Roche

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BY EMAIL

07 Jul 2014

RE: Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukemia [ID650]

Dear Frances,

Our response to the clarification questions for the above technology appraisal is provided below. We would be happy to provide further clarification or information if it would be beneficial.

Kind Regards

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Section A: Clarification on clinical effectiveness data

A1. **Priority question:** Please provide the percentage of patients in each of the World Health Organisation performance statuses (0, 1 and 2) at baseline.

In CLL11 the patient's Eastern Cooperative Oncology Group (ECOG) performance status (also referred to as WHO PS) was recorded at baseline:

ECOG/WHO performance status at baseline, stage 1a & 1b

	Clb **n = 114* (%)**	**GClb** **n = 230* (%)**	**RClb** **n = 222* (%)**
Performance status			
0	40 (35)	81 (35)	69 (31)
1	62 (54)	122 (53)	115 (52)
2	11 (10)	26 (11)	36 (16)
3	1 (1)	1 (<1)	2 (1)
4	0	0	0

*Missing data excluded from the analysis
Extracted from: Roche. Primary Abbreviated Clinical Study Report - BO21004/CLL11 - Stage 1b (RClb vs. Clb) 2013 Mar. Roche. Update Clinical Study Report - BO21004/CLL11: Stage 1a - 1b Update. 2013 Dec.

ECOG/WHO performance status at baseline, stage 2

	GClb **n = 322* (%)**	**RClb** **n = 321* (%)**
Performance status		
0	106 (33)	104 (33)
1	173 (54)	155 (49)
2	41 (13)	55 (17)
3	2 (1)	3 (1)
4	0	0

*Missing data excluded from the analysis
Extracted from: Roche. Primary Clinical Study Report - BO21004/CLL11 - Stage 2 (GClb vs. RClb) 2013 Dec.

A2. **Priority question:** Please clarify whether unsuitability for fludarabine therapies was an inclusion criteria in CLL11.

The CLL11 inclusion criterion of 'Total cumulative illness rating scale (CIRS) Score >6 [excluding illness related to CLL] or creatinine clearance <70 mL/min or both' describes patients who would not be suitable for full-dose fludarabine treatment.

A3. **Priority question:** Please explain why there is a difference in the progression free survival hazard ratios reported from CLL11 in table B26 on pages 102 and 103 (obinutuzumab vs. chlorumbucil 0.183, rituximab vs. chlorumbucil 0.458, and obinutuzumab vs. rituximab 0.388) and in table B41 on page 142 [redacted]

The CLL11 data reported in table B26 are from the May 2013 cut, whereas the data in table B41 relate to the March 2014 cut. These relatively minor differences in the calculated PFS HRs for the same stage of the study can be attributed to the different lengths of follow up.

A4. Please provide results from a corrected search or a corrected search strategy for Embase and MEDLINE for the update of the systematic review (page 255, section 10.3.4). Currently the following errors exist:

a. Line 28 should combine lines 24-27 but instead lines 22-25 have been combined.

b. The final line should combine lines 29 and 36 and 50, but the search actually combines 27 and 34 and 48.

These are typographical errors. The correct strings were combined in the search strategy used for the review. Therefore, there are no studies that were missed. The search strategy utilised is provided in Appendix 1 of this document.

A5. Please confirm that the Kaplan-Meier curves in figure B40 and B41 (pages 161 and 162) relate to the March 2014 data cut off.

This is correct.

Section B: Clarification on cost-effectiveness data

B1. Please explain why 'lymphocytic' is spelt 'lymphocitic' in the MEDLINE and EMBASE searches for the cost effectiveness, measurement and valuation of health effects, and resource identification. If this is an error, please re-run the search and highlight any studies that were missed.

Thank you for identifying this error. The revised searches are provided in Appendix 2 of this document.

B2. Please explain why EMBASE Alert was searched instead of MEDLINE-in-process for cost-effectiveness, measurement and valuation of health effects, and resource identification.

EMBASE, EMBASE Alert and MEDLINE were searched in PROQUEST for the cost-effectiveness, measurement and valuation of health effects, and resource identification searches. MEDLINE-in-process is contained within the MEDLINE database therefore a separate search was not required.

Quality of life

B3. **Priority question:** Please confirm that EQ-5D data were not available for the CLL11 trial.

EQ-5D data was not collected in the CLL11 trial.

B4. **Priority question:** Please explain why the mapping function for mapping EORTC QLQ-C30 onto EQ-5D as reported by Kim S.H., Jo M.W., Kim H.J., and Ahn J.H. (2012) ('Mapping EORTC QLQ-C30 onto EEQ-5D for the assessment of cancer patients.' Health Qual Life Outcomes, vol 10, p151) was not used on the EORTC-QLQ-C30 data from CLL11. Alternatively, please perform this mapping on data from CLL11.

This mapping function was not identified during the development of the submission and so was not used. We are unable to conduct this mapping in the time-frame given for response to these questions. If the Committee consider this mapping preferable to the use of existing alternative utility values we would potentially be able to provide this in response to consultation.

B5. Please provide the NHS EED and EconLit searches for the measurement and valuation of health effects search (section 10.11.4) and the EconLit search and the database provider for EconLit for the resource identification search (section 10.12.4).

Appendix 2 includes the results of the EconLIT searches for the measurement and valuation of health effects search and resource identification.

B6. Please clarify which table is referred to in the first sentence of section 7.4.6 on page 177.

This should be table B49 (above).

B7. Please provide the 9 vignette descriptions mentioned on page 178 and in table B50 on page 179.

These are provided in Appendix 3 of this document.

Adverse events

B8. Please state whether there is any evidence of rare adverse events that might have been missed by the CLL11 trial.

In CLL11 adverse events were reported according to the National Cancer Institute Common Toxicity Criteria (version 4.0) and recorded in the Clinical Study Reports.

All adverse events and serious adverse events occurring after study entry (i.e., date of informed consent) were recorded up to 28 days after completion of study treatment. New Grade 3 and 4 adverse events continue to be reported until 6 months after end of therapy. All unrelated serious adverse events are to be reported up to one year and Grade 3 or 4 infections will be reported up to two years after treatment or until a new anti-leukemic treatment is instituted. However, secondary malignancies and all related serious adverse events will continue to be reported irrespective of whether the patient has received new therapy.

Section C: Textual clarifications and additional points

C1. Please check and clarify the numbering of the figures in your submission. There is inconsistency between the figure numbering in the list of figures on page 2 and the numbering in the text (for example, figure A1 in the content list appears to be titled figure A2 in the text on page 18). The list of figures appears to be incomplete (for example, figure B11 on page 71 is not in the list of figures on page 2).

Thank you for for highlighting these inconsistencies. We have now corrected the numbering of the figures in the attached document.

C2. Please check and clarify the numbering of the tables in your submission. Some table numbering is duplicated in the list of tables in pages 3 to 5 (for example, there are 2 tables referred to as B42 and 2 tables referred to as B47). There are tables in the main text of the submission that do not appear in the list of tables on pages 3 to 5 (for example, tables B43 and B46).

This has been corrected in the attached document.

C3. Please check and clarify the formatting of your submission since there are inconsistencies in the page numbers between an onscreen version and a printed version of the submission.

We are unclear on the precise cause of this. We believe that in Word 2010 unwanted page breaks in cross-references sometimes appear in the printed version of a document. We have now tried to correct these inconsistencies in the document but cannot guarantee that these will not reappear.

C4. Please clarify the wording in the sentence that starts 'The fact that in the Clb and Benda arms the predicted….' (on line 3 of page 163) since there is a typographical error which makes the content of the sentence unclear.

This sentence should read:

"The fact that in the Clb and Benda arms the predicted medians are [redacted] months less than the respective medians for patients over 65 in the Knauf trial (65.4 months OS for Clb in Knauf vs [redacted] in the model, 72.8 months OS for Benda in Knauf vs [redacted] in the model) is somewhat reassuring, since given the increased age and frailty of the CLL11 trial population one would expect their survival prospects to be less."

C5. Please clarify which reference 'Hillmen, 2008' on page 149 refers to and add this to the reference list if it is not included already.

This should be 'Hillmen 2014' (the CLL208 trial publication). This has been amended in the text and PDF attached.

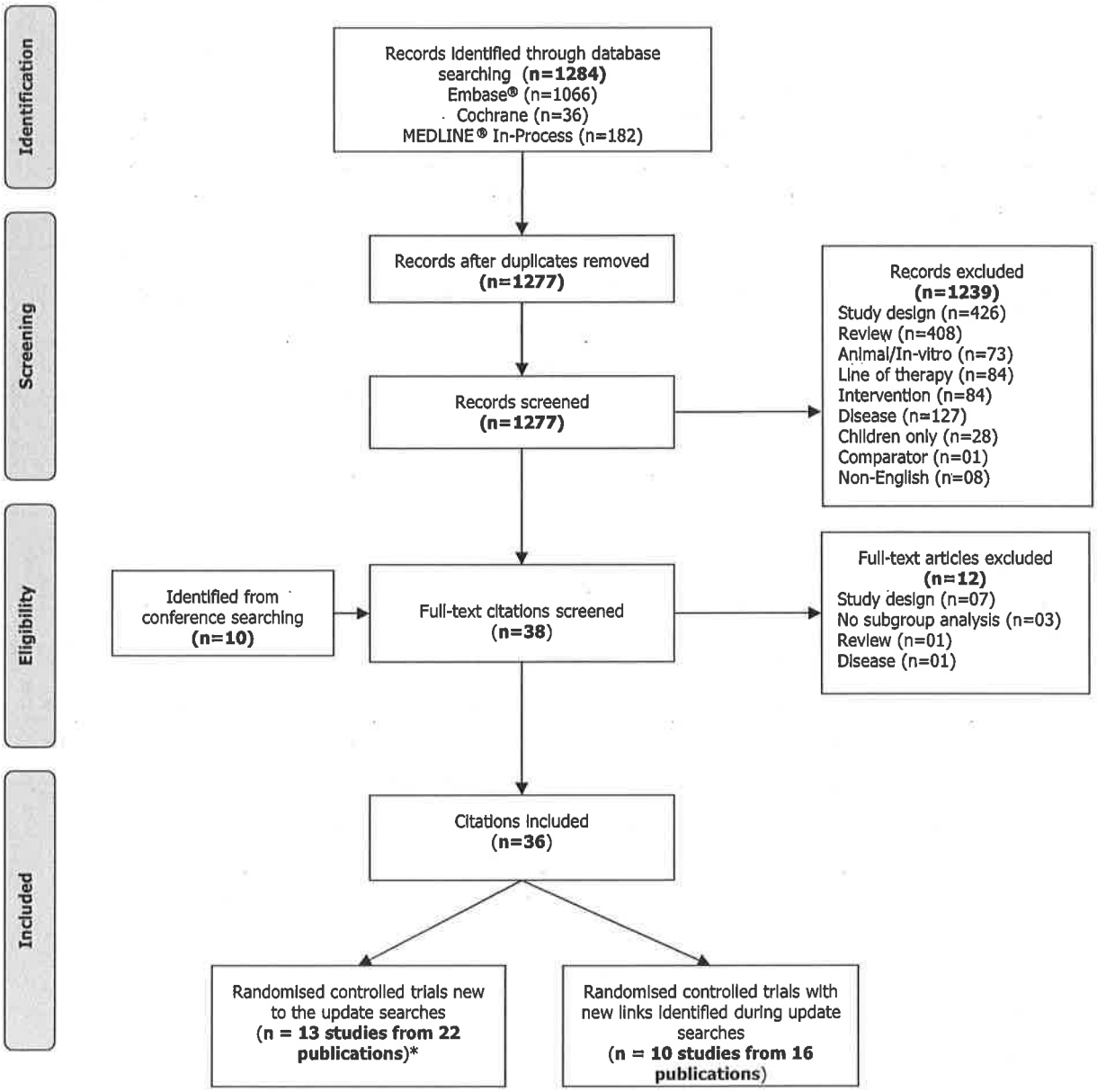
C6. Please lift some of the confidentiality marking in your submission. Following the NICE team review of your submission, we have identified several issues with the confidential marking.

Thank you for identifying these inconsistencies in data marked as CIC. We have subsequently reviewed the submission and removed CIC marking from all the areas highlighted (including inconsistent marking of data presented elsewhere in the submission, marking of data in the public domain and marking of complete blocks of data contain some CIC data).

The clinical trial data from the latest cut of the CLL11 trial should be regarded as CIC and not AIC. This trial is set to be presented at a conference in December 2014 and has not yet been made public (nor has a clinical study report yet been produced for this data-cut). We have received permission to share this information in confidence in order to ensure the Committee have access to the most recent data on the efficacy of obinutuzumab. We do not permit this data to be released or presented publically prior to formal presentation.

Appendix 1 – Amended RCT Search Strategy

Figure 1: Trial flow diagram summarising the flow of randomised controlled trials during the update searches



*Represents two additional references for studies that were identified in the original review but were not extracted due to the unavailability of results

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Table 1: Search strategy for clinical review in Embase® and MEDLINE® (searched through Embase.com on 16 April 2014) for RCTs

#	Search History	Facet	Results
1	'clinical trial'/exp	Study design (RCTs)	959,334
2	'randomization'/de		61,404
3	'controlled study'/de		4,272,155
4	'comparative study'/de		620,235
5	'single blind procedure'/de		17,819
6	'double blind procedure'/de		114,150
7	'crossover procedure'/de		38,298
8	'placebo'/de		249,504
9	'clinical trial' OR 'clinical trials'		1,222,268
10	'controlled clinical trial' OR 'controlled clinical trials'		515,580
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'		25,783
12	'randomisation' OR 'randomization'		79,186
13	Rct		15,927
14	'random allocation'		1,425
15	'randomly allocated'		20,107
16	'allocated randomly'		1,912
17	allocated NEAR/2 random		789
18	random* NEAR/1 assign*		83,002
19	random*		1,003,174
20	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)		204,768
21	placebo*		326,122
22	'prospective study'/de		242,980
23	#1 OR #2 OR #3 OR #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		5,725,012
24	'case study'/de		26,670
25	'case report'		1,936,427
26	'abstract report'/de		89,606
27	'letter'/de		808,910
28	#24 OR #25 OR #26 OR #27		2,693,461
29	#23 NOT #28		5869229
30	'chronic lymphatic leukemia'/de	Disease facet	23252
31	'b cell leukemia'/exp		5032
32	lymphom* near/2 lymphocyt*		7459
33	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')		1133958
34	(chronic OR cronic OR 'well differential')		1223310
35	#33 AND #34		117134
36	OR/30-32, 35		127883
37	'chlorambucil'/syn OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR 'nsc 3088' OR nsc3088	Intervention facet	16597

38	'fludarabine'/syn OR fludara		17996
39	'cladribine'/syn OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251		5070
40	'bendamustine'/syn OR 'cimet 3393' OR cytostasan OR cytostasan OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda		2122
41	'alemtuzumab'/syn OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath		10140
42	'rituximab'/syn OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin		39132
43	'ofatumumab'/syn OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20		1175
44	'lenalidomide'/syn OR 'cc 5013' OR cc5013 OR 'cdc 501' OR 'cdc 5013' OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid		8459
45	'gs 1101'/syn OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib		511
46	'obinutuzumab'/syn OR afutuzumab OR 'ga 101' OR ga101 OR 'r 7159' OR r7159 OR 'ro 5072759' OR ro5072759		405
47	'cyclophosphamide'/syn OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid		171998
48	cop NEAR/2 regimen		75
49	chop NEAR/2 regimen		800
50	Or/37-49		219215
49	#29 AND #36 AND #50 AND [27-2-2013]/sd NOT [16-4-2014]/sd	Combined results	1066

Table 2: Search strategy for clinical review in Cochrane (searched through Cochrane library interface on 16 April 2014)

No.	Query	Results
1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	22
2	'b cell leukaemia' OR 'b cell leukemia'	1410
3	lymphom* near/2 lymphocyt*	90
4	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')	12836
5	(chronic OR cronic OR 'well differential')	67410
6	#4 AND #5	2129
7	OR/1-3, 6	3174
8	MeSH descriptor: [Chlorambucil] explode all trees	227
9	(chlorambucil OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088):ab,ti,kw	436
10	(fludarabine OR fludara):ab,ti,kw	442
11	MeSH descriptor: [Cladribine] explode all trees	65
12	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251): ab,ti,kw	148
13	(bendamustine OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda): ab,ti,kw	50
14	(alemtuzumab OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath): ab,ti,kw	222

No.	Query	Results
15	(rituximab OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin): ab,ti,kw	889
16	(ofatumumab OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20): ab,ti,kw	28
17	(lenalidomide OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid): ab,ti,kw	166
18	('gs 1101' OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib): ab,ti,kw	5
19	(obinutuzumab OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759): ab,ti,kw	19
20	MeSH descriptor: [Cyclophosphamide] explode all trees	3888
21	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid): ab,ti,kw	6763
22	cop NEAR/2 regimen	21
23	chop NEAR/2 regimen	129
24	OR/8-23	8653
25	#7 and #24 from 2013 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	36

Table 3: Search strategy for clinical review in MEDLINE®-In Process (searched through Pubmed.com interface on 16 April 2014)

No	Query	Results
1	"Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh terms]	11520
2	"chronic lymphocytic leukaemia"[All Fields] OR ("leukemia"[All Fields] AND "lymphocytic"[All Fields] AND "chronic"[All Fields] AND "b-cell"[All Fields]) OR "b-cell chronic lymphocytic leukemia"[All Fields] OR ("chronic"[All Fields] AND "lymphocytic"[All Fields] AND "leukemia"[All Fields]) OR "chronic lymphocytic leukemia"[All Fields]	18564
3	Search (#1 or #2)	18564
4	(chlorambucil OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088)	4654
5	(fludarabine OR fludara)	4300
6	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251)	1628
7	(bendamustine OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda)	499
8	(alemtuzumab OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath)	2291
9	(rituximab OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin)	12250
10	(ofatumumab OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20)	7838
11	(lenalidomide OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid)	2150
12	('gs 1101' OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib)	74
13	(obinutuzumab OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759)	81

No	Query	Results
14	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid)	2690626
15	"cop regimen"	44
16	"chop regimen"	374
17	OR/4-16	2713294
18	Search (#3 AND #17)	5078
19	Search (#18 AND (in process[sb] OR pubstatusaheadofprint))	182

Appendix 2 – Revised Economics Search Strategy

Search strategies for cost effectiveness

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), EconLIT and NHS EED were searched for studies assessing the cost-effectiveness of obinutuzumab. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Key word strategies were developed using key references retrieved through initial scoping searches. ProQuest was used to search EMYY, EMBA and MEYY, NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York) and the American Economic Association website was used to search for EconLIT. All databases were searched on 13 May 2014. The title and abstract of each search result were assessed for relevance according to pre-defined inclusion and exclusion criteria (Table 1).

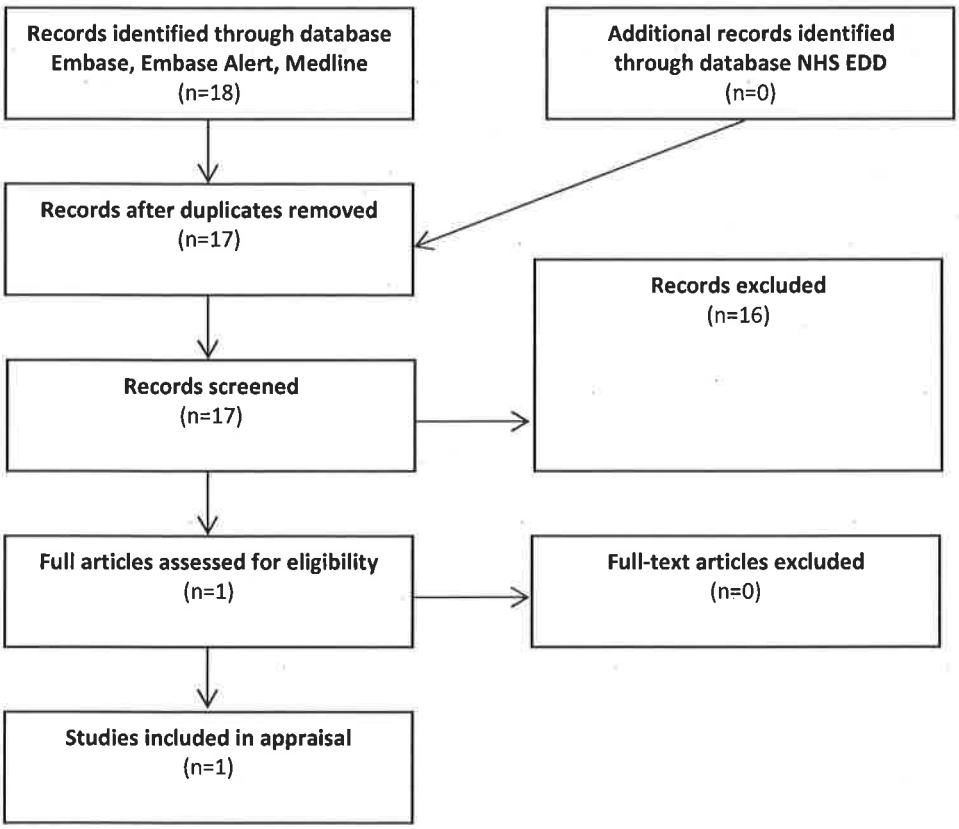
Table 1: Inclusion and exclusion criteria for cost-effectiveness search

Parameter	Inclusion Criteria	Exclusion Criteria
Population	1L CLL patients	Non CLL, non-1L
Intervention	Obinituzumab (GA101)	-
Comparator	Chlorambucil, Rituximab plus Chlorambucil, Bendamustine, Rituximab plus Bendamustine	-
Outcome	Cost per QALY gained,Cost per LY gained	-
Study Design	Economic Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

The above methodology is founded on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008). The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

One study was identified across the four databases, and was determined as relevant by the independent reviewers after being assessed against the inclusion and exclusion criteria. One cost-effectiveness study of GA101 was thus identified.

Figure 1: PRISMA Flow showing economic studies identified through searching of the databases



The Centre for Reviews and Dissemination's website, the American Economic Association website, and the PROQUEST website were searched on 13 May 2014.

The date span of the search: 1992 – 13 May 2014

PROQUEST was searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised in the table below.

Table 2: Cost-effectiveness PROQUEST Search Terms

#	Search History	Facet	Results
S1	(cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness) AND la.exact("ENG")	Modelling	820607
S2	(economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost[*1] OR direct ADJ cost[*1] OR direct ADJ service		873648

	ADJ cost[*1] OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util[*3] OR quality ADJ of ADJ life OR QALY OR QALYs OR QOL OR economic$1 ADJ models OR medical ADJ economics OR pharmaceutical ADJ economics) AND la.exact("ENG")		
S3	(Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR/4 Evaluation) OR EMB.EXACT.EXPLODE("ECONOMIC EVALUATION") OR EMB.EXACT.EXPLODE("PHARMACOECONOMICS") OR EMB.EXACT.EXPLODE("COST UTILITY ANALYSIS") OR EMB.EXACT.EXPLODE("QUALITY ADJUSTED LIFE YEAR") AND la.exact("ENG")		387763
S4	(TI(Markov OR decision ADJ analys[*2]) OR AB(Markov OR decision ADJ analys[*2])) AND la.exact("ENG")		25963
S5	S1 OR S2 OR S3 OR S4		1453220
S6	chronic lymphocitic leukemia	Disease Facet	18
S7	chronic lymphatic leukemia		22411
S8	S6 OR S7		22422
S9	'obinutuzumab'/syn OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759	Intervention Facet	23758
S10	S5 AND S8 AND S9	Combined Result	17

Search strategy for NHS EED and EconLIT – Year 1992 – 13 May 2014

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised below.

Table 3: Cost-effectiveness EconLIT and NHS EED Search Terms

"COST EFFECTIVENESS ANALYSIS" OR "COST UTILITY ANALYSIS" OR "COST BENEFIT ANALYSIS" OR "ECONOMIC MODEL" OR "DE NOVO MODELLING" OR "COST MINIMISATION ANALYSIS" AND (LEUKEMIA OR LYMPHOCYTIC OR CHRONIC OR B-CELL) AND (OBINUTUZUMAB OR AFUTUZUMAB OR GA 101)

No additional searches were undertaken.

Search strategies for Resource identification, measurement and valuation

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)1, EconLIT and NHS EED were searched for studies regarding resource use and costs related to CLL. The complete search strategy is provided in section **Error! Reference source not found.**. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008).

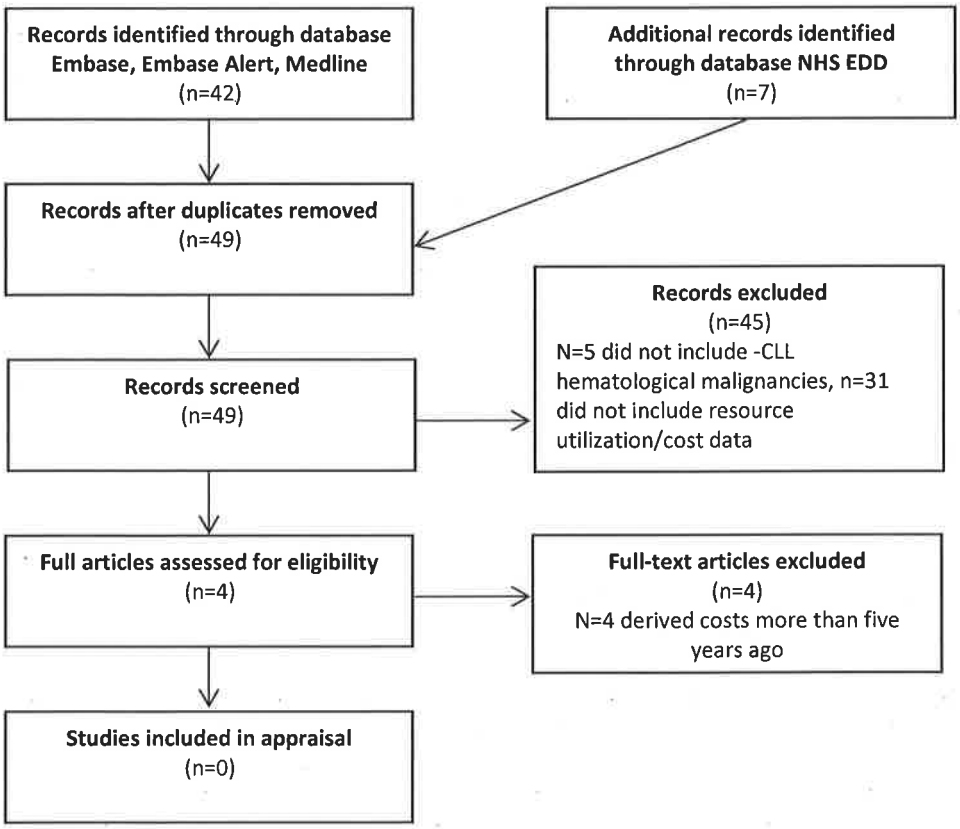
ProQuest was used to search EMYY, EMBA and MEYY. NHS EED was searched using The Centre for Reviews and Dissemination's website. EconLIT was searched using The American Economic Association website. All searches were undertaken on the 13 May 2014 except for the EconLIT search which was undertaken on 02 July 2014. Titles and abstracts were assessed for relevance according to the pre-defined inclusion and exclusion criteria. If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in **Error! Not a valid bookmark self-reference.**.

Table 4: Inclusion and exclusion criteria for resource utilisation studies

Inclusion criteria	Exclusion criteria
CLL Resource utilisation from a UK NHS Perspective	Non-CLL hematological malignancies Resource utilisation from a private/US setting and any other non-UK country. Studies contain costs that are 5 or more years old.

In total 40 articles were identified across the four databases. All were excluded by the independent reviewers.

Figure 2: PRISMA Flow showing resource utilisation studies identified through searching of the databases



The Centre for Reviews and Dissemination's website and the PROQUEST website were searched on 13 May 2014. The American Economic Association website was searched on 02 July 2014.

Search strategy for Embase, Embase Alert and MEDLINE:

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised in the table below.

Table 5: Resource Use PROQUEST Search Terms

#	Search History	Facet	Results
S1	(socioeconomics OR cost ADJ benefit ADJ analysis OR cost ADJ effectiveness ADJ analysis OR cost ADJ of ADJ illness OR cost ADJ control OR economic ADJ aspect OR financial ADJ management OR health ADJ care ADJ cost OR health ADJ care ADJ financing OR health ADJ economics ADJ hospital ADJ cost OR (fiscal OR financial OR finance OR funding) OR cost ADJ minimi?ation ADJ analysis OR (cost ADJ ESTIMATE$) OR (cost ADJ variable$) OR (unit ADJ cost$)) AND la.exact("ENG")	Resource use	318343
S2	(resource ADJ utilis?ation OR nhs ADJ cost$1 OR resource) AND la.exact("ENG")		515877
S3	S1 OR S2		797095
S4	chronic lymphocitic leukemia	Disease Facet	18
S5	chronic lymphatic leukemia		22411
S6	S4 OR S5		22422
S7	(england OR wales OR scotland OR united ADJ kingom OR uk) AND la.exact("ENG")	Country Facet	4292082
S8	S3 AND S6 AND S7	Combined Result	33

Search strategy for NHS EED and EconLIT.

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised below.

Table 6: Resource Use EconLIT and NHS EED Search Terms

"RESOURCE UTILISATION OR NHS REFERENCE COSTS OR COST ANALYSIS"
AND *TITLE ONLY* (LEUKEMIA OR LYMPHOCYTIC OR CHRONIC OR B-CELL)
AND *TITLE ONLY* (ENGLAND OR WALES OR SCOTLAND OR UNITED ADJ KINGOM OR UK).

No additional searches were undertaken.

Search strategies for Measurement and valuation of health effects

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)2, EconLIT and NHS EED were searched for studies assessing utility values for different health states in CLL. The searches were conducted on the 28 January 2014 except for the EconLIT search which was conducted on 02 July 2014. All searches were designed to evaluate all potentially relevant utility scores that have been used in CLL health technology evaluations. The complete search strategy is provided in section **Error! Reference source not found.**. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008). If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 7: Inclusion and exclusion criteria for utility studies

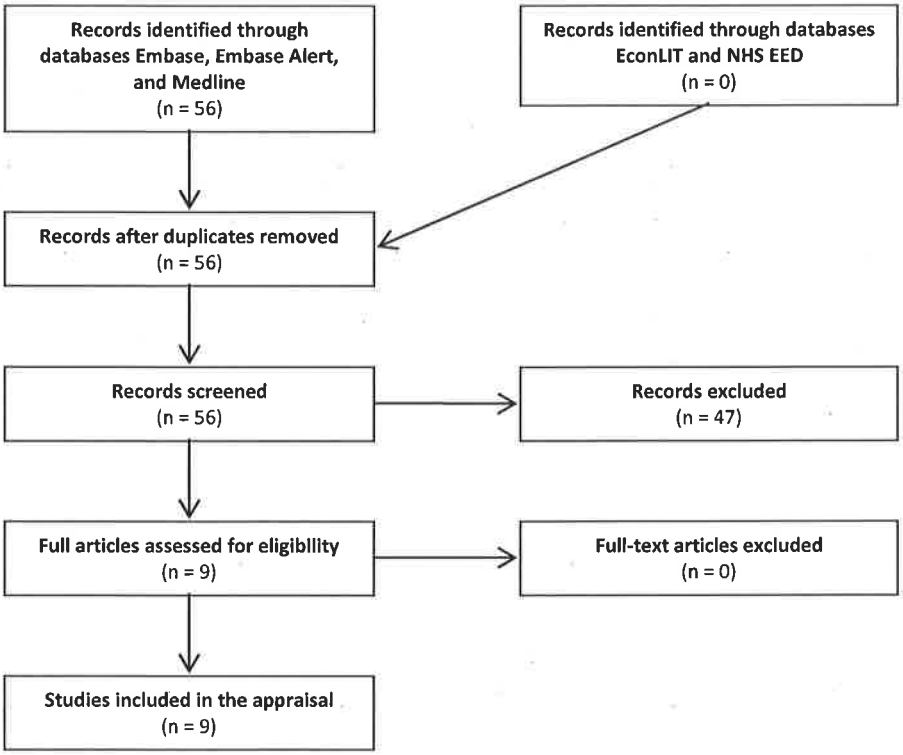
Parameter	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously untreated Chronic Lymphocytic Leukemia (CLL)	Non CLL patients
Intervention	Any	-
Comparator	Any	-
Outcome	Utilities derived via a recognised preference based instrument (EQ5D or SF6D), standard gamble or time trade off conducted using a sample of the general public	Other non-preference based HRQoL measures
Study Design	Utility Studies, Cost-Effectiveness studies containing utility values	-

CLL: Chronic Lymphocytic Leukaemia; EQ5D: EuroQOL five dimensions questionnaire; HRQoL: Health Related Quality of Life; SF6D: six-dimensional health state short form

In total 56 records were identified across the 4 databases. Of these, 47 were excluded by the independent reviewers whilst 9 were deemed potentially relevant and read in full. These 9 were included after being assessed against the exclusion criteria

[2] Note Medline-In-Process is now nested within Medline in the new ProQuest.

Figure 3: PRISMA flow for utility studies identified through database searches



Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), EconLIT and NHS EED were searched for retrieving utility values in CLL in order to inform a health economic model. The searches were conducted on the 28th January 2014.

The search was conducted in PROQUEST using the search terms summarised in the table below.

Table 8: Utility Studies Search terms for PROQUEST

Set#	Searched for	Databases	Results
S1	QUALITY-ADJUSTED-LIFE-YEAR OR QALY[*2] OR QALIES	Embase®, Embase® Alert, MEDLINE®	26051*
S2	SF-6D OR EQ-5D OR EQ-5D-5L OR EUROQOL	Embase®, Embase® Alert, MEDLINE®	11172*
S3	"UTILITY VALUES" OR "UTILITY SCORES"	Embase®, Embase® Alert, MEDLINE®	1737*
S4	"TIME TRADE OFF" OR "STANDARD GAMBLE"	Embase®, Embase® Alert, MEDLINE®	1527*
S5	S1 OR S2 OR S3 OR S4	Embase®, Embase® Alert, MEDLINE®	37427*
S6	CHRONIC LYMPHOCYTIC LEUKEMIA	Embase®, Embase® Alert, MEDLINE®	32154*
S7	CHRONIC LYMPHATIC LEUKEMIA	Embase®, Embase® Alert, MEDLINE®	22033*
S8	S6 OR S7	Embase®, Embase® Alert, MEDLINE®	38933*
S9	S5 AND S8	Embase®, Embase® Alert, MEDLINE®	56*

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Search strategy for NHS EED and EconLIT.

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised below.

Table 9 Utility Studies Search Terms for NHS EED and EconLIT

QUALITY ADJUSTED LIFE YEAR OR QALY OR EQ-5D OR EQ-5D-5L OR EUROQOL OR TIME TRADE OFF OR STANDARD GAMBLE OR UTILITY VALUE OR UTILITY SCORE AND *TITLE ONLY* (LEUKEMIA OR LYMPHOCYTIC OR CHRONIC OR B-CELL)

No additional searches were undertaken.

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in Table 10.

Table 10: Inclusion and exclusion criteria for Utility Studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously untreated Chronic Lymphocytic Leukemia (CLL)	Non CLL patients
Intervention	Any	-
Comparator	Any	-
Outcome	Utilities derived via a recognised preference based instrument (EQ5D or SF6D), standard gamble or time trade off conducted using a sample of the general public	Other non-preference based HRQoL measures
Study Design	Utility Studies, Cost-Effectiveness studies containing utility values	-

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

Appendix 3 – Utility Study Vignettes

Progression free survival on initial therapy IV treatment

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have been told that you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are sometimes limited in the distance you want to go.
- You are able to wash and dress yourself.
- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.
- You experience a reaction when you start treatment which makes you sweat and gives you chills which lasts for a short time during and following treatment.
- You worry about whether your treatment is working and the effect it may have on you and your family.

Progression free survival on initial therapy oral treatment

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to take regular tablets. You have been told that you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are sometimes limited in the distance you want to go.
- You are able to wash and dress yourself.
- You experience sores in your mouth and due to vomiting and feelings of nausea, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.
- You worry about whether your treatment is working and the effect it may have on you and your family.

Progression free survival without therapy

- You have previously received treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. You have completed an initial course of treatment and have been told that your illness has been brought under control.
- You have no physical problems walking about although you do feel more tired than before you became unwell.
- You are able to wash and dress yourself.
- You are able to carry out your usual activities, but you worry about the risk of picking up infections such as coughs and colds from other people.
- You do not experience any pain or discomfort.
- You worry about your illness coming back which would require you to undergo further treatment. You are concerned as to how this may impact you and your family.

Progression after first line treatment

- You have previously received treatment for a serious illness which affects your blood and bone marrow. The treatment worked initially, but now your illness has worsened and you have been told that your illness requires further treatment.
- The illness also caused you to experience uncomfortable lumps around your neck, and a fever which initially got better with treatment but are now returning and becoming uncomfortable again.
- You have no physical problems walking about although you do feel tired which can limit the distance you want to go.
- You are able to wash and dress yourself.
- You are able to carry out your usual activities, but you worry about the risk of picking up infections such as coughs and colds from other people.
- You experience occasional discomfort in you abdomen and pain from the lumps on your neck.
- You worry about having further treatment for your illness as last time it made you feel unwell. This concern is great because you are aware that your illness came back after your first course of treatment. You worry about how this may affect you and your family.

Progression free survival on second line therapy

- You are currently undergoing a second course of treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, fever and night sweats. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have been told that you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are limited in the distance you want to go.
- You are able to wash and dress yourself.
- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up severe infections which may result in you being admitted to hospital.
- You experience occasional discomfort in your abdomen and a reaction when you start treatment which makes you sweat and gives you chills which lasts for a short time during and following treatment.
- You worry about whether your treatment is working and the effect this may have on you and your family. This concern is great because you are aware that your illness came back after your first course of treatment. You worry about how this may affect you and your family.

Progression free survival without second line therapy

- You have previously received a second course of treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, fever and night sweats. You have been told that your illness has been bought under control again.
- You have no physical problems walking about although you do feel more tired than before you became unwell.
- You are able to wash and dress yourself.
- You are able to carry out most of your usual activities, but you worry about the risk of picking up severe infections which may result in you being admitted to hospital.
- You do not experience any pain or discomfort.
- You worry about your illness coming back which would require you to undergo a further course of treatment. This concern is causing you a high level of anxiety because you are aware that your illness came back after the first course of treatment which required you to have a second course of treatment. You worry about your illness getting worse again and the effect this may have on you and your family.

Further progression

- You have undergone a second course of treatment for a serious illness which affects your blood and bone marrow. You have been told that your illness is getting worse again despite previous treatments.
- The illness is causing you to experience uncomfortable lumps around your neck, fever, night sweats and feelings of breathlessness. The previous treatments required you to attend hospital multiple times for short sessions of treatment given through a needle into your vein.
- You have no physical problems walking about although due to tiredness, you are limited in the distance you want to go.
- You are able to wash and dress yourself, although this requires more effort than usual because of your tiredness.
- You are able to carry out your usual activities, but you worry about the risk of picking up another severe infection which may result in you being admitted to hospital.
- You experience occasional discomfort in your abdomen.
- You continually worry about your illness getting worse again and the effect this may have on you and your family. You have concerns about the future and how you will cope.

Progression free survival on initial therapy with increased hospital visits

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have to attend the hospital two days in a row for the first treatment. You are at the hospital for a total of 6 hours on each day. You have been told you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are limited in the distance you want to go.
- You are able to wash and dress yourself.
- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.
- You experience a reaction from the treatment which makes you sweat and gives you chills which lasts for two days following treatment.
- You worry about whether your treatment is working and the effect this may have on you and your family.

Relapsed lines of treatment

- You have undergone multiple courses of treatment for a serious illness which affects your blood and bone marrow. You have been told that your illness is getting worse again despite these previous treatments.
- The illness is causing you to experience uncomfortable lumps around your neck, fever, night sweats and feelings of breathlessness. The treatment required you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. Your disease has returned and you have now been told that there is no further treatment available which could cure it.
- You have some physical problems walking about and mainly due to tiredness and breathlessness, you are limited in the distance you want to go.
- You require minor assistance to wash and dress yourself.
- You are able to carry out your usual activities, but you regularly pick up severe infections which result in you being admitted to hospital.
- You experience occasional discomfort in your abdomen.
- You worry about your illness getting worse and the effect this may have on you and your family, especially as your life span is limited.