Non Hodgkin's Lymphoma:
diagnosis and management

Appendix I: Search Strategies
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Developed for NICE by the National Collaborating Centre for Cancer

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Search strategies

NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Non-Hodgkin's Lymphoma	**Literature search summary**
Question title: Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of suspected non-Hodgkin's lymphoma at first presentation?	

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-3/2015	3840	286	13/03/2015
Premedline	All-3/2015	156	9	18/03/2015
Embase	All-3/2015	3159	200	16/03/2015
Cochrane Library	All-3/2015	74	3	18/03/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-3/2015	5030	187	20/03/2015

Total References retrieved (after de-duplication): 521

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	3/2015-9/2015	22	0	25/09/2105
Premedline	3/2015-9/2015	46	5	25/09/2105
Embase	3/2015-9/2015	132	6	25/09/2105
Cochrane Library	3/2015-9/2015	1	0	25/09/2105
Web of Science (SCI & SSCI) and ISI Proceedings	3/2015-9/2015	173	8	25/09/2105

Total References retrieved (after de-duplication): 13

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

1. exp Lymphoma/di, pa [Diagnosis, Pathology]
2. exp Lymphoma, Non-Hodgkin/di, pa [Diagnosis, Pathology]
3. 1 or 2
4. exp Image-Guided Biopsy/
5. exp Biopsy/
6. (true cut adj biops*).tw.
7. (lymph node adj biops*).tw.
8. core needle biopsy.tw.
9. core biopsy.tw.
10. excision* biopsy.tw.
11. exp Biopsy, Large-Core Needle/
12. exp Flow Cytometry/
13. immunocytochemistry.tw.
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 and 14

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2014	5335	370	30/06/2014
Premedline	All-6/2014	526	24	01/07/2014
Embase	All-6/2014	5102	280	08/07/2014
Cochrane Library	All-6/2014	337	1	10/07/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2014	6586	133	11/07/2014

Total References retrieved (after de-duplication): 607

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	7/2014-9/2015	608	66	25/09/2015
Premedline	7/2014-9/2015	536	41	25/09/2015
Embase	7/2014-9/2015	1288	34	25/09/2015
Cochrane Library	7/2014-9/2015	14	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	7/2014-9/2015	211	14	25/09/2015

Total References retrieved (after de-duplication): 137

Total References search results D1 and D2 combined (after de-duplication): 190

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

1. (diffuse large B-cell or DLBCL).tw.
2. aggressive B-cell*.tw.
3. exp Lymphoma, Large B-Cell, Diffuse/di, ge [Diagnosis, Genetics]
4. exp Burkitt Lymphoma/di, ge [Diagnosis, Genetics]
5. Burkitt Lymphoma.tw.
6. Mediastinal B-cell Lymphoma.tw.
7. or/1-6
8. exp Oligonucleotide Array Sequence Analysis/
9. oligonucleotide array sequence analysis.tw.
10. exp Protein Array Analysis/

11. protein array analysis.tw.
12. exp Gene Expression Profiling/
13. gene expression profil*.tw.
14. exp Germinal Center/
15. germinal centre.tw.
16. activated b-like.tw.
17. exp Molecular Diagnostic Techniques/
18. molecular diagnosis.tw.
19. (DNA sequenc* or DNA microarray*).tw.
20. exp In Situ Hybridization, Fluorescence/
21. (flourescence in situ hybridization or FISH).tw.
22. chromosomal abnormalit*.tw.
23. (chromosomal abnormalit* or genetic abnormalit*).tw.
24. exp Real-Time Polymerase Chain Reaction/
25. (real-time polymerase chain reaction or realtime PCR).tw.
26. exp Translocation, Genetic/
27. (genetic translocation or myc translocation or rearrangement*).tw.
28. exp Genetic Testing/mt [Methods]
29. (genetic test* or genomic test* or phenotypic test*).tw.
30. exp Prognosis/
31. (prognosis or prognostic).tw.
32. (subgroup* or subset* or subtype* or subclassifi*).tw.
33. or/8-32
34. exp Immunohistochemistry/
35. (immunohistochemistry or immunocytochemistry or flow cytometry).tw.
36. exp Antibodies, Monoclonal/ad [Administration & Dosage]
37. exp Antibodies, Monoclonal, Murine-Derived/ad [Administration & Dosage]
38. (?CHOP* or doxorubicin or prednison or vincristine or rituximab).tw.
39. chemotherapy.tw.
40. exp Cyclophosphamide/ad, tu [Administration & Dosage, Therapeutic Use]
41. exp Antineoplastic Combined Chemotherapy Protocols/ad, tu [Administration & Dosage, Therapeutic Use]
42. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. 33 or 42
44. 7 and 43

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on

non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-10/2014	2989	513	29/10/2014
Premedline	2000-10/2014	441	32	10/11/2014
Embase	2000-10/2014	5309	636	07/11/2014
Cochrane Library	2000-10/2014	88	8	10/11/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2000-10/2014	2099	160	10/11/2014

Total References retrieved (after de-duplication): 1018

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2014-9/2015	150	17	25/09/2015
Premedline	11/2014-9/2015	336	27	25/09/2015
Embase	11/2014-9/2015	343	50	25/09/2015
Cochrane Library	11/2014-9/2015	2	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	11/2014-9/2015	281	32	25/09/2015

Total References retrieved (after de-duplication): 90

Total References search results D1 and D2 combined (after de-duplication): 190

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

1. Lymphoma, Large B-Cell, Diffuse/ge [Genetics]

2. Lymphoma, B-Cell/cl [Classification]

3. Burkitt Lymphoma/ge [Genetics]
4. diffuse large B-cell lymphoma*.tw.
5. double-hit lymphoma*.tw.
6. (DLBCL or DHL).tw.
7. aggressive b-cell.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Antibodies, Monoclonal, Murine-Derived/tu [Therapeutic Use]
10. Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
11. Cyclophosphamide/tu [Therapeutic Use]
12. exp Cytogenetic Analysis/
13. DNA-Binding Proteins/an [Analysis]
14. DNA-Binding Proteins/ge [Genetics]
15. Proto-Oncogene Proteins c-bcl-2/ge [Genetics]
16. Proto-Oncogene Proteins c-myc/ge [Genetics]
17. exp In Situ Hybridization, Fluorescence/
18. Flow Cytometry/st [Standards]
19. fluorescent in situ hybridization.tw.
20. FISH.tw.
21. exp Translocation, Genetic/
22. exp Genes, myc/
23. exp Gene Rearrangement/ge [Genetics]
24. exp Chromosome Breakpoints/
25. Myc breakpoint.tw.
26. exp Immunohistochemistry/
27. exp Immunophenotyping/
28. exp Paraffin Embedding/
29. immunohistochemistry.tw.
30. exp Gene Expression Profiling/
31. gene expression pofiling.tw.
32. realtime PCR.tw.
33. exp Sequence Analysis, DNA/
34. DNA sequencing.tw.
35. standard.tw.
36. test* strateg*.tw.
37. therapeutic stratification.tw.
38. (International prognostic index or IPI).tw.
39. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or

31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp Disease-Free Survival/

41. exp Prognosis/

42. Prognosis.tw.

43. exp Survival Rate/

44. exp Treatment Outcome/

45. 40 or 41 or 42 or 43 or 44

46. 39 or 45

47. 8 and 46

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 2000 onwards applied. Rationale: Interventions included in PICO published after 2000. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1997-11/2014	4702	430	24/11/2014
Premedline	1997-11/2014	916	31	25/11/2014
Embase	1997-11/2014	4243	286	10/12/2014
Cochrane Library	1997-11/2014	191	5	25/11/2014
Web of Science (SCI & SSCI) and ISI Proceedings	1997-11/2014	3862	255	22/12/2014

Total References retrieved for topics E1, E2 and E3 (after de-duplication): 1035

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	12/2014-9/2015	93	8	25/09/2015
Premedline	12/2014-9/2015	473	31	25/09/2015
Embase	12/2014-9/2015	330	23	25/09/2015
Cochrane Library	12/2014-9/2015	0	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	12/2014-9/2015	173	15	25/09/2015

Total References retrieved (after de-duplication): 57

Total References retrieved for topics E1, E2 and E3 (after de-duplication): 94

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

1. exp Lymphoma/di, ri [Diagnosis, Radionuclide Imaging]
2. non-hodgkin* Lymphoma.tw.
3. exp Lymphoma, Non-Hodgkin/
4. non hodgkin lymphoma.tw.
5. 1 or 2 or 3 or 4
6. exp Diagnostic Imaging/
7. exp Tomography, Emission-Computed/ or exp Positron-Emission Tomography/
8. PET-CT.tw.
9. (histopathol* adj exam*).tw.
10. (clinical adj assess*).tw.

11. CT.tw.
12. exp Tomography, X-Ray Computed/
13. (Bone marrow adj biops*).tw.
14. pre-treatment staging.tw.
15. Fluorodeoxyglucose F18/du [Diagnostic Use]
16. initial assessment*.tw.
17. Ann Arbor.tw.
18. baseline staging.tw.
19. (18F-Fluorodeoxyglucose or FDG).tw.
20. PET.tw.
21. stage migration.tw.
22. functional imaging.tw.
23. PET-CT enhanced.tw.
24. contrast enhanced CT.tw.
25. radiological follow-up.tw.
26. treatment change*.tw.
27. exp Multimodal Imaging/mt [Methods]
28. exp Neoplasm Staging/mt [Methods]
29. response assessment.tw.
30. diagnostic accuracy.tw.
31. gallium scintigraphy.tw.
32. Monitoring, Physiologic/mt [Methods]
33. Neoplasm Invasiveness/ri [Radionuclide Imaging]
34. exp Image Interpretation, Computer-Assisted/
35. Immunohistochemistry/st [Standards]
36. exp Biopsy/
37. Bone Marrow/ra [Radiography]
38. Bone Marrow/ri [Radionuclide Imaging]
39. Image Enhancement/mt [Methods]
40. exp "Predictive Value of Tests"/
41. Gallium Radioisotopes/du [Diagnostic Use]
42. exp "Reproducibility of Results"/
43. or/6-42
44. 5 and 43
45. limit 44 to yr="1997 -Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 1997 applied. Rationale: Relevant articles on PET published from this point forward. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1998-1/2015	2711	115	11/02/2015
Premedline	1998-1/2015	375	24	18/02/2015
Embase	1998-1/2015	1577	187	19/02/2015
Cochrane Library	1998-1/2015	22	5	23/02/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1998-1/2015	654	118	20/02/2015

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2/2015-9/2015	63	4	25/09/2015
Premedline	2/2015-9/2015	207	15	25/09/2015
Embase	2/2015-9/2015	142	19	25/09/2015
Cochrane Library	2/2015-9/2015	1	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2/2015-9/2015	82	14	25/09/2015

Total References retrieved (after de-duplication): 31

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

1. exp Lymphoma, Large B-Cell, Diffuse/
2. diffuse large b-cell lymphoma.tw.
3. DLBCL.tw.
4. 1 or 2 or 3

5. first-line treatment.tw.

6. progression-free survival.tw.

7. lesion size.tw.

8. Tumour volume.tw.

9. exp Positron-Emission Tomography/

10. (Positron Emission Tomography or PET).tw.

11. PET-CT.tw.

12. exp Fluorodeoxyglucose F18/

13. Fluorine-18-fluorodeoxyglucose.tw.

14. Interim positron emission tomography scan*.tw.

15. Interim 18-FDG-PET.tw.

16. (18F fluoro-2-deoxy-D-glucose positron emission tomography or FDG-PET).tw.

17. early prognosis.tw.

18. Early restaging.tw.

19. predict*.tw.

20. exp Prognosis/

21. CT scan.tw.

22. exp Tomography, X-Ray Computed/

23. interim.tw.

24. or/5-23

25. 4 and 24

26. limit 25 to yr="1998 –Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 1998 applied. Rationale: Whilst the commercial use of PET-CT started after 2000, relevant articles from 1998 onwards on the use of PET for interim assessments. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1997-2/2015	965	86	24/02/2015
Premedline	1997-2/2015	45	8	24/02/2015
Embase	1997-2/2015	822	108	02/03/2015
Cochrane Library	1997-2/2015	12	1	02/03/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1997-2/2015	138	19	03/03/2015

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	3/2015-9/2015	56	4	25/09/2015
Premedline	3/2015-9/2015	25	2	25/09/2015
Embase	3/2015-9/2015	66	8	25/09/2015
Cochrane Library	3/2015-9/2015	1	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	3/2015-9/2015	24	4	25/09/2015

Total References retrieved (after de-duplication): 12

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

1. exp Lymphoma, Large B-Cell, Diffuse/
2. diffuse large b-cell lymphoma.tw.
3. DLBCL.tw.
4. 1 or 2 or 3
5. exp Positron-Emission Tomography/
6. (Positron Emission Tomography or PET).tw.
7. PET-CT.tw.
8. exp Fluorodeoxyglucose F18/

9. Fluorine-18-fluorodeoxyglucose.tw.

10. (18F fluoro-2-deoxy-D-glucose positron emission tomography or FDG-PET).tw.

11. exp Prognosis/

12. CT scan.tw.

13. exp Tomography, X-Ray Computed/

14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. 4 and 14

16. response assessment.tw.

17. (post?therapy or post?treatment).tw.

18. (after or final).tw.

19. residual mass*.tw.

20. (end adj1 treatment).tw.

21. (end adj1 therapy).tw.

22. post?induction.tw.

23. restaging.tw.

24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. 15 and 24

26. limit 25 to yr="1997 –Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 1997 applied. Rationale: Relevant articles on PET published from this point forward. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title: What is the most effective first-line treatment for people with stage IIa follicular lymphoma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2014	2408	323	05/01/2015
Premedline	All-2014	206	35	20/12/2014
Embase	All-2014	4512	457	07/01/2015
Cochrane Library	All-2014	340	75	30/12/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-2014	723	163	07/01/2015

Total References retrieved (after de-duplication): 712

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1/2015-9/2015	37	8	25/09/2015
Premedline	1/2015-9/2015	92	19	25/09/2015
Embase	1/2015-9/2015	201	25	25/09/2015
Cochrane Library	1/2015-9/2015	5	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1/2015-9/2015	38	12	25/09/2015

Total References retrieved (after de-duplication): 44

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

1. exp Lymphoma, Follicular/dt, rt, th [Drug Therapy, Radiotherapy, Therapy]
2. follicular lymphoma*.tw.
3. early stage follicular lymphoma.tw.
4. 1 or 2 or 3
5. first line treatment*.tw.
6. exp Radiotherapy/
7. exp Drug Therapy/
8. exp Antineoplastic Combined Chemotherapy Protocols/
9. exp Interferons/
10. Interferon*.tw.
11. (Observ* or wait* or watch* or defer*).tw.
12. radiotherap*.tw.

13. low dose*.tw.
14. exp Craniospinal Irradiation/ or exp Cranial Irradiation/
15. (irradiat* adj (neck or axilla or supraclavicular fossa)).tw.
16. recurren*.tw.
17. (PET adj staging).tw.
18. exp Immunotherapy/
19. immunotherapy.tw.
20. immunochemotherapy.tw.
21. field radiation therapy.tw.
22. (involved or extended).tw.
23. exp Antibodies, Monoclonal/
24. rituximab.tw.
25. exp Chemoradiotherapy/
26. exp Dose Fractionation/
27. exp Radiotherapy Dosage/
28. exp Neoplasm Recurrence, Local/
29. exp Positron-Emission Tomography/
30. exp Neoplasm Staging/
31. or/5-30
32. 4 and 31

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-9/2014	400	237	02/09/2014
Premedline	All-9/2014	20	12	02/09/2014
Embase	All-9/2014	1242	399	08/09/2014
Cochrane Library	All-9/2014	23	17	08/09/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-9/2014	1222	330	09/09/2014

Total References retrieved (after de-duplication): 769

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2014-9/2015	22	6	25/09/2015
Premedline	10/2014-9/2015	10	5	25/09/2015
Embase	10/2014-9/2015	185	39	25/09/2015
Cochrane Library	10/2014-9/2015	0	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	10/2014-9/2015	98	14	25/09/2015

Total References retrieved (after de-duplication): 47

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

1. exp Lymphoma, Follicular/
2. follicular lymphoma*.tw.
3. 1 or 2
4. exp Transplantation, Autologous/
5. Autologous transplant*.tw.
6. exp Transplantation, Homologous/
7. (allogeneic transplant* or allogenic transplant*).tw.
8. reduced intensity transplant*.tw.
9. Hematopoietic Stem Cell Transplantation/ or Stem Cell Transplantation/ or Bone Marrow Transplantation/ or Graft vs Host Reaction/
10. exp Transplantation Conditioning/
11. exp Peripheral Blood Stem Cell Transplantation/
12. HD-ASCT*.tw.
13. alloHSCT*.tw.
14. ASCT*.tw.
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-1/2015	1069	333	09/02/2015
Premedline	All-1/2015	50	13	24/02/2015
Embase	All-1/2015	2185	563	24/02/2015
Cochrane Library	All-1/2015	555	247	09/02/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-1/2015	1125	225	10/02/2015

Total References retrieved (after de-duplication): 932

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2/2015-9/2015	248 sifted	22	25/09/2015
Premedline	2/2015-9/2015	81	11	25/09/2015
Pubmed	2/2015-9/2015	48	4	25/09/2015
Embase	2/2015-9/2015	306 sifted	28	25/09/2015
Cochrane Library	2/2015-9/2015	46 sifted	1	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2/2015-9/2015	262 sifted	9	25/09/2015

Total References retrieved (after de-duplication): 55

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

1 exp Lymphoma/
2 exp Hematologic Neoplasms/
3 ((hemato$ or haemato$) adj5 (cancer$ or neoplasm$ or malign$)).mp.
4 lymphom$.mp.
5 non-hodgkin$.mp.
6 nonhodgkin$.mp.
7 (non adj hodgkin$).mp.
8 NHL.mp.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Lymphoma, Follicular/
11 ((follicul$ or nodular$ or indolent$) adj2 lymph$).tw.
12 (diffus$ adj lymphom$).tw.
13 ((low-grad$ or low grad$) adj3 lymph$).tw.
14 (follic$ adj2 (center$ or centro$) adj lymph$).tw.
15 (brill-symmer$ or brill symmer$).tw.
16 ((centroblast$ or zentroblast$ or centrocy$ or zentrozyt$ or zentrocyt$) adj lymph$).tw.
17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 9 or 17
19 Watchful Waiting/

20 (watch$ adj2 wait$).tw.
21 (active adj1 (surveillance or monitoring)).tw.
22 (expectant adj (surveillance or monitoring or manag$)).tw.
23 ((defer$ or delay$) adj3 (treatment or therap$)).tw.
24 (watchful adj (observation or surveillance or monitoring)).tw.
25 conservative monitoring.tw.
26 (immediat$ adj (treatment or therap$)).tw.
27 initial* untreat*.tw.
28 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 18 and 28

2. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected. An additional search of the patient population (Medline Line 18 and Embase Line 17) with ScHARR QoL search filter was undertaken to supplement the search result for this topic.

3. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-3/2014	1084	118	15/04/2014
Premedline	All-3/2014	327	13	21/04/2014
Embase	All-3/2014	1760	103	24/04/2014
Cochrane Library	All-3/2014	97	4	24/04/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-3/2014	110	48	24/04/2014

Total References retrieved (after de-duplication): 217

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2014-9/2015	70	14	25/09/2015
Premedline	4/2014-9/2015	304	2	25/09/2015
Embase	4/2014-9/2015	395	16	25/09/2015
Cochrane Library	4/2014-9/2015	1	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	4/2014-9/2015	25	7	25/09/2015

Total References retrieved (after de-duplication): 28

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

1. exp Lymphoma, Follicular/
2. follicular lymphoma*.tw.
3. 1 or 2
4. exp Lymphoma, Large B-Cell, Diffuse/
5. diffuse large b-cell lymphoma*.tw.
6. 4 or 5
7. 3 or 6
8. exp Composite Lymphoma/
9. composite lymphoma*.tw.
10. discordant lymphoma*.tw.
11. 8 or 9 or 10

12. histolog* transform*.tw.
13. Transformed Follicular Lymphoma.tw.
14. (double hit adj lymphoma).tw.
15. c-myc.tw.
16. (lymphoma adj5 bone marrow).tw.
17. exp Cell Transformation, Neoplastic/
18. 12 or 13 or 14 or 15 or 16 or 17
19. 11 or 18
20. 7 or 19
21. exp Transplantation, Autologous/
22. high-dose therapy.tw.
23. autologous stem cell.tw.
24. ASCT.tw.
25. (International prognostic Index or IPI).tw.
26. (autograft or allograft).tw.
27. exp Transplantation, Homologous/
28. (allogeneic transplantation or allgenic transplantation).tw.
29. exp Hematopoietic Stem Cell Transplantation/ or exp Stem Cell Transplantation/
30. allogeneic stem cell.tw.
31. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. exp Radiotherapy/
33. radiotherapy.tw.
34. exp Radioimmunotherapy/
35. 32 or 33 or 34
36. rituximab.tw.
37. 31 or 35 or 36
38. 20 and 37

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-3/2014	835	297	01/04/2014
Premedline	All-3/2014	90	25	01/04/2014
Embase	All-3/2014	1624	191	04/04/2014
Cochrane Library	All-3/2014	70	16	08/04/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-3/2014	1461	298	08/04/2014

Total References retrieved (after de-duplication): 602

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2014-9/2015	51	9	25/09/2015
Premedline	4/2014-9/2015	52	7	25/09/2015
Embase	4/2014-9/2015	358	32	25/09/2015
Cochrane Library	4/2014-9/2015	11	1	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	4/2014-9/2015	96	9	25/09/2015

Total References retrieved (after de-duplication): 42

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

1. Lymphoma, B-Cell, Marginal Zone/dt [Drug Therapy]
2. Mucosal Associated Lymphoid Tissue.tw.
3. MALT.tw.
4. Extranodal marginal zone lymphoma.tw.
5. (gastric adj MALT).tw.
6. or/1-5
7. exp Anti-Bacterial Agents/
8. Antibiotic*.tw.
9. Antimicrobial.tw.
10. exp Amoxicillin/
11. amoxicillin.tw.
12. exp Clarithromycin/
13. clarithromycin.tw.
14. omeprasole.tw.

15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Radiotherapy/
17. Radiotherapy.tw.
18. irradication.tw.
19. 16 or 17 or 18
20. exp Drug Therapy/
21. exp Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
22. exp Chlorambucil/
23. chlorambucil.tw.
24. exp Cyclophosphamide/
25. Cyclophosphamide.tw.
26. 20 or 21 or 22 or 23 or 24 or 25
27. exp Immunotherapy/
28. Immunotherapy.tw.
29. exp Antibodies, Monoclonal/tu [Therapeutic Use]
30. rituximab.tw.
31. (Chemo-immunotherapy or Radio-immunotherapy).tw.
32. exp Radioimmunotherapy/
33. tiuxetan.tw.
34. 27 or 28 or 29 or 30 or 31 or 32 or 33
35. (surgery or operat*).tw.
36. ((watch adj1 wait) or defer* or monitor*).tw.
37. 15 or 19 or 26 or 34 or 35 or 36
38. 6 and 37

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-2014	925	257	13/01/2015
Premedline	2000-2014	106	16	13/01/2015
Embase	2000-2014	2237	248	21/01/2015
Cochrane Library	2000-2014	248	83	26/01/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2000-2014	1646	123	26/01/2015

Total References retrieved (after de-duplication): 550

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1/2015-9/2015	16	4	25/09/2015
Premedline	1/2015-9/2015	67	28	25/09/2015
Embase	1/2015-9/2015	145	28	25/09/2015
Cochrane Library	1/2015-9/2015	1	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1/2015-9/2015	144	17	25/09/2015

Total References retrieved (after de-duplication): 51

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

1. exp Lymphoma, Mantle-Cell/
2. mantle cell lymphoma.tw.
3. (indolent adj10 mantle).tw.
4. (blastoid adj10 mantle).tw.
5. 1 or 2 or 3 or 4
6. first line treatment*.tw.
7. exp Radiotherapy/
8. exp Drug Therapy/
9. exp Antineoplastic Combined Chemotherapy Protocols/

10. (Observ* or wait* or watch* or defer*).tw.
11. radiotherap*.tw.
12. exp Immunotherapy/
13. immunotherapy.tw.
14. immunochemotherapy.tw.
15. exp Antibodies, Monoclonal/
16. rituximab.tw.
17. (Mantle-cell international prognostic index or MIPI).tw.
18. (CHOP or DHAP).tw.
19. R-DHAP.tw.
20. myeloablative radiochemotherapy.tw.
21. (fludarabine or cyclophosphamide).tw.
22. systemic treatment.tw.
23. exp Transplantation, Autologous/
24. autologous stem cell transplantation.tw.
25. (relapse adj10 mantle).tw.
26. exp Cytarabine/
27. (Cytosine arabinoside or Cytarabine).tw.
28. (FCM or MCP or CVP or COP).tw.
29. fitness.tw.
30. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 5 and 30
32. limit 31 to yr="2000 -Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 2000 onwards applied. Rationale: Reliable diagnosis, previously grouped with low grade lymphomas. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-3/2015	1228	260	24/03/2015
Premedline	2000-3/2015	139	21	24/03/2015
Embase	2000-3/2015	3237	355	14/04/2015
Cochrane Library	2000-3/2015	67	21	16/04/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2000-3/2015	902	189	15/04/2015

Total References retrieved (after de-duplication): 571

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2015-9/2015	11	1	25/09/2015
Premedline	4/2015-9/2015	61	7	25/09/2015
Embase	4/2015-9/2015	99	20	25/09/2015
Cochrane Library	4/2015-9/2015	0	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	4/2015-9/2015	28	10	25/09/2015

Total References retrieved (after de-duplication): 25

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

1. exp Lymphoma, Mantle-Cell/
2. (mantle cell lymphoma or MCL).tw.
3. 1 or 2
4. chemotherapy.tw.
5. Antineoplastic Combined Chemotherapy Protocols/ or Antibodies, Monoclonal/ or Antibodies, Monoclonal, Murine-Derived/
6. rituximab.tw.
7. exp Combined Modality Therapy/
8. exp Consolidation Chemotherapy/
9. Consolidation.tw.

10. exp Hematopoietic Stem Cell Transplantation/
11. Stem Cell Transplantation/ or Transplantation, Autologous/ or Transplantation Conditioning/ or Bone Marrow Transplantation/ or Transplantation, Homologous/
12. transplantation.tw.
13. exp Peripheral Blood Stem Cell Transplantation/
14. exp Graft vs Host Disease/
15. exp Bone Marrow Purging/
16. exp Bone Marrow/
17. Bone Marrow.tw.
18. exp Vincristine/
19. exp Neoplasm Recurrence, Local/pc [Prevention & Control]
20. exp Salvage Therapy/
21. high-dose therapy.tw.
22. (autologous or allogeneic).tw.
23. immunochemotherapy.tw.
24. chemoimmunotherapy.tw.
25. ASCT.tw.
26. (mantle cell lymphoma international prognostic index-biological or MIPI-B).tw.
27. Molecular relapse*.tw.
28. alloHCT.tw.
29. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 3 and 29
31. limit 30 to yr="2000 -Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 2000 onwards applied. Rationale: Diagnostic uncertainty before 2000. Any possibly relevant material selected.

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-4/2015	1649	141	21/04/2015
Premedline	2000-4/2015	259	18	21/04/2015
Embase	2000-4/2015	4105	165	12/05/2015
Cochrane Library	2000-4/2015	132	32	12/05/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2000-4/2015	1100	56	13/05/2015

Total References retrieved (after de-duplication): 323

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2015-9/2015	16	1	25/09/2015
Premedline	5/2015-9/2015	123	10	25/09/2015
Embase	5/2015-9/2015	32	2	25/09/2015
Cochrane Library	5/2015-9/2015	0	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	5/2015-9/2015	40	4	25/09/2015

Total References retrieved (after de-duplication): 11

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

1. exp Lymphoma, Mantle-Cell/
2. (mantle cell lymphoma or MCL).tw.
3. 1 or 2
4. chemotherapy.tw.
5. Antineoplastic Combined Chemotherapy Protocols/ or Antibodies, Monoclonal/ or Antibodies, Monoclonal, Murine-Derived/
6. rituximab.tw.
7. exp Consolidation Chemotherapy/
8. exp Interferon-alpha/
9. Interferon.tw.
10. exp Induction Chemotherapy/
11. maintenance.tw.
12. R-CHOP.tw.

13. nucleoside analogue therapy.tw.

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp Watchful Waiting/

16. (Observ* or watch* or wait* or defer*).tw.

17. transplantation.tw.

18. 15 or 16 or 17

19. 15 or 18

20. 3 and 19

21. limit 20 to yr="2000 -Current"

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 2000 onwards applied. Rationale: Diagnostic uncertainty before 2000. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title: What is the effectiveness of consolidation radiotherapy when given following immuno-chemotherapy as first-line treatment for people with advanced stage diffuse large B-cell lymphoma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2003-4/2014	644	104	28/04/2014
Premedline	2003-4/2014	120	17	28/04/2014
Embase	2003-4/2014	1395	184	06/05/2014
Cochrane Library	2003-4/2014	96	23	06/05/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2003-4/2014	1374	180	07/05/2014

Total References retrieved (after de-duplication): 370

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	05/2014-9/215	117	22	25/09/2015
Premedline	05/2014-9/215	110	13	25/09/2015
Embase	05/2014-9/215	374	36	25/09/2015
Cochrane Library	05/2014-9/215	1	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	05/2014-9/215	247	14	25/09/2015

Total References retrieved (after de-duplication): 69

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

1. exp Lymphoma, Large B-Cell, Diffuse/
2. diffuse large B-cell lymphoma.tw.
3. (advanced adj5 B-Cell Lymphoma).tw.
4. DLBCL.tw.
5. (bulk* adj5 B-Cell Lymphoma).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Antineoplastic Combined Chemotherapy Protocols/
8. CHOP.tw.
9. immunochemotherapy.tw.
10. exp Combined Modality Therapy/
11. 7 or 8 or 9 or 10
12. 6 and 11

13. exp Radiotherapy/ or exp Radiotherapy, Adjuvant/
14. (PET or PET-CT).tw.
15. radiotherapy.tw.
16. exp Positron-Emission Tomography/
17. exp Tomography, X-Ray Computed/
18. 13 or 14 or 15 or 16 or 17
19. (second-line adj1 chemotherapy).tw.
20. exp Salvage Therapy/
21. (salvage adj1 chemotherapy).tw.
22. (watch* or wait* or observ* or defer*).tw.
23. transplantation.tw.
24. 19 or 20 or 21 or 22 or 23
25. 18 or 24
26. 12 and 25
27. limit 26 to '2003-Current'

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits from 2003 onwards applied. Rationale: Rationale: Treatment options changed during 2003 with the introduction of Rituximab. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title:

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

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-1/2015	727	193	27/01/2015
Premedline	All-1/2015	174	37	28/01/2015
Embase	All-1/2015	2308	322	04/02/2015
Cochrane Library	All-1/2015	102	4	09/02/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-1/2015	701	170	09/-2/2015

Total References retrieved (after de-duplication): 520

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2/2015-9/2015	14	2	25/09/2015
Premedline	2/2015-9/2015	90	12	25/09/2015
Embase	2/2015-9/2015	141	10	25/09/2015
Cochrane Library	2/2015-9/2015	3	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	2/2015-9/2015	39	7	25/09/2015

Total References retrieved (after de-duplication): 22

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

1. exp Lymphoma, Large B-Cell, Diffuse/
2. diffuse large B-cell lymphoma*.tw.
3. aggressive B-cell.tw.
4. DLBCL.tw.
5. 1 or 2 or 3 or 4
6. exp Central Nervous System/
7. (central nervous system or CNS).tw.
8. (testicular or bone marrow or pharynx or facial sinus or breast or primary bone or paraspinal or epidural or kidney).tw.
9. subclinical CNS.tw.

10. 6 or 7 or 8 or 9
11. 5 and 10
12. (International prognostic index or IPI).tw.
13. exp L-Lactate Dehydrogenase/
14. Extranodal.tw.
15. (Cerebrospinal fluid or CSF).tw.
16. Omaya reservoir.tw.
17. Schedule.tw.
18. exp Antineoplastic Combined Chemotherapy Protocols/
19. Intravenous.tw.
20. CNS prophylaxis.tw.
21. relapse.tw.
22. Parenchymal.tw.
23. Meningeal.tw.
24. exp Risk Factors/
25. exp Prognosis/
26. exp Antibodies, Monoclonal/
27. rituximab.tw.
28. Lactate Dehydrogenase.tw.
29. exp Flow Cytometry/
30. Flow Cytometry.tw.
31. exp Immunophenotyping/
32. Immunophenotyping.tw.
33. predict.tw.
34. exp Methotrexate/ad, tu [Administration & Dosage, Therapeutic Use]
35. Intrathecal.tw.
36. high risk.tw.
37. or/12-36
38. 11 and 37

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected. Do to the close nature of both topic questions the searches were combined to one search.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2015	3659	729	19/06/2015
Premedline	All-6/2015	529	57	23/06/2015
Embase	All-6/2015	7644	1069	06/07/2015
Cochrane Library	All-6/2015	485	79	07/07/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2015	2247	360	07/07/2015

Total References retrieved (after de-duplication): 1657

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	7/2015-9/2015	0	0	25/09/2015
Premedline	7/2015-9/2015	152	7	25/09/2015
Embase	7/2015-9/2015	139	16	25/09/2015
Cochrane Library	7/2015-9/2015	6	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	7/2015-9/2015	11	3	25/09/2015

Total References retrieved (after de-duplication): 19

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

1. exp Salvage Therapy/
2. exp Combined Modality Therapy/
3. exp Bone Marrow Transplantation/
4. reduced intensity transplant*.tw.
5. exp Hematopoietic Stem Cell Transplantation/
6. exp Graft vs Tumor Effect/
7. consolidat*.tw.
8. exp Platinum Compounds/
9. exp Ifosfamide/
10. exp Transplantation, Autologous/
11. Autologous transplant*.tw.
12. exp Transplantation, Homologous/

13. Allogeneic transplant*.tw.
14. Allogenic transplant*.tw.
15. salvage treatment*.tw.
16. salvage*.tw.
17. chemotherap*.tw.
18. exp Antineoplastic Combined Chemotherapy Protocols/
19. exp Drug Therapy/
20. exp Immunotherapy/
21. Chemoimmunotherap*.tw.
22. or/1-21
23. malignant lymphoma.tw.
24. agressive lymphoma.tw.
25. aggressive NHL.tw.
26. indolent Non Hodgkin Lymphoma.tw.
27. Lymphoid malignancy.tw.
28. (DLBCL or NHL).tw.
29. diffuse large b-cell lymphoma*.tw.
30. exp Lymphoma, Large B-Cell, Diffuse/
31. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. (refractory or recurrent or relaps* or remission*).tw.
33. exp Recurrence/
34. 32 or 33
35. 31 and 34
36. 22 and 35

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title: The most effective first-line treatment for people with Burkitt's lymphoma?

Question no: M

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All – 3/2014	936	159	24/03/2014
Premedline	All – 3/2014	33	12	24/03/2014
Embase	All – 3/2014	1995	196	26/03/2014
Cochrane Library	All – 3/2014	69	13	25/03/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All – 3/2014	935	114	26/03/2014

Total References retrieved (after de-duplication): 352

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2014-9/2015	26	8	25/09/2015
Premedline	4/2014-9/2015	39	14	25/09/2015
Embase	4/2014-9/2015	220	20	25/09/2015
Cochrane Library	4/2014-9/2015	8	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	4/2014-9/2015	122	15	25/09/2015

Total References retrieved (after de-duplication): 45

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

1. exp Burkitt Lymphoma/
2. Burkitt Lymphoma.tw.
3. 1 or 2
4. chemotherapy.tw.
5. (first adj line*).tw.
6. exp Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
7. hyper-CVAD.tw.
8. Codox*.tw.
9. exp Antibodies, Monoclonal/tu [Therapeutic Use]
10. monoclonal antibody.tw.
11. exp Antibodies, Monoclonal, Murine-Derived/tu [Therapeutic Use]
12. rituximab.tw.

13. EPOCH-R.tw.

14. Da-epoch*.tw.

15. exp Cyclophosphamide/tu [Therapeutic Use]

16. Chemo-immunotherapy.tw.

17. exp Combined Modality Therapy/

18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 3 and 18

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-4/2014	1285	182	12/05/2014
Premedline	2000-4/2014	27	7	12/05/2014
Embase	2000-4/2014	3031	171	13/05/2014
Cochrane Library	20000-4/2014	50	4	13/05/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2000-4/2014	954	129	13/05/2014

Total References retrieved (after de-duplication): 379

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2014-9/2015	73	24	25/09/2015
Premedline	5/2014-9/2015	16	10	25/09/2015
Embase	5/2014-9/2015	306	21	25/09/2015
Cochrane Library	5/2014-9/2015	22	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	5/2014-9/2015	77	19	25/09/2015

Total References retrieved (after de-duplication): 57

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

1. exp Lymphoma, T-Cell/
2. ((peripheral or mature) adj T-Cell lymphoma).tw.
3. "peripheral T-Cell lymphoma not otherwise specified".tw.
4. (PTCL or PTCL-NOS).tw.
5. Angioimmunoblastic T-Cell lymphoma.tw.
6. AITL.tw.
7. (high grade adj lymphoma).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Drug Therapy, Combination/
10. (CHOP or CHOEP or GEM-P or PEGS or ACVBP or MEGA CHOEP).tw.
11. exp Cyclophosphamide/
12. Cyclophosphamide.tw.

13. exp Vincristine/
14. Vincristine.tw.
15. exp Doxorubicin/
16. Doxorubicin.tw.
17. exp Prednisolone/
18. Prednisolone.tw.
19. exp Etoposide/
20. Etoposide.tw.
21. exp Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
22. Gemcitabine.tw.
23. first-line.tw.
24. (chemo-immunotherapy or immunochemotherapy).tw.
25. exp Antibodies, Monoclonal/
26. Antibodies, Monoclonal.
27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 8 and 27

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits applied. Rationale|: date limit included due to large volume of evidence and significant change in practice post 2000. Any possibly relevant material selected.

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000-4/2014	419	150	20/05/2014
Premedline	2000-4/2014	9	8	20/05/2014
Embase	2000-4/2014	1478	196	22/05/2014
Cochrane Library	2000-4/2014	56	3	22/05/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2000-4/2014	1199	100	22/05/2014

Total References retrieved (after de-duplication): 330

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2014-9/2015	42	18	25/09/2015
Premedline	5/2014-9/2015	13	7	25/09/2015
Embase	5/2014-9/2015	258	74	25/09/2015
Cochrane Library	5/2014-9/2015	22	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	5/2014-9/2015	76	17	25/09/2015

Total References retrieved (after de-duplication): 73

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

1. exp Lymphoma, T-Cell/
2. ((peripheral or mature) adj T-Cell lymphoma).tw.
3. "peripheral T-Cell lymphoma not otherwise specified".tw.
4. (PTCL or PTCL-NOS).tw.
5. Angioimmunoblastic T-Cell lymphoma.tw.
6. AITL.tw.
7. (high grade adj lymphoma).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Transplantation, Homologous/
10. Allogeneic transplant*.tw.
11. exp Transplantation, Autologous/
12. (high adj dose).tw.
13. autologous stem cell transplantation*.tw.

14. first remission*.tw.
15. (ASCT or alloHSCT).tw.
16. (consolidation adj5 ASCT).tw.
17. exp Stem Cell Transplantation/
18. consolidation.tw.
19. reduced intensity.tw.
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. expectant observation*.tw.
22. exp Watchful Waiting/
23. (watch adj wait).tw.
24. 21 or 22 or 23
25. 20 or 24
26. 8 and 25

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only. Date limits applied. Rationale|: date limit included due to large volume of evidence and significant change in practice post 2000. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-9/2014	3169	83	29/09/2014
Premedline	All-9/2014	134	3	13/10/2014
Embase	All-9/2014	3984	50	13/10/2014
Cochrane Library	All-9/2014	659	3	13/10/2014
Psychinfo	All-9/2014	28	8	13/10/2014
Web of Science (SCI & SSCI) and ISI Proceedings	All-9/2014	797	12	13/10/2014

Total References retrieved (after de-duplication): 135

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	9/2014-9/2015	81	7	25/09/2015
Premedline	9/2014-9/2015	100	3	25/09/2015
Embase	9/2014-9/2015	327	22	25/09/2015
Cochrane Library	9/2014-9/2015	0	0	25/09/2015
Psychinfo	9/2014-9/2015	2	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	9/2014-9/2015	116	1	25/09/2015

Total References retrieved (after de-duplication): 31

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

1. Pamphlets/
2. exp Audiovisual Aids/
3. exp Internet/
4. exp Self-Help Groups/
5. (support* adj2 (group* or meet*)).tw.
6. exp Patient Education/mt [Methods]
7. ((inform* or support*) adj2 (tool* or method* or group*)).tw.
8. (leaflet* or diary or diaries or booklet* or guidebook* or sheet* or pamphlet* or flyer* or flier*).tw.
9. (prompt* or coach*).tw.
10. (checklist* or check list*).tw.

11. (written or write).tw.
12. question*.tw.
13. (card* or helpcard*).tw.
14. (video* or tape* or cd* or film* or dvd* or telephone* or phone* or computer* or internet or electronic).tw.
15. (information adj3 need*).tw.
16. information material*.tw.
17. (patient* adj3 information).tw.
18. (information adj3 web*).tw.
19. (information adj3 print*).tw.
20. (information adj3 electronic*).tw.
21. ((patient* or care*) adj pathway*).tw.
22. information deliver*.tw.
23. interactive session*.tw.
24. Health Services Accessibility/
25. Office Visits/
26. Remote Consultation/
27. Physician-Patient Relations/
28. Nurse-Patient Relations/
29. Professional-Patient Relations/
30. Professional-Family Relations/
31. ((patient* or consumer* or carer* or caregiver* or spouse* or famil* or relati*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
32. ((personal or interpersonal or individual*) adj2 (decision* or choice* or preference* or support* or participat* or educat*)).tw.
33. Patient Education as Topic/
34. exp social support/
35. exp hotlines/
36. ((hot or help* or tele* or phone) adj (line* or support)).tw.
37. Communication/
38. (communicat* or talking).tw.
39. exp Self-Help Groups/
40. Psychoeducation/
41. Psychotherapy/
42. ((psychosocial or psycho*) adj2 (support* or educat* or need*)).tw.
43. Stress, Psychological/
44. Counseling/
45. "watch and wait".mp.

46. observ.tw.

47. exp Decision Making/

48. exp Fertility/re [Radiation Effects]

49. or/1-48

50. exp Lymphoma, Non-Hodgkin/di, mo, nu, pc, px, rh, th [Diagnosis, Mortality, Nursing, Prevention & Control, Psychology, Rehabilitation, Therapy]

51. 49 and 50

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected. As the subject specific Psychinfo database is relevant for this topic, it was searched and the results included.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

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

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-5/2015	1788	112	21/05/2015
Premedline	All-5/2015	184	32	27/05/2015
Embase	All-5/2015	4558	184	08/06/2015
Cochrane Library	All-5/2015	64	1	08/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-5/2015	877	54	08/06/2015

Total References retrieved (after de-duplication): 271

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2015-9/2015	89	3	25/09/2015
Premedline	6/2015-9/2015	152	2	25/09/2015
Embase	6/2015-9/2015	189	6	25/09/2015
Cochrane Library	6/2015-9/2015	4	0	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	6/2015-9/2015	16	3	25/09/2015

Total References retrieved (after de-duplication): 11

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

1. exp Lymphoma, Large B-Cell, Diffuse/
2. DLBCL.tw.
3. diffuse large b-cell lymphoma.tw.
4. large-cell lymphoma.tw.
5. (Aggressive adj3 lymphoma).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Remission Induction/
8. remission*.tw.
9. disease relapse*.tw.
10. exp Follow-Up Studies/
11. (follow-up or follow up).tw.
12. exp Neoplasm Recurrence, Local/

13. exp Recurrence/
14. recurrence.tw.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. posttherapy surveillance.tw.
17. posttreatment follow-up test*.tw.
18. (detection adj2 relapse*).tw.
19. (monitor* or surveillance*).tw.
20. risk reduction.tw.
21. (blood count or fbc or cbc).tw.
22. haemoglobin.tw.
23. (leukocyte count or platelet* count).tw.
24. exp L-Lactate Dehydrogenase/
25. (lactate dehydrogenase or ldh).tw.
26. exp Liver Function Tests/
27. exp Kidney Function Tests/
28. exp Tomography, X-Ray Computed/
29. exp Fluorodeoxyglucose F18/du [Diagnostic Use]
30. (Positron Emission Tomography or PET).tw.
31. exp Positron-Emission Tomography/
32. exp Multimodal Imaging/
33. CT scan.tw.
34. X-ray.tw.
35. PET-CT.tw.
36. exp Physical Examination/
37. exp "Signs and Symptoms"/
38. (sign* or symptom*).tw.
39. exp Time Factors/
40. exp Risk Factors/
41. exp "Predictive Value of Tests"/
42. exp Monitoring, Physiologic/
43. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. 15 or 43
45. 6 and 44

2. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on

non-hodgkin’s lymphoma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title: What is the effectiveness of surveillance protocols for late adverse effects of treatment in people with non-hodgkin's lymphoma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-3/2015	2508	306	13/04/2015
Premedline	All-3/2015	93	34	12/03/2015
Embase	All-3/2015	2336	273	20/04/2015
Cochrane Library	All-3/2015	226	35	12/03/2015
Psycinfo	All-3/2015	112	68	12/03/2015
AMED	All-3/2015	42	12	12/03/2015
CINAHL	All-3/2015	119	44	16/06/2015
Web of Science (SCI & SSCI) and ISI Proceedings	All-3/2015	1429	239	21/04/2015

Total References retrieved (after de-duplication): 687

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2015-9/2015	295 sifted	10	25/09/2015
Premedline	4/2015-9/2015	99	22	25/09/2015
Pubmed	4/2015-9/2015	23	6	25/09/2015
Embase	4/2015-9/2015	305 sifted	26	25/09/2015
Cochrane Library	4/2015-9/2015	16 sifted	1	25/09/2015
AMED	4/2015-9/2015	1 sifted	0	25/09/2015
Psycinfo	4/2015-9/2015	22 sifted	3	25/09/2015
Cinahl	4/2015-9/2015	16 sifted	2	25/09/2015
Web of Science (SCI & SSCI) and ISI Proceedings	4/2015-9/2015	67 sifted	12	25/09/2015

Total References retrieved (after de-duplication): 54

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

1 exp Lymphoma/
2 exp Hematologic Neoplasms/
3 ((hemato$ or haemato$) adj5 (cancer$ or neoplasm$ or malign$)).mp.
4 lymphom$.mp.
5 non-hodgkin$.mp.
6 nonhodgkin$.mp.
7 (non adj hodgkin$).mp.
8 NHL.mp.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Aftercare/
11 (aftercare or after-care or followup or follow-up or surveillance).m_titl.
12 ((post-treatment or posttreatment) adj1 evaluation$).mp.
13 ((post-treatment or posttreatment) adj1 care).mp.

14 ((post-treatment or posttreatment) adj1 monitoring).mp.
15 10 or 11 or 12 or 13 or 14
16 9 and 15
17 Survivors/
18 "survivor*".m_titl.
19 (late adj effect$).m_titl.
20 17 or 18 or 19
21 9 and 20
22 16 or 21

2. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

3. Health Economics Literature search details

The health economics search undertaken across the population identified any general health economics papers on non-hodgkin's lymphoma.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Non-Hodgkin's Lymphoma Literature search summary

Question title: Scoping Search

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2013	320	91	10/09/2013
Pre-Medline	All-2013	18	6	12/09/2013
Cochrane Library	All-2013	162	114	12/09/2013

Total References retrieved (after de-duplication): 207

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

1. exp Lymphoma, Non-Hodgkin/
2. NHL*.tw.
3. (non-hodgkin* adj lymphoma*).tw.
4. exp Lymphoma, B-Cell/
5. exp Lymphoma, T-Cell/
6. exp Burkitt Lymphoma/
7. exp Lymphoma, Mantle-Cell/
8. exp Lymphoma, Follicular/
9. exp Lymphoma, B-Cell, Marginal Zone/
10. exp Waldenstrom Macroglobulinemia/
11. exp Lymphoma, Large B-Cell, Diffuse/
12. or/1-11
13. Health Planning Guidelines/
14. Practice Guidelines/
15. Guidelines as topic/
16. guideline$.ti.
17. guideline.pt.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18

2. Health Economics Literature search details

SIGN Health Economics filter was added to search.

SCHARR Quality of Life filter was added to search.

The search was limited to the years 2011-2013 and for the update search until 25/9/2015.

Database name	No of references found	Finish date of search
Medline	100	12/09/2013
Premedline	22	12/09/2013
NHSEED + HTA	107	12/09/2013

Update Search

Database name	No of references found	Finish date of search
Medline	90	25/9/2015
Premedline	34	25/9/2015
NHSEED + HTA	1	25/9/2015

Review Protocols

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

A	**Topic:** The specific information and support needs of people with non-Hodgkin's lymphoma and their carer's at the time of diagnosis and treatment planning, as well as during and after treatment.
Review question	What are the information and support needs of patients with a diagnosis of non-Hodgkin's lymphoma and their carers?
Guideline subgroup	*Lead:* Jackie
	Subgroup: Gillian, Jennie, Tessa, Kate
Economic Priority	High *(high cost of implementation of support needs, large population, low feasibility for modelling)*

Background *(~half a page of A4)*

Living with Non-Hodgkin's Lymphoma (NHL) or supporting someone who has NHL having access to the right information at the right time is essential. Information about the diagnostic tests, disease itself, treatment options, complications associated with NHL, available clinical trials and practical issues is vital. Patients with NHL and those supporting them must cope with the stresses created by a potentially physically demanding illness and health impairment. These effects may be magnified if the right information and support is not available.

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

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

PICO Table

Population	Themes		Outcomes
Adults and young people (16 years and	Information, communication and	Note. Watch and wait/observation,	1. Health Related

older) with NHL *(see included subtypes below)* and their carers: • At diagnosis • During treatment • After treatment • At point of consideration of palliative care	support needs associated with NHL cancer diagnosis and treatment *e.g. psychological difficulties; living with watch and wait/observation; therapeutic decision making.*	fertility issues.	Quality of Life 2. Patient satisfaction/ experience 3. Treatment decision making 4. Patient reported outcomes 5. Social/psychological impact 6. Informed decision making

Additional Comments on PICO

Note for LB: Evidence by subtype of NHL when there are differences
Note for LB: background text suggests that treatment may be influenced by age and co-morbidities, LB asked for clarification from the GDG and had the following response: Concern is both age and fitness of the patient, also there is lack of willingness to give radiotherapy in certain areas due to higher risk of secondary cancers in under 25 year olds
Sifting update: LB excluded articles where either the sum of the NHL patients was less than 50% of the total sample and/or when the study did not provide results broken down according to NHL and other malignancies (so NHL sample could be extracted).

	Details	**Additional Comments**
Type of review	Qualitative review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional, case series, case reports, audit	Include quantitative and qualitative evidence if available
Publication status	Peer reviewed journals, conference proceedings/abstracts, published audits	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms	Information needs for patients with NHL *, cancer	

	patient experience*, psychological needs* providing information*, support needs for patients with NHL*	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Schattner**, A. What do patients really want to know.? OJM (2002)95 (3):135-136 – **Audit Commission.** What seems to be the matter: Communication between Hospital and Patients. London. HMSO, 1993 – **George** CF, Waters WE, Nicholas JA. Prescription information leaflets: a pilot study in general practice. Br Med J 1983: 28:1193 – 1196 – **Bunker** TD. An information leaflet for surgical patients. Annuals of the Royal College of Surgeons of England 1983; 65: 242 – 243	
Amendments		

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

B	**Topic:** The role of image-guided core biopsy compared with excision biopsy in the diagnosis of non-Hodgkin's lymphoma
Review question	***Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of suspected non-Hodgkin's lymphoma at first presentation?***
Guideline subgroup	*Lead:* Andrew
	Subgroup: Chris, Bhuey, Jackie
Economic Priority	Medium *(small amounts of money in comparison to rest of patient pathway)*

Background *(~half a page of A4)*

A surgically excised tissue biopsy is widely accepted as the gold standard for the diagnosis of lymphoma. This is because of the range of investigative techniques that can be performed and the information that can be obtained from this type of biopsy is greater than for other biopsy techniques. This includes an assessment of the micro-structure of the lymph node (loss of normal tissue architecture is a primary indicator of a malignant process and the potential to obtain better quality material for molecular diagnostic tests and flow cytometry. Where the disease process is focal an excision biopsy is more likely to be diagnostic by virtue of the volume of tissue obtained and excision biopsies are typically less prone to processing artefacts which can impair morphological interpretation.

The major disadvantages of an excision biopsy are the need for general anaesthesia and the delays that can result from the need to obtain a surgical opinion. These issues can be addressed by using needle core biopsies, but at the expense of a reduction in the range of quality of investigations that can be performed. This is important because it reduces the degree of confidence that can be placed in the diagnosis and judging when a needle core biopsy is adequate to support the immediate treatment of the patient is subjective and can be very difficult.

The critical question to be addressed is the circumstances where the loss of information and diagnostic confidence can be justified by logistical benefits and patient convenience. The main determinants will be the site of disease, urgency of treatment and patient preference and fitness. Strategies that can be used to improve the diagnostic value of needle core biopsies include taking a parallel aspirate and peripheral blood samples for flow cytometry and molecular diagnostic and much greater integration of the results of imaging and pathological investigations. Experience also suggests that advanced molecular diagnostic techniques (high throughput sequencing and expression profiling) can often be performed on reasonably sized needle cores and the growing availability of these techniques may change the balance between excision and needle core biopsies.

Possible Recommendation: Surgical excision biopsy is the gold standard for the diagnosis of lymphoma. Needle core biopsies are an acceptable alternative to excision biopsies where a surgical intervention would entail unacceptable risk or delay. Where needle core biopsies are used the diagnosis should be supported by molecular or flow cytometric data in addition to routine histology and immunocytochemistry. Institutions should have failure criteria in place to ensure timely surgical biopsy where necessary.

Additional background information supplied by topic lead:
As well as concordance in final diagnosis between a needle biopsy and excision the level of certainty in diagnosis in an important variable which is almost impossible to measure. Deciding whether a needle biopsy is adequate for diagnosis is one of the most challenging aspects of haematopathology practice and is highly subjective.
Most people with lymphadenopathy do not have lymphoma or any type of malignancy. To avoid unnecessary surgical intervention it is essential that investigations to exclude common infections and routine blood count and biochemical analysis are performed. In some clinical situation, where lymphoma is suspected, investigation of the peripheral or bone marrow using sensitive and specific flow cytometric techniques may be a preferable route to diagnosis.
An excision biopsy of a lymph node (or other tissue) allow assessment of micro-architecture, provides adequate material for immunocytochemistry, flow cytometry if received unfixed, FISH studies and extraction of DNA and RNA for molecular diagnostics. Concordance between the results of these investigations provides a high level of confidence in the diagnosis. Focal disease within an enlarged node is also more likely to be detected. Current international guidelines (Lugano 2014 and ESMO 2015) regarded excision biopsies as the procedure of choice. Needle core biopsies vary in the gauge of needle used, the number of cores taken and the length of the core. This is a major factor confounding any meaningful comparison of excision and needle core biopsies. Where multiple 10-15 mm core have been taken the amount of tissue may be similar to some excision biopsies in terms of the information obtained and level of certainty in the diagnosis. However, single thin cores of 5mm or less are common and this severely compromises all of the investigation listed above. The problem is compounded by routinely cutting step levels through these blocks, which results in a significant amount of the available tissue being discarded; this is common practice in many pathology departments.
An additional factor, in the near future, will be the need for a much higher standard of tissue collection and handling to support the diagnostics required for precision medicine. It is likely that unfixed tissue will be required to support sequencing based techniques and that conditions under which samples are collected, transported and stored will become much more rigorous than is the case at present. This will increase the requirement for excision biopsies to be performed.

PICO Table

Population	Index Test	Reference Standard	Outcomes
Adults and young people (16 years and older) presenting with suspected lymphoma (at initial presentation)	Core biopsy • Image • Needle • True cut	Excision biopsy • Surgical • Lymph node biopsy	1. Diagnostic accuracy 2. Healthy related quality of life 3. Patient preference 4. Patient

			satisfaction 5. Accuracy of classification of NHL 6. Speed of diagnosis 7. Sample adequacy 8. Diagnostic yield 9. Morbidity due to test

Additional Comments on PICO

Note for LB – present outcomes by type of NHL malignancy subtypes included in scope
Note for LB – Level of confidence in diagnosis might be an outcome

Exclude: fine needle aspiration biopsy. Rationale: FNA biopsy does not provide an adequate sample (cells and not tissue) resulting in less pathology to work with. FNA not considered reliable alone for diagnosing NHL.

	Details	**Additional Comments**
Type of review	Diagnostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional, audit	Case series with one intervention or case reports will not be included due to no comparison to the reference standard
Publication status	Peer reviewed journals, conference proceedings/abstracts, audits	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and	

	synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality.	
Identified papers	– **Clarke**, C.A., Glaser, S.L., Dorfman, R.F., Bracci, P.M., Eberle, E., and Holly, E.A. (2004). Expert review of non-Hodgkin's lymphomas in a population-based cancer registry: reliability of diagnosis and subtype classifications. Cancer Epidemiol. Biomarkers Prev. 13, 138–143. – **Ireland**, R. (2011). Haematological malignancies: the rationale for integrated haematopathology services, key elements of organization and wider contribution to patient care. Histopathology 58, 145–154. – **LaCasce**, A.S., Kho, M.E., Friedberg, J.W., Niland, J.C., Abel, G.A., Rodriguez, M.A., Czuczman, M.S., Millenson, M.M., Zelenetz, A.D., and Weeks, J.C. (2008). Comparison of Referring and Final Pathology for Patients With Non-Hodgkin's Lymphoma in the National Comprehensive Cancer Network. J Clin Oncol 26, 5107–5112. – **Lester**, J.F., Dojcinov, S.D., Attanoos, R.L., O'Brien, C.J., Maughan, T.S., Toy, E.T., and Poynton, C.H. (2003). The clinical impact of expert pathological review on lymphoma management: a regional experience. Br J Haematol 123, 463–468. – **Proctor**, I.E., McNamara, C., Rodriguez-Justo, M., Isaacson, P.G., and Ramsay, A. (2011). Importance of Expert Central Review in the Diagnosis of Lymphoid Malignancies in a Regional Cancer Network. J Clin Oncol.	
Amendments		

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

D1	**Topic:** The role of genetic and molecular testing in the diagnosis and prognosis of non-Hodgkin's lymphoma (for example, FISH [fluorescence in situ hybridisation] and gene expression profiling).
Review question	***D1 - What is the most effective genomic/phenotypic testing strategy to diagnose the subtypes of aggressive b-cell non-Hodgkin's lymphoma?***
Guideline subgroup	*Lead:* Andrew
	Subgroup:, Ian, Graham
Economic Priority	Low *(no data yet)(applicable to all in common type – moderate costs on genetic tests but falling rapidly)*
Background *(~half a page of A4)*	

There are two broad categories of investigation that will be considered within this question. These are techniques which identify genetic abnormalities that underlie the development and progress of the lymphoma and techniques that investigate the patterns of genes expressed in the tumour; this is to some extent linked to the underlying genetic abnormalities. Genetic abnormalities can be investigated by detecting structural abnormalities in chromosomes (FISH, conventional or array based cytogenetics) or by determining the sequence of individual genes. Gene expression is determined by detecting the mRNA produced when a gene is transcribed (RQ-PCR and various types of gene expression profiling) or by detecting the protein product (flow cytometry and immunocytochemistry). The key development in this area is the introduction of high throughput sequencing (NGS) and mRNA based gene expression profiling. These systems allow many patient samples to be analysed simultaneously for many targets that would previously have required individual tests (this varies by platform but can hundreds or thousands). The cost of these techniques is falling rapidly and providing a laboratory has the throughput to support frequent runs the cost per test is now comparable to conventional diagnostics while providing a much richer data source. These techniques are unlikely to be suitable for small laboratories because of need for high throughput and the requirement for specialist informatics support. This has driven the development of surrogate markers which seek to replicate the results of molecular diagnostic using immunocytochemistry which is, of course, widely available. There are significant concerns about the technical reliability and reproducibility of immunocytochemistry, particularly in applications that have a major impact on treatment.

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

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

1. The distinction between Diffuse Large B-cell Lymphoma (DLBCL), Burkitt Lymphoma (BL) and Mediastinal B-cell Lymphoma (subtype of DLBCL).

This has critical treatment implications. The distinction between BL and DLBCL is based at present on the demonstration of a chromosomal rearrangement of MYC in the absence of other chromosomal abnormalities (as shown by FISH) and with an appropriate phenotype (immunocytochemistry or flow cytometry) (Mead et al., 2008). It is recognized that this approach is probably not optimal to assign patients to receive R-CODOXM/IVAC or similar and newer gene expression profiling and sequencing based approach are now being introduced (Hummel et al., 2006; Dave et al., 2006; Schmitz et al., 2012). Mutational and gene expression based definitions of Mediastinal B-cell lymphoma have been proposed but are at an experimental stage of development (Rosenwald et al., 2003; Lenz et al., 2008a).

2. The Sub-classification of DLBCL

The subdivision of DLBCL into ABC and GCB type by gene expression profiling was a landmark discovery (Alizadeh et al., 2000; Wright et al., 2003; Lenz et al., 2008b; Care et al., 2013; Barrans et al., 2012).This is not only a powerful prognostic factor but each category has a distinctive pattern of mutations and these include the pathways targeted by a variety of novel drugs. It is very likely that the treatment of these two sub-categories will diverge in the near future. Accurate and cost effective targeting of these agents will require a combination of gene expression and mutational analysis and integration of these techniques into single treatment related biomarker for these drugs is an area of active investigation. The effectiveness in using immunocytochemistry as a surrogate biomarker is a controversial area (Hans et al., 2004; Barrans et al., 2012; Castillo et al., 2012; Ott et al., 2010; de Jong et al., 2007).
An additional area, which is now a subject of very active investigation, is whether patterns of mutations and other genetic abnormalities become the primary means of diagnosis of lymphoma and other types of haematological malignancy and the demonstration of these abnormalities would be an obligatory part of diagnosis. This has wide implications.

Possible Recommendation: Gene Expression profiling, molecular cytogenetic data and mutational analysis should become the standard of care for all patients with Diffuse Large B-cell Lymphoma.

PICO Table

Population	Index test	Reference standard	Outcomes
Adults and young people (16 years and older) presenting with new aggressive b-cell non-Hodgkin's lymphoma.	Gene expression profiling • Patterns of genes/genes in list form Fluorescence in situ hybridisation (FISH) Realtime PCR DNA sequencing Immunohistochemistry	Where reported: gene expression as the reference standard For aggressive b-cell lymphoma have a comparison of each other	1. Diagnostic accuracy 2. Reproducibility 3. Turnaround time for test

Additional Comments on PICO

Note for LB – present outcomes by aggressive b-cell NHL malignancy subtypes included in scope
Note for LB – make note of different platforms used in the gene expression (illumina, affymetrix, agilent)

	Details	Additional Comments
Type of review	Diagnostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison to the reference standard.
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		

Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes unrelated to diagnosis. The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality. The diagnostic/QUADAS-2 Quality checklist from the NICE Guidelines Manual (appendix F) will be used.	
Identified papers	– **Alizadeh**, A.A., Eisen, M.B., Davis, R.E., Ma, C., Lossos, I.S., Rosenwald, A., Boldrick, J.C., Sabet, H., Tran, T., Yu, X., et al. (2000). Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403, 503–511. – **Barrans**, S., Crouch, S., Smith, A., Turner, K., Owen, R., Patmore, R., Roman, E., and Jack, A. (2010). Rearrangement of MYC Is Associated With Poor Prognosis in Patients With Diffuse Large B-Cell Lymphoma Treated in the Era of Rituximab. J Clin Oncol. – **Barrans**, S.L., Crouch, S., Care, M.A., Worrillow, L., Smith, A., Patmore, R., Westhead, D.R., Tooze, R., Roman, E., and Jack, A.S. (2012). Whole genome expression profiling based on paraffin embedded tissue can be used to classify diffuse large B-cell lymphoma and predict clinical outcome. Br. J. Haematol. 159, 441–453. – **Care**, M.A., Barrans, S., Worrillow, L., Jack, A., Westhead, D.R., and Tooze, R.M. (2013). A Microarray Platform-Independent Classification Tool for Cell of Origin Class Allows Comparative Analysis of Gene Expression in Diffuse Large B-cell Lymphoma. PLoS ONE 8, e55895. – **Castillo**, J.J., Beltran, B.E., Song, M.-K., Ilic, I., Leppa, S., Nurmi, H., Seki, R., Uccella, S., Li, J.-M., Treaba, D.O., et al. (2012). The Hans algorithm is not prognostic in patients with diffuse large B-cell lymphoma treated with R-CHOP. Leukemia Research. – **Dave**, S.S., Fu, K., Wright, G.W., Lam, L.T., Kluin, P., Boerma, E.J., Greiner, T.C., Weisenburger, D.D., Rosenwald, A., Ott, G., et al. (2006). Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 354, 2431–2442. – **Hans**, C.P., Weisenburger, D.D., Greiner, T.C., Gascoyne, R.D., Delabie, J., Ott, G., Muller-Hermelink, H.K., Campo, E., Braziel, R.M., Jaffe, E.S., et al. 00000000000 – **Hummel**, M., Bentink, S., Berger, H., Klapper, W., Wessendorf, S., Barth, T.F., Bernd, H.W., Cogliatti, S.B., Dierlamm, J., Feller, A.C., et al. (2006). A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 354, 2419–2430. – **De Jong**, D., Rosenwald, A., Chhanabhai, M., Gaulard, P., Klapper, W., Lee, A., Sander, B., Thorns, C., Campo, E., Molina, T., et al. (2007). Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications--a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 25, 805–812. – **Lenz**, G., Wright, G.W., Emre, N.C., Kohlhammer, H., Dave, S.S., Davis, R.E., Carty, S., Lam, L.T., Shaffer, A.L., Xiao, W., et al. (2008a). Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A 105,	

	13520–13525. – **Lenz**, G., Wright, G., Dave, S.S., Xiao, W., Powell, J., Zhao, H., Xu, W., Tan, B., Goldschmidt, N., Iqbal, J., et al. (2008b). Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 359, 2313–2323. – **Mead**, G.M., Barrans, S.L., Qian, W., Walewski, J., Radford, J.A., Wolf, M., Clawson, S.M., Stenning, S.P., Yule, C.L., and Jack, A.S. (2008). A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 112, 2248–2260. – **Ott**, G., Ziepert, M., Klapper, W., Horn, H., Szczepanowski, M., Bernd, H.-W., Thorns, C., Feller, A.C., Lenze, D., Hummel, M., et al. (2010). Immunoblastic morphology but not the immunohistochemical GCB/non-GCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL. Blood blood–2010–03–276766. – **Rosenwald**, A., Wright, G., Leroy, K., Yu, X., Gaulard, P., and Gascoyne, R.D. (2003). Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 198, 851–862. – **Schmitz**, R., Young, R.M., Ceribelli, M., Jhavar, S., Xiao, W., Zhang, M., Wright, G., Shaffer, A.L., Hodson, D.J., Buras, E., et al. (2012). Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature. – **Wright**, G., Tan, B., Rosenwald, A., Hurt, E.H., Wiestner, A., and Staudt, L.M. (2003). A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. Proc. Natl. Acad. Sci. U.S.A 100, 9991–9996.
Amendments	

D2	**Topic:** The role of genetic and molecular testing in the diagnosis and prognosis of non-Hodgkin's lymphoma (for example, FISH [fluorescence in situ hybridisation] and gene expression profiling).
Review question	***D2 What is the most effective genomic/phenotypic testing strategy to determine therapeutic stratification and prognostic subtypes of aggressive b-cell non-Hodgkin's lymphoma?***
Guideline subgroup	*Lead:* Andrew
	Subgroup: Kim, Ian, Graham
Economic Priority	Low *(no data yet)(applicable to all in common type – moderate costs of genetic tests but falling rapidly)*
Background *(~half a page of A4)*	

There are two broad categories of investigation that will be considered within this question. These are techniques which identify genetic abnormalities that underlie the development and progress of the lymphoma and techniques that investigate the patterns of genes expressed in the tumour; this is to some extent linked to the underlying genetic abnormalities. Genetic abnormalities can be investigated by detecting structural abnormalities in chromosomes (FISH, conventional or array based cytogenetics) or by determining the sequence of individual genes. Gene expression is determined by detecting the mRNA produced when a gene is transcribed (RQ-PCR and various types of gene expression profiling) or by detecting the protein product (flow cytometry and immunocytochemistry). The key development in this area is the introduction of high throughput sequencing (NGS) and mRNA based gene expression profiling. These systems allow many patient samples to be analysed simultaneously for many targets that would previously have required individual tests (this varies by platform but can hundreds or thousands). The cost of these techniques is falling rapidly and providing a laboratory has the throughput to support frequent runs the cost per test is now comparable to conventional diagnostics while providing a much richer data source. These techniques are unlikely to be suitable for small laboratories because of need for high throughput and the requirement for specialist informatics support. This has driven the development of surrogate markers which seek to replicate the results of molecular diagnostic using immunocytochemistry which is, of course, widely available. There are significant concerns about the technical reliability and reproducibility of immunocytochemistry, particularly in applications that have a major impact on treatment.

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

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

1. Identifying very poor prognosis Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL with an abnormality of the MYC gene and one of several additional genetic abnormalities detectable by FISH have a very poor clinical outcome ('double and triple hit lymphomas') and there is no consensus on treatment of these patients (Barrans et al., 2010; Savage et al., 2009; Aukema et al., 2010; Wu et al., 2010). This group is likely to expand when mutation of specific genes are added to the abnormalities detectable by FISH. Again, attempts to replicate this by immunocytochemistry have been reported (Green et al., 2012).

2. Identifying very good prognosis DLBCL

The International Prognostic Index (IPI) has been used for many years to stratify patients with DLBCL. There is preliminary data that a statistical modification of the IPI (use of continuous variables) combined with gene expression and mutational analysis can identify a set of patients with a very high probability of cure by R-CHOP. This has important implication for trial design, the application of new therapies and patient information.

Possible Recommendation: Gene Expression profiling, molecular cytogenetic data and mutational analysis should become the standard of care for all patients with Diffuse Large B-cell Lymphoma.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) presenting with new aggressive b-cell non-Hodgkin's lymphoma (narrowed to DLBCL at GDG6, see below).	Gene expression profiling – Patterns of genes/genes in list form Fluorescence in situ hybridisation (FISH) Realtime PCR	Standard procedure (International Prognostic Index [IPI], stage, age)	1. Prediction of survival (Overall/Progression free survival) 2. Health-related quality of life 3. Turnaround time for test

	DNA sequencing Immunohistochemistry		

Additional Comments on PICO

Note for LB – present outcomes by aggressive b-cell NHL malignancy subtypes included in scope
Note for LB – make note of different platforms used in the gene expression (illumina, affymetrix, agilent)
GDG6: 06.11.14
Following on from the discussions and draft recommendations made for topic D1, the GDG proposed to the following additional inclusion criteria to be applied during sifting to ensure that the evidence appraised is appropriate to the proposed question:

- *Patients with diffuse large B-cell lymphoma*
- *Sample size ≥100*
- *Conference abstracts ≤3 years since publication (GDG reasoned that most abstracts who make to full publication will have done so within by 3 years)*
- *Reported patient characteristics need to include the component parts of the International Prognostic Index (IPI)*

Subgroup email communication December 2014:
Following on from screening the search, MSH confirmed with the subgroup that the target comparisons are GCB v non-GCB; GCb v ABC v Type 3; MYC translocation v MYC no translocation; BCL2 translocation v BCL2 no translocation; BCL6 translocation v BCL6 no translocation, and that this is limited to patients who have been treated with rituximab (phone conversation with AJ on 8/12/14). That means that gene (protein) expression results are not included and neither are results on double-hit lymphomas.
It was not feasible to undertake any meta-analyses due to the between-study variation in terms of which covariates the reported multivariate estimates were adjusted for.
Following discussion at the GDG meeting, 26.01.2015, it was decided to also look at the following comparisons:
- patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18) translocation (Double hit)
- patients with MYC translocation versus patients with a MYC translocation AND a BCL6/3q27 translocation (Double hit)
- patients with MYC translocation versus patients with a MYC translocation AND a BCL2/T(14,18) translocation AND a BCL6/3q27 translocation (Triple hit)

	Details	**Additional Comments**
Type of review	Prognostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will	

	routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000 Rationale: Interventions included in PICO published after 2000	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Aukema**, S.M., Siebert, R., Schuuring, E., van Imhoff, G.W., Kluin-Nelemans, H., Boerma, E.-J., and Kluin, P.M. (2010). Double hit B-cell lymphomas. Blood blood–2010–09–297879. – **Barrans**, S., Crouch, S., Smith, A., Turner, K., Owen, R., Patmore, R., Roman, E., and Jack, A. (2010). Rearrangement of MYC Is Associated With Poor Prognosis in Patients With Diffuse Large B-Cell Lymphoma Treated in the Era of Rituximab. J Clin Oncol. – **Barrans**, S.L., Crouch, S., Care, M.A., Worrillow, L., Smith, A., Patmore, R., Westhead, D.R., Tooze, R., Roman, E., and Jack, A.S. (2012). Whole genome expression profiling based on paraffin embedded tissue can be used to classify diffuse large B-cell lymphoma and predict clinical outcome. Br. J. Haematol. 159, 441–453. – **Green**, T.M., Young, K.H., Visco, C., Xu-Monette, Z.Y., Orazi, A., Go, R.S., Nielsen, O., Gadeberg, O.V., Mourits-Andersen, T., Frederiksen, M., et al. (2012). Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. – **Hans**, C.P., Weisenburger, D.D., Greiner, T.C., Gascoyne, R.D., Delabie, J., Ott, G – **Savage**, K.J., Johnson, N.A., Ben-Neriah, S., Connors, J.M., Sehn, L.H., Farinha, P., Horsman, D.E., and Gascoyne, R.D. (2009). MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 114, 3533–3537. – **Wu**, D., Wood, B.L., Dorer, R., and Fromm, J.R. (2010). “Double-Hit” mature B-cell lymphomas show a common immunophenotype by flow cytometry that includes decreased CD20 expression. Am. J. Clin. Pathol 134, 258–265.	
Amendments		

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

E1	**Topic:** The role of PET-CT in initial staging, evaluation interim response to treatment and post-treatment assessment for people with non-Hodgkin's lymphoma.
Review question	E1: What is the staging value of pre-treatment functional imaging with PET-CT compared with other initial assessments for people with different subtypes of non-Hodgkin's lymphoma?
Guideline subgroup	*Lead:* Bhuey
	Subgroup: Peter, Tessa, Jennifer
Economic Priority	High *(feasibility issues/lack of data)*

Background *(~half a page of A4)*

Pre-treatment staging defines disease extent enabling appropriate therapy. The Ann Arbor staging system was originally developed to define patients who may be candidates for radiation therapy from those who would benefit from systemic treatment. Originally relying on physical examination and bone marrow assessment, the system has evolved over the last 40 years to include anatomical Computed Tomography (CT), which is currently routinely used for baseline staging in lymphoma. CT relies on lesion size however, and numerous studies demonstrate that metabolic imaging with Positron Emission Tomography (PET-CT) is more accurate than CT for detecting sites of disease involvement in a number of lymphoma histological subtypes. Discordance between PET-CT and CT occurs in a proportion of patients at staging, predominantly in favour of PET-CT (with patients typically being upstaged by the detection of involved nodes 1cm or smaller in short axis on CT or the detection of extranodal involved sites); however in most patients stage is not usually changed, treatment is changed in an even smaller proportion and there is no evidence for a change in patient outcome as a result of this staging PET-CT data.

Most lymphomas are PET 18F-Fluorodeoxyglucose (FDG) avid, including high grade (HG) aggressive disease such as diffuse large B cell lymphoma (DLBCL), Burkitt's lymphoma and aggressive T-cell lymphomas, as well as low grade lymphoma such as follicular lymphoma (FL). Mantle cell lymphoma (MCL) also demonstrates FDG uptake, with more variable accuracy for mucosal associated lymphoid tissue (MALT) lymphoma. PET can be useful detecting high grade transformation, by defining biopsy site/s considered suspicious for transformation, however is not reliable for differentiating FL from HG lymphoma, because FL demonstrates high PET FDG activity levels.

Pre-treatment PET-CT scan can be useful for interpreting subsequent post therapy PET-CT scans, however is not considered mandatory in HG lymphomas because these subtypes are usually intensely FDG avid, hence the post-therapy scan can be interpreted based on response evaluation criteria. Pre-treatment PET-CT may be of particular value in patients who appear to have stage I or II disease and where radiation therapy is being considered as part of treatment, including FL where the patient is considered to have stage I disease and radiotherapy is part of the treatment option. Additional sites of occult disease detected by PET leading to stage migration (upstaging) would result in a change of management approach.

Possible recommendations: PET-CT is not routinely standard in the pre-treatment staging of non-Hodgkin's lymphoma (DLBCL, FL, MCL, MALT, Burkitt's lymphoma and peripheral T-cell

lymphomas). Pre-treatment PET-CT should be considered in patients who appear to have Stage I or II disease and for whom radiation therapy is being considered as part of patient management.

PICO Table

Population	Index test	Reference standard	Outcomes
Adults and young people (16 years and older) presenting with newly diagnosed non-Hodgkin's lymphoma.	Functional imaging with FDG PET-CT enhanced Functional imaging with FDG PET-CT not-enhanced Contrast enhanced CT	Standard staging CT Bone marrow biopsy Positive test on imaging results: • Histopathological examination • Bone marrow biopsy Positive CT but Pet negative Negative test on imaging results: • Clinical and radiological follow-up	1. Diagnostic accuracy 2. Test-related morbidity 3. Health-related quality of life 4. Bone marrow involvement 5. Upstaging 6. Down-staging 7. Treatment management change

Additional Comments on PICO

Note for LB – present information by subtypes included in scope.
Papers may include Hodgkin's lymphoma.
Note for LB – Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project)
Note for LB – make note of any outcomes related to treatment management changes
Note for LB – If PET-CT enhanced the paper will state this, if just PET-CT then it is not enhanced.
Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294).
Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)

	Details	Additional Comments
Type of review	Diagnostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison to the reference standard

Publication status	Peer reviewed journals	Will not look at conference proceedings/abstracts as there will not be enough detail provided for this diagnostic question (decision made at GDG 3 06.06.14)
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	1997 Rationale: Relevant articles on PET published from this point forward	Date amended to 1997 by the sub-lead due to relevant articles published from this point
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). The QUADAS-2 tool for studies of diagnostic test accuracy will be used to assess study quality.	
Identified papers	Please note a number of references used for E1 are also applicable to E2 & E3. – **Kostakoglu** L, Cheson BD. State-of-the-art research on "lymphomas: role of molecular imaging for staging, prognostic evaluation, and treatment response." Front Oncol. 2013 Sep 4;3:212. eCollection 2013. – **Seam** P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007 Nov 15;110(10):3507-16. Epub 2007 Aug 20. – **Juweid** ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007 Feb 10;25(5):571-8. Epub 2007 Jan 22. – **Cheson** BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb	

10;25(5):579-86. Epub 2007 Jan 22.
- **Khan** AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood. 2013 Jul 4;122(1):61-7. doi: 10.1182/blood-2012-12-473389. Epub 2013 May 9.
- **Avigdor** A. Staging DLBCL: bone marrow biopsy or PET-CT? Blood. 2013 Jul 4;122(1):4-5. doi: 10.1182/blood-2013-05-502575.
- **Ghielmini** M, Vitolo U, Kimby E, et al. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol. 2013 Mar;24(3):561-76. doi: 10.1093/annonc/mds517. Epub 2012 Nov 21.
- **Elstrom** R, Guan L, Baker G, et al. Utility of FDG-PET in lymphoma by WHO classification. Blood. 2003 May 15;101(10):3875-6. Epub 2003 Jan 16.
- **Wirth** A, Foo M, Seymour JF, et al. Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2008 May 1;71(1):213-9. doi: 10.1016/j.ijrobp.2007.09.051. Epub 2008 Mar 4.
- **Friedberg** JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012 Sep 20;30(27):3368-75. doi: 10.1200/JCO.2011.40.6546. Epub 2012 Aug 20.
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Amendments	

E2	**Topic:** The role of PET-CT in initial staging, evaluation interim response to treatment and post-treatment assessment for people with non-Hodgkin's lymphoma.
Review question	E2: What is the prognostic value of an interim assessment using functional imaging with PET-CT during the treatment of diffuse large B-cell non-Hodgkin's lymphoma?
Guideline subgroup	*Lead:* Bhuey
	Subgroup: Peter, Tessa, Jennifer
Economic Priority	High *(feasibility issues/lack of data)*

Background *(~half a page of A4)*

The current evidence base in this area is largely limited to Diffuse Large B-Cell Lymphoma (DLBCL), with very limited evidence or current clinical application in other and lower grade NHL subtypes, this review question will therefore consider DLBCL only.

Only a proportion of patients with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) are potentially cured with a prolonged progression-free survival (PFS) when treated with rituximab-CHOP like regimens. A prolonged PFS is then achieved only in a proportion of treatment resistant or relapsed patients following salvage therapy (high-dose therapy followed by autologous stem cell transplantation). A tool which is able to reliably predict an unfavourable outcome early in the management of these patients may lead to risk-adapted change in therapy. Anatomical Computed Tomography (CT) is conventionally used for interim response evaluation, assessing changes in lesion size. Tumour volume reduction may require time however, with metabolic changes on Positron Emission Tomography (PET-CT) preceding anatomical volume changes. In aggressive NHL, including DLBCL, rapid reduction in FDG (Fludeoxyglucose) uptake during chemotherapy with a negative interim PET-CT scan seems to predict a favourable outcome. In the rituximab (immunochemotherapy treatment) era, the positive predictive value (the ability of a positive PET scan to predict persistent disease or future relapse) appears more variable however.

Currently there is insufficient evidence to escalate/ de-escalate therapy (change patient management) in patient groups based on the results of an interim PET-CT scan. There is also currently no evidence to suggest that early therapy change in poorly responding patients will translate into improved patient outcomes in DLBCL. The interim PET-CT scan can be helpful in patients with equivocal CT findings and in those patients where sites of disease involvement cannot be assessed with anatomical imaging, to confirm patients are responding to treatment and to exclude progression.

Possible Recommendation: PET-CT is not generally routinely indicated for interim response evaluation in DLBCL due to insufficient evidence to change patient management based on the PET-CT result. Interim PET-CT may be performed in patients with indeterminate interim CT findings to confirm patients are responding to treatment and exclude disease progression.

PICO Table

Population	Factors	Outcomes
Adults and young people (16 years and older) currently undergoing first-line treatment for Diffuse	Functional imaging with FDG PET-CT enhanced • PET+ • PET-	1. Overall survival 2. Progression-free survival 3. Health-related

Large B-cell non-Hodgkin's lymphoma. Subgroups: • Stages: o Early stage nodal disease o Advanced • Time point of scan • When during the interval of treatment is the scan conducted • Treatment use (esp. Rituximab)	Functional imaging with FDG PET-CT not-enhanced • PET+ • PET- No functional imaging with PET-CT scan • Alternative scanning: CT scan	quality of life 4. Treatment management change

Additional Comments on PICO
Note for LB – When reviewing papers please note whether PET-CT scan data was blinded. *Note for LB – Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project)* *Note for LB – Make a note of treatment type prior to scan* *Query – Should we note treatment type due to the variable results since use of Rituximab because not all patients will be receiving Rituximab under the recommendations of the TA65 (localised only as part of ongoing or new clinical studies). – Not a problem as all patients will receive rituximab now as the TA was for a specific stage which is rarely diagnosed.* Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294). Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)

	Details	**Additional Comments**
Type of review	Prognostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, observational studies	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and	

	used as appropriate.	
Date limits of search	1998 Rationale: Whilst the commercial use of PET-CT started after 2000, relevant articles from 1998 onwards on the use of PET for interim assessments.	Date changed to 1998 by sub-group lead as relevant articles published from this point forward
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Terasawa** T, Lau J, Bardet S, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma : **A systematic review**. J Clin Oncol. 2009 Apr 10;27(11):1906-14. doi: 10.1200/JCO.2008.16.0861. Epub 2009 Mar 9. – **Horning** SJ, Juweid ME, Schoder H, et al. Interim positron emission tomography scans in diffuse large B-cell lymphoma: an independent expert nuclear medicine evaluation of the Eastern Cooperative Oncology Group E3404 study. Blood. 2010 Jan 28;115(4):775-7; quiz 918. doi: 10.1182/blood-2009-08-234351. Epub 2009 Sep 18. – **Pregno** P, Chiappella A, Bello M, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. Blood. 2012 Mar 1;119(9):2066-73. doi: 10.1182/blood-2011-06-359943. Epub 2012 Jan 10. – **Haioun** C, Itti E, Rahmouni A, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood. 2005 Aug 15;106(4):1376-81. Epub 2005 Apr 28. – **Casasnovas** RO, Meignan M, Berriolo-Riedinger A, et al. SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. Blood. 2011 Jul 7;118(1):37-43. doi: 10.1182/blood-2010-12-327767. Epub 2011 Apr 25. – **Safar** V, Dupuis J, Itti E, et al. Interim [18F]fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. J Clin Oncol. 2012 Jan 10;30(2):184-90. doi: 10.1200/JCO.2011.38.2648. Epub 2011 Dec 12. – **Juweid** ME, Wiseman GA, Vose JM, et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. J Clin Oncol. 2005 Jul 20;23(21):4652-61. Epub 2005 Apr 18. – **Moskowitz** CH. Interim PET-CT in the management of diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:397-401. doi: 10.1182/asheducation-2012.1.397.	

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Amendments	

E3	**Topic:** The role of PET-CT in initial staging, evaluation interim response to treatment and post-treatment assessment for people with non-Hodgkin's lymphoma.
Review question	E3: What is the prognostic value of functional imaging with PET-CT performed after the various types of treatment for non-Hodgkin's lymphoma are completed?
Guideline subgroup	*Lead:* Bhuey
	Subgroup: Peter, Tessa, Jennifer
Economic Priority	High *(feasibility issues/lack of data)*

Background *(~half a page of A4)*

Achieving complete remission (CR) after first-line systemic therapy is important in aggressive non-Hodgkin lymphoma (NHL) patients for example, as this usually leads to a longer progression-free survival (PFS), whereas incomplete response is usually associated with poorer patient outcomes. Computed Tomography (CT) is usually used for response assessment in patients at treatment completion. However, in the common situation of residual mass(es) at the 'end of treatment', anatomical CT imaging cannot accurately discriminate remaining active lymphoma from either necrotic tumour or inactive treatment related fibrosis. Defining the true nature of residual mass is important, enabling consolidation treatment in patients with remaining active disease, and avoiding unnecessary further therapy/ treatment related morbidity in patients in complete remission. The positive predictive value (PPV) of CT (the ability of a positive CT scan to predict persistent disease or future relapse) is low.

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

The PET 'end of treatment' result correlates with patient outcome in aggressive NHL. The role of PET in low grade NHL is less well characterized, although early limited data suggests that post-induction PET assessment may also represent an independent predictor of progression free survival (PFS) in follicular lymphoma (FL), differentiating patient cohorts destined to have a longer or shorter remission. Any potential role for potential patient treatment/ management modifications based on post-induction PET results in FL is currently unknown.

Possible recommendations: PET is strongly recommended (substantial clinical benefit) for restaging aggressive NHL, including DLBCL and Burkitt's lymphoma at the end of treatment (residual mass assessment). Further data is required regarding a potential role of post induction PET in FL, PET not currently being routinely indicated for end of treatment response in FL. PET is not routinely indicated for end of treatment response in mantle cell lymphoma or low grade NHL such as MALT.

PICO Table

Population	Factors	Outcomes

Adults and young people (16 years and older) with non-Hodgkin's lymphoma who have completed planned first-line treatment (RCHOP, rituximab plus any chemo, any radiotherapy).
 	
Subgroups:
• Stages:
  ○ Early
  ○ Advanced
• Residual mass on CT
• Time interval of scan (current practice in the UK 4 weeks after chemo, 3 months after radiotherapy)
• Treatment type
	Functional imaging with FDG PET-CT enhanced
	• PET+
	• PET-
	
	Functional imaging with FDG PET-CT not-enhanced
	• PET+
	• PET-
	
	No functional imaging with PET-CT scan
	• Alternative scanning: CT scan
		1. Diagnostic accuracy (accuracy often based on PFS)
		2. Overall survival
		3. Progression-free survival
		4. Health-related quality of life
		5. Treatment management change

Additional Comments on PICO

Note for LB – Present outcomes by NHL subtypes included in scope.
Note for LB – Please note the different criteria used when scoring a positive and negative PET-CT scan (e.g. IWG 2007; Deauville, International harmonisation project)
Sifting update (July 2015): search produced 1028 hits, 294 potentially relevant articles from title and abstract sift so conference abstracts (decision made at GDG 06.06.14) and articles with <40 participants were not ordered (n=136/294).
Sifting update (July 2015): Full text articles with <40 participants were not appraised due to low frequency of outcome events (i.e. positive PET/CT scan)

	Details	Additional Comments
Type of review	Prognostic review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, observational studies	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD,	

	CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	1997 Rationale: Relevant articles on PET published from this point forward	Date amended to 1997 by the sub-lead due to relevant articles published from this point
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Trotman** J, Fournier M, Lamy T, et al. Positron Emission Tomography-Computed Tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: Analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol. 2011 Aug 10;29(23):3194-200. doi: 10.1200/JCO.2011.35.0736. Epub 2011 Jul 11. – **Dupuis** J, Berriolo-Riedinger A, Julian A, et al. Impact of [(18)F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. J Clin Oncol. 2012 Dec 10;30(35):4317-22. doi: 10.1200/JCO.2012.43.0934. Epub 2012 Oct 29. – **Tychyj-Pinel** C, Ricard F, Fulham M, et al. PET/CT assessment in follicular lymphoma using standardized criteria: central review in the PRIMA study. Eur J Nucl Med Mol Imaging. 2014 Mar;41(3):408-15. doi: 10.1007/s00259-013-2441-8. Epub 2014 Jan 17. – **Halasz** LM, Jacene HA, Catalano PJ, et al. Combined modality treatment for PET-positive non-Hodgkin lymphoma: favorable outcomes of combined modality treatment for patients with non-Hodgkin lymphoma and positive interim or postchemotherapy FDG-PET. Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):e647-54. doi: 10.1016/j.ijrobp.2012.01.060. Epub 2012 May 18. – **Terasawa** T, Nihashi T, Hotta T, et al. 18F-FDG PET for posttherapy assessment of Hodgkin's disease and aggressive Non-Hodgkin's lymphoma: A systematic review. J Nucl Med. 2008 Jan;49(1):13-21. Epub 2007 Dec 12. – **Liu** H, Johnson JL, Koval G, et al. Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma : final results of CALGB 59909. Haematologica. 2012 Apr;97(4):579-85. doi: 10.3324/haematol.2011.050203. Epub 2011 Nov 18. – **Zinzani** PL, Tani M, Trisolini R, et al. Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma. Haematologica. 2007 Jun;92(6):771-7.	

- **Naumann** R, Vaic A, Beuthien-Baumann B, et al. Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. Br J Haematol. 2001 Dec;115(4):793-800.
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- **Hutchings** M, Barrington SF. PET/CT for therapy response assessment in lymphoma. J Nucl Med. 2009 May;50 Suppl 1:21S-30S. doi: 10.2967/jnumed.108.057190. Epub 2009 Apr 20.
- **Zhu** Y, Lu J, Wei X, et al. The predictive value of interim and final [18F] fluorodeoxyglucose positron emission tomography after Rituximab chemotherapy in the treatment of non-Hodgkin's lymphoma: a meta-analysis. Biomed Res Int. 2013;2013:275805. doi: 10.1155/2013/275805. Epub 2013 Aug 14.
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	for malignant lymphoma. Nucl Med Commun. 1998 Nov;19(11):1055-63.
Amendments	

Topic F: The frequency and nature of follow-up for people with non-Hodgkin's lymphoma after attainment of remission.

F	**Topic:** The frequency and nature of follow-up for people with non-Hodgkin's lymphoma after attainment of remission.
Review question	***In patients in remission after treatment with curative intent for non-Hodgkin's lymphoma, what are the optimal method(s), frequency and duration of follow-up?***
Guideline subgroup	*Lead:* Kim
	Subgroup: Bhuey, Tessa, Ian, Jackie *(Gillian after October 2014)*
Economic Priority	Medium *(costly as affects majority of patients, but not suitable for modelling)*

Background *(~half a page of A4)*

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

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

With regards to patients in complete remission after first line treatment, regular blood tests (full blood count and serum LDH) and surveillance scanning (CT or PET-CT) appear to have limited benefit (Elis et al, Am J Hematol, 2002; Cheah et al, Ann Hematol, 2014). Data obtained from retrospective series indicate that most lymphoma relapses are detected by signs and symptoms regardless of the imaging schedule (Goldschmidt et al, Ann Hematol, 2011). Some papers suggest that imaging detection is associated with a lower disease burden and improved survival (El-Galaly et al, amm J Hematol), others have found no survival benefit associated with early detection using sensitive techniques such as PET-CT (Goldschmidt et al, Ann Hematol, 2011). Apart from concerns about the cost-effectiveness of imaging surveillance, there are also concerns about the radiation exposure and risk of second cancers (Guttikonda et al, Eur j Radiol, 2014; Cheah et al, BJC, 2013; Avivi et al, Am J Hematol, 2013) associated with long-term scanning.

Some studies suggest that certain blood tests may have utility during follow-up (e.g. detection of lymphopenia after RCHOP for DLBCL has been shown to be associated with a high risk of relapse; Porrata et al, Leukemia, 2010), but in general the value of blood tests during follow-up is poorly understood. Common practice includes the measurement of serum LDH and full-blood count but this practice is not evidence-based. For example, baseline serum LDH is a validated prognostic biomarker in patients with NHL, however LDH measured during follow-up has low sensitivity and specificity for predicting disease progression or relapse (Hong et al, Acta

Heamatol, 2013).

Since this is a relatively under-researched topic, it is likely that our recommendations for follow-up will be based on retrospective data, consensus practise and expert opinion.

Additional background supplied by topic lead:

People with DLBCL in complete metabolic remission after treatment have an excellent prognosis with a low relapse rate and a 5-year overall survival rate of approximately 80%. Follow-up is routinely offered to this patient group, and is aimed at disease surveillance for early detection of relapse, monitoring of late effects, patient education and reassurance. The optimal follow-up strategy has not been well defined. However, since most relapses occur in the first 2 years after treatment, most people are seen frequently during this period, typically 2-3 monthly, followed by 6-12 monthly visits for up to 5 years. Centres with an interest in late effects of treatment may offer longer follow-up. The nature of follow-up is variable and may include a history, physical examination, blood tests and routine surveillance scanning in the form of CT or PET-CT.
The majority of relapses are clinically suspected in symptomatic patients attending early or at their scheduled visits. LDH has not been found to be useful for detecting DLBCL relapse. In certain settings, routine scanning may be advocated for early detection and initiation of salvage therapy that would not be feasible with a larger burden of disease, or to produce a lower secondary IPI and better associated outcomes. However, scan detected relapse before clinical manifestations only happens in a minority of cases (1-2%) and no studies have demonstrated a survival advantage following treatment for scan detected relapse in asymptomatic people compared to clinically suspected relapse. Imaging costs, radiation exposure and patient anxiety factors must also be taken into account when considering the role and impact of routine scan surveillance, as well as the high false positive rate of PET-CT in RCHOP compared to CHOP treated patients and the potential trigger of unnecessary investigations.

PICO Table			
Population	**Intervention**	**Comparison**	**Outcomes**
Adults and young people (16 years and older) in remission after treatment with curative intent for non-Hodgkin's lymphoma. Exclude: • Allograft • People who were treated for non-Hodgkin's lymphoma below the age of 16 years	Follow-up protocol of tests including: Blood test: • Full blood count (FBC) • Complete blood count (CBC) • Haemoglobin/haemoglobin • White blood count/leukocyte count • Platelets/platelet count Serum biochemistry: • Lactate dehydrogenase (LDH) • Liver function tests (LFTs) • Renal/kidney function tests CT scan X-ray PET scan or PET-CT (PET/CT) scan Medical history (review of symptoms) and physical examination Patient reported symptoms	No follow-up Presentation with symptoms Each other (including frequency and duration of follow-up, setting of follow-up)	1. Recurrence 2. Overall survival 3. Disease progression 4. Disease-specific survival 5. Test related complications 6. Health-related quality of life 7. Patient experience 8. Patient preference 9. Number of scans
Additional Comments on PICO			
Note for LB – Present outcomes by NHL subtypes included in scope. *Note for LB – Question is assessing which tests, when, how often and how long follow-up should be.* Discussion on PICO at GDG meeting 26.01.15: - GDG decided to limit population to patients in complete remission after first-line treatment for DLBCL. Additional text provided in background by topic lead discussing refined population. - Do not include results that compare the different blood tests listed under interventions in the PICO above (e.g., full blood count versus platelets only) Notes to MSH (26.01.15): - Follow up starts at the end of the last cycle of chemotherapy - Follow up ends at relapse or death. Late effects/survivorship (topic R) is separate from follow			

up and runs alongside follow up.
- Outcomes are all clinical outcomes, thus no sensitivity and specificity to be reported.

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison. Qualitative and quantitative
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms	Surveillance imaging	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	Please note various references listed in E1 are also relevant for this surveillance question. Some further references pertinent to imaging aspects: – **Zinzani** PL, Stefoni V, Tani M, et al. Role of [18F]fluorodexoyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol. 2009 Apr 10;27(11):1781-7. doi: 10.1200/JCO.2008.16.1513. Epub 2009 Mar 9. – **Kostakoglu** L, Cheson BD. State-of-the-art research on "lymphomas: role of molecular imaging for staging, prognostic	

	evaluation, and treatment response." Front Oncol. 2013 Sep 4;3:212. eCollection 2013. – **Seam** P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007 Nov 15;110(10):3507-16. Epub 2007 Aug 20. – **Ghielmini** M, Vitolo U, Kimby E, et al. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol. 2013 Mar;24(3):561-76. doi: 10.1093/annonc/mds517. Epub 2012 Nov 21. – **Weeks** JC, Yeap BY, Canellos GP, et al. Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete response. J Clin Oncol. 1991 Jul;9(7):1196-203. – **Cheah** CY, Hofman MS, Dickinson M, et al. Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. Br J Cancer. 2013 Jul 23;109(2):312-7. doi: 10.1038/bjc.2013.338. Epub 2013 Jun 27. – **Liedtke** M, Hamlin PA, Moskowitz CH, et al. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. Ann Oncol. 2006 Jun;17(6):909-13. Epub 2006 May 3. – **Tilly** H, Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May;21 Suppl 5:v172-4. doi: 10.1093/annonc/mdq203. – **Elis** A, Blickstein D, Klein O, et al. Detection of relapse in non-Hodgkin's lymphoma: role of routine follow-up studies. Am J Hematol. 2002 Jan;69(1):41-4. – **Petrausch** U, Samaras P, Haile SR, et al. Risk-adapted FDG PET/CT based follow up in patients with diffuse large B-cell lymphoma after first line therapy. Ann Oncol. 2010 Aug;21(8):1694-8. doi: 10.1093/annonc/mdq015. Epub 2010 Feb 5. – **Truong** Q, Shah N, Knestrick M, et al. Limited utility of surveillance imaging for detecting disease relapse in patients with non-Hodgkin lymphoma in first complete remission. Clin Lymphoma Myeloma Leuk. 2014 Feb;14(1):50-5. doi: 10.1016/j.clml.2013.08.009. Epub 2013 Oct 10.
Amendments	

Topic G: The most effective first-line treatment for early-stage follicular lymphoma.

G	**Topic:** The most effective first-line treatment for early-stage follicular lymphoma.
Review question	What is the most effective first-line treatment for people with stage IIa follicular lymphoma?
Guideline subgroup	*Lead:* Peter
	Subgroup: Ian, Graham, Kate
Economic Priority	Low *(Low prevalence rate, inexpensive treatment)*

Background *(~half a page of A4)*

Conventionally early stage follicular Non-Hodgkin's Lymphoma (NHL) has been considered potentially curable by local treatment using radiotherapy, distinct from more advanced disease which is regarded as a chronic disorder with prolonged periods of control but rarely complete eradication. Relatively low dose radiotherapy delivering 24Gy is effective in follicular lymphoma and if the disease is truly localised and encompassed in the radiation field then long term cure is possible. Acute toxicity is low. There is limited data on long term effects. Most cases will involve irradiation to the neck, axilla or supraclavicular fossa. Localised mediastinal or abdominopelvic presentations of follicular lymphoma are rare and so the more serious long term effects of radiotherapy such as cardiac deaths and second malignancies of the breast and lung are not major concerns.

There are two other approaches to the management of early stage follicular lymphoma:

1. In some patients there will be apparent complete removal at surgical biopsy. Observation rather than radiotherapy has been proposed as appropriate in these patients and series of observation only patients suggest this may be successful with no need for further treatment in around 70% of patients.
2. After radiotherapy long term cure rates vary between 40 and 70%. Recurrence is rarely in the radiation field but represents the presence of undetected occult disease which later becomes manifest. The increased accuracy of staging with PET may help select patients better for local treatment. The use of chemotherapy with or without radiotherapy as initial treatment or the use of immunotherapy with radiotherapy has been proposed to address disease outside the presenting region. There is however currently limited data to guide this approach.

A recommendation should therefore address the ongoing role of local radiotherapy in early stage follicular lymphoma in the era of PET staging and whether it is possible to select patients who may be safely observed on the one hand or on the other have higher risk features which may benefit from adjuvant immunotherapy or immunochemotherapy.

PICO Table

Population	Intervention	Comparator	Outcomes
Adults and young people (16 years and older) newly diagnosed with stage IIa follicular Non-Hodgkin's Lymphoma Subtypes: • Symptomatic • *Not 'b' symptoms but bulky disease, painful, discomfort* • *Symptomatic criteria's: Bnli criteria; GELF criteria* • Asymptomatic (including vital organ compromised)	Radiotherapy • Various dose levels • Types of field radiation therapy (involved, extended) Chemotherapy Immuno-chemotherapy • (Rituximab) Rituximab Radio-immuno therapy Observation/watch and wait	Each other	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health related quality of life 7. Patient preference

• Flipi • Nodal/extra nodal • Above/below diaphragm Exclude: • Grade 3b • All other			

Additional Comments on PICO

Note for LB – Where reported record results by subtypes included in PICO

Query – Should we record use of PET scanning?

Many comparative studies pre rituximab era

06.06.14: Decision to limit population to Stage IIa only for the following reasons:

- *Stage I1: These patients are generally treated with radiotherapy. GDG believe that there will be no data to answer issue of which type of therapy after surgery and that treatment within this group of patients within the UK is not an issue in current practice*
- *Stage IIa: Different countries are treating patients differently (US immediate radiotherapy, UK considered advanced disease: asymptomatic do nothing, symptomatic do something), uncertainty in practice so there is a need to know which treatment strategy to take.*

06.06.14: Due to potential need to include non-comparative studies a sample size limit of ≥40 will be applied.

Jan 2015: LB excluded conference abstracts if they did not state stage information.

Sifting update: LB will report data where the n of stage II patients is >50% of the entire sample when data is not reported according to disease stage II.

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design filter	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Non-comparative studies with sample sizes ≥40.	GDG believe that there is unlikely to be any RCTs
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		

Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers		
Amendments		

Topic H: The role of autologous and allogeneic transplantation in people with follicular lymphoma.

H	**Topic:** The role of autologous and allogeneic transplantation in people with follicular lymphoma.
Review question	Is autologous transplantation, allogeneic transplantation or no transplantation the most effective treatment for people with follicular lymphoma at various time points?
Guideline subgroup	*Lead:* Karl
	Subgroup: Gillian, Graham, Morag, Kate
Economic Priority	High *(expensive treatment)*

Background *(~half a page of A4)*

Follicular lymphoma is a comparatively indolent disorder in most patients. Because of this, survival will be relatively prolonged in the majority, and responses to subsequent salvage therapies the rule rather than the exception. Nevertheless, conventional immune-chemotherapy is not considered curative. Although escalation to high dose therapy with autologous stem cell transplantation (ASCT) in selected patients has been historically considered to offer improved progression free survival rather than cure, several series have reported that a proportion of patients achieve very durable remissions and may indeed never relapse. Given the older age of most patients with follicular lymphoma (median age of onset 60 years), it has also been argued that cure should not be the therapeutic goal for most patients with the disorder, as control of the disease and maintenance of health-related quality of life may allow patients to live with their disease until other medical issues intervene.

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

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

morbidities. Current practice therefore varies widely across the UK.

This is one area in which pharmaco-economic analyses may help to define future practice given the often closely balanced clinical issues. Current improvements in pharmacological therapies also complicate the picture. Whilst on the one hand they may offer improved rates of progression free survival, making transplantation strategies less appealing, this will undoubtedly come at considerable financial cost. A better understanding of the cost-effectiveness of transplant approaches is therefore important for the integration of these newer therapies over coming years.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with follicular non-Hodgkin's lymphoma. Exclude: • Grade IIIB • Transformed FL • Composite/discordant FL Subgroups: • • Line of treatment • Length of first remission • FLIPI score (early/late/ low/high risk) • Use of Rituximab • Quality of response to pre-transplant therapy	Autologous transplantation Allogeneic/ Allogenic/ reduced intensity transplantation	No transplantation *(record what was used)* – Rituximab – Interferon Each other	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health-related quality of life

Additional Comments on PICO

Note for LB – Record what the 'no transplantation' comparison was
Note for LB – Report the stage of treatment (e.g. first response, second response, beyond second response)
Note for LB – Where available report evidence by age
Note for LB: Allo transplantation no comparative data so look for trials

- ***TA 137:*** *Rituximab relapsed stage III or IV FL, review analyses and recommendations need to take in to account the following recommendations:*
  - *Rituximab recommended as an option for the induction of remission and/or maintenance therapy in people with relapsed stage III or IV follicular NHL.*
  - *Rituximab recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular NHL when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).*
- *Following GDG 3 LB has included the following exclusion criteria*
  - *Sample size ≥40 (non-comparative studies)*

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Non-comparative studies due to a lack of comparative studies especially for the intervention allogeneic transplantation.	
Publication status	Peer reviewed, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Lenz** et al Blood 2004; 104: 2667-2674 – **Sebban** et al Blood 2006; 108: 2540-2544 – **Gyan** et al Blood 2009; 113: 995-1001 – **Montoto** et al Haematologica 2013; 98: 1014-1021 – **Schouten** et al JCO 2003; 21: 3918-3927 – **Villa** et al JCO 2013; 31: 1164-1171 – **Eide** et al BJH 2011; 152: 600-610 – **Williams** et al JCO 2001; 19: 727-735 – **Ban-Hoefen** et al Leuk Lymphoma 2012; 53: 830-835 – **van Besien** et al Blood 1998; 92: 1832-1836 – **Morris** et al Blood 2004; 104: 3865-3871 – **Robinson** et al Blood 2002; 100: 4310-4316 – **Faulkner** et al Blood 2004; 103; 428-434 – **Thomson** et al JCO 2010; 28: 3695-700 – **Robinson** et al BMT 2013; doi: 10.1038/bmt.2013.83 – **Rezvani** et al JCO 2008; 26: 211-217	
Amendments		

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

I	**Topic:** The role of immediate compared with deferred chemotherapy (watch and wait) in treating advanced asymptomatic follicular lymphoma.
Review question	Is immediate treatment or deferred chemotherapy (watch and wait) the more effective treatment for people with advanced asymptomatic follicular lymphoma?
Guideline subgroup	*Lead:* Peter
	Subgroup: Chris, Ian, Kate, Jackie
Economic Priority	High *(cost of Rituximab but watch & wait a small cost)*

Background *(~half a page of A4)*

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

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

Diagnostic procedures have also improved. It is recognised that follicular lymphoma may transform to a more aggressive lymphoma, usually diffuse large B cell lymphoma (DLBCL), and also that some cases of follicular lymphoma will have coexisting DLBCL within the lymphoma population. In both of these settings watch and wait would not be considered.

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

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with advanced asymptomatic follicular non-Hodgkin's lymphoma (≥ Stage II).	Chemotherapy • Immunotherapy (+/- Rituximab) •	Watch and wait *(deferred chemotherapy)* Active surveillance/ active monitoring No treatment	1. Overall survival 2. Progression free survival 3. Treatment related mortality 4. Treatment related

Include: • Stage II and above Exclude: • Grade IIIb • Transformed FL, composite/discordant FL/DLBCL	Radio-immunotherapy •	Each other	morbidity 5. Health-related quality of life 6. Patient satisfaction 7. Patient preference 8. Time to first treatment 9. Time to second treatment 10. Transformation to aggressive lymphoma 11. Treatment free survival 12. Response to next line of treatment

Additional Comments on PICO
Note for LB – Look at Stage II separately *Note for LB – Record Flipi scores separately* *Note for LB – Radiotherapy could be counted as no treatment or as an intervention* *06.06.14: KR noted that we should included 'each other' in the comparison column as there are studies that look at rituximab versus chemotherapy* *06.06.14: TA137: Rituximab induction of remission (maintenance therapy) in people with relapsed stage II or IV FL. LB asked GDG if there was overlap and the GDG added 'newly diagnosed' to the population, with this inclusion there is no overlap with the TA.*

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison.
Publication status	Peer reviewed, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	

Date limits of search	N/A	
Useful search terms	Flipi II	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Ardeshna** K, Qian W, Smith P et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial Lancet Oncology 2014 Published online March 4, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70027-0 – Portlock et al. Ann Intern Med 1979 – Young et al. Semin Hematol.1988 – Horning et al. N.Engl.J.Med 1984 – Brice et al. J Clin Oncol 1997 – O'Brien et al. Q J Med 1991 – Ardeshna et al. Lancet 2003	
Amendments	06.06.14: – TA ID434: Bendamustine 1st-line advanced indolent NHL – LB asked GDG: Can advanced asymptomatic also be advanced indolent and would bendamustine be used in patients with follicular lymphoma? – GDG: Yes but the literature search will probably not pick up anything in this population as only just publishing work	

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

J	**Topic:** The most effective first-line treatment for people with MALT lymphoma, including the role of antibiotic therapy, radiotherapy and chemo-immunotherapy.
Review question	***What is the most effective first-line treatment for people with MALT lymphoma?***
Guideline subgroup	*Lead:* Chris
	Subgroup: Jennifer, Peter, Gillian
Economic Priority	Low *(inexpensive treatments)*

Background *(~half a page of A4)*

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

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

features of high-grade histology at the time of initial presentation; transformation may occur throughout the disease course.

Diagnosis is based on history, physical exam, radiologic imaging studies, histopathologic and immunohistochemical evaluation of the biopsy specimen, and special molecular laboratory techniques.

Treatment is based on the site of disease and severity of symptoms at presentation. Surgery, radiation therapy, immunotherapy and chemotherapy have all been studied. Unlike many other lymphomas anti-microbial therapy is an important consideration in *H pylori* associated gastric lymphomas- eradication therapy is the mainstay of treatment for localized *H pylori*-positive gastric MALT lymphoma. It remains controversial as to whether other infectious agents may have a pathogenic role in the development of MALT lymphomas at other disease sites.
Regrettably, there is only one randomised trial in the setting of gastric MALT lymphoma not responding to anti-microbial therapy. It is speculated that there is significant variation in practice because of this.

Additional background supplied by topic lead:
Background information: Helicobacter pylori put in italics throughout
Surgery for patients with MALT lymphoma of the stomach should be reserved only for those patients with life-threatening complications such as perforation or massive haemorrhage. Surgery has not been demonstrated to improve disease control, compared to more conservative therapies.

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

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

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

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with newly diagnosed Mucosal/Mucosa Associated Lymphoid Tissue (MALT) non-Hodgkin's lymphoma. Subgroups: • Stages Include: • Gastric MALT • Non-gastric MALT (Salivary glands, lung,	Antibiotic therapy • Antimicrobial • E.g. amoxicillin, clarithromycin, omeprazole • Helicobacter eradication therapy (gastric MALT only) Radiotherapy Chemotherapy • E.g. chlorambucil, CVP • Fludarabine	Each other	1. Progression free survival 2. Overall survival 3. Disease free survival 4. Treatment related morbidity (radiation, dumping syndrome, B12 deficiency) 5. Health-related quality of life 6. Response to first-line therapy

intestinal tract, thyroid gland, breast tissue, genitourinary tract pulmonary/ocular adnexa, orbit) Exclude: • Splenic • Primary Nodal • Skin non-gastric MALT • Transformed lymphoma	Immunotherapy • Rituximab Chemo-immunotherapy • Rituximab and chlorambucil • CVP and rituximab • +/- Rituximab for chemotherapy above Radio-immunotherapy • Ibritumomab tiuxetan (Zevalin) Surgery Watch and wait/Observation		

Additional Comments on PICO

Note for LB – Note for each study how risk is defined (early/low risk, advanced/high risk)
Note for LB – Bendamustine is excluded from the protocol due to Proposed TA ID434
12.05.14:

- *Search generated large evidence base of 600 articles with over 80 that met the minimum criteria of the PICO table, therefore applied an exclusion criteria to the case series with sample sizes less than 50 due to the small sample sizes per intervention included in these studies.*

06.06.14:
Spoke to Chris regarding the studies concerning non-gastric extranodal MALT: 6 case series assessed interventions for one non-gastric extranodal site only each. Chris suggested we focus on the papers assessing interventions for more than one site (except for gastric MALT) due to variation in the treatments for individual sites of non-gastric MALT.
For publications concerning antibiotic therapy non-comparative studies were reviewed to enable updates of two systematic reviews

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional, non-comparative studies (see PICO additional comments section)	
Publication status	Peer reviewed, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline &	

	Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Zucca** E, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. J Clin Oncol. 2013 Feb 10;31(5):565-72.	
Amendments	11.05.14: The search produced a large evidence base of 600 articles with over 80 that met the minimum criteria of the PICO table. LB suggested to the subgroup that it would be best to exclude the case series with sample sizes less than 50 due to the small sample sizes per intervention included in these studies.	

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

K1	**Topic:** The most effective first-line treatment for people with mantle cell lymphoma, including the choice of first-line treatment, the role of consolidation of high-dose therapy with stem cell support and the role of maintenance treatment.
Review question	K1: What is the most effective first-line treatment for people with mantle-cell lymphoma?
Guideline subgroup	*Lead:* Chris
	Subgroup: Kim, Graham, Ian
Economic Priority	Low *(low prevalence rate, low cost of interventions)*
Background *(~half a page of A4)*	

There is no accepted standard of care for patients with mantle cell lymphoma (MCL). The paucity of randomised control data, the relative infrequency of this lymphoma subtype, historical problems in identifying this entity correctly and finding trials with only MCL patients included have all contributed to this.
The majority of patients have advanced stage disease and require systemic treatment. The regimens that have been studied are mostly similar to those used in other B-cell lymphomas-chemotherapy with or without rituximab. The disease is generally considered incurable with conventional chemotherapy. In everyday practice the choice of therapy often depends on whether the patient is fit and considered for intensification with high-dose chemotherapy and autologous stem cell transplantation (ASCT). Several groups have demonstrated excellent activity of cytarabine (cytosine arabinoside)-based combinations, admittedly with greater toxicity than other chemotherapy options combined with ASCT.
It may be that newer agents will have a profound impact on the first-line treatment of MCL, on the basis of results of phase 1 studies reported in relapsed MCL patients. Recommendations at this point in time are likely to be dependent on factors such as patient fitness, the MCL prognostic index and the intention of therapy.
Note that a small number of patients present with limited stage disease and are frequently considered for radiotherapy. There is also an 'indolent' form of MCL which may be observed without therapy.

PICO Table

Population	Intervention	Comparator	Outcomes

Adults and young people (16 years and older) newly diagnosed with Mantle-cell lymphoma
 	
Subgroups:
• Stages
• Variants:
  ○ Blastoid
  ○ Non-blastoid: Indolent (e.g. Small cell)
  ○ Fitness
 	
Exclude:
• Cyclin D1 negative detected by any method
• Presence of a 11:14 translocation
	Radiotherapy
	
	Chemotherapy
	
	Chemo-immunotherapy
	• R-CHOP/CHOP
	• Cytarabine (Cytosine arabinoside)
	• Rituximab
	• Fludarabine/ FCM/rituximab
	• MCP/rituximab
	• CVP/ COP
	
	Watch and wait/observation (for indolent patients)
		Each other	1. Overall survival
			2. Disease free survival
			3. Progression free survival
			4. Treatment related mortality
			5. Treatment related morbidity
			6. Health related quality of life

Additional Comments on PICO

Note for LB – Where results present by age
Note for LB – Present results by subtype reported in the literature (make note of when they include blastoid)

Note for LB – Report when proliferation index reported in literature
Note for LB – Report when Mantle-cell international prognostic index (MIPI) reported in literature

Note for LB - Due to the development of a NICE technology appraisal (Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. NICE technology appraisal ID: 609) the choice of first-line treatment (K1) cannot include Bendamustine. K2 and K3 can include Bendamustine.

Note for LB – Minimal residual disease status should not be included as an outcome of interest as it is not helpful to answer question

Note for GDG4: Proposed TA under consultation: Bortezomib for previously untreated mantle cell lymphoma. TA scope states that current studies include bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, compared with R-CHOP, in adults with previously untreated stage II, III or IV mantle cell lymphoma for whom bone marrow transplants are unsuitable.

Note for GDG: LB asked the subgroup about the inclusion of non-comparative studies as the comparative studies appraised accounted for all the interventions included in the PICO. Chris replied with the following:

Comments on the non-comparative studies:

- HyperCVAD+R studies are represented in the RCT group, with R-CHOP as comparator
- R-DHAP- this regimen is not represented elsewhere in the studies earmarked for analysis- it contains agents which are used in the United Kingdom, albeit in a regimen that is not used for the purpose of primary therapy for this condition. We agreed to look at Ara C and Ritux in the PICO.
- MCL2- this is a very important study but you have included the Abrahamsson study, which subsumes this work, in your review.
- RCHOP- already included in comparison to other studies
- RCHOP (+ consolidation with Y-90-Ibritumamab tiuxetan)- I think you can leave out Zevalin studies
- CHOP- can be excluded as this is no longer relevant with rituximab data that has been published; in addition, you have included R-CHOP in the studies to be examined.

In summary and in response to your question, the only paper from the non-comparative studies list that I would consider looking at would be the R-DHAP paper.

	Details	**Additional Comments**
Type of review	Interventional review	
Language	English language only – literature of interest published in English language journals	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Non-comparative studies (minimum sample size ≥40)	Very few RCTs
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will	

	routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000 Reliable diagnosis, previously grouped with low grade lymphomas	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Kluin-Nelemans** HC1, et al. N Engl J Med. 2012 Aug 9;367(6):520-31. Treatment of older patients with mantle-cell lymphoma. – **Delarue** R1, Haioun C, Ribrag V, Brice P, Delmer A, Tilly H, Salles G, Van Hoof A, Casasnovas O, Brousse N, Lefrere F, Hermine O; Groupe d'Etude des Lymphomes de l'Adulte (GELA). CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood. 2013 Jan 3;121(1):48-53. doi: 10.1182/blood-2011-09-370320. Epub 2012 Jun 20.**Le Gouill**, S., et al (2010) High response rate after 4 courses of R-DHAP in untreated mantle cell lymphoma (MCL) patients in the ongoing phase III randomized GOELAMS and GELA LyMa trial. Blood (ASH Annual Meeting Abstracts), 116, 1758. – **Hermine**, O., et al (2010) Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) Is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: results of the MCL younger trial of the European mantle cell lymphoma network (MCL net). Blood (ASH Annual Meeting Abstracts), 116, 110. – Guideline 422 [a] 2012 Blackwell Publishing Ltd. – **Rule**, S., Smith, P., Johnson, P., Bolam, S., Follows, G.A., Gambell, J. Hillmen, P., Jack, A., Johnson, S., Kirkwood, A., Kruger, A., Seymour, J.F., British Journal of Haematology, 2012, – **Rule et al.** (2011) The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): results of the randomised UK national cancer research institute (NCRI) trial. Blood (ASH Annual Meeting Abstracts), 118, 440.	
Amendments		

K2	**Topic:** The most effective first-line treatment for people with mantle cell lymphoma, including the choice of first-line treatment, the role of consolidation of high-dose therapy with stem cell support and the role of maintenance treatment.
Review question	K2: What is the effectiveness of first-line consolidation of high-dose therapy with autologous or allogeneic transplantation in people with mantle-cell lymphoma?
Guideline subgroup	*Lead:* Karl
	Subgroup: Graham, Kim, Ian, Chris
Economic Priority	Medium *(low prevalence of disease, high cost of interventions)*

Background *(~half a page of A4)*

Mantle cell lymphoma accounts for 5-10% of NHL diagnoses, occurring predominantly in those over the age of 50 years. Historically it has been considered to combine adverse features of both low grade and high grade NHL in that cure is elusive despite attainment of apparent complete clinical responses following immunochemotherapy, but clinical progression often relatively aggressive. Most patients present with advanced disease (stage IV), and bone marrow involvement is common. Median overall survival with chemoimmunotherapy is between 3 and 4 years. Since more intensive induction regimens are associated with higher overall response rates, strategies involving consolidation of first response with high-dose therapy followed by autologous transplantation (ASCT) have been investigated. This improves survival when compared to historical control groups (median overall survival >10 years), although no randomised data are available. This approach has therefore become accepted standard of care for those deemed eligible for ASCT. Nevertheless, late relapses beyond 5 years do occur, with no clear plateau on survival curves suggestive of definitive cure. Furthermore, patient groups with worse prognoses can be identified, for example, those with high MIPI-B (mantle cell lymphoma international prognostic index-biological) scores have 10-year overall survival rates of <25%. Molecular relapses after ASCT can be successfully treated with rituximab, but whether this improves overall survival outcomes and whether it translates to measurable clinical benefits as a maintenance therapy remains unclear. New agents clearly have activity in this disease, but their impact on the role of ASCT remains unknown.

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

PICO Table

Population	Intervention	Comparator	Outcomes
Adults and young people (16 years and older) who have responded to induction therapy for Mantle-cell lymphoma.	Autologous transplantation Allogeneic/(Allogenic/ reduced intensity transplantation)	Each other No transplantation Maintenance rituximab	1. Overall survival 2. Disease free survival 3. Progression free survival

Subgroups: • Mantle cell International Prognostic Index (MIPI) • Response to induction therapy (Complete Response/Partial Response) • Blastoid/Non-blastoid			4. Treatment related mortality 5. Treatment related morbidity 6. Health related quality of life

Additional Comments on PICO

Note for LB – Report age categories when reported in literature
Note for LB – Where reported make note of the Mantle cell International Prognostic Index (MIPI)
Note for LB – Report response to induction therapy (CR/PR)
Note for LB – Report subtype of MCL (Blastoid, non-blastoid)
Note for LB: n≥40 sample size
Note for LB: Aim for comparator studies but look for all trials with sample size ≥40.
UPDATE:

- Review included comparative evidence from one RCT and 10 retrospective reviews so non-comparative evidence was not included

No comparative or non-comparative evidence (sample size ≥40) could be found for allogeneic transplantation.

	Details	**Additional Comments**
Type of review	Interventional review	
Language	English language only – literature of interest published in English language journals	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Single arm trials with a sample size n≥40	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000 Rationale: Diagnostic uncertainty before 2000	

Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Dreyling** M. Blood. 2005 Apr 1;105(7):2677-84. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. – **Fenske** TS et al. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. J Clin Oncol. 2014 Feb 1;32(4):273-81. – **Kruger** WH. Ann Hematol.Ann Hematol. 2014 Apr 30. Allogeneic stem cell transplantation for mantle cell lymphoma-final report from the prospective trials of the East German Study Group Haematology/Oncology (OSHO). This may fall below our limit (n=39) but is the only current prospective trial of allo in first line treatment that I'm aware of. The UK study (n=25) finished recruitment last year but will not have final follow-up until Sept 2015. – **Decaudin**, D., Brousse, N., Brice, P., Haioun, C., Bourhis, J.H., Morel, P., Van Hoof, A., Souleau, B., Quesnel, B. & Gisselbrecht, C. (2000) Efficacy of autologous stem cell transplantation in mantle cell lymphoma: a 3-year follow-up study. Bone Marrow Transplantation, 25, 251–256. – **Khouri**, I.F., Saliba, R.M., Okoroji, G.J., Acholonu, S.A. & Champlin, R.E. (2003) Long-term follow-up of autologous stem cell transplantation in patients with diffuse mantle cell lymphoma in first disease remission: the prognostic value of beta2-microglobulin and the tumor score. Cancer, 98, 2630–2635. – **Lefrere**, F., Delmer, A., Levy, V., Delarue, R., Varet, B. & Hermine, O. (2004) Sequential chemotherapy regimens followed by high-dose therapy with stem cell transplantation in mantle cell lymphoma: an update of a prospective study. Haematologica, 89, 1275–1276. – **Ganti**, A.K., Bierman, P.J., Lynch, J.C., Bociek, R.G., Vose, J.M. & Armitage, J.O. (2005) Hematopoietic stem cell transplantation in mantle cell lymphoma. Annals of Oncology, 16, 618–624. – **Dietrich**, S., Tielesch, B., Rieger, M., Nickelsen, M., Pott, C., Witzens-Harig, M., Kneba, M., Schmitz, N., Ho, D. & Dreger, P. (2010) Patterns and outcome of relapse after autologous stem cell transplantation for mantle cell lymphoma. Cancer, 117, 1901–1910. – **Reddy**, N., Greer, J.P., Goodman, S., Kassim, A., Morgan, D.S., Chinratanalab, W., Brandt, S., Englehardt, B., Oluwole, O., Jagasia, M.H. & Savani, B.N. (2012) Consolidative therapy with stem cell transplantation improves survival of patients with mantle cell lymphoma after any induction regimen. (Abstract). Experimental hematology, 40, 359–366. – **Gianni**, A.M., Magni, M., Martelli, M., Di Nicola, M., Carlo-Stella, C., Pilotti, S., Rambaldi, A., Cortelazzo, S., Patti, C., Parvis, G., Benedetti, F., Capria, S., Corradini, P., Tarella, C. & Barbui, T. (2003) Long-term remission in mantle cell lymphoma following	

	high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood, 102, 749–755. – **Ladetto**, M., Magni, M., Pagliano, G., De Marco, F., Drandi, D., Ricca, I., Astolfi, M., Matteucci, P., Guidetti, A., Mantoan, B., Bodoni, C.L., Zanni, M., Boccadoro, M., Gianni, A.M. & Tarella, C. (2006) Rituximab induces effective clearance of minimal residual disease in molecular relapses of mantle cell lymphoma. Biology of Blood and Marrow Transplantation, 12, 1270–1276. – **Andersen**, N.S., Pedersen, L.B., Laurell, A., Elonen, E., Kolstad, A., Boesen, A.M., Pedersen, L.M., Lauritzsen, G.F., Ekanger, R., Nilsson-Ehle, H., Nordstrom, M., Freden, S., Jerkeman, M., Eriksson, M., Vaart, J., Malmer, B. & Geisler, C.H. (2009) Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma. Journal of Clinical Oncology, 27, 4365–4370. – **Milpied**, N., Gaillard, F., Moreau, P., Mahe, B., Souchet, J., Rapp, M.J., Bulabois, C.E., Morineau, N. & Harousseau, J.L. (1998) High-dose therapy with stem cell transplantation for mantle cell lymphoma: results and prognostic factors, a single center experience. Bone Marrow Transplantation, 22, 645–650. – **Kroger**, N., Hoffknecht, M., Kruger, W., Zeller, W., Renges, H., Stute, N., Zschaber, R. & Zander, A.R. (2000) Allogeneic bone marrow transplantation for refractory mantle cell lymphoma. Annals of Hematology, 79, 578–580. – **Peniket**, A.J., Ruiz de Elvira, M.C., Taghipour, G., Cordonnier, C., Gluckman, E., de Witte, T., Santini, G., Blaise, D., Greinix, H., Ferrant, A., Cornelissen, J., Schmitz, N. & Goldstone, A.H. (2003) An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplantation, 31, 667–678. – **Izutsu**, K., Kanda, Y., Ohno, H., Sao, H., Ogawa, H., Miyazaki, Y., Kawa, K., Kodera, Y., Kato, S., Morishima, Y. & Hirai, H. (2004) Unrelated bone marrow transplantation for non-Hodgkin lymphoma: a study from the Japan Marrow Donor Program. Blood, 103, 1955–1960. – **Ganti**, A.K., Bierman, P.J., Lynch, J.C., Bociek, R.G., Vose, J.M. & Armitage, J.O. (2005) Hematopoietic stem cell transplantation in mantle cell lymphoma. Annals of Oncology, 16, 618–624. – **Maris**, M.B., Sandmaier, B.M., Storer, B.E., Chauncey, T., Stuart, M.J., Maziarz, R.T., Agura, E., Langston, A.A., Pulsipher, M., Storb, R. & Maloney, D.G. (2004) Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood, 104, 3535–3542. – **Cook**, G., Smith, G.M., Kirkland, K., Lee, J., Pearce, R., Thomson, K., Morris, E., Orchard, K., Rule, S., Russell, N., Craddock, C. & Marks, D.I. (2010) Outcome following Reduced-Intensity Allogeneic Stem Cell Transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): a study of the British Society for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation, 16, 1419–1427. – **Tam** CS et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. 2009 Apr 30;113(18):4144-52.
Amendments	

K3	**Topic:** The most effective first-line treatment for people with mantle cell lymphoma, including the choice of first-line treatment, the role of consolidation of high-dose therapy with stem cell support and the role of maintenance treatment.
Review question	K3: What is the effectiveness of first-line maintenance strategies compared with observation for people with mantle-cell lymphoma?
Guideline subgroup	*Lead:* Chris
	Subgroup: Graham, Ian, Kim
Economic Priority	Medium *(Low prevalence of disease, expensive treatment due to duration)*

Background *(~half a page of A4)*

Mantle cell lymphoma (MCL) is a distinct type of B-cell lymphoma genetically characterized by the t(11;14) translocation and cyclin D1 over-expression in the majority of cases. Although the median overall survival of patients has improved it is still has one of the poorest outcomes among the B-cell lymphomas. Choice of initial therapy for MCL is complex due to the lack of available randomised trials. The role of maintenance therapy (defined as any treatment which is given regularly, usually following induction therapy, in order to optimise patient outcomes) remains unclear. Interferon alpha has been studied by various groups but the overall effect on MCL outcomes coupled with the side effect profile has meant that this treatment has not been widely adopted.

Maintenance therapy is topical in MCL for several reasons. Progression free survival is significantly prolonged by the use of maintenance with rituximab, with acceptable toxicity, in other lymphoma subtypes. A recent study in MCL has demonstrated that maintenance rituximab almost doubled the duration of remission in patients responding to a regimen used regularly in older patients, compared with maintenance interferon. Although this study administered rituximab maintenance until patients progressed (or withdrew due to toxicity or patient preference),. In addition, overall survival was also significantly improved among patients who responded to R-CHOP chemotherapy, though this benefit could not be demonstrated in patients receiving nucleoside analogue therapy. Finally, consolidation and maintenance strategies are of interest in a condition which is incurable using conventional methods and which has a median age of onset of 61 years of age. Hence, many patients may be unsuitable for aggressive therapy but may benefit from long term maintenance treatments.

PICO Table

Population	Intervention	Comparator	Outcomes
Adults and young people (16 years and older) who have responded to induction treatment for Mantle-cell lymphoma Subgroups: • Type of induction treatment e.g.	Rituximab Interferon alfa	Each other Observation/watch and wait Auto- Transplantation	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment

ASCT versus chemotherapy			related morbidity 6. Health related quality of life

Additional Comments on PICO

Note for LB – Record length of time for maintenance treatment (duration of maintenance)
Date limit: 2000 (rationale: Diagnostic uncertainty before 2000)

	Details	Additional Comments
Type of review	Interventional review	
Language	English language only – literature of interest published in English language journals	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison. Subgroup suggest there are very few RCTs
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000 Rationale: Diagnostic uncertainty before 2000	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	

Identified papers	– **Kluin-nelemans** et al. (2012). Treatment of Older patients with mantle Cell lymphoma; New England Journal of Medicine. August 2012. – **Dietrich** S. Et al. (2014). Rituximab maintenance therapy after autologous stem cell transplantation prolongs progression-free survival in patients with mantle cell lymphoma. Leukemia. 2014 Mar;28(3):708-9.
Amendments	

Topic L: The most effective first-line treatment for peripheral T-cell lymphoma.

L1	**Topic:** The most effective first-line treatment for peripheral T-cell lymphoma.
Review question	***L1 - What is the most effective first-line treatment for people with peripheral T-cell lymphoma?***
Guideline subgroup	*Lead:* Graham
	Subgroup: Kim, Andrew
Economic Priority	Low *(low number affected, inexpensive treatments)*

Background *(~half a page of A4)*

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

The cure rate, and survival rates for PTCL are worse than for the more common high grade B-cell NHL with data from the International Peripheral T-cell Lymphoma project showing that at 5 years after diagnosis, only 30-40% of patients are still alive and only 20-30% of patients have not relapsed. First line treatment for these patients consists of combination chemotherapy. The most frequently used regimen is CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) which although reasonably well tolerated is associated with infections, nerve damage and (more rarely) cardiac damage. The reason for this regimen being standard of care is historical. Before the routine use of immunohistochemistry in diagnostics, T-cell and B-cell high grade lymphomas were treated together. Randomised clinical trials confirmed that CHOP was superior to a number of other, more intensive, combination chemotherapy regimens. With improvement in diagnostics, T-cell lymphomas could be reliably identified as a subset. Until rituximab was available for routine use as part of therapy for B-cell lymphomas, some trials included high grade T-cell and B-cell lymphomas together although interpreting the results for T-cell lymphomas is difficult due to their relatively small number. Current high grade lymphoma trials involve T-cell and B-cell lymphomas separately although randomised trials for T-cell lymphomas have not been completed due to small numbers of patients (although some are on-going).

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

T-cell lymphoma subtypes. Single centre series suggest gemcitabine containing chemotherapy regimens are effective (such as GEM-P) but other results (for example using the PEGS regimen) are disappointing. In the UK, the use of CHOP, CHOEP and gemcitabine-containing regimens is highly variable.

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

Additional background supplied by topic lead: Peripheral T-cell lymphoma is a rare subtype of lymphoma. Clinical trials investigating this entity are therefore limited in both number and quality. First line treatment has historically been with CHOP chemotherapy but, although the therapy for high grade B-cell lymphomas has advanced with the addition of rituximab, no such advance has been observed in T-cell lymphomas. No multicentre phase III clinical trial has been performed comparing first line chemotherapy regimens. A single institution randomised study suggested a benefit for the regimen CMED over CHOP but the authors themselves acknowledged that this needed to be verified in a multi-centre study. Other studies are mainly retrospective and of poor quality thus not challenging the use of CHOP firstline. In the UK many centres would perform an autologous stem cell transplant in first remission so this guideline should be read in conjunction with L2.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) with new peripheral/mature T-cell non-Hodgkin's lymphoma. Include: • Peripheral T-cell not otherwise specified (PTCL-NOS) • Angio-immunoblastic	Chemotherapy • CHOP • Etoposode (CHOEP) • Gemcitabine-based • GEM-P • PEGS • ACVBP • Mega CHOEP • CHOP14 Chemo-immunotherapy • Alemtuzumab (Campath) (trials in progress)	Each other	1. Overall survival 2. Overall response 3. Complete response 4. Disease free survival 5. Progression free survival 6. Treatment related mortality 7. Treatment related morbidity 8. Health-related quality of life

Additional Comments on PICO

Note for LB – Look at stage after appraisal of evidence
Note for LB – mature and peripheral are the same terms
Following on from GDG 4 the following criteria was applied to the database:

- ***Exclude meeting abstracts due to limited data available to appraise***
- ***Exclude "aggressive NHL" only include PTCL***
- ***Exclude pre 2000***
- ***Sample size ≥40 (single arm trials)***

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	

Study design	Following GDG4: All study designs to be considered	Following GDG4: No filter on study design
Publication status	Peer reviewed journals	
Other criteria for inclusion/exclusion of studies	Following on from GDG 4 the following criteria was applied to the database: • Exclude meeting abstracts due to limited data available to appraise • Exclude "aggressive NHL" only include PTCL • Exclude pre 2000 Sample size ≥40 (single arm trials)	
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000	22.07.14 date limit included due to large volume of evidence and significant change in practice post 2000
Useful search terms	Mature and peripheral are the same terms	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Arkenau HT et al.** 'Gemcitabine, cisplatin and methylprednisolone for the treatment of patients with peripheral T-cell lymphoma: the Royal Marsden Hospital experience.' Haematologica. 2007 Feb;92(2):271-2. – **d'Amore F et al.** 'Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01.' J Clin Oncol. 2012 Sep 1;30(25):3093-9. (NB although the title doesn't mention it, this is one of the biggest reports of using CHOEP as first line treatment.) – **Mahadevan D, et al.** 'Phase 2 trial of combined cisplatin, etoposide, gemcitabine, and methylprednisolone (PEGS) in peripheral T-cell non-Hodgkin lymphoma: Southwest Oncology Group Study S0350.' Cancer. 2013 Jan 15;119(2):371-9. – **Pfreundschuh M, et al**. 'Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL.' Blood. 2004 Aug 1;104(3):634-41. – **Pfreundschuh M et al.** 'Two-weekly or 3-weekly CHOP	

	chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL.' Blood. 2004 Aug 1;104(3):626-33. – **Richard I. Fisher et al** 'Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma'. N Engl J Med 1993; 328:1002-1006 – **Schmitz et al** 'Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patient with T-cell lymphoma treated in studies of the German high grade Non-Hodgkin Lymphoma Study Group.' Blood. 2010 Nov 4;116(18):3418-25. – **Vose et al.** International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes. J Clin Oncol. 2008 Sep 26(25): 4124-4130. – **Yim KL, Ashley S.** 'Assessment of gemcitabine, cisplatin and methylprednisolone (GEM-P) combination treatment for non-Hodgkin T cell lymphoma.' Med Oncol. 2012 Dec;29(5):3535-9.
Amendments	

L2	**Topic:** The most effective first-line treatment for peripheral T-cell lymphoma.
Review question	***L2 - What is the effectiveness of high-dose consolidation of first-line therapy with autologous or allogeneic transplantation in people with peripheral T-cell lymphoma?***
Guideline subgroup	*Lead:* Karl
	Subgroup: Graham, Morag, Kim
Economic Priority	Medium *(rare but expensive)*

Background *(~half a page of A4)*

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

The cure rate, and survival rates for Peripheral T-cell lymphoma (PTCL) are worse than for the more common high grade B-cell NHL with data from the International Peripheral T-cell Lymphoma project showing that at 5 years after diagnosis, only 30-40% of patients are still alive and only 20-30% of patients have not relapsed. First-line treatment for these patients consists of combination chemotherapy. In an effort to improve the cure rate, high dose therapy with autologous stem cell transplantation (ASCT) in first remission has been employed for those who have responded to first-line chemotherapy. No randomised trials have been performed to investigate the role of either ASCT or allogeneic transplantation (alloHSCT) in PTCL. The best evidence comes from prospective, single arm studies, or from analyses of Registry data. Both have significant potential weaknesses, making definitive conclusions impossible and current practice contentious. The largest study employing consolidation ASCT performed by the Nordic group yielded 5 year Progression Free Survival and Overall Survival of 44% and 51% respectively. However, other studies that have sought to compare the outcome of patients receiving ASCT with those receiving chemotherapy alone by case-matched analyses showed no improvement with ASCT. Therefore, different centres utilise different approaches with some routinely offering ASCT in first remission whilst others do not. As with other lymphomas it is also possible to identify groups of patients with worse prognostic features. The possible role of

alloHSCT has therefore been explored as consolidation either in those with higher risk features, or in younger patients in whom the toxicities and non-relapse-related procedural mortality are likely to be lower. The introduction of less toxic 'reduced intensity' alloHSCT regimens has more recently allowed evaluation of its role in older patients up to the age of 65 years.

The main alternative management strategy to transplantation is expectant observation following induction chemotherapy. Whilst this may appear economically favourable, it is important to acknowledge the subsequent costs of increasingly expensive salvage regimens in those destined to relapse, in many cases given with the intent to consolidate 2nd remission by either ASCT or alloHSCT.

Additional background supplied by topic lead: The cure rate, and survival rates for Peripheral T-cell lymphoma (PTCL) are worse than for the more common high grade B-cell NHL with data from the International Peripheral T-cell Lymphoma project showing that at 5 years after diagnosis, only 30-40% of patients are still alive and only 20-30% of patients have not relapsed. First line treatment for these patients consists of combination chemotherapy (see L1). In an effort to improve the cure rate, high dose therapy with autologous stem cell transplantation (ASCT) in first remission has been employed for those who have responded to first line chemotherapy. No randomised trials have been performed to investigate the role of either ASCT or allogeneic transplantation (alloHSCT) in PTCL. The 'best' evidence comes from prospective, single arm studies, or from analyses of Registry data. Both have significant potential weaknesses (all were graded as very poor in the current analysis), making definitive conclusions impossible, and current practice contentious. The largest study employing consolidation ASCT performed by the Nordic group yielded 5y PFS and OS of 49% and 52% for AITL and 38% and 47% for PTCL-NOS respectively (NLG-T-01; d"Amore F et al, Journal of Clinical Oncology 2012; 30(25);3093-9). This, together with similar outcome data in single arm studies reported by other groups, has led to adoption of ASCT as 'standard' consolidation by many centres. However, other studies that have sought to compare the outcome of patients receiving ASCT with those receiving chemotherapy alone by case-matched analyses showed no improvement with ASCT. Therefore, different centres utilise different approaches with some routinely offering ASCT in first remission whilst others do not.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have undergone first-line treatment for peripheral/mature T-cell non-Hodgkin's lymphoma. Include: • Peripheral T-cell not otherwise specified (PTCL-NOS) • Angio-immunoblastic Subgroups: • Response to first-line treatment • PTCL subtypes	Autologous transplantation Allogeneic/allogenic/reduce intensity transplantation	No transplantation • Expectant observation (Clinic appointments, scans) Each other	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health-related quality of life

Additional Comments on PICO

Note for LB – Look at stage after appraisal of evidence
Note for LB – mature and peripheral are the same terms

Note for LB – most studies look at all PTCL subtypes. Anaplastic lymphoma kinase (ALK) positive Anaplastic large cell lymphoma (ALCL) has a relatively good prognosis so inclusion of these patients is likely to bias results in favour of the treatment intervention. Some studies specifically exclude these patients. These studies also have a bias towards young people. Exclude papers that only include ALK + ALCL but make note when papers have these populations included in the populations included in PICO (could use GRADE to downgrade evidence in these circumstances).

Following on from GDG 4 the following criteria was applied to the database:

- ***Exclude meeting abstracts due to limited data available to appraise***
- ***Exclude "aggressive NHL" only include PTCL***
- ***Exclude pre 2000***
- ***Sample size ≥40 (single arm trials)***

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All Languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Single arm trials n≥40	
Publication status	Peer reviewed journals, conference proceedings/abstract	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2000	22.07.14 data limit included due to large volume of evidence and significant change in practice post 2000
Useful search terms	Mature and peripheral are the same terms	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	

Identified papers	– **Corradini et al.** 'Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation.' Leukemia 20 (2006): 1533-38 – **d'Amore et al.** 'Up-Front Autologous Stem-Cell Transplantation in – Peripheral T-Cell Lymphoma: NLG-T-01' J Clin Oncol 30 (2012): 3093-99 – **Mournier et al.** 'Prognostic factors in patients with aggressive non-Hodgkin's lymphoma treated by front-line autotransplantation after complete remission: a cohort study by the Groupe d'Etude des Lymphomes de l'Adulte'. J Clin Oncol 22, 2826-2834 – **Rodrı́guez et al.** 'Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group'. Eur J Haematol 79 (2007): 32-38
Amendments	

Topic M: The most effective first-line treatment for people with Burkitt lymphoma?

M	**Topic:** The most effective first-line treatment for Burkitt lymphoma.
Review question	***What is the most effective first-line treatment for people with Burkitt lymphoma?***
Guideline subgroup	*Lead:* Kim
	Subgroup: Chris, Ian, Andrew
Economic Priority	Low *(rare)*
Background *(~half a page of A4)*	

Burkitt's lymphoma (BL) is a rare and highly aggressive subtype of B-cell Non-Hodgkin's Lymphoma (NHL). Cure rates with intensive first-line treatment are high, especially for younger patients and those with low risk disease (Castillo et al, Cancer 2013), although the outlook is generally very poor for patients who relapse as few patients respond to salvage therapy.

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

An accurate diagnosis of BL is central to appropriate management. Consensus diagnostic criteria are based on the results of the LY10 trial and include the presence of a highly proliferative germinal centre phenotype B-cell lymphoma lacking BCL2expression and with IGH-MYC rearrangements as the only FISH detectable abnormality. Controversy surrounds the management of lymphomas morphologically resembling BL, including the 2008 World Health Organisation (WHO) entity 'B-cell lymphoma, unclassifiable, with features intermediate between BL and DLBCL, and tumours which lack myc rearrangements but have gene expression patterns resembling BL. There is no clear guidance on how best to manage the Burkitt-like tumours and, at least for the present time, recommendations emerging from this guideline should be restricted to cases adhering to the strict diagnostic criteria for BL outlined above.

Addressing the question of most effective treatment for BL will involve comparative appraisal of mostly non-randomised phase I/II data and must take into consideration the toxicity of treatment and rate of relapse, including central nervous system relapse. Unfortunately, there is a paucity of Health Related Quality of Life (HRQOL) data to assist selection. Recommendations are likely to be based on patient age and disease risk.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with Burkitt's lymphoma. Exclude: • Endemic Burkitt's • DLBC-Burkitt's • Tumours which lack myc rearrangements but have gene expression patterns resembling BL • Post-transplant lymphoproliferative	Chemotherapy • Codox-m/IVAC +/- • Hyper-Cvad • GALGB 9251 • LMB/A *(+ year)* • SFOP (French) • BFM (German) Chemo-immunotherapy • Dose-Adjusted EPOCH-Rituximab (Da-epoch-R) • Chemotherapy regimens+/- Rituximab	Each other	1. Overall survival 2. Treatment related mortality 3. Treatment related morbidity 4. Health-related quality of life 5. Central Nervous System (CNS) progression

disease • L3 ALL			

Additional Comments on PICO

Note for LB – Note for each study how risk is defined (early/low risk, advanced/high risk)
Note for LB – Endemic Burkitt's out due to no standard treatment, prevalence predominately sub-Saharan Africa.
Note for LB – DLBC-Burkitt's may crop up due to diagnostic uncertainty
Note for LB – Where noted categorise by MYC in results
Note for LB – after discussing with Kim, exclude papers which only have HIV BL populations (these papers were exploring the ways to treat HIV BL populations prior to acknowledging no need to treat these patients differently to BL populations). Only include papers where population has some sporadic BL.
06.06.14: GDG felt that the evidence base of comparative studies is not enough to aid them when drafting the recommendations and asked to include single arm trials on the interventions where we have no comparative evidence. In order to ensure that the single arm trials included are relevant to the questions they added additional inclusion criteria:

- *Modern diagnostic criteria (WHO 2008)*

07.06.14: Following discussions at GDG3 a decision was made to review the non-comparative evidence for interventions for which no comparative evidence was found and the following criteria was applied to the database:

1. Modern diagnostic criteria
   - If reference is a conference abstract, needs to provide information on diagnosis in order to assess diagnostic criteria
2. Publication date: >2006
3. Interventions for which no comparative studies were found in the original review:
   - SFOP
   - Da-epoch-r

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Non-comparative studies sample size ≥40 (06.06.14)	
Publication status	Peer reviewed, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	

Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers		
Amendments		

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

N	**Topic:** The role of consolidation radiotherapy in first-line treatment of diffuse large B-cell lymphoma.
Review question	***What is the effectiveness of consolidation radiotherapy when given following immuno-chemotherapy as first-line treatment for people with advanced stage diffuse large B-cell lymphoma?***
Guideline subgroup	*Lead:* Peter
	Subgroup: Graham, Kim, Bhuey, Jennifer
Economic Priority	Medium *(common issue, radiotherapy inexpensive, transplantation expensive)*

Background *(~half a page of A4)*

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

Radiotherapy has been used in the past after primary chemotherapy for advanced DLBCL in cases where there is limited residual disease and to sites of bulk at presentation. These are most likely to be the focus for relapse in the future. In general a reduction in local relapse has been shown from this approach but no consistent effect upon survival is seen. The majority of published studies in this setting will reflect both the pre-rituximab era and the pre-Positron Emission Tomography (PET) era. Computed Tomography (CT) has conventionally been used for response assessment at treatment completion, however this anatomical technique cannot accurately discriminate remaining active lymphoma (residual disease) from post treatment necrotic tumour or inactive fibrosis. In contrast post-therapy metabolic imaging, PET-CT, has a

high negative predictive value (the ability of a negative PET scan to exclude persistent disease or future relapse). The small false negative rate with PET is mostly related to its inability to detect microscopic disease which results in future relapse. Current practice following immunochemotherapy is for patients with residual disease to be considered for salvage intensive chemotherapy using an autograft or allograft. However there remains a subgroup of older patients or those with significant co-morbidity who will not be able to proceed with salvage chemotherapy to whom radiotherapy will be offered.

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

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) diagnosed with advanced diffuse large B-cell lymphoma who have responded to first-line immuno-chemotherapy. Include: • Advanced: Bulky stage I, Bulky Stage II, Stage IIb, Stage III, Stage IV	Radiotherapy • Various dose levels • Fields (involved, extended)	No treatment/ observation/watch and wait Second-line chemotherapy/Salvage chemotherapy Transplantation ~~(combined with chemotherapy?)~~ Note: Record if transplantation was in combination with chemotherapy	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health-related quality of life 7. Patient satisfaction 8. Patient preference 9. Overall response rate (complete remission [CR] or partial remission [PR])

Additional Comments on PICO

Note for LB – Present outcomes by included stages
Note for LB – Use International prognostic index (IPI)
Note for LB – Record the response measurement (e.g. PET, CT, PET-CT)
Note for LB – Record variation in reporting of bulky (7.5cm, 10cm)
Note for LB – Consolidated radiotherapy – achieved remission
Note for GDG/subgroup: LB removed the transplantation combined with chemotherapy text in the comparison. Transplantation papers will not change dependent on chemotherapy and therefore LB will record if the transplantation included chemotherapy when reviewing the articles
06.06.14:
- Spoke to Graham regarding FL grade 3. Exclude 3b as this is not considered transformation.

07.06.14:
- Following on from discussions at GDG3 inclusion criteria of sample size n>40 for single arm trials has been applied. This was taken from the inclusion criteria of K2 which is also a consolidation with transplant question in a different population

20.06.14:
Exclusion of ‘double-hit’ lymphomas: Email to Graham regarding inclusion of articles with populations with 'double hit' NHL. Graham replied that 'double hit' refers to 2 genetic changes, 1 involving BCL2 gene (which is the classic follicular lymphoma gene) and one involving c-myc (of Burkitt fame). It's rare, and a very nasty disease with poor outcomes. Usually the double hits arise de novo, with no prior history of follicular. Occasionally you can get a true c-myc driven transformation which therefore becomes a double hit. So on balance I would say it's not part of the population as usually it arises de novo.

Discussion sub-group via email: due to low event rates the decision was made that for comparative non-RCT studies a minimum sample size of ≥30 in each group was required for inclusion.

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Single arm trials with n≥40.	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2003 Rationale: Treatment options changed during 2003 with the introduction of Rituximab.	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	

Identified papers	– **Held** G, Murawski N, Ziepert M et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B cell lymphoma. J Clin Oncol. Published Ahead of Print as 10.1200/JCO.2013.51.4505
Amendments	

Topic O: The initial treatment of composite/discordant and transformed follicular lymphoma.

O	**Topic:** The initial treatment of composite/discordant and transformed follicular lymphoma.
Review question	***What is the effectiveness of first-line consolidation with high-dose therapy with autologous or allogeneic transplantation in people with histological transformation of follicular lymphoma to diffuse large B-cell lymphoma or concurrent presentation with follicular lymphoma & diffuse large B-cell lymphomas, compared with other strategies?***
Guideline subgroup	*Lead:* Graham
	Subgroup: Karl, Andrew, Kate
Economic Priority	High *(common and expensive treatment)*

Background *(~half a page of A4)*

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

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

Some cases of transformed follicular lymphoma are associated with particularly poor survival. For example, those associated with c-myc rearrangement (producing a so-called ‘double hit’ lymphoma). These are rare so little data exists to guide management. Many centres consolidate remission with either autologous or allogeneic stem cell transplant and there are reports of positive outcomes using either approach.

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

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

Traditionally patients with composite lymphoma are usually treated as for other high grade transformation events. However, when the low grade component is in the marrow the outcome with immunochemotherapy alone is very encouraging. It would be a valuable task of this review to assess the evidence for this common approach to the two situations presented above.

Additional background supplied by topic lead: Follicular lymphoma is the commonest subtype of indolent Non-Hodgkin Lymphoma in the UK. Although in the majority of patients, the disease remains indolent throughout its natural history, approximately 30% of patients experience a high grade transformation event. In the majority of cases this is characterised by the development of diffuse large B-cell lymphoma which requires prompt treatment with systemic chemotherapy. Most series define transformed follicular lymphoma as the diagnosis of high grade lymphoma at least 6 months after the diagnosis of follicular lymphoma was made. This is to distinguish transformed lymphoma from concurrent high grade and low grade lymphoma which may either be concordant (two different lymphomas in the same place, for example seen in the same lymph node section) or discordant (two different lymphomas seen in different places for example high grade in a lymph node and low grade in the bone marrow).

For patient who are fit enough, the standard of care for treatment of diffuse large B-cell lymphoma is rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). This is irrespective of whether the high grade lymphoma has arisen de novo, occurs concurrently with indolent lymphoma or has transformed from an indolent lymphoma. Alternative regimens are used in those not suitable for an anthracycline or who have been exposed to a dose of anthracyclines in the past which excludes further use of these agents. Failure to respond to first line immunochemotherapy is defined as primary refractory disease and is generally considered to have a poor prognosis.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have undergone first-line treatment for histological transformation of follicular lymphoma to diffuse large B-cell lymphoma or concurrent presentation with follicular lymphoma & diffuse large B-cell lymphomas.	Autologous transplantation Allogeneic (Allogenic/ reduced intensity transplantation)	No transplant Radiotherapy Maintenance therapy (Rituximab) Each other	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health-related quality of life 7. Patient satisfaction 8. Patient preference 9. Diagnosis at relapse

Additional Comments on PICO

Note for LB –Present results by isolated disease limited stage versus advanced stage
Note for LB – Record previous treatment for follicular lymphoma (prior to transformation)
Note for LB – Record transformation Flipi
Note for LB – Record time to transformation
Note for LB – Where available present results by composite versus discordant

Note for LB – Could be chemotherapy or immuno-chemotherapy. Present where possible by treatment type
Note for LB – Present evidence where possible by the two possible situations mentioned in the background
06.06.14:
- *Spoke to Graham regarding FL grade 3. Exclude 3b as this is not considered transformation.*

07.06.14:
Following on from discussions at GDG3 inclusion criteria of sample size n>40 for single arm trials has been applied. This was taken from the inclusion criteria of K2 which is also a consolidation with transplant question in a different population

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional Single arm trials n≥40 (07.06.14)	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Guirguis** HR et al. 'Survival of patients with transformed lymphoma in the rituximab era.' Ann Hematol. 2014 Jan 11. – **Villa** D et al. 'Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group.' J Clin Oncol. 2013 Mar 20;31(9):1164-71. – **Wirk** B et al. 'Outcomes of hematopoietic cell transplantation for diffuse large B cell lymphoma transformed from follicular	

	lymphoma.' Biol Blood Marrow Transplant. 2014 Mar 15. pii: S1083-8791(14)00163-3.
Amendments	

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

P	**Topic:** The most appropriate salvage strategies, including indication for autologous and allogeneic transplantation, for people with diffuse large B-cell lymphoma.
Review question	***What is the most appropriate salvage strategy for people with relapsed/refractory diffuse large B-cell lymphoma?***
Guideline subgroup	*Lead:* Karl
	Subgroup: Morag, Gillian, Graham
Economic Priority	High *(possible expensive treatment)*

Background *(~half a page of A4)*

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

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

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

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

response to salvage. The role of allogeneic transplantation (alloHSCT) in these patients remains incompletely defined. The graft-versus-lymphoma effect is less well demonstrated in DLBCL than in other lymphomas. Furthermore, the non-relapse-related procedural mortality associated with such transplants is relatively high in patients with DLBCL (>20% in most series). Nevertheless, a number of published series indicate plateaus in the survival curves for patients undergoing alloHSCT, and it continues to be considered a clinical option in such cases. Some reserve alloHSCT for patients who have failed a prior ASCT, recognizing that only a minority will be salvaged to a position in which they can undergo such a procedure.

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) who have relapsed/refractory diffuse large B-cell lymphoma. Exclude: • Transformed follicular • Low grade (indolent) lymphoma • Composite low/high grade lymphoma • Central Nervous System lymphoma	Chemo-immunotherapy Chemo-immunotherapy with autologous transplantation Chemo-immunotherapy with allogeneic/ allogenic/ reduced intensity transplantation Chemo-immunotherapy with autologous transplantation followed by allogeneic/allogenic/ reduced intensity transplantation at relapse	Each other	1. Overall survival 2. Disease free survival 3. Progression free survival 4. Treatment related mortality 5. Treatment related morbidity 6. Health-related quality of life 7. Response to chemo-immunotherapy

Additional Comments on PICO

Note for LB – Record duration of response
Note for LB – Record time to relapse
Note for LB – Where available report by age
Note for LB – Record response to chemo-immunotherapy
Note for LB – For the third intervention: These are patients presenting for an allogeneic transplantation but with a history of past autologous transplantation. Therefore I will need to record any past transplantations patients may have had.
27.07.2015: Email communication with the subgroup (KP, GC) confirmed that immunotherapy agents to be considered are restricted to rituximab, which came into use circa 2002.

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison.
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for		

inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Aksentijevich**,I. et al. (2006) Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. *Biol.Blood Marrow Transplant.*, 12, 965-972. – **Ardeshna**,K.M., et al. (2005) Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br.J.Haematol.*, 130, 363-372. – **Armitage**,J.O., et al. (2003) Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J.Clin.Oncol.*, 21, 897-906. – **Bacher**,U., et al. (2012) Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: myeloablative or reduced intensity? *Blood*, 120, 4256-4262. – **Bishop**,M.R., et al. (2008) Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation. *Ann.Oncol.*, 19, 1935-1940. – **Biswas**,T., et al. (2010) Involved field radiation after autologous stem cell transplant for diffuse large B-cell lymphoma in the rituximab era. *Int.J.Radiat.Oncol.Biol.Phys.*, 77, 79-85. – **Blay**,J., et al. (1998) The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. Parma Group. *Blood*, 92, 3562-3568. – **Bloor**,A.J., et al. (2008) High response rate to donor lymphocyte infusion after allogeneic stem cell transplantation for indolent non-Hodgkin lymphoma. *Biol.Blood Marrow Transplant.*, 14, 50-58. – **Coiffier**,B., et al. (2010) Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*, 116, 2040-2045. – **Corradini**,P., et al. (2007) Allogeneic stem cell transplantation	

following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia*, 21, 2316-2323.

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- **Freytes**,C.O et al. (2012) Outcome of lower-intensity allogeneic transplantation in non-Hodgkin lymphoma after autologous transplantation failure. *Biol.Blood Marrow Transplant.*, 18, 1255-1264.
- **Friedberg**,J.W., et al. (2001) The impact of external beam radiation therapy prior to autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Biol.Blood Marrow Transplant.*, 7, 446-453.
- **Gisselbrecht**,C., et al. (2010) Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J.Clin.Oncol.*, 28, 4184-4190.
- **Gisselbrecht**,C., et al. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J.Clin.Oncol.*, 30, 4462-4469.
- **Guglielmi**,C., et al. (1998) Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial. *J.Clin.Oncol.*, 16, 3264-3269.
- **Haioun**,C., et al. (2001) Tandem autotransplant as first-line consolidative treatment in poor-risk aggressive lymphoma: a pilot study of 36 patients. *Ann.Oncol.*, 12, 1749-1755.
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- **Hamlin**,P.A., et al. (2003) Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*, 102, 1989-1996.
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- **Hoppe**,B.S., et al. (2009) The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. *Bone Marrow Transplant.*, 43, 941-948.
- **Jabbour**,E., et al. (2004) Outcome of elderly patients with aggressive Non-Hodgkin's lymphoma refractory to or relapsing after first-line CHOP or CHOP-like chemotherapy: a low probability of cure. *Leuk.Lymphoma*, 45, 1391-1394.
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- **Philip**,T., et al. (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N.Engl.J.Med.*, 333, 1540-1545.
- **Rapoport**,A.P., et al. (1997) Autotransplantation for relapsed or refractory non-Hodgkin's lymphoma (NHL): long-term follow-up and analysis of prognostic factors. *Bone Marrow Transplant.*, 19, 883-890.
- **Rezvani**,A.R., et al. (2008) Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: a multicentre experience. *Br.J.Haematol.*, 143, 395-403.
- **Robinson**,S.P., et al. (2002) Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. *Blood*, 100, 4310-4316.
- **Rodriguez**,J., et al. (2004) Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO

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- **Vose**,J.M., et al. (1992) Progressive disease after high-dose therapy and autologous transplantation for lymphoid malignancy: clinical course and patient follow-up. *Blood*, 80, 2142-2148.
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- **Vose**,J.M., et al. (2001) Autologous transplantation for diffuse aggressive non-Hodgkin's lymphoma in patients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. *J.Clin.Oncol.*, 19, 406-413.
- **Wendland**,M.M., et al. (2007) The impact of involved field radiation therapy in the treatment of relapsed or refractory non-Hodgkin lymphoma with high-dose chemotherapy followed by hematopoietic progenitor cell transplant. *Am.J.Clin.Oncol.*, 30, 156-162.
- **Wildes**,T.M., et al. (2008) Comorbidities, not age, impact

	outcomes in autologous stem cell transplant for relapsed non-Hodgkin lymphoma. *Biol.Blood Marrow Transplant.*, 14, 840-846. – **Zijlstra**,J.M., et al. (2006) 18F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. *Haematologica*, 91, 522-529.
Amendments	

Topic Q: Indications and methods for central nervous system prophylaxis for people with diffuse large B-cell lymphoma.

Q1	**Topic:** Indications and methods for central nervous system prophylaxis for people with diffuse large B-cell lymphoma.
Review question	***What are the risk factors associated with central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma?***
Guideline subgroup	*Lead:* Chris
	Subgroup: Peter, Kim, Jennifer, Graham
Economic Priority	Low

Background *(~half a page of A4)*

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

There is significant controversy regarding which factors most reliably identify patients at high risk of this complication. Clarification is also needed regarding the value of the various prophylaxis strategies when contemporary chemotherapy regimens incorporating rituximab are used. Traditionally, involvement of > 1 extranodal site and an elevated lactate dehydrogenase level identifies individuals at highest risk (i.e. > 20% risk of the event). In addition, certain solitary extra-nodal sites (e.g. testis, kidney and breast) have been regarded as imputing higher risk. Due to the current lack of consensus, a wide variation of practise occurs across the UK with some centres only giving CNS directed prophylaxis to those with the highest risk (such as testicular involvement). Other centres would include patients with epidural disease, paranasal sinus involvement, bone marrow involvement and involvement of kidney or breast.

A significant number of patients with high risk features may already have subclinical CNS disease at presentation. Detection of this at a time when effective therapy may be applied requires innovative strategies. Immunophenotyping by flow cytometry is a promising approach. Widespread use of this technique may redefine what risk and prophylaxis really mean. Low sensitivity of current laboratory methods in predicting CNS involvement, including cytological assessment of cerebrospinal fluid (CSF), also raises issues about overtreatment of patients allocated a high risk status. Intra-thecal and parenterally administered prophylaxis imparts small but definite risks to the patient. In addition, the administration of such prophylaxis is resource intensive. Intrathecal drug delivery requires an elaborate governance structure to avoid the wrong drug being administered, and intravenous administration requires an in-patient stay.

PICO Table

Population	Factors	Outcomes
Adults and young people (16 years and older) newly diagnosed with diffuse large B-cell lymphoma.	Patient characteristics Disease characteristics International prognostic index (IPI) score Lactate Dehydrogenase (LDH) Extranodal disease Cerebrospinal fluid (CSF) detection of occult disease Disease site: • Testicular, bone marrow, pharynx, facial sinus, breast, primary bone, para-spinal, epidural, kidney	1. CNS relapse a. Time to relapse b. Sites of relapse • Isolated to CNS compared to systemic relapse • General relapse • Parenchymal • Meningeal

Additional Comments on PICO

Note for LB – First-line treatment only
Date limit: publications ≥2003
Sifting update: Fletcher et al. (2014) systematic review concerning prognostic factors for CNS relapse had the following inclusion criteria:

- ≥18 years with histologically proven aggressive B-cell lymphoma
- Trials conducted from 1994-2013

Exclusion criteria:

- Immuno-compromised patients, studies with T-cell lymphoma as primary histology, patients with primary CNS lymphoma, Studies performed on patients with intravascular lymphoma or the very 'aggressive' lymphomas (BL or Burkitt-like histology), trials adding chemotherapy without known/appreciable CNS penetration, trials not reporting CNS related data, lack of peer review or clear peer review process, publications including <25 patients.

I used the Fletcher et al. (2014) systematic review and ordered all papers included in the review. I then re-sifted and ordered all articles published from 2013 onwards.

	Details	Additional Comments
Type of review	Risk profiling	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort	
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of	

	Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	2003 Rationale: Treatment options changed during 2003 with the introduction of Rituximab which in turn may influence the factors associated with central nervous system relapse	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers		
Amendments		

Q2	**Topic:** Indications and methods for central nervous system prophylaxis for people with diffuse large B-cell lymphoma.
Review question	***What is the efficacy of central nervous system prophylaxis for people with diffuse large B-cell lymphoma?***
Guideline subgroup	*Lead:* Chris
	Subgroup: Peter, Kim, Jennifer, Graham
Economic Priority	High *(Frequent issue and logistically difficult to deliver, expensive)*
Background *(~half a page of A4)*	

Although subgroups of patients with diffuse large B-cell lymphoma (DLBCL) with a relatively high risk of Central Nervous System (CNS) recurrence (i.e. ≥ 20%) can be identified, the current evidence base supporting the use of prophylactic strategies in patients receiving modern chemo-immunotherapy is limited. Excluding testicular DLBCL, the evidence for intra-thecal prophylaxis in this setting is controversial, consequently practice varies between complete opt-out, intrathecal prophylaxis (1-6 doses), intravenous high dose methotrexate, or a combination of the latter two.

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

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

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

PICO Table

Population	Intervention	Comparison	Outcomes
Adults and young people (16 years and older) newly diagnosed with diffuse large B-cell lymphoma. Subgroups: • Risk factors of Central Nervous System (CNS) relapse	CNS prophylaxis: Intrathecal chemotherapy • Number of administrations • Omaya reservoir/ no reservoir • Drug type and dosage • Schedule (early or after chemotherapy) Intravenous chemotherapy • Number of cycles • Drug type and dosage • Schedule (early or after chemotherapy)	No CNS prophylaxis Each other	1. 1. CNS relapse • Time to relapse • Sites of relapse a. Isolated b. General relapse c. Parenchymal d. Meningeal 2. Overall survival 3. Treatment related mortality 4. Treatment related morbidity 5. Health related quality of life

Additional Comments on PICO

Note for LB – papers may be pre or post Rituximab
Post GDG 1 LB removed people who have received CNS prophylaxis from the population as the comparison is 'no CNS prophylaxis' so we have to have a population that reflects this.

27.04.15: LB email to subgroup: There are 7 non-comparative studies with >40 patients. Given the amount of comparative evidence included in the review I suggested that these non-comparative studies should not be included in the review. Subgroup agreed to exclusion of these articles.

	Details	Additional Comments
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional	Case series with one intervention or case reports will not be included due to no comparison.
Publication status	Peer reviewed journals, conference proceedings/abstracts	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	
Useful search terms		
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **Benevolo** G , Stacchini A , Spina M , et al . Final results of a multicenter trial addressing role of CSF fl ow cytometric analysis in NHL patients at high risk for CNS dissemination . Blood 2012 ; 120 : 3222 – 3228 . – **Schmitz** N, Zeynalova S, Glass B, et al. CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade Non-Hodgkin Lymphoma Study Group. Ann Oncol 2012;23:1267–1273.	
Amendments		

Topic R: The survivorship issues for people treated for non-Hodgkin's lymphoma

R	**Topic:** The survivorship issues for people treated for non-Hodgkin's lymphoma.
Review question	What is the effectiveness of surveillance protocols for late adverse effects of treatment in people with non-Hodgkin's lymphoma?
Guideline subgroup	*Lead:* Gillian
	Subgroup: Chris, Kim, Morag, Tessa
Economic Priority	Medium *(high cost of surveillance, large population, low feasibility for modelling)*

Background *(~half a page of A4)*

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

Chemotherapy and radiotherapy can cause physical problems long after the treatment has ended. Heart damage, peripheral neuropathy, cognitive disorders, second cancers, infertility, chronic tiredness and inability to do day to day tasks are some of the late side effects that can happen after lymphoma treatment. People can also have long term psychological and emotional late effects following NHL treatment, such as depression, anxiety and even post- traumatic stress disorder, affecting families and carers too. A study looking at the quality of life of long term NHL survivors found that 10 years after treatment 23% of participants had poor or worsening physical and mental health. This suggests that late effects can continue for many years.

The statistics also show more older people are now diagnosed, treated and achieve long term disease free survival from NHL. This has implications as older people often have other health problems, such as heart disease and diabetes. A national cancer survey, where NHL patients contributed, said that their cancer treatment had made these other health problems worse and reduced their quality of life.

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

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

PICO Table

Population	Intervention	Comparator	Outcomes
Adults and young people (16 years and older) treated for non-Hodgkin's lymphoma Subgroups: • Type of treatment	Surveillance programs specific to NHL: • Immuno-deficiency/infection	None Each other	1. Overall survival 2. Late-event rate 3. Cause-specific survival

• Risk of relapse • Co-morbidity Exclude: • People who were treated for non-Hodgkin's lymphoma below the age of 16 years	• Cardiac Disease (including heart failure, coronary artery disease) • Fertility issues • Secondary cancers Follow-up setting: • General Practice • Specific hospital clinics		4. Treatment related morbidity 5. Health related quality of life 6. Patient satisfaction 7. Patient preference 8. Psychological well-being

Additional Comments on PICO
Note for LB – Record where reported the results by subgroups presented in the PICO *Note for LB – Record number of relapses (for risk of relapse subgroups in PICO)* *Note for LB – Record the follow-up setting* *Note for LB – Record incidence of heart failure and coronary cardiac/artery disease separately*

	Details	**Additional Comments**
Type of review	Interventional review	
Language	All languages	
Study design	Systematic reviews, Randomised Control Trial, Cohort, Case-control, cross-sectional, audit, service development reports	Case series with one intervention or case reports will not be included due to no comparison. May be qualitative evidence available to assess HRQoL.
Publication status	Peer reviewed journals, conference proceedings/abstracts, audits, service development reports	
Other criteria for inclusion/exclusion of studies		
Search strategy	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Date limits of search	N/A	

Useful search terms	Neoplasms*/drug therapy, survivors*, radiotherapy/*adverse effects, cancer/neoplasm, lymphoma, survivorship, nurse led services, service development, follow up care, anthracyclines/adverse effects, neoplasms*/radiotherapy	
Review strategies	Relevant studies will be identified, assessed and synthesised using the appropriate quality checklists according to the NICE Guideline Manual (2012). GRADE methodology will be used to assess study quality for the outcomes.	
Identified papers	– **John** C and Armes J (2013) Developing a nurse-led survivorship service for patients with lymphoma. *European Journal of Oncology Nursing* 17(5): 521-527 – **Carver** JR, Szalda D and Ky B (2013) Asymptomatic cardiac toxicity in long-term cancer survivors: defining the population and recommendations for surveillance. *Seminars In Oncology* 40(2): 229-238 – **Walsh** MC (2010) Impact of treatment-related cardiac toxicity on lymphoma survivors: an institutional approach for risk reduction and management. *Clinical Journal Of Oncology Nursing* 14(4): 505-507 – **Suter** TM and Ewer MS (2013) Cancer drugs and the heart: importance and management. *European Heart Journal* 34(15): 1102-1111	
Amendments		

Excluded Health Economic Studies

1. Andresen, S., et al. The impact of high-dose chemotherapy, autologous stem cell transplant and conventional chemotherapy on quality of life of long-term survivors with follicular lymphoma. Leukemia and Lymphoma 2012. 53(3): 386-393

Reason for exclusion: QOL over- cross referred to clinical evidence review

2. Athanasakis, K., et al. "Rituximab Sc Vs Rituximab Iv for non-Hodgkin's Lymphomas (Nhls): an Economic Evaluation for the Greek Healthcare System." Value in Health 18.7 (2015): A444.

Reason for exclusion: Not specific to any PICO – cost-minimisation analysis of different modes of rituximab delivery

3. Auweiler, P. W., et al. "Cost effectiveness of rituximab for non-Hodgkin's lymphoma: a systematic review. [Review]." Pharmacoeconomics 30.7 (2012): 537-49.

Reason for exclusion: Not specific to PICOs- focus on rituximab CE studies overview

4. Beveridge, R., et al. "Economic impact of disease progression in follicular non-Hodgkin lymphoma." Leukemia & Lymphoma 52.11 (2011): 2117-23.

Reason for exclusion: Not specific to PICO- not specific to IIA/first line treatment

5. Blaes, A. H., et al. "Quality of life appears similar between survivors of indolent and aggressive non-Hodgkin lymphoma." Leukemia & Lymphoma 52.11 (2011): 2105-10.

Reason for exclusion: Not economic paper reports QOL of long term survivors only

6. Blommestein, H. M., et al. "Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: results of a population-based study." European Journal of Haematology 92.5 (2014): 398-406.

Reason for exclusion: Not specific to PICO-focus on rituximab as maintenance treatment in relapsed/refractory FL who responded to second line chemotherapy

7. Boland A., et al. “Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.” Health Technol Assess. 2009 Sep;13 Suppl 2:41-8.

Reason for exclusion: Not specific to PICOs- focus on use of rituximab in relapsed or refractory stage III or IV with chemotherapy or chemotherapy alone

8. Braga et al. 2010

Reason for exclusion: Not specific PICO- not specific to IIA/ or to first line

9. Castro Gomez, A. J., et al. "[Cost-effectiveness analysis of maintenance therapy with rituximab in patients with follicular lymphoma responding to induction therapy at the first line]. [Spanish]." Revista Espanola de Salud Publica 86.2 (2012): 163-76.

Reason for exclusion: Not specific PICO- not specific to IIA/

10. Chan, K. K., et al. "Cost-utility analysis of primary prophylaxis versus secondary prophylaxis with granulocyte colony-stimulating factor in elderly patients with diffuse aggressive lymphoma receiving curative-intent chemotherapy (Provisional abstract)." Journal of Clinical.Oncology 30.10 (2012): 1064-71.

Reason for exclusion: Not specific to PICO- focus on use of GCSF with curative intent chemotherapy

11. Chen, Q., et al. "Comparing the cost-effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma." Value in Health 18.2 (2015): 189-97.

Reason for exclusion: Not specific to any PICO – rituximab maintenance and radioimmunotherapy consolidation for people with FL in first remission

12. Chrischilles E.A., et al. “Impact of age and colony-stimulating factor use on hospital length of stay for febrile neutropenia in CHOP-treated non-Hodgkin's lymphoma.” Cancer Control. 2002;9(3):203-11

Reason for exclusion: Cost only paper-not specific to PICOs- focus on neutropenia costs

13. Compaci, G., et al. "Effectiveness of telephone support during chemotherapy in patients with diffuse large B cell lymphoma: the Ambulatory Medical Assistance (AMA) experience." International Journal of Nursing Studies 48.8 (2011): 926-32.

Reason for exclusion: Not an economic paper

14. Deconinck, E., et al. "Cost effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation (Structured abstract)." Pharmacoeconomics. 28.1 (2010): 35-46.

Reason for exclusion: Not specific to PICO- not specific to IIA/first line treatment

15. Dewilde S1, Woods B Castaigne JG Parker C Dunlop W. "Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales." Journal of Medical Economics 17.2 (2014): 111-24.

Reason for exclusion: Not specific PICO- not specific to IIA/looks at bendamustine

16. Doorduijn, J., Buijt, I., van der Holt, B., Steijaert, M., Uyl-de Groot, C. and Sonneveld, P. (2005), “Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy”. European Journal of Haematology, 75: 116–123.

Reason for exclusion: Not specific to PICOs- reports QOL/QALYs only

17. Doorduijn, J. K., et al. "Economic evaluation of prophylactic granulocyte colony stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma (Provisional abstract)." Haematologica 89.9 (2004): 1109-17.

Reason for exclusion: Not specific to PICOs- focus on GCSF during chemotherapy in elderly patients with aggressive NHL

18. Doss, S., et al. "NICE guidance on rituximab for first-line treatment of symptomatic stage III-IV follicular lymphoma in previously untreated patients." Lancet Oncology 13.2 (2012): 128-30.

Reason for exclusion: Report of NICE appraisal TA 243of rituximab as first line treatment

19. Dranitsaris, G., C. Altmayer, and I. Quirt. "Cost-benefit analysis of prophylactic granulocyte colony-stimulating factor during CHOP antineoplastic therapy for non-Hodgkin's lymphoma (Structured abstract)." Pharmacoeconomics. 11.6 (1997): 566-77.

Reason for exclusion: Not specific to PICOs- focus on GCSF during CHOP for NHL

20. Dundar, Y., et al. "Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma (Structured abstract)." Health Technology Assessment.Database.3 (2009): 23.

Reason for exclusion: Not specific to PICO- focus on ERG report on to CE of rituximab in combination with CVP Vs. CVP in first line treatment

21. Errante, D., E. Vaccher, and U. Tirelli. "Are hematopoietic colony-stimulating factors useful in association with chemotherapy in the treatment of HIV-related non-Hodgkin's lymphomas? (Structured abstract)." Annals.of Oncology 7.3 (1996): 233-37.

Reason for exclusion: Not specific to PICOs- focus on use of GCSF in HIV related NHL

22. Fagnoni, P., et al. "Cost effectiveness of high-dose chemotherapy with autologous stem cell support as initial treatment of aggressive non-Hodgkin's lymphoma (Provisional abstract)." Pharmacoeconomics. 27.1 (2009): 55-68.

Reason for exclusion: Not specific to PICO- focused on first-line treatment for transplantation in FL – does not meet topic H

23. Ferrara, F. and R. Ravasio. "Cost-effectiveness analysis of the addition of rituximab to CHOP in young patients with good-prognosis diffuse large-B-cell lymphoma (Structured abstract)." Clinical.Drug Investigation. 28.1 (2008): 55-65.

Reason for exclusion: Not specific to PICOs- focus on young patients receiving rituximab with CHOP in good prognosis DLBCL

24. Ramos, Font C., A. C. Rebollo-Aguirre, and Portero R. Villegas. "Utility of 90Y-Ibritumomab Tiuxetan (Zevalin) in the treatment of adult patients with non-Hodgkin lymphoma (Structured abstract)." Health Technology Assessment.Database.3 (2010).

Reason for exclusion: Spanish TA- focus on radioimmunotherapy in NHL – executive summary only available in English

25. Foster T., et al. Economic burden of follicular non-Hodgkin's lymphoma. Pharmacoeconomics. 2009;27(8):657-79.

Reason for exclusion: Review (non-systematic) –review of different treatments and across NHL types/stages

26. Greenhalgh, J., et al. "Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma : a NICE single technology appraisal." Pharmacoeconomics 31.5 (2013): 403-13.

Reason for exclusion: Reports NICE TA appraisal-not specific to IIA

27. Griffiths, R. I., et al. "Impact on medical cost, cumulative survival, and cost-effectiveness of adding rituximab to first-line chemotherapy for follicular lymphoma in elderly patients: an observational cohort study based on SEER-medicare (Provisional abstract)." Journal of Cancer Epidemiology 2012:978391.3 (2012).

Reason for exclusion: Not specific to PICO- not specific to IIA

28. Griffiths, R. I., et al. "Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma." Cancer 118.24 (2012): 6079-88.

Reason for exclusion: Not specific to PICO- focus on addition of rituximab to first-line chemotherapy

29. Groot, M. T., Lugtenburg, P. J., Hornberger, J., Huijgens, P. C. and Uyl-de Groot, C. A. (2005), Cost-effectiveness of rituximab (MabThera®) in diffuse large B-cell lymphoma in the Netherlands. European Journal of Haematology, 74: 194–202.

Reason for exclusion: Not specific to PICOS- focus on Rituximab with CHOP vs. CHOP in DCLBC.

30. Gruschkus, S. K., et al. "Cost-effectiveness of white blood cell growth factor use among a large nationwide cohort of elderly non-Hodgkin's lymphoma patients treated with chemotherapy." Value in Health 14.2 (2011): 253-62.

Reason for exclusion: Not specific to PICOs- focus on sue of prophylaxis CSF in elderly NHL patient receiving chemotherapy

31. Hackshaw, A., J. Sweetenham, and A. Knight. "Are prophylactic haematopoietic growth factors of value in the management of patients with aggressive non-Hodgkin's lymphoma? (Structured abstract)." British.Journal of Cancer 90.7 (2004): 1302-05.

Reason for exclusion: Not specific to PICOs- focus on GCSF

32. Hagemeister, F. B. "'Watch and wait' as initial management for patients with follicular lymphomas: still a viable strategy?. [Review]." Biodrugs 26.6 (2012): 363-76.

Reason for exclusion: Not an economic paper

33. Hara, T., et al. "Low-dose granulocyte colony-stimulating factor overcomes neutropenia in the treatment of non-Hodgkin's lymphoma with higher cost-effectiveness (Provisional abstract)." International.Journal of Hematology. 82.5 (2005): 430-36.

Reason for exclusion: Not specific to PICOs focus on GCSF with chemotherapy

34. Hashino, S., et al. "Cost benefit and clinical efficacy of low-dose granulocyte colony-stimulating factor after standard chemotherapy in patients with non-Hodgkin's lymphoma (Provisional abstract)." International.Journal of Laboratory.Hematology. 30.4 (2008): 292-99.

Reason for exclusion: Not specific to PICOs- focus on GCSF after standard chemotherapy

35. Hornberger, J. C. and J. H. Best. "Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma (Structured abstract)." Cancer 103.8 (2005): 1644-51.

Reason for exclusion: Not specific to PICO- focus on addition of rituximab to CHOP in DCBCL- entered into model at first line (event-free)

36. Hornberger, J., et al. "Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma (Structured abstract)." Leukemia and Lymphoma 49.2 (2008): 227-36.

Reason for exclusion: Not specific to PICO- focus on addition of rituximab to CVP in patients with advanced F

37. Hornberger, J., et al. "Cost-effectiveness of rituximab as maintenance therapy in patients with follicular non-Hodgkin lymphoma after responding to first-line rituximab plus chemotherapy." Leukemia & Lymphoma 53.12 (2012): 2371-77.

Reason for exclusion: Not specific to any PICO – rituximab maintenance in FL

38. Hui, J., E. Przespo, and A. Elefante. "Pralatrexate: a novel synthetic antifolate for relapsed or refractory peripheral T-cell lymphoma and other potential uses. [Review]." Journal of Oncology Pharmacy Practice 18.2 (2012): 275-83.

Reason for exclusion: Not an economic paper

39. Jerijs et al. 1999

Reason for exclusion: Not specific to PICO included acute lymphoblastic lymphoma- cost analysis only

40. Johnston, K. M., et al. "Cost-effectiveness of the addition of rituximab to CHOP chemotherapy in first-line treatment for diffuse large B-cell lymphoma in a population-based observational cohort in British Columbia, Canada (Provisional abstract)." Value.in Health 13.6 (2010): 703-11.

Reason for exclusion: Not specific to PICOs- addition of ritiuximab to CHOP in DLBCL

41. Johnston, K. M., et al. "Cost-effectiveness of rituximab in follicular lymphoma. [Review]." Expert Review of Pharmacoeconomics & Outcomes Research 12.5 (2012): 569-77.

Reason for exclusion: Not specific to PICOs- focus on rituximab in addition to chemotherapy- review

42. Kasteng, F., et al. "Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden (Structured abstract)." Acta Oncologica. 47.6 (2008): 1029-36.

Reason for exclusion: Not specific to PICOS- stage not defined, focus on rituximab after second line treatment with

43. Khera, N., et al. “Costs of second allogeneic hematopoietic cell transplantation.” Transplantation. 2013; 96(1): 108–115

Reason for exclusion: Not specific to PICO- looked at impact of different clinical characteristics on costs of allogeneic transplantation- no specific NHL-leukaemia/MDS or lymphoma /MM or other included

44. Khor, S., et al. "Real world costs and cost-effectiveness of Rituximab for diffuse large B-cell lymphoma patients: a population-based analysis." BMC Cancer 14 (2014): 586.

Reason for exclusion: Compares R-CHOP to CHOP, no transplantation

45. Knight, C., et al. "Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation (Structured abstract)." Health Technology Assessment.Database.3 (2004): 1.

Reason for exclusion: Not specific to PICO-SHARR model to look at R-CHOP vs. CHOP based on ROCHE model

46. Kymes, S. M., et al. "Economic evaluation of plerixafor for stem cell mobilization." American Journal of Managed Care 18.1 (2012): 33-41.

Reason for exclusion: Not specific to PICO- focus on addition of GCSF + plerixafor vs. GCSF alone prior to stem cell mobilisation

47. Leahy, M. F. and J. H. Turner. "Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients." Blood 117.1 (2011): 45-52.

Reason for exclusion: Not specific to PICOS compares I-rituximab versus rituximab

48. Lee, S. M., et al. "Recombinant human granulocyte colony-stimulating factor (filgrastim) following high-dose chemotherapy and peripheral blood progenitor cell

rescue in high-grade non-Hodgkins lymphoma: clinical benefits at no extra cost (Structured abstract)." British.Journal of Cancer 77.8 (1998): 1294-99.

Reason for exclusion: Not specific to PICOs- focused on GCSF treatment

49. Lee, S., et al. "Primary prophylaxis with granulocyte colony-stimulating factor (GCSF) reduces the incidence of febrile neutropenia in patients with non-Hodgkin lymphoma (NHL) receiving CHOP chemotherapy treatment without adversely affecting their quality of life: cost-benefit and quality of life analysis." Supportive Care in Cancer 21.3 (2013): 841-46.

Reason for exclusion: Not specific to PICOs- focused on GCSF treatment

50. LeGouill S., et al. High response rate after 4 courses of R-DHAP in untreated mantle cell lymphoma (MCL) patients in the ongoing phase III randomized GOELAMS and GELA LyMa Trial. Blood (2010) 16

Reason for exclusion: Not an economic paper- cross referred to clinical evidence review selection

51. Limat, S., et al. "Cost-effectiveness of CD34(+) dose in peripheral blood progenitor cell transplantation for non-Hodgkin's lymphoma patients: a single centre study (Structured abstract)." Bone Marrow Transplantation 25.9 (2000): 997-1002.

Reason for exclusion: Not specific to PICO not FL specific

52. Limat, S., et al. "Effect of cell determinant (CD)34(+) cell dose on the cost and consequences of peripheral blood stem cell transplantation for non-Hodgkin's lymphoma patients in front-line therapy (Structured abstract)." European.Journal of Cancer 36.18 (2000): 2360-67.

Reason for exclusion: Not specific to PICO not FL specific

53. Messori, A., et al. "Cost-effectiveness of autologous bone marrow transplantation in patients with relapsed non-Hodgkin's lymphoma (Structured abstract)." Bone Marrow Transplantation 19.3 (1997): 275-81.

Reason for exclusion: Not specific to PICO- type of NHL not defined

54. Micallef, I. N., et al. "Cost-effectiveness analysis of a risk-adapted algorithm of plerixafor use for autologous peripheral blood stem cell mobilization." Biology of Blood & Marrow Transplantation 19.1 (2013): 87-93.

Reason for exclusion: Not relevant to PICO- not NHL specific

55. Moulin-Romsee et al. 2008

Reason for exclusion: Reports costs but no quality of life data; early treatment-response assessment

56. Ibritumomab tiuxetan for NHL - horizon scanning review (Structured abstract). Health Technology Assessment.Database.3 (2002): 4.

Reason for exclusion: Not specific to PICOs- horizon scanning- no cost effectiveness evidence presented- cost of drug only presented

57. Temsirolimus (Torisel) for mantle cell lymphoma - relapsed and/or refractory: horizon scanning technology briefing (Project record). Health Technology Assessment.Database.3 (2009).

Reason for exclusion: Not relevant to PICOs- horizon scanning of Bortezomub in relapsed. Refractory FL- cost of drug only presented

58. NICE technology appraisal guidance (TA65). Rituximab for aggressive non-Hodgkin's lymphoma

Reason for exclusion: Existing NICE guidance.

59. Olin, R.L., et al. “Determinants of the optimal first-line therapy for follicular lymphoma: A decision analysis.” Am J Hematol. 2010 Apr; 85(4): 255–260.
Reason for exclusion: Not specific PICO- not specific to IIA/

60. Papaioannou, D., et al. "Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. [Review]." Health Technology Assessment (Winchester, England) 16.37 (2012): 1-253.
Reason for exclusion: TA review- Rituximab for first line treatment

61. Pohar, R., M. Clark, and E. Nkansah. "Radioimmunotherapies for non-hodgkin lymphoma: systematic review of clinical effectiveness, cost-effectiveness, and guidelines (Structured abstract)." Health Technology Assessment.Database.3 (2009).
Reason for exclusion: Canadian agency for drugs and technologies in health report- not specific to PICOs –focus on radio immunotherapies in NHL in general

62. Prajogo, J., et al. "Modelling cost-effectiveness of high-dose chemotherapy as treatment for relapsed aggressive non-Hodgkin lymphoma in an Australian setting (Provisional abstract)." Internal.Medicine Journal 39.8 (2009): 519-26.
Reason for exclusion: Not specific to PICO- NHL in general- focused on high dose vs. standard chemotherapy

63. Ray, J. A., et al. "An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-Hodgkin's lymphoma in the UK (Structured abstract)." Value.in Health 13.4 (2010): 346-57.
Reason for exclusion: Abstract- duplication of paper below

64. Ray, J. A., Carr, E., Lewis, G. and Marcus, R. “An Evaluation of the Cost-Effectiveness of Rituximab in Combination with Chemotherapy for the First-Line Treatment of Follicular Non-Hodgkin's Lymphoma in the UK.” Value in Health (2010), 13: 346–357
Reason for exclusion: Not specific PICO- not specific to IIA/

65. Sabater et al [year unknown- abstract]
Reason for exclusion: Not specific PICO- not specific to IIA/

66. Samaras, P., et al. "Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation (Provisional abstract)." Oncology 79.1-2 (2010): 93-97.
Reason for exclusion: Not specific to NHL- reports resource use/cost summary only

67. Schulman, K. A., et al. "Prospective economic evaluation accompanying a trial of GM-CSF/IL-3 in patients undergoing autologous bone marrow transplantation for Hodgkins and non-Hodgkins-lymphoma (Structured abstract)." Bone Marrow Transplantation 21.6 (1998): 607-14.
Reason for exclusion: Not specific to PICO- includes Hodgkin’s Lymphoma

68. Smith, T. J., et al. "Economic analysis of a randomized clinical trial to compare filgrastim-mobilized peripheral-blood progenitor-cell transplantation and autologous bone marrow transplantation in patients with Hodgkins and non-Hodgkins lymphoma (Structured abstract)." Journal of Clinical.Oncology 15.1 (1997): 5-10.

Reason for exclusion: Not relevant to PICO- HL +NHL

69. Soini, E. J., J. A. Martikainen, and T. Nousiainen. "Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up (Structured abstract)." Annals.of Oncology 22.5 (2011): 1189-97.

Reason for exclusion: Not specific to PICO- stage not clear (abstract- duplicates paper below)

70. Soini, E. J., J. A. Martikainen, and T. Nousiainen. "Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up." Annals of Oncology 22.5 (2011): 1189-97..

Reason for exclusion: Not specific to PICO- stage not clear

71. Soini, E. J., et al. "Economic evaluation of sequential treatments for follicular non-hodgkin lymphoma." Clinical Therapeutics 34.4 (2012): 915-25.

Reason for exclusion: Not specific to PICO- not specific to IIA/first line treatment

72. Sweetenham, J., et al. "Cost-minimization analysis of CHOP, fludarabine and rituximab for the treatment of relapsed indolent B-cell non-Hodgkin's lymphoma in the UK (Structured abstract)." British.Journal of Haematology. 106.1 (1999): 47-54.

Reason for exclusion: Not specific to PICO- focus on indolent relapsed B cell lymphoma and comparison of CHOP or fluradarbine with rituximab

73. Uyl-de-Groot, C. A., et al. "Costs of peripheral blood progenitor cell transplantation using whole blood mobilised by filgrastim as compared with autologous bone marrow transplantation in non-Hodgkin's lymphoma (Structured abstract)." Pharmacoeconomics. 15.3 (1999): 305-11.

Reason for exclusion: Not specific to PICO-focused on ABMT versus whole blood transplantation – cost analysis only

74. Uyl-de-Groot, C. A., et al. “Costs of introducing autologous BMT in the treatment of lymphoma and acute leukaemia in The Netherlands.” Bone Marrow Transplant. 1995 Apr;15(4):605-10.

Reason for exclusion: Not specific to PICOs- NHL type unclear

75. Van Agthoven M et al. “Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial.” Eur J Cancer. 2001;37(14):1781-9.

Reason for exclusion: Not specific to PICO- covered Hodgkin’s lymphoma as well as NHL- cost analysis and QOL reported as disaggregated outcomes

76. Van Agthoven M et al. “Cost analysis of common treatment options for indolent follicular non-Hodgkin's lymphoma.” Haematologica January 2005 90(10): 1422-1432

Reason for exclusion: Not specific to PICO- cost analysis across disease pathway

77. Wake, B., et al. "Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation (Structured abstract)." Health Technology Assessment.Database.3 (2002): 1.

Reason for exclusion: Not specific to PICO Focus on rituximab as 3rd line treatment

78. Weycker, D., et al. "Economic costs of chemotherapy-induced febrile neutropenia among patients with non-Hodgkin's lymphoma in European and Australian clinical practice." BMC Cancer 12 (2012): 362.
Reason for exclusion: Not specific to any PICO- focus on neutropenia

79. Wirt, D. P., et al. "Cost-effectiveness of interferon alfa-2b added to chemotherapy for high-tumor-burden follicular non-Hodgkin's lymphoma (Structured abstract)." Leukemia and Lymphoma 40.5-6 (2001): 565-79.
Reason for exclusion: Not specific to PICO or first line treatment

80. Woronoff-Lemsi, M. C., et al. "Cost comparative study of autologous peripheral blood progenitor cells (PBPC) and bone marrow (ABM) transplantations for non-Hodgkin's lymphoma patients (Structured abstract)." Bone Marrow Transplantation 20.11 (1997): 975-82.
Reason for exclusion: Not specific to PICOs

81. Yakushijin, Y., et al. "Usage of granulocyte colony-stimulating factor every 2days is clinically useful and cost-effective for febrile neutropenia during early courses of chemotherapy." International Journal of Clinical Oncology 16.2 (2011): 118-24.
Reason for exclusion: Not specific to PICOs-focus on treatment of febrile neutropenia

82. Zumberg, M. S., et al. "GM-CSF versus G-CSF: engraftment characteristics, resource utilization, and cost following autologous PBSC transplantation (Structured abstract)." Cytotherapy. 4.6 (2002): 531-38.
Reason for exclusion: Not specific to PICOs – included multiple myeloma and Hodgkin’s lymphoma

83. Zurawska, U., et al. "Hepatitis B virus screening before chemotherapy for lymphoma: a cost-effectiveness analysis." Journal of Clinical Oncology 30.26 (2012): 3167-73.
Reason for exclusion: Not specific to any PICO- focus on Hep B screening prior to chemotherapy in DLBCL