

Fludarabine phosphate for the first-line treatment of Chronic Lymphocytic Leukaemia

NICE STA Submission

Academic in Confidence Data

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Executive Summary

The decision problem considered is the clinical and cost-effectiveness of fludarabine, or fludarabine plus cyclophosphamide (FC), relative to chlorambucil in the treatment of first-line patients with Binet Stage A progressive, or Binet Stages B and Cⁱ, Chronic Lymphocytic Leukaemia (CLL) in England & Wales.

A consistent body of good quality clinical evidence has found that fludarabine and FC increase response rates and extend progression-free survival and QOL when used as a first-line treatment for CLL. An economic evaluation finds FC is highly cost effective, giving an incremental cost per QALY (quality adjusted life year) of £2,600. The cost effectiveness of fludarabine monotherapy compared to chlorambucil is estimated to be around £19,600 per QALY gained in the base case. Approximately 500 patients currently receive FC first-line in England & Wales and following a positive recommendation from NICE this is expected to increase to around 2,200 with a modest impact to the overall budget impact after 5 years (approximately £709,000 per annum by the fifth year).

CLL, which is both incurable and life-threatening, is the most common adult leukaemia occurring in Western countries (2). Incidence peaks at between 60-80 years and the majority of patients present at diagnosis with early stage disease, classified as Binet Stage A (6). It has been shown that currently there is no advantage from immediate treatment (4). Instead, chemotherapy is generally reserved for more advanced disease at diagnosis (Binet stage B or C), or when there are signs of disease progression (7). Patients ultimately relapse following initial therapy and typically go on to receive second-line and third-line chemotherapies. Until sufficient data are found to show that treatment prolongs survival, the main outcomes that should be considered are progression-free survival and health related quality of life.

The current, most widely used first-line treatment in the NHS is chlorambucil (8), which offers overall response rates from approximately 37-71% (9;10). Responses to chlorambucil may not be durable, and the proportion of complete responses is low, which means that repeated courses are sometimes employed. Chlorambucil is normally well tolerated.

Fludarabine is an established second-line therapy in England and Wales (8) and its use in this context was recommended by NICE in 2001. Due to its effectiveness as a second-line agent, a number of randomised studies in the first-line setting were initiated. Since fludarabine has a synergistic effect with other chemotherapies, notably cyclophosphamide, the FC combination was also investigated.

A systematic review of the clinical literature found 7 RCTs (randomised control trials) comparing

ⁱ This differs from the licensed indication which includes patients with Binet stage C or Binet stage A/B where the patient has disease related symptoms or evidence of progressive disease. Expert clinical opinion is that these differences do not have a significant impact on the relevance to usual practice in the UK. Please see section 3.2.3 Q 75 for additional information.

fludarabine with chlorambucil or FC (1;9-14). Over 2,400 patients were included in these studies and the ranges of overall response rates for the three therapies were: C:37%-71%, F:49.6%-85.7%, FC:70-94%; complete response rates were: C:4%-37%, F:0-46%, FC:22.4%-37.5%. None of the studies have shown a significant overall survival benefit for fludarabine or FC compared to chlorambucil, either because they were not powered to do so, or median survival has not yet been reached. This is also compounded by the crossover of treatment following relapse in CLL clinical trials, meaning that a survival benefit generated by a first-line therapy will be difficult to attribute to that particular therapy. Generally, fludarabine and FC were associated with more toxicity than chlorambucil although when quality-of-life (QoL) was directly measured across the three treatments in a single study, it was found to be similar for all three (15;16). As the QoL associated with each treatment is equivalent in a given health state, eg. 'progressive disease' or 'progression-free', any overall gain in QoL associated with a therapy has to be achieved via higher response rates and more durable progression-free periods; these gains are observed with fludarabine and FC compared to chlorambucil (9;11).

Evidence of cost-effectiveness

A systematic review of the cost-effectiveness literature found only 2 evaluations that considered the economic implications relating to the decision problem (5;17). One of these evaluations estimated the incremental cost per QALY of fludarabine monotherapy over chlorambucil to be £48,000 (5), but neither evaluation could reach a conclusion as to whether fludarabine monotherapy represented a cost-effective regimen with any certainty due to the lack of appropriate data at the time of publication. With the recent availability of new clinical data it was appropriate to undertake a new economic evaluation.

It was clear from the RCTs identified in the systematic review that the LRF (Leukaemia Research Fund) CLL4 study (11) was the most appropriate data source to inform the decision problem in the base-case analysis. This is because it is the only study to compare directly all three therapies of interest, it is the largest study (777 evaluable patients), and it is primarily UK based (88% patients). Furthermore, it is likely to be comparable to UK clinical practice since current guidelines have recommended that all patients, not contraindicated to fludarabine, be entered into the study (7). The data owners kindly made the patient-level data available for the purposes of this STA (Single Technology Assessment) (18).

A Markov model was built to estimate the incremental cost per QALY of fludarabine and FC compared to chlorambucil. The model took a life-time (approximately 20 year) time horizon, composed of 260 28 day cycles, and discounted future costs and benefits at 3.5%. As the choice of first-line treatment regimen influences the choice of therapeutic options available later in the disease pathway and because CLL is a chronic disease for which there is no cure, the model also considered progression of patients through second-line and subsequent treatment until death from CLL or other cause.

The model considered patients with CLL at Binet Stage B, C or A with progressive features, eligible for chemotherapy and who had not received previous chemotherapy or radiotherapy for their CLL. Treatments compared were: chlorambucil, fludarabine, or FC. The main outcome was the difference

between groups in cost per Quality Adjusted Life Year (QALY) gained. The model considered the costs of initial chemotherapy, subsequent therapy and of ongoing medical management.

The duration of first-line therapy and associated response rates, response duration and mortality were taken directly from the CLL4 dataset. However patient level data were not available for second and subsequent lines of treatment and therefore response rates and duration were estimated from a comprehensive search of the published literature. Follow up from CLL4 is not yet mature enough to demonstrate any potential advantage in overall mortality. To avoid overstatement of benefit, a conservative assumption was used and so overall survival was assumed to be equal for all three arms.

Costs associated with first-line treatment were estimated by conducting a detailed audit of 113 patients from the CLL4 study. This audit collected resource use data on chemotherapy drug usage, hospital contacts, tests and investigations, co-medication use and adverse events. Health related quality of life data collected in the CLL4 study showed a significant difference in QoL between patients with active disease and those that were progression free; there was not a significant difference between treatments (15). On this basis QALY estimates were calculated by taking published utility estimates for patients with active disease and those progression-free, and multiplying utilities by the expected time in each of the states. Extensive one way sensitivity analyses were conducted.

The modelled estimates of the mean costs of treatment and QALYs for a hypothetical cohort of 1,000 patients are shown below.

Table 1: Expected costs, QALYs and incremental cost-effectiveness of a hypothetical cohort of 1,000 patients with CLL

Treatment given	Costs	QALYs	ICER
Chlorambucil	£ 11,659,803	5,096	
Fludarabine	£ 17,590,562	5,399	£ 19,613
Fludarabine + cyclophosphamide	£ 13,657,485	5,864	£ 2,602

* QALY = Quality Adjusted Life Year; ICER = Incremental Cost-Effectiveness Ratio for treatment compared to chlorambucil

Sensitivity analysis found that the incremental cost per QALY gained with FC compared to chlorambucil is around £2,600 in the base case and under £5,000 for the majority of scenarios tested within the model. This finding was found to be robust to a wide range of patient groups and structural and data assumptions.

A probabilistic sensitivity analysis was performed, including variation in response rates to therapy, duration of response, quality of life and cost inputs. A cost-effectiveness acceptability curve (CEAC) was calculated, showing the estimated likelihood that fludarabine will be preferred to chlorambucil; FC preferred to chlorambucil and FC preferred to fludarabine at different levels of willingness to pay for a QALY gained. The CEAC indicates that the model found a high degree of confidence that the cost per QALY gained comparing FC with C is below £10,000.

The incremental cost per QALY gained with fludarabine monotherapy compared to chlorambucil is

sensitive to model inputs, including the likelihood that extended progression-free survival will translate into extended survival, and to variation in assumed second-line treatment used.

An estimated 3,200 patients in England and Wales receive initial treatment for CLL annually. Introducing fludarabine plus cyclophosphamide instead of chlorambucil as first-line treatment is estimated to increase NHS expenditure by around £3.3 million in the first year. The budget impact is modelled to be negligible by the fifth year, (from £23.5m if current practice continues to £24.2m if FC is incorporated into routine clinical practice) as reduced expenditure on second-line therapy partly offsets the higher cost of FC at first-line.

Discussion

A consistent body of good quality clinical evidence has found that, in comparison to the current standard treatment chlorambucil, FC increased response rates and extended progression-free survival and QOL when used as a first-line treatment for CLL.

The economic modelling suggests that the better response achieved is sufficient to outweigh any higher toxicity and that FC offers attractive cost-effectiveness in this patient group. Furthermore, the more durable responses observed with fludarabine and FC, compared to chlorambucil, lead to a delay in the need for subsequent therapy.

The cost-effectiveness of fludarabine as monotherapy in the model was generally found to be less attractive than FC however; fludarabine still represents a cost-effective alternative to chlorambucil.

No therapy has yet been found to significantly extend overall survival in this patient population and extended follow up of existing study cohorts will be needed to generate evidence to address this point. Should the benefits seen in progression-free survival translate into improvements in overall survival then the cost-effectiveness of fludarabine will be materially better than that reported here.

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Abbreviations

AIHA	Autoimmune Haemolytic Anaemia
ATP	Adenosine Triphosphate
BCSH	British Committee for Standards in Haematology
CAP	Cyclophosphamide, Adriamycin, Prednisone combination
CEAC	Cost-Effectiveness Acceptability Curve
CHOP	Cyclophosphamide, Vincristine, Prednisone, Adriamycin combination
CLB	Chlorambucil
CLL	Chronic Lymphocytic Leukaemia
CLL4	Leukaemia Research Fund sponsored trial comparing chlorambucil to fludarabine and FC
CR	Complete Response
CTC	Common Toxicity Criteria
CVP	Cyclophosphamide, Vincristine and Prednisone combination
DAT	Direct Antiglobulin Test
DNA	Deoxyribonucleic acid
DR	Duration of Response
HDMP	High-Dose MethylPrednisolone
ECOG	Eastern Cooperative Oncology Group (US)
EORTC	European Organisation for Research and Treatment of Cancer
FC	Fludarabine, Cyclophosphamide combination
GVHD	Graft versus Host Disease
HCHS	Hospital and Community Health Services
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention To Treat
IV	Intravenous
IWCLL	International Workshop on CLL
LRF	Leukaemia Research Fund
MRC	Medical Research Council
MRD	Minimal Residual Disease
NCI	National Cancer Institute (US)
NICE	National Institute for Health & Clinical Excellence
nPR	nodular Partial Response
NR	Non-Responders

NZ	New Zealand
OR	Overall Response
OS	Overall Survival
PFS	Progression-free Survival
POACH	Cyclophosphamide, Vincristine, Prednisone, Adriamycin, Ara-C combination
PR	Partial Response
PSA	Probabilistic Sensitivity Analysis
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RNA	Ribonucleic acid
SPC	Summary of Product Characteristics
TRM	Treatment Related Mortality
TTF	Time to Treatment Failure
US	United States
WHO	World Health Organisation

Definition of terms

The following definitions are used *within the context of this submission document*, eg within this document the term 'salvage' refers to therapy administered to patients refractory or relapsed following second-line treatment, whereas in clinical practice patients may receive 3 or 4 lines of treatment before being considered to receive 'salvage' therapy. For a glossary of general terms relating to CLL please refer to Appendix 8.

First-line	Therapy administered when patient first becomes symptomatic, often after a period of 'watch & wait'
Overall Survival (OS)	Percentage of patients (in a study or modelled cohort) who have survived for a defined period of time
Progression-free survival (PFS)	Interval between diagnosis, or the initiation of therapy and diagnosis of progression. The exact definition may vary between papers and studies making it necessary to check which definition is being used within a particular study
Refractory	Patient has not responded to therapy or <i>Relapsed</i> from therapy within 6 months
Relapsed	Recurrence of CLL following a <i>Response</i> to therapy
Remission	Specified time period over which an improvement in disease (to meet specified criteria) is maintained
Response	Improvement in disease to meet relevant specified criteria (clinical factors and symptoms). Response may be complete (CR), partial (PR) or overall (OR = CR + PR)
Response Rate	Percentage of patients in a study or modelled cohort experiencing a response
Salvage	Therapy administered when patients have become <i>Refractory</i> to or relapsed following second-line treatment
Second-line	Therapy administered when patients have become <i>Refractory</i> to or relapsed after first-line treatment

1. Background

The purpose of the background section is to summarise and contextualise the decision problem. It should contain the following information.

1.1. *Summary of decision problem*

The purpose of this section is to summarise the decision problem and state the key factors that are addressed in the submission: 1. intervention 2. Population, including subgroups 3. Relevant comparator(s) 4. Outcomes 5. Key issues.

1. Intervention

The intervention considered in the decision problem is fludarabine phosphate (fludarabine) used as a monotherapy or in combination with cyclophosphamide (FC). Next to chlorambucil, FC and fludarabine are the most commonly used first-line therapies in the UK with approximately 16% and 8% of projected patients receiving each treatment respectively (8). Cyclophosphamide monotherapy and chlorambucil in combination with either cyclophosphamide or fludarabine, are not generally used to treat CLL. Cyclophosphamide monotherapy may sometimes be used as a palliative treatment, as are chlorambucil and corticosteroids, but they do not produce high remission rates and do not noticeably improve the prognosis of the disease (19).

It has been demonstrated that the fludarabine-chlorambucil combination does not increase response rates and is associated with excessive rates of life-threatening toxic events when compared to single-agent fludarabine or chlorambucil (9). Various other drugs have been tried in combination with fludarabine (20-23) but cyclophosphamide was identified as the most promising with laboratory studies confirming synergistic effects (24;25). A number of randomised controlled studies have therefore been initiated to measure the safety, efficacy and tolerability of fludarabine monotherapy and FC in chemotherapy naïve patients with CLL. Data from these studies have recently confirmed that fludarabine, and particularly FC, offer significantly superior outcomes compared to chlorambucil (1;11-14).

Current guidelines do not recommend first-line treatment with other interventions (eg. high-dose chlorambucil, alemtuzumab, rituximab monotherapy, cladribine, fludarabine in combination with rituximab) until further evidence is available (7).

2. Population

Chemotherapy naïve patients considered in the decision problem should be in line with the fludarabine licence (See Appendix 7, fludarabine SPC) and therefore have B-cell CLL with

'sufficient bone marrow reserves'. First-line treatment should only be initiated in those with:

- i) Advanced disease (Binet stage C), or
- ii) Binet stage A/B with disease related symptoms or evidence of progression.

The principal data source informing the economic evaluation of this submission is the CLL4 RCT (11). It should be noted that there are some minor differences between the entry criteria for this study and the licensed indication for fludarabine, namely:

- a) CLL4 allowed enrolment of patients with Binet stage B without progressive features and
- b) CLL4 did not specify that patients should have 'sufficient bone marrow reserves'.

Expert clinical opinion is that these differences do not have a significant impact on the relevance of the data source to usual practice in the UK (Personal communication with D Catovsky).

The proposed patient population is also within the indication for cyclophosphamide. Cyclophosphamide has a broad indication covering a 'range of neoplastic conditions, including leukaemias,...'. The licence also states that, 'Cyclophosphamide is frequently used in combination chemotherapy regimens involving cytotoxic drugs.' (See Appendix 8, cyclophosphamide SPC).

3. Relevant Comparator(s)

Chlorambucil is the relevant comparator in the decision problem because over 60% of projected patients undergoing first-line chemotherapy for CLL in England and Wales receive this drug either alone or in combination with prednisolone (There is no difference in response rate, progression-free interval or survival, between chlorambucil or chlorambucil plus prednisolone (7;26)). When the first-line patients receiving FC and fludarabine monotherapy are considered alongside those receiving chlorambucil, the comparators in the decision problem encompass 85% of projected treated patients in 2005 (8).

4. Outcomes

Beyond a cure, the ultimate outcome for a life-threatening disease such as CLL is increased survival. To date, this outcome has not been proven; either because studies have not been powered to detect a difference or data are too immature. In addition cross-over treatments used following a first or subsequent relapse is a hallmark of CLL clinical trials meaning that any overall survival gain observed is difficult to attribute to a particular therapy in the study. Therefore, the main outcomes that should be considered are progression-free survival and health-related quality of life (HRQoL). Progression-free survival is defined as the period of survival during which the patient is experiencing a response (response criteria are clinically defined according to the internationally recognised

NCI criteria). HRQoL is a multidimensional construct that includes symptoms of the disease, toxicity associated with therapy, and functional, emotional and social factors that reflect the well-being of the patient (27). Current clinical guidelines are mindful of the consideration that should be given to treating CLL with the minimum treatment-related toxicity and the aim for prolonged progression-free survival in the hope that this will translate into superior overall survival (7).

A number of recent, randomised comparative trials, have shown that fludarabine and FC offer significantly greater response rates and longer durations of response than chlorambucil (see Table 20 & Table 21) (1;9;11;13;28). These outcomes translate into increased progression-free survival. It is known that patients who are in remission have a significantly higher quality of life (QoL) than those with progressive disease (15;16). The primary outcome of treatment is therefore to induce the best and most durable response possible with the minimum toxicity. Prolonging the duration of response has the additional benefit of increasing the time spent off treatment, which is of benefit to patients and the health care system.

5. Key Issues

Despite the proven enhanced activity of fludarabine and FC compared to chlorambucil a number of uncertainties remain:

- Fludarabine and FC have a higher acquisition cost than chlorambucil and this additional cost needs to be evaluated relative to the clinical benefits
- As fludarabine and FC are more potent interventions they can be associated with greater toxicity and the need for higher levels of prophylaxis to prevent and manage infections
- The effect of the different treatment strategies on patients' HRQoL
- Whether improved response rates and more durable responses eventually translate into improved overall survival
- The response to therapies given after first-line treatment and the effect of this on outcomes and overall survival
- Effectiveness of therapy on subgroups with known prognostic characteristics, eg age, grade of disease at diagnosis, genetic markers.

Summary

The decision problem is to evaluate the clinical and cost-effectiveness of fludarabine and FC relative to chlorambucil in the treatment of first-line patients with CLL in England & Wales.

1.2. *Description of technology under assessment*

6. Give the brand name, approved name and where appropriate, therapeutic class.

Fludara

Brand name: Fludara[®] / Fludara[®] oral

Approved name: Fludarabine phosphate

Therapeutic class: Antimetabolite (bnf: 8.1.3)

Product Licence Holder: Schering Health Care Ltd

Cyclophosphamide

Brand name: non-proprietary

Approved name: Cyclophosphamide monohydrate

Therapeutic class: Alkylating drugs (bnf: 8.1.1)

Product Licence Holder: Pharmacia Limited

Brand name: Endoxana[®]

Approved name: Cyclophosphamide

Therapeutic class: Alkylating drugs (bnf: 8.1.1)

Product Licence Holder: Baxter Healthcare Ltd

7. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If yes, please give the date it received it. If no, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Fludara[®] gained marketing authorisation for first-line CLL in 2003

Cyclophosphamide has marketing authorisation for use in combination chemotherapy regimens involving other cytotoxic drugs.

Endoxana[®] has had a marketing authorisation for use as a chemotherapy since 1989.

8. Does the technology have regulatory approval outside of the UK?

Yes. Fludarabine phosphate and cyclophosphamide are available in all major European countries, Canada and the USA.

9. If the technology has not been launched, please supply the anticipated launch date for the UK.

Not applicable, as therapies already launched.

10. Is the technology subject to any other form of Health Technology Assessment either in the UK or elsewhere? If so, what is the timescale for completion?

Schering Health Care made a submission to the Scottish Medicines Consortium (SMC) on 5 June 2006. Assuming standard SMC timelines are followed, then guidance will be issued on the SMC website in October 2006.

There are no other on-going health technology assessments that we are aware of.

11. What is the principal mechanism of action of the technology?

Fludarabine phosphate is a nucleotide analogue of adenosine arabinoside. In cells, the active metabolite 2F-Ara-ATP competes directly with dATP (deoxyadenosine triphosphate) and ATP for incorporation into an elongating nucleic acid chain. Once in the DNA or RNA strand, it is an effective chain terminator, thereby inactivating DNA or RNA synthesis and triggering subsequent cell apoptosis (29). It also inhibits DNA and RNA polymerases, DNA primase, DNA ligase and ribonucleotide reductase - enzymes involved in cellular replication (30).

12. For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained release tablet), strength(s) and pack size(s) will be available?

Fludarabine is available in the following formulations:

- i) Vial containing 50mg fludarabine phosphate powder for reconstitution
- ii) Film-coated tablets containing fludarabine phosphate 10 mg
Available in 15 and 20 tablet packs

Cyclophosphamide (non-proprietary) is available in the following formulations:

- i) 500-mg or 1-g vial containing cyclophosphamide powder for reconstitution
- ii) Sugar-coated tablets containing cyclophosphamide (anhydrous) 50 mg
Available in 20 tablet packs

Cyclophosphamide (Endoxana[®]) is available in the following formulations:

- i) 200-mg or 500-mg or 1-g vial containing cyclophosphamide powder for reconstitution
- ii) Sugar-coated tablets containing cyclophosphamide 50 mg,
Available in 100 tablet packs

13. What is the acquisition cost of the technology (minus VAT)? If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs. For devices, provide the list price and average selling price.

Fludarabine phosphate –
1x 50 mg vial = £156.00
15 tablet pack (10mg) = £279.00
20 tablet pack (10mg) £372.00

Cyclophosphamide –
500-mg vial = £2.88
1-g vial = £5.04
20 tablet pack 50 mg = £2.12

Cyclophosphamide (Endoxana®)
200-mg vial = £1.86
500-mg vial = £3.25
1-g vial = £5.67
100 tablet pack 50 mg = £12.00

Source: BNF 50, September 2005

14. What are the (proposed) main indication(s)?

Fludarabine

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.

First-line treatment with fludarabine should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C) or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

(See Appendix 7, fludarabine SPC)

Cyclophosphamide

Alkylating, antineoplastic agent. Cyclophosphamide has been used successfully to induce and maintain regressions in a wide range of neoplastic conditions, including leukaemias, lymphomas, soft tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular, breast and lung carcinomas.

Cyclophosphamide is frequently used in combination chemotherapy regimens involving other cytotoxic drugs.

(See Appendix 8, cyclophosphamide SPC)

15. What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Fludarabine monotherapy

Intravenous - 25 mg fludarabine phosphate/m² body surface given as a bolus injection or by IV infusion daily for 5 consecutive days every 28 days.

Oral - 40 mg fludarabine phosphate/m² body surface given daily for 5 consecutive days every 28 days.

The duration of treatment depends on the success of treatment and the tolerability of the drug. Fludarabine by bolus injection, IV infusion, or oral delivery is usually administered until best response is achieved (complete or partial remission) and then discontinued. In the largest RCT comparing fludarabine with chlorambucil in first-line CLL, the range and mean number of cycles (1 cycle = 5 days consecutive administration every 28 days) was 1-8 and 5.3 respectively (CLL4 patient level data, 2006).

Fludarabine in combination with cyclophosphamide

Intravenous – 25mg fludarabine phosphate/m² body surface plus 250mg cyclophosphamide/m² body surface given as a bolus injection or IV infusion daily for 3 days, every 28 days.

Oral – 24mg fludarabine phosphate/m² body surface plus 150mg cyclophosphamide/m² body surface each day for 5 days.

The duration of treatment depends on the success of treatment and the tolerability of the drug. FC by bolus injection, IV infusion, or oral delivery is usually administered until best response is achieved (complete or partial remission) and then discontinued. In the largest RCT comparing FC with chlorambucil in first-line CLL, the range and mean number of cycles (1 cycle = 3 or 5 days consecutive administration every 28 days) was 1-8 and 4.6 respectively (CLL4 patient level data, 2006).

16. What other therapies, if any, are likely to be prescribed as part of a course of treatment?

No other active chemotherapies are likely to be prescribed with fludarabine either as a monotherapy or in combination with cyclophosphamide.

Low-dose use of prophylactic co-trimoxazole has been recommended to prevent infection in patients receiving fludarabine alone or in combination (7;31). Other supportive drugs such as further antibiotics, antifungals and antivirals are considered on an individual basis to manage specific events (7;31).

17. For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? If yes, provide details.

Patients undergoing treatment with fludarabine should be closely monitored for response and toxicity and individual dosing adjusted accordingly. In the event of blood transfusions being required, patients treated with fludarabine or FC should receive irradiated blood products to prevent the rare but well documented occurrence of transfusion associated graft versus host disease (7).

No additional tests or investigations are required over and above routine care of patients undergoing chemotherapy for CLL.

18. For pharmaceuticals, please provide a Summary of Product Characteristics (SPC) or draft SPC as an appendix to the submission.

Please see Appendices:
7 – SPC Fludarabine phosphate
8 – SPC Cyclophosphamide

19. For devices, please provide the (anticipated) CE marking, including the indication for use, (draft) technical manual and details of any different versions of the same device, as an appendix to the submission.

Pharmaceutical product so not applicable

20. What is the current usage of the technology in the NHS? Include details of use in ongoing clinical trials.

IMS data for 2005 suggest that approximately 270 (8%) patients starting first-line therapy for CLL were receiving fludarabine monotherapy. Similarly, 516 (16%) were receiving fludarabine plus cyclophosphamide. (8) It should be noted that many of these patients may have been entered in the CLL4 study.

In the second-line setting the usage of fludarabine alone and in combination with FC was 27% and 4% of patients respectively.

No significant clinical trials that relate to the decision problem are on-going or expected to complete in the near future (see Table 2).

Table 2: On-going studies of fludarabine in CLL and NHL expected to complete in 2006/2007

Study ref.	Indication	Randomised therapies		Number of patients		Phase	Expected completion
				Planned	To date		
303530	CLL	fludarabine		10	<i>CIC information removed</i>	Post mktg	31.05.06
309123	Indolent lymphoma	fludarabine		40	<i>CIC information removed</i>	Phase II	18.11.07
308580	NHL	fludarabine		60	<i>CIC information removed</i>	Phase II	22.01.07

1.3. *Context*

21. Please provide a brief overview of the disease and current treatment options.

Chronic Lymphocytic Leukaemia (CLL)

CLL is the most common adult leukaemia occurring in Western countries (2), accounting for 40% of all leukaemias in individuals over the age of 65 years (32). The disease occurs in approximately 2.7 people per 100,000 population (33). As with many malignancies, the incidence increases with age, peaking between 60 and 80 years. Twice as many males as females are affected (34). Approximately 25% of cases present under the age of 55 years (7). In younger people the disease tends to be more aggressive (35). Approximately 95% of CLL cases are of B-cell origin (B-CLL).

CLL is a chronic, life-threatening and incurable illness (36). Nevertheless, early symptoms are usually minimal and diagnosis may often only arise from a chance finding of either a high lymphocyte count (lymphocytosis) on a routine blood test or a lymph node swelling (lymphadenopathy) upon physical examination. As the disease advances, patients may experience tiredness, shortness of breath, weight loss, bleeding or bruising owing to lack of platelets (thrombocytopenia), and recurrent or persistent infections (37;38). Infection, ranging from moderate to life threatening, is a major cause of morbidity in CLL, affecting up to 80% of patients during the course of their illness and accounting for up to 60% of CLL-related deaths (37). This susceptibility to infection results from functional incompetence of B-lymphocytes in B-CLL and a later decline in T-lymphocyte function (39). Chemotherapy often enhances this effect, further increasing the risk of infective and other complications. Immune abnormalities in CLL also result in an increased incidence of autoantibody production and autoimmune disorders, such as autoimmune haemolytic anaemia (39). The stage of the disease and number of previous therapies is clearly correlated with the incidence of infection, other complications, and median survival in CLL patients (37;38;40;41).

The clinical course of CLL is highly variable with survival from the initial diagnosis ranging from as little as several months to as long as 20 or more years (42). The clinical stages of the disease, as defined by the Binet (43) and Rai (44) staging system (see Table 3 & Table 4 respectively) and are key prognostic factors at diagnosis. The Binet system is most commonly used in Europe. It was originally developed for newly diagnosed patients and is therefore of limited usefulness in previously treated patients, where age, type of CLL and response to prior therapy is of greater prognostic significance (45). The International Workshop on CLL (IWCLL) has recommended the integration of the Rai and Binet systems in the following manner: Binet stage A = Rai stages 0 – I; Binet stage B = Rai stage I – II; and Binet stage C = Rai stages III – IV.

Table 3: Chronic lymphocytic leukaemia - Binet staging system

Stage	Criteria	Median Survival (years)
Stage A	No anaemia, no thrombocytopenia, fewer than 3 lymphoid areas* enlarged	14
Stage B	No anaemia, no thrombocytopenia, 3 or more lymphoid areas enlarged	5
Stage C	Anaemia (Hb<10g/dL) and/or platelets <100 x 10 ⁹ /L	2.5

*Lymphoid areas considered are: cervical, axillary and inguinal lymphadenopathies (where uni-or bilateral), spleen and liver.
 Adapted from: NCI PDQ CLL Treatment

Table 4: Chronic lymphocytic leukaemia - Rai staging system

Stage	Criteria	Median Survival (years)
Stage 0	Absolute lymphocytosis (>15,000/mm ³). No adenopathy, hepatosplenomegaly, anaemia, or thrombocytopenia.	12.5
Stage I	Absolute lymphocytosis with lymphadenopathy. No hepatosplenomegaly, anaemia, or thrombocytopenia.	8.5
Stage II	Absolute lymphocytosis with either hepatomegaly or splenomegaly, with or without lymphadenopathy.	6
Stage III	Absolute lymphocytosis and anaemia (haemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.	1.6
Stage IV	Absolute lymphocytosis and thrombocytopenia (<100,000/mm ³) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anaemia.	1.6

Adapted from: NCI PDQ CLL Treatment (46)

Current treatment options

The majority of patients present at diagnosis with Binet Stage A CLL (6).

A substantial number of these patients will have survival times comparable with an age-matched population and therefore do not require immediate treatment, although they should be monitored at regular intervals (frequently referred to as 'watch and wait').

A meta-analysis performed by the CLL Trialists' Collaborative Group (CLL-TG) in 1999 showed that, on the basis of the data available at the time, there was no survival advantage from immediate treatment of early stage disease and that there might be a disadvantage (4).

Treatment, with chemotherapy, is generally reserved for more advanced disease at diagnosis (Binet stage B or C, Rai stage I to IV) or when there are signs of disease progression, systemic symptoms, bone marrow impairment, hypersplenism, or autoimmune phenomena such as haemolytic anaemia. As yet, there are no curative therapies for CLL and first-line treatment with currently available agents ultimately results in the patient relapsing and requiring a cascade of further therapies i.e. second-line and salvage chemotherapy.

Until a therapy is found to prolong survival, the current aim of treatment is to:

- achieve complete remissions
- prolong the duration of response, and hence the time spent off treatment
- manage the complications of the disease
- reduce symptoms
- maintain or improve quality of life.

First-line treatment

"First-line" treatment for patients with intermediate and advanced stage disease has for many years consisted of an alkylating agent, usually chlorambucil, either alone or in combination with steroids (47;48). Current BCSH guidelines endorse the use of chlorambucil and recommend that first-line patients who are not contraindicated for fludarabine be entered into the CLL4 study for randomisation to chlorambucil or fludarabine. The guidelines also state that chlorambucil remains an option for those not wishing to enter the study (7). Overall response rates associated with chlorambucil regimens range from as high as 70% in Stage A disease to as low as 30% in stages B and C (9;49;50). Responses to chlorambucil may not be durable, and the proportions of complete responses are low, and so repeated courses of treatment are sometimes employed (51). Chlorambucil is normally well tolerated with myelosuppression being the most common adverse effect, although it is not without concerns especially in high-dose regimens (52;53).

Other alkylating agent-based regimens that have been used as initial therapy are cyclophosphamide, vincristine, and prednisone (CVP) (54); cyclophosphamide, vincristine, prednisone, and adriamycin with or without ara-C (CHOP, POACH) (55;56); and cyclophosphamide, adriamycin, and prednisone (CAP) (57). These combinations do not produce superior response rates or any advantage in survival rates over chlorambucil (4) and therefore are not used as first-line treatments in the UK (8).

Since their introduction in the early 1990's, purine analogues (fludarabine, cladribine and pentostatin) have been increasingly studied as first-line therapy. Of these analogues, fludarabine is the most widely used and tested. Various fludarabine-based combinations of chemotherapies have been studied in the first-line setting. The combination with the most data is the combination of fludarabine with cyclophosphamide (FC) (1;11;13;21).

Second-line treatment

Over the past 15 years fludarabine has become the treatment of choice for patients with relapsed or refractory disease (51;58;59).

In 2001, NICE recommended fludarabine as second-line therapy for B-cell CLL in preference to CHOP, CAP or CVP combination chemotherapy (33). The oral formulation of fludarabine was preferred to the intravenous formulation on the basis of more favourable cost-effectiveness. IMS data indicate that at least 60% of projected patients in the UK in 2005 were receiving fludarabine monotherapy or the FC combination as a second-line treatment (8).

When fludarabine has been used as a first-line therapy, current guidelines suggest either re-treatment (assuming an initial response lasting >1 year) or treatment with the combination chemotherapy, FC or CHOP (7).

Salvage treatment

Patients who have become refractory to purine analogues and alkylating agents have a poor prognosis. Alemtuzumab is highly efficacious in this population (60-64), particularly in cases with heavy bone marrow disease and / or p53 abnormalities (65). Overall response rates are achieved in 22 to 54% of this difficult to treat group, with overall median survival not reached after 6 years' follow up in MRD-negative responders. High-dose methylprednisolone, given alone or in combination with other chemotherapies, is also a useful treatment strategy in refractory CLL producing response rates of 77% (66). More recently chemoimmunotherapy combinations have been investigated. These include the combination of alemtuzumab and fludarabine (67) (Sayala 2005), alemtuzumab and FC (68), and CHOP with rituximab (28) producing overall response rates of 44%, 100% and 69% respectively. In addition, different monoclonal antibodies have been combined. An OR

rate of 65% was achieved in a study investigating the efficacy of a combination of alemtuzumab, rituximab and FC in 44 patients (69).

Other therapies

Transplantation is a possible therapy in CLL but current guidelines suggest that the increased morbidity and mortality of high-dose chemo-radiotherapy associated with this option mean that it is not recommended except in young, fit patients (7).

Where there is massive splenomegaly, marked hypersplenism or autoimmune haemolysis unresponsive to steroids and alkylating agents, splenectomy may be beneficial (70). However, there are no randomised studies comparing the procedure to other therapies and it is not a main treatment option in UK guidelines (7).

Local radiotherapy may be of value in shrinking large splenic or lymphatic masses which are causing pressure symptoms e.g. abdominal pain (26) but the systemic nature of CLL means that cytotoxic chemotherapy remains the main approach to treatment (7).

22. What was the rationale for the development of the new technology?

Rationale for the development of fludarabine as a first-line agent.

Fludarabine has become the established second-line treatment offering better response rates and more durable responses than alternatives (30;71;72). It was therefore postulated that in the first-line setting fludarabine may also offer similar benefits over the mainstay treatment chlorambucil, and that these superior response rates and durations might translate into improved survival. Experts also considered that when used in combination, the unique mode of action of fludarabine, which affects DNA and RNA synthesis, could potentiate the effect of other drugs (31). A natural starting point for clinicians seeking to combine fludarabine would have been to combine it with chlorambucil, the most widely used first-line agent. However, as was demonstrated by the large US study (9), the fludarabine-chlorambucil combination did not increase response rates when compared to single-agent fludarabine or chlorambucil, and caused excessive rates of life-threatening toxic effects. Various other drugs including doxorubicin (22) and epirubicin (23) have been tried in combination with fludarabine, however it is the fludarabine combination with cyclophosphamide that has proved to be the most promising (20;21). Laboratory studies confirm the synergistic effects of these two drugs (24;25). For these reasons a number of randomised studies in the first-line setting were started to measure the efficacy and safety of fludarabine with or without cyclophosphamide compared to chlorambucil.

23. What is the suggested place in therapy for this technology with respect to treatments currently available?

The majority of patients with Binet Stage C and those with Stage B/A with symptomatic

disease or progressive CLL will require a disease control strategy (ie, not transplant). Currently, many of these patients receive chlorambucil as their first-line chemotherapy (8). Comparative trials have shown improved efficacy with fludarabine and FC versus chlorambucil in this patient population (9;11;14). Therefore, the suggested place of fludarabine and/or FC is as a replacement for chlorambucil in these patients who have sufficient bone marrow reserves and in whom there is no contraindication to fludarabine (eg, severe renal impairment or an autoimmune cytopenia).

24. Describe any current variation in services and/or uncertainty about best practice, including cost effectiveness.

Clinical variation / uncertainty

There is little variation in the management of patients with CLL. Current guidelines are clear on the first-line use of fludarabine and FC, stating that patients who are ineligible for transplant and have no contraindications to fludarabine should be entered into the LRF CLL4 study to be randomised to chlorambucil, fludarabine or FC. The uncertainty around the net level of benefit offered by fludarabine and FC compared to chlorambucil (higher response rates and extended duration of response vs increased potential toxicity from more aggressive therapy) is being quantified by results from CLL4 which has now closed to recruitment.

Cost effectiveness

Two published economic evaluations of fludarabine in the first-line treatment of CLL have been identified (5;17), and only one of these calculated an ICER. There was no comparison made between the FC combination and chlorambucil. Although the baseline cost/QALY was £48,000 Hancock et al concluded that there was considerable uncertainty leading to the evidence for cost utility to be inconclusive (5). To reduce uncertainty, the report recommended that patients should be entered in to the LRF CLL4 study. For a fuller description of Hancock et al, see section 3.1.

25. Provide details of any relevant guidelines or protocols.

Relevant guidelines or protocols for first-line therapy of CLL

Current guidelines for UK Haematologists for the management of CLL, compiled on behalf of the British Committee for Standards in Haematology (BCSH) (7), recommend that all patients ineligible for a transplant and in whom there is no contraindication to fludarabine should be entered into the LRF CLL 4 study. Since CLL4 has now closed to recruitment and initial findings have been reported it is expected that revised guidelines will be available in due course.

1.4. *Comparator(s)*

26. Describe the relevant comparator(s) and provide a justification for your selection. In some cases, comparisons with more than one comparator or combination-therapy comparators will be necessary. The Institute considers the most relevant comparators to be those that the new technology is attempting to displace from UK practice.

The most relevant comparator in the first-line setting is chlorambucil. Prior to the advent of fludarabine and FC, chlorambucil, was recognised worldwide as the standard treatment for initial therapy in CLL patients. In the UK, approximately 60% of projected patients continue to receive chlorambucil in the first-line setting (8). This is supported by current guidelines for the management of CLL (7).

27. What are the main differences in the indications, contraindications, cautions, warnings and adverse effects between the proposed technology and the main comparator(s)?

Chlorambucil, fludarabine and cyclophosphamide are all licensed for the initial treatment of CLL. As with any chemotherapy, these agents can exert toxic effects and as such should only be administered under the supervision of a qualified physician experienced in assessing the risks and benefits to the individual patient (ref BNF Section 8.1: General Guidance on the use of cytotoxic drugs).

Fludarabine, when given as a single-agent or in combination with cyclophosphamide, more frequently causes severe neutropenia than chlorambucil (see Section 2; Table 11). More hospitalisations for neutropenia were reported in the fludarabine and FC arms in the CLL4 study (11), which may have an impact on overall costs of therapy. Although there were more neutropenias and hospitalisations this did not translate into statistically significant differences in symptomatic infections.

Many clinicians advocate prophylaxis against opportunistic infections with fludarabine-containing regimens, which has been shown to be more severe than with chlorambucil (9).

Patients who require blood transfusion and who are undergoing, or who have received, treatment with fludarabine should receive irradiated blood products to avoid transfusion-related graft-versus-host disease (7) (See Appendix 7, fludarabine SPC).

2. Clinical Evidence

2.1. *Identification of studies*

28. Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.

Literature search strategy

The literature search aimed to identify all literature relating to studies involving treatment of previously untreated chronic lymphocytic leukaemia with chlorambucil, fludarabine or FC. This was then narrowed to randomised clinical trials (RCTs) comparing at least two of these interventions. The search was conducted this way in the event that there were insufficient RCTs and there was a need to include non-randomised or single arm studies.

29. The specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least: Medline, Embase, Medline (R) In-Process, The Cochrane Library

Twelve electronic bibliographic databases were searched, covering biomedical, science, and health economic literature. The health economic sources were searched for completeness but details of the cost-effectiveness literature search can be found in Section 3.1.

1. MEDLINE (1966 – January 2006) through PubMed
2. OLDMEDLINE (1950 – 1965) through PubMed
3. Medline® In-Process through PubMed
4. Embase (Datastar) 1974 – January 2006
Cochrane Library 2005 Issue 5 including:
 5. The Cochrane Database of Systematic Reviews (Cochrane Reviews)
 6. Database of Abstracts of Reviews of Effects (DARE)
 7. The Cochrane Central Register of Controlled Trials (CENTRAL)
 8. The Cochrane Database of Methodology Reviews (Methodology Reviews)
 9. The Cochrane Methodology Register (Methodology Register)

10. Health Technology Assessment Database (HTA)
11. NHS Economic Evaluation Database (NHS EED)
12. Health Economic Evaluation Database (HEED)

For details of other sources searched please see question 33 and also Appendix 1

30. The date the search was conducted

The searches for the clinical evidence and cost-effectiveness sections were conducted in January 2006.

31. The date span of the search

Due to the many years that chlorambucil has been available, no date restrictions were applied to the search in order that all relevant studies involving chlorambucil could be included.

32. The complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)

A combination of thesaurus terms (such as MeSH headings) and free-text searching was used to maximise the pool of reference material.

MEDLINE, EMBASE and other search strategies are included in Appendix 2

33. Details of any additional searches, for example searches of company databases (include a description of each database)

The reference lists of relevant articles identified in the database searches were hand-searched, and various health research-related resources were consulted via the internet. These resources included health economics and health technology assessments, guideline-producing agencies, research registers and haematology specialist conference proceedings. These additional resources are listed in Appendix 1. No additional company databases were searched.

34. The inclusion and exclusion criteria

No language restrictions were applied to any of the searches.

Free text search terms were limited to the title or the abstract as it was felt that relevant papers would at least carry the term in the title or abstract.

Studies were restricted to human studies not animal studies.

Inclusion criteria

Table 5: Inclusion Criteria

Interventions:	Fludarabine, fludarabine plus cyclophosphamide, chlorambucil
Population:	Previously untreated patients with B-cell CLL
Outcomes:	No restriction was made according to the outcomes measured
Design:	RCTs; trials were accepted as RCTs if the allocation of subjects to treatment groups was described as either randomised and/or double-blind.

Exclusion criteria

There was no specific exclusion criteria applied to the search, beyond the restrictions described above.

35. The data abstraction strategy.

The references identified from the literature searches were screened in two stages – screened for relevance first by title and then by abstract. It was not always possible to identify RCTs or papers involving untreated patients from titles alone, hence the title screening stage was used essentially to reject studies that were clearly irrelevant. Following this, abstracts of all studies that used relevant interventions in the relevant populations were screened. For studies that did not provide abstracts, the full papers were screened. Reviews were included as an additional checking process to ensure no studies had been missed. Several studies/papers did not meet the inclusion criteria at the full-paper screening stage. Details of such studies and the reason for their exclusion are listed in Appendix 3.

Data were extracted by one reviewer using customised data extraction forms (Appendix 4). Where full results were not available, as much data relating to results and quality of the study was extracted. A second reviewer checked the search and data extraction strategy and also validated the screening process described in Figure 1.

Where available the following data were reviewed:

- Baseline characteristics
- Response rates and type

- Duration of response
- Progression-free survival
- Overall survival
- Adverse events
- Quality of life

Quality Assessment Strategy

The RCTs were assessed using the checklists proposed by NICE (see section 2.4 Critical Appraisal).

Blinding of the quality assessors to author, institution, or journal was not considered necessary.

The quality assessment of studies included in the review of clinical effectiveness was carried out by two researchers.

2.2. Study selection

2.2.1. Complete RCT list

36. Provide a list of all RCTs that compare the intervention with other therapies, including placebo. The list must be complete and will be validated by searches conducted by the Evidence Review Group. Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

The electronic literature searches identified 395 potentially relevant articles. Of these, 21 articles related to 10 trials comparing fludarabine or FC with other therapies in patients with previously untreated CLL (Table 6 NB: Table lists 22 references as Eichhorst 2006 (1), an update to Eichhorst 2003a (73), was made available to the authors after the search had been completed). Some of these studies, having recently been completed, are in the process of reporting and being published in full (11-14), hence abstracts have been included as the key references. Other sources i.e. earlier reporting of data, are listed in the table for ease of cross-reference.

Table 6: RCTs involving fludarabine

Key Reference	Title	Interventions
Catovsky (2005)(11) [Hillmen, 2005; Catovsky 1999](31;74)	Early results from LRF CLL4: A UK Multicenter Randomized Trial.	fludarabine vs chlorambucil vs fludarabine + cyclophosphamide
Eichhorst (2006, 2003a)(1;73)	Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia.	fludarabine vs fludarabine + cyclophosphamide
Eichhorst, (2005b)(12) [Eichhorst 2003b, Schmitt 2002] (75;76)	Comparison of the Efficacy and Toxicity of Fludarabine in First-line Therapy of Younger versus Elderly Patients With Advanced CLL: Results of a Meta-Analysis of Two Phase III Trials of the German CLL Study Group.	fludarabine vs chlorambucil
Flinn (2004)(13)	Fludarabine and Cyclophosphamide Produces a Higher Complete Response Rate and More Durable Remissions Than Fludarabine In Patients With Previously Untreated CLL: Intergroup Trial E2997.	fludarabine vs fludarabine + cyclophosphamide
Karlsson (2004)(14)	Cladribine or Fludarabine or High-Dose Intermittent Chlorambucil as First-Line Treatment of Symptomatic CLL? First Interim Analysis of Data from the International Randomized Phase III Trial.	cladribine vs fludarabine vs chlorambucil (high-dose)
Leporrier (2001)*(77) [Leporrier 1997; Binet 1993,1994](78-80)	Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients.	Fludarabine vs CAP vs CHOP
Rai (2000) (9) [Rai 1995, 1996](81)	Fludarabine compared with chlorambucil as primary therapy for Chronic Lymphocytic Leukemia.	fludarabine vs chlorambucil vs fludarabine + chlorambucil
Jaksic (2000)**(53) [Jaksik 1996, 1998](47;82)	Fludarabine versus high-dose continuous chlorambucil in untreated patients with B-CLL: results of the CLL1 EORTC randomized trial.	fludarabine vs chlorambucil (high-dose)
Spriano M (2000)(10)	Multicentre prospective randomised trial of fludarabine in previously untreated patients with active B-CLL: final report.	fludarabine vs chlorambucil + prednisone
Johnson 1996*(71)	Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia.	fludarabine vs CAP

*The search identified RCTs comparing fludarabine with other interventions e.g. CHOP, CAP. Since these are not relevant to our decision problem, these studies were excluded at this stage. This resulted in two studies being excluded (71;77).

**In order to compare efficacy between studies, response rate and/or type of response (complete or partial) had to be reported according to NCI criteria. This led to the exclusion of one study (53). This was because response was defined according to Total Tumour Mass (TTM) reduction, an evaluation not used in any other study.

2.2.2. Relevant RCT list

37. List all randomised trials that compare the technology directly with the main comparator(s). If there are none, state this. Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

Thirteen articles related to 7 trials comparing fludarabine with FC and/or chlorambucil were included (Table 7). A further relevant paper (1)(Eichhorst 2006) was published in full during the review process but after the search had been performed. This provided updated information on the Eichhorst (73)2003a abstract and hence was included to make 14 articles in total.

Table 7: RCTs comparing fludarabine with chlorambucil and / or fludarabine and cyclophosphamide

Author	Randomised Therapies			No of patients
Catovsky 2005; Hillmen 2005; Catovsky 1999; CLL4 patient-level data (2006) (11;18;31;74)	chlorambucil	fludarabine	fludarabine + cyclophosphamide	783
Eichhorst 2006 Eichhorst 2005b, 2003a (1;12;73)		fludarabine	fludarabine + cyclophosphamide	375
Eichhorst 2005 Eichhorst 2003b; Schmitt 2002(12;75;76)	chlorambucil	fludarabine		191
Flinn 2004(13)		fludarabine	fludarabine + cyclophosphamide	278
Karlsson 2004*(14)	chlorambucil	fludarabine		150
Rai 2000** Rai 1995, 1996(9;81;83)	chlorambucil	fludarabine		509
Spriano 2000(10)	chlorambucil + prednisone	fludarabine		150

* Also included an arm with cladribine

**Also included an arm with fludarabine + chlorambucil

LRF CLL4 Study (11;18;31)

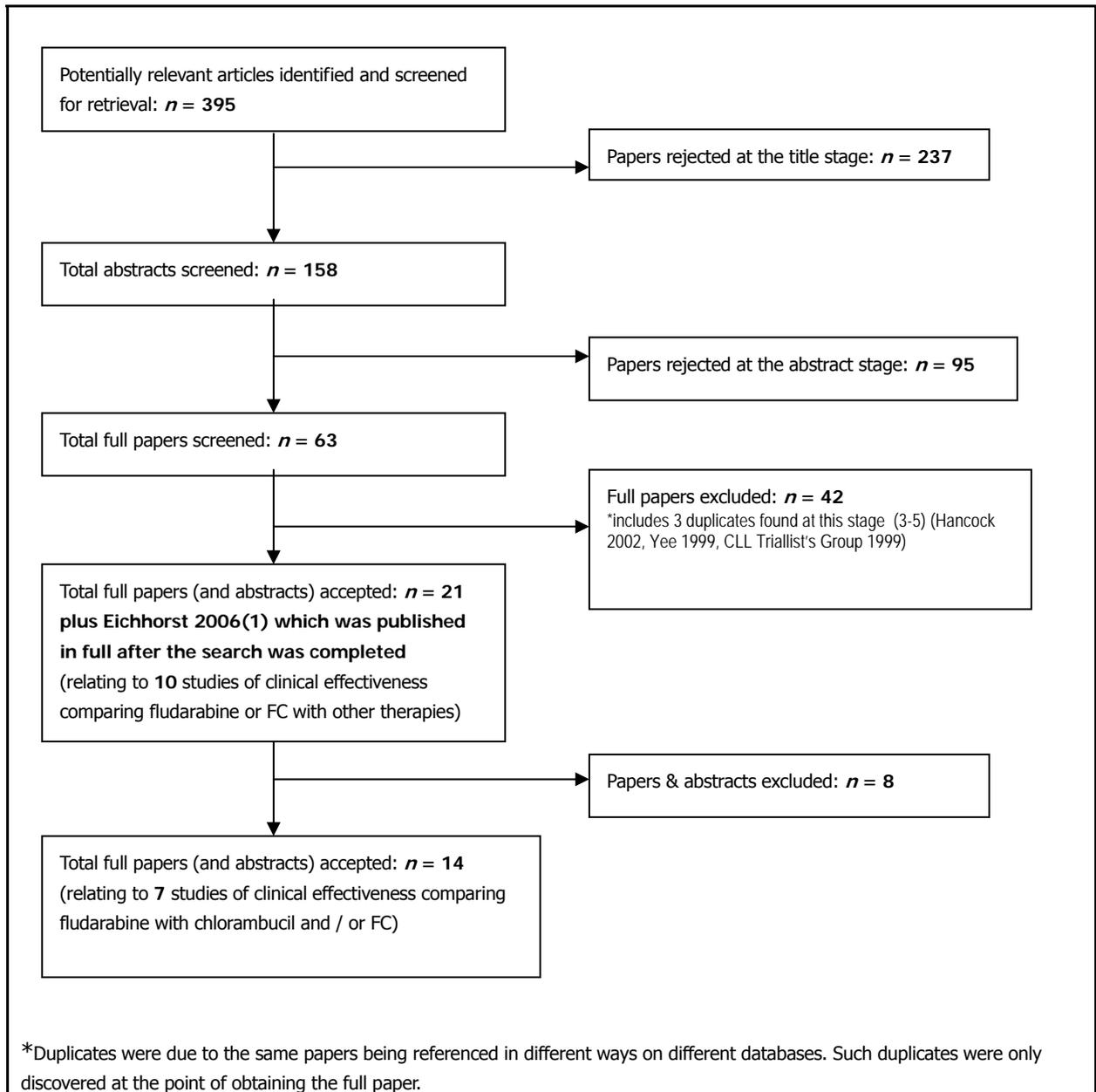
It was clear from the list of relevant RCTs that the Leukaemia Research Fund (LRF) CLL4 study was the most appropriate data source to inform the decision problem. This is because it is the only study to compare chlorambucil with both fludarabine and FC in the first-line setting, it is the largest study, it is primarily UK based (88% patients) and is recent. Although CLL4 is now closed to recruitment, the trial is on-going with patients entering randomisation to second-line treatment and follow up. Therefore, only abstract-level data had been published. Considering the value of CLL4 in answering the decision problem, Schering contacted the data owners and principal investigator to ask if appropriate data could be made available to inform this STA. Permission was kindly given towards the end of January 2006 and patient-level data from first-randomisation to second-line randomisation (or last visit if still in remission, or death, if sooner) were supplied to Fourth Hurdle Consulting to inform the economic evaluation. Throughout this submission document the abstracts for CLL4 and, where relevant, the patient-level data are reported side-by-side and are referenced as 'Catovsky et al 2005' (11) and 'CLL4 patient-level data 2006' (18) respectively. Academic in confidence data from CLL4 are reported in red underlined type.

38. Please provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 6–12 months.

Other than more complete analyses of the studies already mentioned, eg UK CLL4 (11), German CLL Study Group CLL4 & 5 (1;75) (Eichhorst 2006, Eichhorst 2003b), there are no relevant ongoing studies from which significant additional evidence will be available in the next 12 months.

39. A flow diagram of numbers of number of studies included and excluded at each stage should be provided as per the QUORUM statement.

Figure 1: Summary of study selection and exclusion: electronic literature searches



2.3. Summary details of RCTs

40. As a minimum, the summary should include information on the following aspects of the study but the list is not exhaustive. Where there is more than one RCT please tabulate the information.

2.3.1. Methods

41. Describe the trial design (e.g. degree and method of blinding and randomisation) and interventions.
Please see Table 8: Study Characteristics

2.3.2. Population

42. Provide details of the inclusion and exclusion criteria and describe the patient characteristics at baseline. Highlight any differences between study groups.

Please see Table 8: Study Characteristics and Table 9: Study Population

2.3.3. Patient numbers

43. Provide details of the numbers of patients eligible to enter the trial, randomised, and allocated to each treatment. Provide details of patients who crossed over treatment groups and dropped out from the trial. This information should be presented as a CONSORT flow chart.

Please see Table 8: Study Characteristics and Appendix 5: CONSORT Flow Charts

2.3.4. Outcomes

44. Provide details of the outcomes investigated and the measures used to investigate those outcomes. This may include therapeutic outcomes and patient-related outcomes such as assessment of quality of life, social outcomes etc. and any arrangements to measure concordance. Where appropriate, also provide details of the principal outcome measure(s) including details of length of follow-up, timing of assessments, scoring methods, evidence of validity and current status of the measure (e.g. approval by professional bodies, licensing authority, etc.).

Data on all the relevant RCTs have been tabulated in the following tables:

Table 8: Study Characteristics

Table 9: Study Population

Table 10: Study Outcomes (1)

Table 11: Study Outcomes (2)

Data from CLL4 are sourced from both the abstracts and the patient-level dataset, with additional or more recent data drawn from the patient level data as appropriate. In addition to the summary data on CLL4 presented in the tables, a brief outline of this data source is

provided at the end of Section 2.4.

CONSORT flow charts have been prepared for RCTs identified in the literature search where possible, please see appendix 5.

Table 8: Study Characteristics

Study	Study Site	Recruitment	Study Design	Outcome measures	Patient No.s (see Append 5)	Mean age (range) years	Interventions	Mean number of cycles
Catovsky (2005)(11)	UK (88%) and 12% from Argentina, Italy Russia NZ, Ireland	Feb 1999 – Oct 2004	Multicentre, prospective, randomised (randomised via Clinical Trials Support Unit, Oxford)	OS, OR, PFS	783 (194 F vs 387 ChI vs 196 FC)	NR	<ul style="list-style-type: none"> Fludarabine iv (for first 2 years) and/or from 2001, Fludarabine oral, Dosage - <i>as per SPC</i> Chlorambucil 10mg/m² days 1-7 Fludarabine 25mg/m² iv + cyclophosphamide 250mg/m² (both days 1-3) or Fludarabine 24mg/m² oral + cyclophosphamide 150mg/m² (both days 1-5) 	NR
CLL4 Patient level data (2006) (18)	As above	As above	As above	As above	As above	64 years (35 – 86 years)	As Above	Treated patients only: CLB: 6.9 (range 1-18) F: 5.3 (range 1-8) FC: 4.6 (range 1-8)
Eichhorst 2006(1)	Germany / Austria	July 1999 – July 2003	Multicentre, randomised (randomised via Institute of Medical Statistics & Epidemiology, Munich)	PFS, OS, Duration of response	375 (182 F vs 180 FC; 13 excluded due to ineligibility)	F 59 (43 – 65) FC 58 (42 – 64)	<ul style="list-style-type: none"> Fludarabine 25mg/m²/day iv as per SPC Fludarabine 30mg/m² iv + cyclophosphamide 250mg/m² (both days 1-3) every 28 days 	MEDIAN 6 cycles of each therapy given Mean 5.2 cycles of fludarabine administered.
Eichhorst 2005b(12)	Germany / Austria	July 1999 – July 2003	Multicentre, randomised*	PFS, OS, Duration of response	191 (92F, 99 ChI)	71 (65 – 79)	<ul style="list-style-type: none"> Fludarabine 25mg/m²/day iv as per SPC Chlorambucil 0.4mg/kg days 1 and 15 (escalation up to 0.8mg/kg) 	4.9 cycles of fludarabine administered.
Flinn 2004(13)	US	Dec 1999 – March 2004	Randomised, prospective, multicentre *	CR, PFS, OS	278 (137F vs 141 FC)	62 (34 – 86)	<ul style="list-style-type: none"> Fludarabine 25mg/m²/day iv as per SPC Fludarabine 20mg/m² iv days 1-5 + cyclophosphamide 600mg/m² iv day 1 	57% received the maximum of 6 cycles

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Study	Study Site	Recruitment	Study Design	Outcome measures	Patient No.s (see Append 5)	Mean age (range) years	Interventions	Mean number of cycles
Karlsson 2004(14)	Scandinavia, Australia, UK	November 1997 -	Multicentre, Randomised, prospective *	Response, survival, toxicity	150	Median age = 63 yrs	<ul style="list-style-type: none"> Fludarabine iv as per SPC Chlorambucil 10mg/m² orally day 1-10 Cladribine 5mg/m² day 1-5 	Up to 6 courses
Rai 2000(9)	US	Oct 1990 - Dec 1994	Randomised, prospective, multicentre (randomised via CALGB Statistics Centre)	PFS, Response	544 (195F, 200ChI, 149FChI*) *FChI closed due to excessive toxicity.	F 64 (33-88) ChI 62 (36-89) FChI 63 (32-83)	<ul style="list-style-type: none"> Fludarabine 25mg/m²/day iv as per SPC Chlorambucil 40mg/m²day 1 Fludarabine 20mg/m² days 1-5 iv + chlorambucil 20mg/m² day 1 	NR
Spriano 2000(10)	Italy	Oct 1994-	Randomised prospective multicentre*	Response, Toxicity	150 (75F vs 75ChI+P)	NR	<ul style="list-style-type: none"> Fludarabine 25mg/m²/day iv as per SPC Chlorambucil 30mg/m² days 1and15 + Prednisone 40mg/m² days 1-5 and 15-19 every 4 weeks 	NR

* Blinding or randomisation methods not reported

Table 9: Study Population

Study	Inclusion & Exclusion Criteria	Baseline characteristics & comparability	Concomitant therapy	Timing of Assessments
Catovsky (2005, 1999)(11;31)	Typical inclusion and exclusion criteria for 1 st line treatment	Male 2.8: 1 Female Binet A 25%, Binet B 45%, Binet C 30%. 1/3 cases <60yrs, 1/3 aged 60-<70, 1/3 ≥ 70yrs.	Allopurinol for first 7 days. Antiemetics (but not steroids) for FC patients; Stage C patients – Prednisone 30mg/m ² daily for 3 weeks; Antibiotic prophylaxis – cotrimoxazole 480mg bd 3x week for pts receiving F or FC. For all patients : - Other antibiotics at first evidence of infection or unexpected fever. Antifungals for oral candidiasis / mucositis. Antivirals for herpes infections. Gamma globulin infusion for pts with low immunoglobulins and a history of repeated respiratory infections; Influenza vaccine. Growth factors. Blood Products as necessary.	Monthly
CLL4 Patient level data ITT, n=777 (2006) (18)	As above	34.4% <60yrs, 36.5% 60-<70, 29.0% ≥ 70yrs.	As above	As above
Eichhorst 2006(1)	Only previously untreated CLL ≤ 65 years of age were included in the study	Male 70.4%F 75%FC Binet A 11.2%F 7.4%FC Binet B 53.6%F 57.6%FC Binet C 35.2%F 35.0%FC Rai 0 2.4%F 3.1%FC Rai I or II 56.6%F 58.2%FC No significant difference in main clinical features or risk categories.	Anti-infective prophylaxis and growth factors were not given routinely.	After each cycle
Eichhorst 2005b(12)	Only previously untreated CLL > 65 years of age were included in the study.	Binet A 11%F, Binet B 52% F; Binet C 35%F. No significant difference in main clinical features or risk categories.	Anti-infective prophylaxis and growth factors were not given routinely.	NR

Study	Inclusion & Exclusion Criteria	Baseline characteristics & comparability	Concomitant therapy	Timing of Assessments
Flinn 2004(13)	Typical inclusion and exclusion criteria*	70% males; 30% females; 56% Rai stage 0-II; 44% stage III-IV	Filgrastim 5mg/kg starting day 8 for FC pts	NR
Karlsson 2004(14)	Typical inclusion and exclusion criteria*	No significant differences in age, Binet stage, or time from diagnosis to inclusion between groups.	NR	NR
Rai 2000(9)	Typical inclusion and exclusion criteria*	Rai I - II / III - IV F 61 39 % ChI 59 41 % FChI 61 39 % No imbalances among the three groups with respect to clinical features and risk categories.	Allopurinol, 300mg/day days -1 - 8 for the first 3 treatment cycles.	monthly
Spriano 2000(10)	NR	Previously untreated patients with active B-CLL, Rai intermediate or high risk stages	NR	Evaluated for response after 6 th cycle

*Typical Inclusion Criteria: Binet stage A, B or C or Rai stage 0-IV with progressive disease; ECOG performance status 0-2; Life expectancy >6 months

Typical Exclusion Criteria: Patients with other life threatening diseases e.g. cancer, patients unwilling or unable to give informed consent; Renal failure (creatinine clearance <30ml/min); Hepatic enzymes / bilirubin >2x upper normal limit unless due to CLL; Autoimmune Haemolytic Anaemia or Thrombocytopenia; Severe organ dysfunction.

Table 10: Study Outcomes (1)

Study	Overall Response	Complete Response	Partial Response	Median Duration of Response	Median Progression-free survival	Median Overall survival
Catovsky (2005)(11)	77% F 69% Chl 90.5% FC (out of 661 patients with available data)	15% F 8% Chl 37.5% FC	62%F 61% Chl 53% FC	NR	Not reached yet At 3 years: 31% F 23% chl 62% FC	NR
CLL4 Patient level data, ITT (n=777) (2006)* (18)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	NR	NR	NR
CLL4 Patient level data evaluable (n=720) (2006)* (18)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	NR	NR	NR
Eichhorst 2006(1)	82.9% F (n=136) 94.5% FC (n=155) (P=0.001) (out of 328 patients with available data)	6.7% F (n=11) 23.8% FC (n=39) (P<0.001)	78% F (n=128) 78% FC (n=128) (P=1)	NR	20 months F 48 months FC (P=0.001)	Not reached yet. 3 yr survival: 80.7% F 80.3% FC
Eichhorst 2005b(12)	85.7% F NR Chl	10.4%F NR Chl	75.3%F NR Chl	NR	18.7 months F NR Chl	29 months F NR Chl
Flinn 2004(13)	49.6% F 70% FC (p=0.001 Fischer exact test) (246 of patients with available data)	5.8% F 22.4% FC (p=0.0002 Fischer exact test)	43.8% F 48% FC	NR	Preliminary estimates 17.7 months F 41.0 months FC (p<0.001)	NR
Karlsson 2004(14)	67% F 57% Chl 74% Cladribine (139 evaluable of 150)	0% F 4% Chl (n=2) 4% Cladribine (n=2)	67% F (n=30) 53% Chl (n=25) 70% Cladribine (n=33)	NR	NR	NR

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Study	Overall Response	Complete Response	Partial Response	Median Duration of Response	Median Progression-free survival	Median Overall survival
Rai 2000(9)	63% F 37% ChI 61% FChI (p<0.001)	20% F 4% ChI 20% FChI (p<0.001)	43% F 33% ChI 41% FChI	25 months F 14 months ChI (p<0.001)	20 months F 14 months ChI (p<0.001)	66 months F 56 months ChI 55 months FChI No significant differences.
Spriano 2000(10)	71%F 71%ChI + P (142 evaluable for response)	46% F 37% ChI + P	25% F 34% ChI + P	28 months F 21 months ChI+P (p=0.007)	NR	NR

*Response status available for 682 patients out of 777 in patient-level dataset supplied (783 were randomised into the study as reported by Catovsky et al (2005) but 6 were excluded)); Response rates were calculated for the analysis on the assumption that all missing patients were non-responders

Table 11: Study Outcomes (2)

	Haematological Toxicity				Infections	Non-haematological toxicity	Quality of Life method	Comments
	Thrombocytopenia	Neutropenia	Anaemia	AIHA				
Catovsky (2005, 1999)(11; 31)	NR	40% F 29% Chl 55% FC	NR	10% F 13% Chl 4% FC	NR	More nausea/vomiting & alopecia with FC	EORTC QoL-C30 questionnaire	More hospitalisations with F and FC
CLL4 Patient level data, ITT (n=777) (2006) * (18)	10.8% F 11.6% Chl 15.3% FC	<i>AIC information removed</i>	NR	<i>AIC information removed</i>	NR	<i>AIC information removed</i>	EORTC QoL-C30 questionnaire	None
CLL4 Patient level data evaluable (n=720) (2006) * (18)	11.7% F 12.7% Chl 16.1% FC	<i>AIC information removed</i>	NR	<i>AIC information removed</i>	NR	<i>AIC information removed</i>	EORTC QoL-C30 questionnaire	None
Eichhorst 2006(1)	CTC Grade 3 or 4: 12.7% F 15.6% FC (P=0.44) NCI grade 3 or 4 23.3% F 34.9% FC (P=0.02)	CTC Grade 3 or 4: 26% F 55.5% FC (P<0.001)	CTC Grade 3 or 4: 11.6% F 8.1% FC (P=0.28) NCI grade 3 or 4 5.2% F 2.4% FC (P=0.17)	All grades: F arm 7.7% vs 2.8% FC (P=0.06); CTC Grade 3 or 4 AIHA 3.8%F vs 2.2% FC (P=0.37)	CTC Grade 3 or 4: 8.7% F 8.7% FC (P=1)	Gastrointestinal CTC Grade 3 or 4: 1.7% F 5.8% FC (P=0.05)	None	Toxicity avail in 346 pts 3 treatment related deaths due to infection or haemolysis (Fludara).

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	Haematological Toxicity				Infections	Non-haematological toxicity	Quality of Life method	Comments
	Thrombocytopenia	Neutropenia	Anaemia	AIHA				
Eichhorst 2005b(12)	NR	NR	NR	NR	CTC Grade 3 or 4: 6.9% F	NR	EORTC QoL-C30 questionnaire	3 treatment related deaths due to infection or haemolysis (Fludara).
Flinn 2004(13)	NR	NR	NR	NR	11% F 17% FC (p=0.21) 2 deaths (1 in each arm, G3/4 neutropenia)	Grade 3 or higher: 13% F 17% FC (p=0.48)	None	Toxicity data available on 127 FC and 125 F patients
Karlsson 2004(14)	NCI grade 3: 24% F 25% ChI 36% Cladribine NCI grade 4: 5% F 20% ChI 11% Cladribine	NR	NR	4 pts F 3 pts Cladribine	NCI grade 3 or 4: 28% F 25% ChI 30% Cladribine	NR	None	
Rai 2000(9)	13% F 14% ChI 43% FChI	27% F 19% ChI 43% FChI	NR	NR	16% F 9% ChI 28% FChI	NR	transfusion requirements, incidence of infection, performance status	Toxicity evaluated for adverse events 170 F, 178 ChI, 129 FChI

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	Haematological Toxicity				Infections	Non-haematological toxicity	Quality of Life method	Comments
	Thrombocytopenia	Neutropenia	Anaemia	AIHA				
Spriano 2000(10)	NR	NR	NR	NR	NR	NR	None	"Toxicity was comparable in the two treatment groups"

* Toxicity rates calculated from the patient-level dataset on the assumption that those with missing data have no toxicity

2.3.5. Statistical analysis and definition of study groups

45. State the primary hypothesis or hypotheses under consideration and statistical analysis used in testing hypotheses. Also provide details of the power of the study and a description of sample size calculation including assumptions. Provide details of how the analysis took account of patients who withdrew (e.g. a description of the intention-to treat analysis including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken.

Table 12: Statistical analysis of studies

Study	Study Design	Hypothesis under consideration	Statistical Analysis used	Power of study	Evaluated as ITT?	Withdrawals	Subgroups
Catovsky 2005(11) (31)	Multicentre, prospective, randomised	Not explicitly stated. Objectives of study included: To ascertain if fludarabine / FC improve survival compared to chlorambucil. To compare response rates, duration of remission and toxicity	ITT log rank survival. Chi-square tests compare response, toxicity & QoL differences.	Fludarabine based treatments (all) vs chl: Study was designed to detect an absolute difference of 15%, from 40% to 55%, in survival at 5 years using a 2-sided p-value, or 65% power to detect a 10% difference. F vs FC : 65% power to detect 15% difference	Yes	661/783 pts available data (178 F, 309 Chl, 176 FC)	Age Genetic risk groups
Eichhorst 2006(1)	Multicentre, randomised	Not explicitly stated. Endpoints included response rates, overall survival, progression-free survival and treatment-free survival	All tests were two-sided. SPSS V12.0 used. Time to event – Kaplan-Meier method; Treatment comparison tested with log-rank test. Treatment arms compared by Chi-square test	NR	Yes	11 patients lost to follow-up; Survival data available in 351 patients, response data available in 328 patients;	Analysis by Binet stage. NB: All patients were <66
Eichhorst 2005b(12)	Multicentre, randomised	NR	NR	NR	Yes	NR	NR

Study	Study Design	Hypothesis under consideration	Statistical Analysis used	Power of study	Evaluated as ITT?	Withdrawals	Subgroups
Flinn 2004(13)	Randomised, prospective, multicentre	Null hypothesis: No difference between groups in CR rate	Fisher exact test for difference in CR rates and OR	NR	Yes	9 ineligible / declined protocol treatment. Response data available on 246 of 278 patients (121F, 125FC)	NR
Karlsson 2004(14)	Multicentre, randomised, prospective	Not explicitly stated. Response rates reported	NR	NR	NR	Interim analysis on first 150 patients. 139 evaluable – 5 excluded for not fulfilling eligibility criteria and 6 for incomplete reporting	NR
Rai 2000(9)	Randomised, prospective, multicentre	Not explicitly stated. Primary end-point was progression-free survival	Chi square test used to compare response rates. All time to event distributions were calculated by Kaplan Meier method and compared with the use of the log-rank test, with one or two degrees of freedom. All statistical tests were 2-sided.	Adequate power to detect difference in CR rates and PFS. Not powered enough to show difference in overall survival.	Yes. All patients who withdrew were followed for PFS.	Survival data avail 507/509 pts; response 474 pts; 477 toxicity; 355 for PFS (from F and ChI groups).	Response according to Rai Stage
Spriano 2000(10)	Randomised prospective multicentre	Not explicitly stated. Response rate reported	NR	NR	NR	142 evaluable for response (69F; 73ChI +P)	NR

2.4. *Critical appraisal*

For each of the following methodological topics, choose the description that best fits each trial. If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. Your results will be validated by the assessor.

Available data from the clinical studies relevant to questions 46-53 have been summarised in Table XX: Critical Appraisal. An overview of CLL4 is also presented at the end of this Section.

2.4.1. Randomisation

46. Which of the following best describes the randomisation?

- A) No details of randomisation are available, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).
- B) An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/ nblended trial; treatment assignment kept in consecutive 'sealed' envelopes and open/ nblended trial).
- C) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care.

2.4.2. Adequacy of follow-up

47. Which of the following best describes the adequacy of follow-up?

- A) There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.
- B) There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.
- C) Trial outcome(s) were assessed in all treated and control subjects.

2.4.3. Blinding of outcomes assessment

48. Which of the following best describes the blinding of the outcomes assessment?

A) There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer; measurement of vertebral height on an X-ray).

B) The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

2.4.4. Other

49. Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.

50. Was the trial conducted in the UK (or were one or more centres of the multinational trial located in the UK)? If not, where was the trial conducted and is clinical practice likely to differ from UK practice?

51. How do the subjects included in the trial compare with patients who are likely to receive the drug in the UK? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity, setting.

52. For pharmaceuticals, what dosage regimens were used in the trial? Are they within those detailed in the Summary of Product Characteristics?

53. What was the median (and range) duration of follow-up in the trial?

Table 13: Critical Appraisal

Study	Randomisation	Adequacy of follow-up	Blinding of outcomes assessment	Other				
				Parallel group or cross-over Comment on likelihood of carry-over effect.	Location effects & comparability with potential UK patient population	Dosage regimens	Median duration of follow-up	Comments
Catovsky (2005) (11)	C	C (follow-up period not complete)	A	Parallel-group	88% of patients were from the UK. No location effect. Majority of subjects reflect the characteristics of the intended population.	Fludara and Chlorambucil as per standard practice. FC reduced cyclophosphamide dosage compared to initial US studies (O'Brien 2001)	21 months	661/783 pts available for response data (178 F, 309 ChI, 176 FC)
CLL4 Patient level data (2006) (18)	As above	As above	As above	As above	As above	As above	45 months	777/783 pts available for ITT analysis 720/783 available for economic model
Eichhorst 2006(1)	C	B	Uncertain; possibly A	Parallel-group	Germany – no difference in clinical practice or patients compared to intended population in UK	Fludara dose higher in FC arm than in LRF CLL4.	22 months	11 patients lost to follow-up; Survival data available in 351 patients, response data available in 328 patients.
Eichhorst 2005b(12)	Unknown	Unknown	Uncertain; possibly A	Parallel-group	Germany – no difference in clinical practice or patients compared to intended population in UK.	Chlorambucil different regimen but equivalent dosing over a cycle.	22 months	

Study	Randomisation	Adequacy of follow-up	Blinding of outcomes assessment	Other				
				Parallel group or cross-over Comment on likelihood of carry-over effect.	Location effects & comparability with potential UK patient population	Dosage regimens	Median duration of follow-up	Comments
Flinn 2004(13)	A (no details given)	Uncertain; possibly B	Uncertain; possibly A	Unknown	US – no difference in clinical practice or patients compared to intended population in UK	Fludara dose lower in FC arm than Eichhorst & LRF CLL4 (Catovsky 2005) studies. Cyclophosphamide dose equivalent per cycle but taken in 1 day.	NR	9 ineligible / declined protocol treatment. Response data available on 246 of 278 patients (121F, 125FC)
Karlsson 2004(14)	A (no details given)	Unknown	Uncertain; possibly A	Parallel-group	Where? No location effect	Chlorambucil was given for 3 extra days per cycle than UK standard dosing.	NR	5 ineligible patients and 6 incomplete data reporting. 139 evaluable pts to date
Rai 2000(9)	Uncertain; possibly B	Uncertain; possibly B	A, although centralised review for specimens from CR patients	Cross-over design for patients NR or relapsing < 6 months. Therefore possibility of carry-over effect. For patients relapsing > 6 months treated as per initial therapy.	US – no difference in clinical practice or patients compared to intended population in UK	Chlorambucil was given at a lower dose than UK standard dosing.	62 months	Survival data available for 507/509 pts; response 474 pts; 477 toxicity; 355 for PFS (from F and Chl groups).
Spriano 2000(10)	A (no details given)	B	Uncertain; possibly A	Unknown	Italy – no difference in clinical practice or patients compared to intended population in UK	Chlorambucil was given at a slightly lower dose per cycle when compared with UK standard dosing.	NR	142 evaluable for response (69F; 73Chl +P)

Leukaemia Research Fund (LRF) CLL4 Study

Follow up in the LRF CLL4 study is on-going and the trial has therefore, to date, only been published in abstract form (11;15;16;74). However, as it was identified in the systematic review as the best data source for informing the decision problem, and that patient level data had been made available to inform the economic analysis, a more extensive report of its methods are presented here. The same headings and format are followed as for the previous studies.

METHODS

CLL4 was a prospective, randomised, multi-centre, comparative trial comparing chlorambucil, fludarabine, and FC in the first-line setting. (NB: Follow-up is on-going).

The study had Multi-Centre Research Ethics Committee and local ethics committee approval. Participating centres were mainly in the UK but also included Argentina, Italy, Russia, New Zealand and Ireland. All eligible patients gave their written, informed consent to participate in the study.

Patients and treating physicians were not blinded to regimen received. Eligible patients were randomised to chlorambucil or fludarabine and those randomised to fludarabine were further randomised to fludarabine monotherapy or FC. Randomisation was undertaken by the Clinical Trials Service Unit in Oxford. Treatment was allocated by computer, balancing treatment with groups by age (<60, 60-69, 70+), stage of disease and sex.

The specific regimens used for the 3 first-line interventions are presented in Table 14. It was recommended that all patients received annual flu vaccines and that Stage C patients were pre-treated with prednisolone (30mg/m² daily for 3 weeks plus 1 week trailing off) before starting randomised therapy. Prophylaxis with low-dose cotrimoxazole (eg. Septrin 480mg twice daily 3 days per week) was recommended during treatment with fludarabine or FC and for at least 6 months post treatment. Antiemetics were recommended for those receiving FC (corticosteroids were not permitted as part of the antiemetic regimen to avoid affecting the response to treatment and to avoid additive immunosuppression). Other supportive measures including, antibiotics, antifungals, antivirals, gamma-globulin infusion, growth factors, blood products and allopurinol were permitted according to local treatment guidelines and as required.

Fludarabine and FC were given intravenously until early 2001 when the oral formulation of fludarabine became available and from then until recruitment closed in October 2004 both iv and oral were used without any protocol driven restriction, eg patients experiencing nausea or diarrhoea with the oral formulation could switch to the iv.

Subjects failing to respond or relapsing and requiring a change of treatment (relapse within one year of treatment) were randomised to second-line treatment. Initial therapy could be repeated if, following a response, a relapse occurred after 1 year of remission, provided the therapy had been well tolerated and was not associated with major toxicity. Second-line treatment was guided either by DiSC assay (84) or by physician's choice according to protocol guidelines. Mature patient-level data on second-randomisation are not yet available and therefore not provided in this submission.

Table 14: First-line regimens administered in CLL4

Therapy	Dose	Duration
chlorambucil	10mg/m ² per day for 7 days. Repeated every 4 weeks*	Repeat until maximum response is achieved, or up to one year (exceptionally treatment could continue for a few more months if beneficial response continuing)**
fludarabine	IV 25mg/m ² per day for 5 days, or Oral 40mg/m ² per day for 5 days. Repeated every 4 weeks*	Minimum of 3 months and maximum of 6 (exceptionally patients experiencing continuous response may receive up to 8 months)**
FC	IV F 25mg/m ² plus Cyclo 250mg/m ² per day for 3 days or, Oral F 24mg/m ² plus C 150mg/m ² per day for 5 days. Repeated every 4 weeks*	Minimum of 3 months and maximum of 6 (exceptionally patients experiencing continuous response may receive up to 8 months)**

*Downward dose modifications and/or a delay in between doses were permitted if the treating physician considered that falling blood counts were due to treatment and not the underlying disease

**Patients showing no response or progressive disease after 3 cycles were discontinued.

POPULATION

Inclusion criteria: Patients with previously untreated B-cell CLL, diagnosed by a persistent lymphocytosis (>10x 10⁹/L) and bone marrow infiltration of at least 40%, who require treatment, with Binet stage A progressive, stage B or stage C disease.

Exclusion criteria were: Other life threatening disease, unwilling / unable to give consent, renal failure, hepatic enzymes and bilirubin >2x upper normal limit (unless due to CLL), pregnancy or risk thereof, patients not expected to complete the study, diagnosis other than CLL after central review of markers and morphology.

Table 15: Baseline characteristics of the CLL4 patient-level data, n=777, 2006

	chlorambucil		fludarabine		FC	
	No	%	No	%	No	%
Male	286	73.9	142	73.2	145	74.0
Female	101	26.1	52	26.8	51	26.0
Age (range)	35-85		38-85		43-86	
Binet						
A progressive	96	24.8	46	23.7	49	25.0
B	172	44.4	91	46.9	89	45.4
C	119	30.7	57	29.4	58	29.6

Table 16: Baseline characteristics of patients included in the model, n=720

	chlorambucil		fludarabine		FC	
	No	%	No	%	No	%
Male	268	75.5	130	72.6	140	75.3
Female	87	24.5	49	27.4	46	24.7
Age (range)	35-85		38-85		43-86	
Binet						
A progressive	90	25.4	43	24.0	46	24.7
B	157	44.2	87	48.6	85	45.7
C	108	30.4	49	27.4	55	29.6

NB: Data in this table are after allowing for drop-outs and missing data from the patient level dataset (Please see table 19 for details of these)

See Appendix 5 for CONSORT flow chart of patient numbers for CLL4 patient level data set.

OUTCOMES

The endpoints from CLL4 were survival, response to therapy, duration of response, toxicity and quality of life (see Table 17).

The response criteria used are the same as, or more demanding, than those set by the NCI (National Cancer Institute) for the design and conduct of clinical trials in CLL (85). Response was assessed by bone marrow trephine biopsy to enable comparison with original pre-treatment specimen (the distinction between a CR and a nPR (nodular partial response) can only be made with a trephine biopsy). Patients were monitored at baseline, each treatment cycle, 3, 6 and 12 months and annually thereafter (for up to 5 years) unless they progressed or relapsed.

Toxicity was measured in terms of haematological and non-haematological. Haematological thresholds are shown in Table 17 and the degree of non-haematological toxicity was according to WHO grading (See Table 18).

The European Organisation for Research and Treatment of Cancer Core-questionnaire (EORTC QLQ-C30) was used for measuring quality of life. As a cancer specific instrument it has been widely used in clinical trials, is appropriate for self-administration, and demands little time to complete. It incorporates five functional scales (physical, role, cognitive, emotional, and social) three symptom scales (fatigue, pain, and nausea and vomiting) a global health-status scale, and a number of single items commonly reported by cancer patients (eg. loss of appetite, diarrhoea). Subjects were asked to complete a quality of life instrument at baseline, month 3, month 6, month 12, and annually thereafter.

Routine follow-up for patients not requiring treatment or disease related visits was annually for 5 years for survival, disease status, toxicity and QoL. Follow-up for survival will continue indefinitely, and all entered patients have been flagged at the NHS central registry so that only the few who emigrate are likely to be lost.

Table 17: Study endpoints from CLL4

Endpoint	Measure/Timing of assessments
Survival	On-going with annual follow up indefinitely
Response (complete) CR	All of the following must be true: <ul style="list-style-type: none"> i) Absence of lymphadenopathy by physical examination and appropriate imaging; no hepato- or splenomegaly; absence of constitutional symptoms; blood counts: Neutrophils $\geq 2.0 \times 10^9/l$, Platelets $\geq 100 \times 10^9/l$, Haemoglobin $\geq 13g/dl$ for men and $\geq 11g/dl$ for women, Lymphocytes $< 3.5 \times 10^9/l$ ii) Bone marrow aspirate normal cellularity $< 30\%$ lymphocytes and no evidence of lymphocytic infiltration in trephine biopsy.
Response (nodular partial) nPR	As CR including the BM aspirate, but evidence of discrete or moderately large nodules of residual CLL in a trephine biopsy. Minimal interstitial lymphocyte infiltration may be present.
Response (partial) PR	All of the following must be true: <ul style="list-style-type: none"> i) At least 50% reduction in organomegaly ii) Blood lymphocytes $< 15 \times 10^9/l$, neutrophils $\geq 2.0 \times 10^9/l$ or 50% improvement from baseline, platelets $\geq 100 \times 10^9/l$ or 50% improvement from baseline, haemoglobin $\geq 12g/dl$ for men or $\geq 11g/dl$ for women or 50% improvement from baseline, not supported by transfusion
No response	Defined as any response which does not include the above
Progression (relapse in those who reached CR or PR)	At least one of the following: <ul style="list-style-type: none"> i) A persistent rise in lymphocyte count with doubling time < 12 months ii) A downward trend in the Hb and/or platelets iii) $\geq 50\%$ increase in size of liver and/or spleen and/or lymph nodes. Appearance of lymphadenopathy, hepatomegaly or splenomegaly is not previously present iv) Constitutional symptoms attributable to the disease, eg pyrexia, night sweats, weight loss, once other causes have been excluded
Toxicity	Toxicity during treatment was collected as: Haematological: Neutropenia ($< 1 \times 10^9/l$), Thrombocytopenia ($< 50 \times 10^9/l$), Haemolytic anaemia (yes/no) Non-haematological events (graded by WHO): Nausea/vomiting, Alopecia, Mucositis, Diarrhoea, Other. The number of febrile episodes requiring antibiotics and the number of days in hospital were also collected. All life-threatening, lethal and unexpected adverse events were reported to the CTSU or trial co-ordinator within 24 hours.
Quality of Life	The EORTC QLQ-C30 (version 2.0) was used to determine whether there is any difference in QoL of patients according to treatment arm and whether QoL correlates with baseline characteristics and/or with treatment outcome (response). The instrument was administered at baseline, 3, 6 and 12 months, and annually thereafter.

Table 18: WHO Grading of non-haematological toxicities

WHO Grade	1	2	3	4
Nausea / vomiting	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Alopecia	Minimal hair loss	Moderate, patchy alopecia	Severe alopecia	Total alopecia
Oral	Soreness / erythema	Erythema, ulcers, can eat solids	Ulcers, requires liquid diet	Feeding not possible
Diarrhoea	Transient <2 days	Tolerable but > 2 days	Intolerable, requiring therapy	Haemorrhagic dehydration
Cardiac Function	Asymptomatic, but abnormal cardiac sign	Transient symptomatic dysfunction, no therapy required	Symptomatic dysfunction, responsive to therapy	Symptomatic dysfunction, not responsive to therapy

CRITICAL APPRAISAL

Randomisation in CLL4 was secure with the sequence kept away from the clinical area and administered by the Clinical Trials Service Unit in Oxford.

Follow up is on-going in CLL4. However, based on the patient level data available in January 2006 there had been some drop outs and there was some missing data, eg treatment dates not recorded. The rates were approximately equivalent in each of the study arms and are presented in Table 19.

Table 19: Drop outs and missing data in the patient level data

	chlorambucil	fludarabine	FC
Total patients randomised	387	194	196
No treatment given	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
Treatment other than randomised given	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
No data available	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
Died before first dose	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
Patients included in analysis	355 (92%)	179 (92%)	186 (95%)

Although CLL4 was randomised to parallel groups it was of open-label design. However the measurement technique for response required blood counts to meet specific levels and the protocol recommended that response be measured by bone marrow trephine biopsy to enable comparison with the original pre-treatment status.

There is no reason to believe, or evidence to show, that subjects included within CLL4 are any different from those who will receive fludarabine or FC in the UK in routine clinical practice.

Chemotherapy regimens used within CLL4 are in line with those in the SPC. For details of the regimens please see Table 14 in section 2.3.1

2.5. *Results of the comparative randomised trials*

As in previous sections of this STA document, data from the CLL4 patient level data set that were provided in January 2006 are presented as 'academic in confidence' alongside the abstract published in 2005 by Catovsky et al (11).

54. Provide the results for all relevant outcome measure(s). If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible.

For each outcome:

- describe the unit of measurement
- report the size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic
- provide a 95% confidence interval
- provide the number of patients included in the analysis
- state whether 'intention-to-treat' was used for the analysis
- discuss and justify definitions of any clinically important differences.

55. Where interim trial data are quoted this should be clearly stated along with the point at which data were taken and the time remaining until completion of that trial. Analytical adjustments should be described to cater for the interim nature of the data.

56. If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.

57. Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

Effectiveness of fludarabine and FC compared with chlorambucil

Fludarabine and FC have been compared with chlorambucil in 5 studies (9-12;14). In two additional studies (1;13) fludarabine has been compared with FC. One study compares all three regimens (11).

In the earlier US study (9) fludarabine was also combined with chlorambucil, however patients randomised to this treatment experienced severe toxicity and the combination arm was discontinued. In addition, fludarabine combined with chlorambucil did not produce superior response rates (see Section 2.3.4 Study Outcomes (1)) compared to single agent fludarabine and will not be discussed further in this review as it is not regarded as a likely therapeutic option for previously untreated CLL patients (9).

Five out of the seven studies report preliminary results (10-14), as yet unpublished except as abstracts. Results must therefore be interpreted with caution within this systematic review. However, unpublished data from the LRF CLL4 study (11) have been made available for the health economic analysis and these are reported as academic in confidence here and used to inform the cost-effectiveness analysis (see Section 3).

For studies containing a randomisation to chlorambucil, the aims were to assess whether fludarabine produces higher response rates than chlorambucil, and if so, whether these lead to more durable remissions and prolonged survival. The inclusion of the FC arm in the LRF CLL4 study (11) and the comparison between fludarabine and FC, omitting a chlorambucil randomisation (1;13) were to test whether the combination conferred any additional survival benefit over fludarabine single-agent, given the early observations that the proportion of ORs and CRs was significantly enhanced with the FC combination (21).

All studies aimed to compare the associated toxicities of the different treatment modalities. Three studies also included a quality of life analysis, two involving the EORTC-QoL-C30 questionnaire (11;12) and one (9) using an assessment of transfusion requirements, performance status and the incidence of infection as a means of gauging the patient's quality of life during treatment.

Reporting size of effect

Response rates, duration of response and survival are the main measures of effect reported in studies investigating treatments for CLL, therefore relative risks and hazard ratios have not been calculated.

Overall Response

In all studies, except Spriano (10) where it was the same in both arms, overall response (measured according to NCI criteria) was greater in the fludarabine arm than in the

chlorambucil arm (see Table 20). Findings from the German studies indicate that fludarabine is equally effective in younger patients (<66 years) and older patients (>65 years) with CLL (12). In studies comparing fludarabine with FC, the combination achieved higher overall response rates.

Table 20: Overall response reported from RCTs comparing fludarabine with chlorambucil and / or fludarabine-cyclophosphamide combination in previously untreated CLL

Study	Overall Response (%) (no of evaluable patients)			
	F	FC	Chl	
Catovsky 2005(11)	77 (n=178)	90.5 (n=176)	69 (n=309)	NR
CLL4 Patient level data ITT n=777 (2006) (18)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	NR
CLL4 Patient level data evaluable n=720 (2006) (18)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	NR
Eichhorst 2006 (ITT) (1)	82.9 (n=182)	94.5 (n=180)	-	P=0.001
Eichhorst 2005 (ITT)(12)	85.7 (n=92)	-	NR (n=99)	-
Flinn 2004 (ITT)(13)	49.6 (n=121)	70 (n=125)	-	P=0.001
Karlsson 2004(14)	67% (n=45)	-	57% (n=47)	-
Rai 2000 (ITT)(9)	63 (n=170)	-	37 (n=181)	P<0.001
Spriano 2000(9;10)	71 (n=69)	-	71 (n=73)	-

The lower overall response rate reported in the Flinn study (13) is postulated by Eichhorst et al (1) to be due to a higher proportion of elderly or high-risk patients in the study.

Complete Response and Progression-Free Survival

All studies aimed to detect whether the higher overall response rates observed for fludarabine translates into a greater number of complete responses i.e. more complete disease eradication. The hypothesis is that a better quality of response gives rise to a

longer duration of response or median progression-free survival (PFS), and ultimately overall survival was tested.

Table 21: Complete response rates, and median progression-free survival reported in RCTs comparing fludarabine with chlorambucil and / or FC combination in previously untreated CLL

Study	Complete Responses (%)				
	Median PFS	F	FC	ChI	
Catovsky 2005(11)	CRs Median PFS No of evaluable pts	15 not reached (n=178)	37.5 not reached (n=176)	8 not reached (n=309)	
CLL4 Patient level data ITT n=777 (2006) (18)	CRs (NPs) Median PFS No of evaluable pts	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
CLL4 Patient level data in analysis n=720 (2006) (18)	CRs (NPs) Median PFS No of evaluable pts	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
Eichhorst 2006 (ITT)(1)	CRs Median PFS No of evaluable pts	7 20 months (n=182)	24 48 months (n=180)	-	P<0.001 P=0.001
Eichhorst 2005 (ITT)(12)	CRs Median PFS No of evaluable pts	10.4 18.7months (n=92)	-	? ? (n=99)	-
Flinn 2004** (ITT)(13)	CRs Median PFS No of evaluable pts	5.8 17.7 months (n=121)	22.4 41 months (n=125)	-	P=0.0002 P<0.001
Karlsson 2004(14)	CRs Median PFS No of evaluable pts	0 NR 45		4 NR 47	-
Rai 2000 (ITT)(9)	CRs Median PFS No of pts	20 20 months (n=170)	-	4 14 months (n=181)	P<0.001 P<0.001
Spriano 2000(10)	CRs Median PFS No of evaluable pts	46 not reported (n=69)	-	37 not reported (n=73)	-

*Preliminary estimates for median PFS

With the exception of Karlsson 2004 (14), which was still recruiting patients, all studies comparing either fludarabine or the FC combination with chlorambucil demonstrate higher CR rates for the fludarabine-containing arms (Table 21). From the data available so far, fludarabine-induced responses are more durable than responses from chlorambucil, as demonstrated by a longer median PFS in the fludarabine arm (20 months vs 14 months) (9). When fludarabine is combined with cyclophosphamide, the FC combination induces significantly more CRs than fludarabine or chlorambucil (see Table 21) and available data from these studies is indicating major differences in median PFS (1;13). Whereas fludarabine response typically lasted about 20 months, patients treated with the fludarabine-cyclophosphamide combination have a significantly longer response to therapy without relapse of over 40 months (1;11;13).

Overall Survival

Fludarabine and fludarabine-combinations have been the main focus of attention in clinical trials to try and achieve an improvement in overall survival. In earlier studies (9), although fludarabine resulted in higher response rates and improved progression-free survival compared to chlorambucil, there was no statistically significant difference in overall survival (see Table 22). This has been related to the crossover nature of the studies and the high response rate to second-line treatment with fludarabine +/- cyclophosphamide in patients who had failed chlorambucil.

It remains to be seen whether more recent studies will demonstrate a difference in overall survival. Although it is certainly a key endpoint in their design and statistical power considerations, period of follow-up is too short presently to report fully matured overall survival data for most RCTs included in this review.

Table 22: Overall Survival in patients treated with fludarabine, chlorambucil or fludarabine-cyclophosphamide as a first-line therapy in RCTs

Study	Median Overall Survival (months)			Duration of follow up (months)
	F	FC	ChI	
Catovsky 2005(11)	Not reached yet (n=176)	Not reached yet (n=176)	Not reached yet (n=309)	21
CLL4 Patient level data (2006) (18)	<i>AIC information removed</i> (n=194)	<i>AIC information removed</i> (n=196)	<i>AIC information removed</i> (n=387)	45
Eichhorst 2006(1)	Not reached yet (n=182)	Not reached yet (n=180)	-	22
Eichhorst 2005(12)	29m (n=92)	-	? (n=99)	22
Flinn 2004(13)	Not reached yet (n=121)	Not reached yet (n=125)	-	Not reported
Karlsson 2004(14)	Not reached yet		Not reached yet	Not reported
Rai 2000(9)	66m (n=170)	-	56 (n=181)	62
Spriano 2000(10)	Not reported (n=69)	-	Not reported (n=73)	Not reported

The lack of cure and the recurring nature of CLL means that first-line patients will eventually relapse and be given additional treatments, the treatment given will depend on individual patient need and prognosis and will therefore not be the same for all subjects. For this reason, a survival benefit created by a first-line therapy will often be difficult to prove, especially since technologies and treatments for relapsing and salvage CLL patients are also continuing to improve response quality and duration.

Toxicity and Side effects

These are reviewed in Section 2.8 Comparative Safety.

Quality of Life

Three RCTs included quality of life assessments (9;11;12).

The US study reported by Rai (9) claimed to assess patients' quality of life by way of monitoring transfusion requirements, performance status and the incidence of infection. No data was reported regarding transfusions or performance status. On retrospective review of patient notes, 16% of the 170 patients who received fludarabine evaluated for adverse events and 9% of the 178 patients who received chlorambucil had major infections.

The German study, by Eichhorst et al (12) compared fludarabine with chlorambucil in older patients (>65) using the EORTC QLQ-C30 questionnaire. It has yet to report any quality of life data.

The EORTC QLQ-C30 questionnaire (version 2.0) was also used in the UK CLL4 study. Initial results on the first treatment year were presented at the ASH annual meeting in 2005 (15;16). All patients were asked to complete the questionnaires at the start of therapy (baseline), at 3, 6, and 12 months, and annually thereafter. Statistical significance was determined by the use of ANOVA. Patient compliance was high with 599 questionnaires completed at baseline, 557 at 3 months, 559 at 6 months and 470 at 12 months corresponding to 77%, 74%, 77% and 78% of those who had so far reached the time period and remained alive (Updated data from February 2006 are shown in Table 25). Quality of life results were the same for each treatment group at baseline and at 12 months and they correlated with quality of response. Further analyses of quality of life parameters are likely to become available within the next year.

Table 23: Mean QoL Scores by Treatment Group

		Functioning Scales					
		Physical	Role	Emotional	Cognitive	Social	Global Health
	No.	B 12M	B 12M	B 12M	B 12M	B 12M	B 12M
Chl	175	81 78	74 75	75 78	83 82	79 77	66 69
F	92	82 82	72 74	80 81	82 82	80 79	64 68
FC	94	80 77	77 73	78 81	85 82	82 76	66 68
	361						

Table 24: Mean QoL Scores by Response to Treatment

	No.	Functioning Scales					Global Health
		Physical	Role	Emotional	Cognitive	Social	
		B 12M	B 12M	B 12M	B 12M	B 12M	B 12M
CR/NPR	159	84 84	76 80	78 84	86 85	82 83	67 73
PR	125	79 76	73 73	78 78	82 79	80 77	63 68
NR/PD	56	77 74	71 61	74 74	81 79	74 65	65 60
	340		p=0.02	p=0.03			p=0.002

Abbreviations: B = baseline; 12M = 12 months.

P-values compare response groups with respect to the change in scores from baseline to 12 months.

Table 25: Questionnaires Completed by Each Patient Feb 06

Questionnaires Completed	No. patients	% patients
0	<i>AIC information removed</i>	<i>AIC information removed</i>
1 or more	<i>AIC information removed</i>	<i>AIC information removed</i>

Table 26: Questionnaires Completed at Each Time-Period by early Feb06

Time Period	Completed	% Completed of those expected to date
Baseline	<i>AIC information removed</i>	<i>AIC information removed</i>
Month 3	<i>AIC information removed</i>	<i>AIC information removed</i>
Month 6	<i>AIC information removed</i>	<i>AIC information removed</i>
Year 1	<i>AIC information removed</i>	<i>AIC information removed</i>
Year 2	<i>AIC information removed</i>	<i>AIC information removed</i>
Year 3	<i>AIC information removed</i>	<i>AIC information removed</i>
Year 4	<i>AIC information removed</i>	<i>AIC information removed</i>
Year 5	<i>AIC information removed</i>	<i>AIC information removed</i>

Time Period	Completed	% Completed of those expected to date
Total	<i>AIC information removed</i>	<i>AIC information removed</i>

Figures in brackets are for patients who remain alive (not reported to have died) by the time-period in question.

2.6. *Meta-analysis*

58. Where more than one study is available consideration should be given to undertaking a meta-analysis. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate the trial results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate
- Tabulate and/or graphically display the individual and combined results.

Seven studies were identified reporting results relevant to this review. Six of these studies were available in abstract form only. Abstracts generally do not report sufficient information to act as a basis for formal meta-analysis. A meta-analysis has not been performed within this review.

A meta-analysis was attempted by Zhu et al (86), comparing fludarabine with alkylator-based regimens including single-agent chlorambucil. The findings concluded that 'fludarabine as an induction agent for patients with CLL yields a better clinical response with acceptable toxicity when compared with alkylator-based therapy, but without survival benefit by 5 – 6 years of follow up.'

Despite criticisms of the inclusion of abstracts of some studies, and inconsistencies in approach to trial inclusion, when Richards (87) appraised the above meta-analysis, it was considered likely that the conclusion that complete response rates are higher with fludarabine than standard dose chlorambucil is robust. It was also agreed that for survival, the result was inconclusive.

A sensitivity analysis using pooled response data from all the RCTs is reported in the economic analysis reported in section 3 of this document.

2.7. *Indirect/mixed treatment comparisons*

59. In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest consideration should be given to using indirect/mixed treatment comparisons. Give a full description of the methodology used and provide a justification for the approach.

Not applicable

2.8. *Comparative safety*

60. Give a brief overview of the safety of the technology compared to the comparator(s). Give incidence rates if appropriate.

Evidence from comparative trials and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate a relative lack of adverse effects commonly associated with the comparator or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are primarily designed to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to incidence of an adverse effect) these should be reported here in the same detail as described previously (section 3) for efficacy trials.

In the meta-analysis (86), comparing fludarabine with chlorambucil and other alkylator-containing regimens, it was shown that fludarabine was a well-tolerated chemotherapy with an acceptable level of toxicity. This is the general conclusion from many reviews of the literature and non-randomised studies (72;88-91).

The fludarabine-cyclophosphamide combination has also been found to have an acceptable toxicity profile (21), although it causes more haematological toxicity, infections (although no statistically significant difference in symptomatic infection) and gastrointestinal toxicity than the fludarabine single-agent regimen.

Haematological Toxicity

The meta-analysis (86) highlighted the fact that patients treated with fludarabine experience more severe myelosuppression i.e. thrombocytopenia and neutropenia, but that the difference was not statistically significant. Anaemia did not appear to be any more frequent or severe with fludarabine than chlorambucil, CHOP or CAP. More hospitalisations for neutropenia were reported in the fludarabine and fludarabine-cyclophosphamide arms in the recent LRF CLL4 study, but less thrombocytopenia and significantly less haemolytic anaemia in the FC treatment group (11), which may have an impact on overall costs of therapy. Severe myelotoxicity was more frequent in the fludarabine-cyclophosphamide arm, particularly neutropenia, in the German CLL4 study(1).

Table 27: Haematological toxicity reported in RCTs comparing fludarabine with chlorambucil or other combination regimens

Study		Patients with Grade III-IV events, %			
		Fludarabine	Chlorambucil	FC	
Catovsky 2005* (11)	Neutropenia	40 all grades	29 all grades	55 all grades	
	Thrombocytopenia				
CLL4 Patient level data ITT, n=720 (2006) (18)	Neutropenia	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
	Thrombocytopenia	11 all grades	12 all grades	15 all grades	
CLL4 Patient level data in analysis, n=777 (2006) (18)	Neutropenia	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
	Thrombocytopenia	12 all grades	13 all grades	16 all grades	
Eichhorst 2006# (1)	Neutropenia	26.7	-	55.5	P<0.001
	Thrombocytopenia	12.7		15.6	
Rai 2000# (9)	Neutropenia	27	19	-	P=0.08
	Thrombocytopenia	13	14		P=0.81

*WHO toxicity grades

CTC Common Toxicity Criteria

Autoimmune Haemolytic Anaemia (AIHA)

There is much debate around whether fludarabine triggers haemolytic anaemia in more patients than other therapies, and whether this is more severe. Regardless of whether patients have received treatment, autoimmune complications such as autoimmune haemolytic anaemia (AIHA) are a recognised feature of CLL, although AIHA is more common among treated patients (92). Relevant to this review, AIHA has been reported in patients treated with alkylating agents, and purine analogues (92).

In the UK CLL4 trial (93) where newly diagnosed CLL patients were randomised to fludarabine, chlorambucil or fludarabine-cyclophosphamide treatment arms, AIHA was reported in 9/123 (7.3%), 23/218 (10.5%) and 3/129 (2.3%) patients respectively. When patients were analysed according to direct antiglobulin test (DAT) status, AIHA was found to occur more frequently after chlorambucil than after fludarabine or fludarabine-cyclophosphamide, in both groups, especially in DAT positive cases. The incidence of AIHA was significantly lower in patients receiving the fludarabine-cyclophosphamide combination and, coupled with the observation that 7 out of 9 patients who were DAT positive at study entry changed to DAT negativity, the authors suggest a protective role for this combination.

A lower incidence of AIHA was also reported in the fludarabine-cyclophosphamide combination arm, when compared to fludarabine single agent, in the German CLL4 study (73). No conclusions on the severity of AIHA could be drawn, although two patients died of AIHA complications following treatment with fludarabine.

Infections

Infections have not yet been reported separately for CLL4 but toxicity data show a trend of increasing percentage of patients with febrile episodes associated with Fludara and FC although the difference is not significant (chlorambucil 26%; fludarabine 28%; FC 36%). In the US study (9) comparing fludarabine with chlorambucil, the risk of severe infection was lower with chlorambucil (grade 3 or 4 in 9% patients) than with fludarabine (grade 3 or 4 in 16% of patients); this difference was statistically significant. However, Karlsson et al, using a higher dose of chlorambucil than Rai et al, concluded that there was no difference in infections between fludarabine and chlorambucil with the percentage of patients experiencing NCI grade II-IV infections being 25% and 28% for fludarabine and chlorambucil respectively (14).

When compared with CHOP, fludarabine was found to have comparable immunosuppressive toxicity (77).

The German study group (1) found that the number of severe infections and opportunistic infections was similar across the fludarabine and fludarabine-cyclophosphamide arms. Other studies (13;21) report a higher incidence of infections with the FC combination; however these studies both use a higher dose of cyclophosphamide than CLL4 or the German study.

A separate analysis, comparing fludarabine treatment in younger (<66yrs) and older patients (>65yrs) (12) found a similar incidence and severity of infections in both groups.

Many clinicians advocate prophylaxis against opportunistic infections, in order to reduce infection risk with fludarabine or fludarabine-cyclophosphamide regimens.

Non-Haematological Toxicity

Studies including the fludarabine-cyclophosphamide regimen, report more gastrointestinal effects than is typically observed in fludarabine-treated patients. For example, the German study group (1) reported nausea, vomiting, mucositis and gastritis in 5.8% patients receiving the FC combination whereas these effects were observed in only 1.7% patients treated with fludarabine single-agent. A similar effect was noted in the UK CLL4 study (11) and also a higher rate of alopecia was noted with FC than with fludarabine or chlorambucil in the CLL4 study.

2.9. *Interpretation of clinical evidence*

61. Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The CLL4 study, as the pivotal source of evidence for the decision problem, is highly relevant as the protocol was written largely to help answer the problem, ie. whether fludarabine, either alone or in combination with cyclophosphamide, offers a superior therapy option (in terms of overall survival, response rate, duration of response, toxicity and QoL) compared to chlorambucil in first-line CLL (11). It is the largest study in this patient population and 88% of the 777 evaluable patients are from the UK. (11) For these reasons it has been used as the principle data source on outcomes and resource use for the *de novo* economic assessment in section 3.

Data on a further 1,300 patients entered into RCTs are available in the first-line CLL population treated with either chlorambucil or fludarabine +/- cyclophosphamide. With the exception of one study where the response rate for the 69 patients in the fludarabine arm was equal to that of chlorambucil (10), the studies have shown consistently higher responses in the patients treated with fludarabine containing regimens than in those treated with chlorambucil. As in CLL4 these studies have also collected outcomes of direct relevance to patients with CLL, eg response rates, durations of response (progression-free survival) and toxicity(1;9;11-14).

As yet, none of the studies have shown a significant overall survival benefit over chlorambucil since the data are not mature enough or the studies were not powered to show a difference. However, significant improvements in progression-free survival and time without treatment, which are associated with a better quality of life for patients (15;16), are consistently observed with fludarabine containing regimens (1;9;11-14).

A higher level of toxicity is associated with fludarabine and FC than chlorambucil but when patient QoL has been directly measured in the trial setting, it has shown a similar level for all three treatments (15;16).

62. Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, issues relating to conduct of the trial versus clinical practice or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

There is no reason to believe why the patients selected for CLL4 will be any different to those expected in clinical practice in England & Wales. Clinical guidelines produced at the time CLL4 was recruiting specified that eligible patients (i.e. ineligible for transplant and no contraindication to fludarabine) be offered entry into the study (7). If patients did not wish to be randomised, the guidelines state that fludarabine and chlorambucil remain as options. The dose of fludarabine used in CLL4 is the same as that specified in the SPC.

3. Cost effectiveness

3.1. *Published cost-effectiveness estimates*

3.1.1. Identification and description of studies

63. Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced and the rationale for any inclusion and exclusion criteria used should be provided.

The search strategy aimed to identify analyses, either published or unpublished, describing the cost-effectiveness of the initial treatment of Chronic Lymphocytic Leukaemia with chlorambucil, fludarabine or fludarabine plus cyclophosphamide.

64. The specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter).

Searches were undertaken in

- Medline via Pubmed
- Embase via Datastar
- OHE HEED (Health Economic Evaluation Database)
- NHS Economic Evaluation Database (NHS EED)
- Cochrane Library 2005, Issue 4

In addition the reference lists of relevant articles were hand searched

65. The date the search was conducted

The search for cost-effectiveness data was performed in January 2006

66. The date span of the search

No date restriction was placed on the search

67. The complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)

Search strategies for MEDLINE, EMBASE, and the Cochrane Library are presented in Appendix 2. Textwords used to search OHE HEED and NHS EED were: 'fludarabine', 'CLL', 'chronic lymphocytic leukaemia', 'chronic lymphocytic leukemia', WITH 'cost', 'cost-utility', 'cost-effectiveness', 'economic', 'quality of life', or 'utility'.

68. Details of any additional searches, for example searches of company databases. Include a description of each database

None

69. The inclusion and exclusion criteria

In anticipation of there being a limited amount of data the inclusion criteria were left intentionally wide in the initial search, i.e. any document that included a relevant search term was considered. This resulted in the identification of 115 possible titles. 14 duplicates were removed leaving 101 titles for screening. 94 titles were then rejected leaving 7 abstracts. Four abstracts were rejected and 3 full papers obtained (5;94;95). A further 4 papers were identified from hand searching (17;96-98). These 7 papers were reviewed and 5 rejected (See Table 28).

Ultimately only two papers were found that reported on the cost-effectiveness of fludarabine in comparison to chlorambucil in the first-line treatment of CLL, and gave sufficient detail to inform the decision problem; these were the West Midlands HTA Collaboration report by Hancock et al (5) and an earlier DEC report by Best et al (17).

Figure 2: Summary of cost effective study selection and exclusion

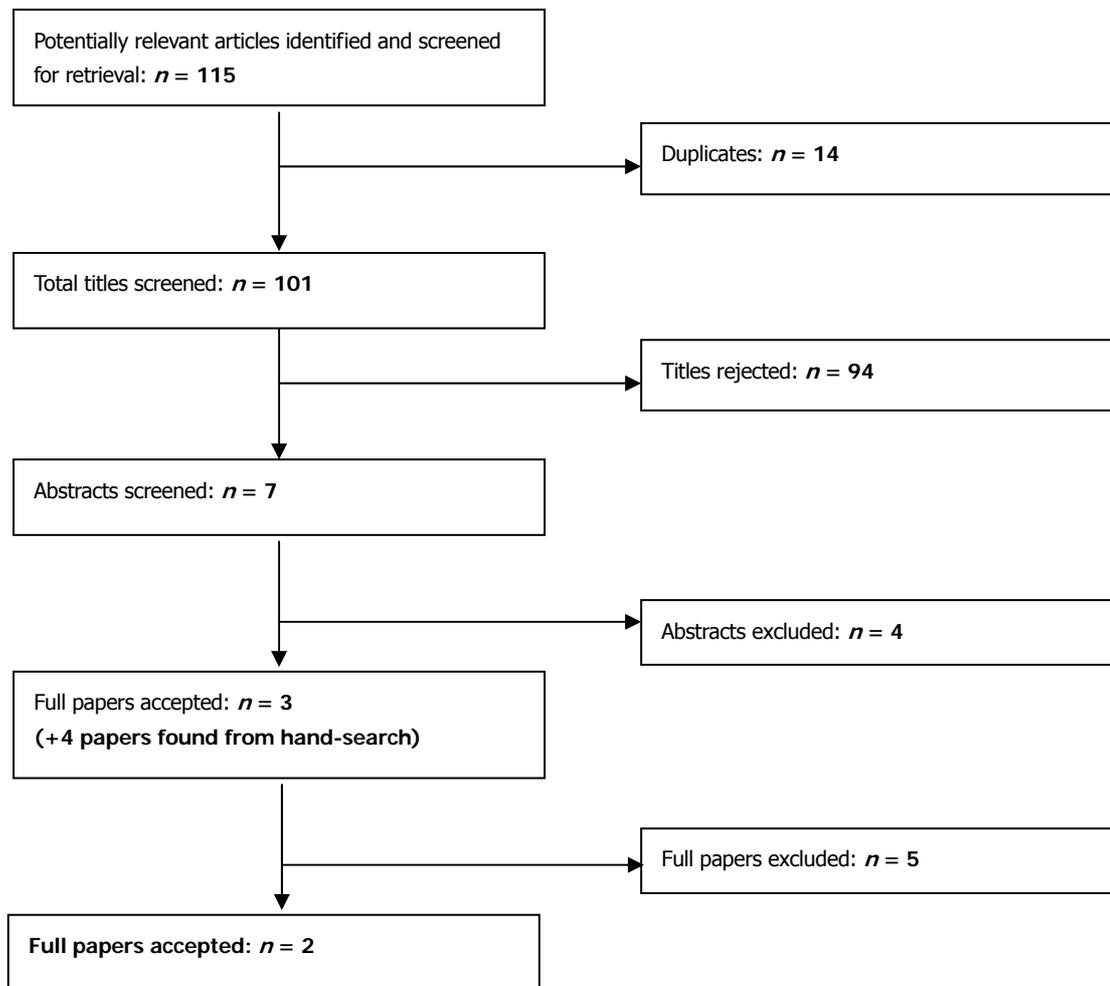


Table 28: Full papers rejected

Reference	Reason for exclusion
Marchetti M, Barosi G, Liberato LN. Fludarabine for chronic lymphocytic leukemia. (2001) N Engl J Med. 344: 1166–1167. (96)	Italian study which was not relevant to the UK. Only a short editorial provided. Could not validate conclusions because of the limited information.
Mason JM, Drummond MF, Bosanquet AG, Sheldon TA. (1999) The DiSC assay. A cost-effective guide to treatment for chronic lymphocytic leukemia? Int J Technol Assess H Care. 15:173–184.(94)	Neither fludarabine nor chlorambucil was the focus of this research. Research focused on DiSC assay.
Redaelli A, Stephens JM, Laskin BL, Pashos CL, Botteman MF. (2003) The burden and outcomes associated with four leukemias: AML, ALL, CLL and CML. Expert Rev Anticancer Ther;3(3):311-29. (97)	Review of other studies, most of which focused on cost-identification and cost comparison.
Stephens JM, Gramegna P, Laskin B, Botteman MF, Pashos CL. (2005) Chronic lymphocytic leukemia: economic burden and quality of life: literature review. Am J Ther. 12(5):460-6. (95)	Review of other studies most of which focused on cost-identification and cost comparison.
Weeks JC, Tierney MR, Weinstein MC. (1991) Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. N Engl J Med. 325:81–86.(98)	Neither fludarabine nor chlorambucil was the focus of this research. The cost effectiveness model created focused on intravenous immune globulin and a theoretical control group.

70. The data abstraction strategy.

Narrative descriptions of the two studies that considered the cost-effectiveness of the decision problem are provided in section 3.1.2.

3.1.2. Description of identified studies

71. Please provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales.

1. The WMHTAC report

A report considering the effectiveness and cost-utility of fludarabine as first-line therapy for the treatment of CLL was published in 2002 by the West Midlands Health Technology Assessment Collaboration (WMHTAC) as Hancock et al (5). Hancock *et al's* search identified

five comparative clinical trials but only one (9) compared fludarabine to the UK-relevant first-line therapy chlorambucil. Furthermore, they found no useful, previously conducted economic evaluations of fludarabine in first-line CLL. Due to the then lack of available data on which to base an evaluation, the authors stated that their intention when deciding to construct a simple economic model was, "as much to indicate the impact of uncertainty as to provide definitive estimates of cost-utility" (pp 33).

Hancock *et al*/used a simple decision analytical model to compare fludarabine and chlorambucil with respect to three health states:

- Death
- Survival with disease progression and
- Progression-free survival

For the base case comparison a three-year time frame was chosen. Utility estimates for the health states of 'progressive disease' and 'progression-free' were made on the basis of an earlier study in the QoL of oncology (99) and the authors' own assumptions. A one-way sensitivity analyses was conducted to estimate the impact of uncertainty on the base-case estimates. On average, over three years Hancock *et al*/estimated that:

- Fludarabine treatment results in 1.9 QALYs
- Chlorambucil treatment results in 1.82 QALYs
- A gain of 0.08 QALY is achieved at a cost of £3830
- Incremental Cost per QALY of £48,000

The estimates in the sensitivity analyses found that fludarabine treatment can vary from being inefficient to justifiable in terms of cost utility.

The authors recommended that the use of fludarabine as first-line therapy for CLL was 'borderline' because of the relatively high cost per QALY. The study had several limitations which should be noted:

- Information on key aspects of effectiveness and cost was limited. The cost analysis did not consider costs arising from adverse events in chlorambucil treated patients; it also did not quantify the costs saved by treatment producing more frequent responses and responses of longer duration in terms of delay for further treatment;
- The cost estimates for fludarabine in the first-line setting are questionable because they were based on second-line use;
- Dosing schedules were fixed when the reality of clinical practice is that these will change depending on response;
- The exact resource commitment and cost of treating side effects was not conducted.

Hancock *et al*/concluded that there were continuing areas of high uncertainty around the balance between oral and iv administration of fludarabine, AE rates, survival, QoL and costs. They recognised that the then on-going CLL4 trial was a major study which could inform future estimates by answering many of the issues surrounding uncertainty,

particularly the balance of AEs to increased response rates.

2. Wessex DEC report

An earlier report which investigated the economic impact of fludarabine in first-line CLL was published in 1995 by The Development and Evaluation Committee (DEC) of the South and West Regional Health Authority (17). The authors of this report assessed the cost-effectiveness of iv fludarabine used for first-line, second-line, and heavily pre-treated patients, with that of chlorambucil plus prednisone (C+P). Only the data on first-line patients are presented here as these relate to the decision problem of this STA.

We did not have access to the methodology appendices supporting the report by Best et al but some details on the methodology used to estimate QALY gains were provided in the WMHTAC report by Hancock et al. It appears that the single effect incorporated into the cost-utility estimate was an increase in time free of progressive disease after treatment (32 months vs 24 months, for fludarabine and chlorambucil + prednisone respectively). Using an approximation of the utility associated with remission as 0.96, and with disease as 0.81, and estimates of proportions achieving remission as 74% and 77% for fludarabine and chlorambucil + prednisone respectively, QALY gains of 0.29 and 0.23 were suggested, again for fludarabine and chlorambucil + prednisone respectively.

Table 29: Key values from the Wessex DEC

	Fludarabine iv	C+P
Cost of therapy	£6810	£410
Health gain (compared to no treatment)	0.29 QALYs	0.23 QALYs
Cost per QALY	£23,480	£1,780

The Wessex report concluded that it could not be proven that fludarabine is more cost-effective than current first-line treatment (chlorambucil + prednisone). However, there are several shortcomings of the report:

- Since no RCT data comparing fludarabine with chlorambucil were available at the time the report was written, the effectiveness data were drawn from case series or used just one relevant arm taken from studies against other, inappropriate comparators;
- The basis of the utility estimates is unclear. From the report it is not apparent how the measurements were derived;
- The study did not report the incremental cost-effectiveness of fludarabine compared to C+P;
- The analysis did not consider the use of oral fludarabine;
- A standard duration of treatment was used with no account for response rate, ie. in clinical practice patients will receive treatment until the best response is achieved.

Conclusion of economic evaluation

The literature on the QoL and cost-effectiveness of first-line treatments for CLL is very limited. There are no published, robust evaluations of the cost-effectiveness of fludarabine or FC as first-line treatments for CLL in comparison with chlorambucil. The evaluation studies by Hancock et al and Best et al were constructed from a UK clinical practice perspective but were limited by the lack of available data at the time of their publication. With the completion of CLL4 and other RCTs in the first-line setting there are now more extensive and appropriate data sources on which to base economic evaluations.

3.2. *De novo economic evaluation*

72. In the absence of a relevant published economic evaluation, manufacturers should submit their own economic evaluation.

The lack of published and robust cost-effectiveness analyses that considered the decision problem meant that a new evaluation was required for this submission. In recent years several large RCTs investigating the efficacy of chlorambucil, fludarabine and FC have been completed and reported (1;9-14) (see clinical section). Of these studies the largest, and most applicable to UK clinical practice, is the LRF CLL4 study by Catovsky et al. This was also the only RCT identified that compared all three treatments within the same study and therefore it was considered the most appropriate on which to base any new economic modelling. To date, this study has been published only in abstract form (11;15;16;74).

Aware of the importance of the data from this study in answering the decision problem, the owners (UK NCRI CLL Trials Group and the Adult Leukaemia Working Party) kindly made the patient-level clinical data available to Schering. Broadly, the data supplied encompassed: treatment given, adverse events, response rates and quality-of-life. These data were available for all 783 patients from initial randomisation until second-line treatment, end of follow-up, or death, depending on which occurred first. Furthermore, a micro costing study was undertaken (CLL4 audit – see Appendix 9) on a sample of 113 patients from CLL4 which was used to inform the costing of the whole study thereby ensuring that the costs and the effectiveness data were drawn from the same source. Further details are given in the description of the model (section 3.28).

3.2.1. A note on the Reference Case

73. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'Reference Case' (see NICE 'Guide to the Methods of Technology Appraisal'). Reasons for deviating from it should be clearly explained. Particularly important features of the reference case include:

Attribute	Reference case	Comment on whether de Novo evaluation meets reference case requirements
Comparator(s)	Alternative therapies including those routinely used in NHS	Met: Chlorambucil is the most widely used first-line therapy in the NHS with over 60% of patients receiving the drug.
Perspective costs	NHS and PSS	Met: Direct NHS costs considered
Perspective benefits	All health effects on individuals	Met: QALY benefits to treated patients are considered

Form of EE	CEA	Met: Incremental cost-utility analysis undertaken
Time horizon	Sufficient to capture differences in costs and outcomes	Met: Lifetime to account for subsequent treatments
Synthesis of evidence	Systematic review	Base case uses results from most relevant single study. A systematic review of other studies relevant to the decision problem was undertaken to populate a sensitivity analysis
Outcome measure	QALYs	Met: QALYs estimated
Health states for QALY measurement	Described using a standardised and validated instrument	Not met: Baseline utility was taken from a study using the EQ-5D in patients with NHL (the NHL study also used the EORTC QLQ-C30 instrument which was used in CLL4; this allowed a baseline comparison). However, utility values for the states of progressive disease and progression-free disease were based on previous economic evaluations in the literature. Sensitivity analysis showed that the cost-effectiveness ratio was not highly sensitive to the utility estimates
Benefit valuation	Time Trade Off or Standard Gamble	
Source of preference data	Sample of public	
Discount rate	Health benefits and costs 3.5%	Met: QALYs and costs discounted at 3.5%
Equity	No special weighting	Met: No special weighting
Sensitivity analysis	Probabilistic sensitivity analysis	Met: PSA included

3.2.2. Technology

74. How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

Table 30: Frequency and duration of therapies used in the CLL4 study and economic evaluation

In the model fludarabine is used alone or in combination with cyclophosphamide for the first-line treatment of CLL in patients with Binet stage A progressive disease or Binet stage B or C (see question 75 for details of included patients and licensed indication). Dosing within the evaluation is that used in the CLL4 study. Frequency and duration of treatment are given in Table 30.

Therapy	Dose per cycle	Per protocol Duration
chlorambucil	10mg/m ² per day for 7 days. Repeated every 4 weeks	Repeat until maximum response is achieved, or up to one year (exceptionally treatment could continue for a few more months if beneficial response continuing)*
fludarabine	IV 25mg/m ² per day for 5 days, or Oral 40mg/m ² per day for 5 days. Repeated every 4 weeks	Minimum of 3 months and maximum of 6 (exceptionally patients experiencing continuous response may receive up to 8 months)*
FC	IV F 25mg/m ² plus Cyclo 250mg/m ² per day for 3 days or, Oral F 24mg/m ² plus C 150mg/m ² per day for 5 days. Repeated every 4 weeks	Minimum of 3 months and maximum of 6 (exceptionally patients experiencing continuous response may receive up to 8 months)*

*Patients showing no response or progressive disease after 3 cycles should be discontinued.

Fludarabine is administered under the supervision of an expert physician in a specialist setting. Concomitant treatments are individualised to the requirements of the patient and include hospital contacts, scans and investigations and medications to prevent and manage adverse events. These concomitant activities are typical of chemotherapies but the cost is potentially substantial. To quantify these costs an audit of resource use in a subgroup of patients included in the CLL4 study was conducted (see section 3.2.9) and is fully described in Appendix 9.

3.2.3. Evaluation design and structure

- **Patients**

75. What group(s) of patients is /are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the decision problem; in other words, specify the data-gap.

In the SPC fludarabine is indicated for:

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment with fludarabine should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C) or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

Contraindications are:

- Hypersensitivity to fludarabine phosphate or to any of the excipients
- Renal impairment with creatinine clearance < 30 ml/min
- Decompensated haemolytic anaemia
- Pregnancy and lactation

The main data source for the model was the CLL4 study. In the CLL4 study inclusion was permitted for:

All patients with B-cell CLL, previously untreated, diagnosed by a persistent lymphocytosis (greater than $10 \times 10^9/l$) and bone marrow infiltration of at least 40%, who require treatment, with stage A progressive, stage B or stage C disease using the International (Binet) Staging System.

The CLL4 study excluded:

- Patients with other life-threatening diseases; eg cancer;
- Patients unwilling or unable to give informed consent;
- Renal failure (creatinine clearance < 30 ml/min);
- Hepatic enzymes and bilirubin greater than twice the upper limit of normal, unless due to CLL;
- Pregnant women or women at risk of pregnancy;
- Patients who for other reasons are not expected to complete the study;
- Patients with a diagnosis other than CLL after central review of markers and morphology.

Potential differences between the main data source used and the indicated population that

might influence the relevance of the analysis are therefore:

1. The study allowed enrolment of patients with Binet stage B without progressive features who are not covered by the licensed indication
2. The study did not allow enrolment of patients with hepatic impairment who might be included in the licensed indication.

Expert clinical opinion is that these differences do not have a significant impact on the relevance of the data source to usual practice in the UK (Personal communication with Prof D Catovsky).

76. Was the analysis carried out for any subgroups of patients? If so, how was this subgroup identified, what clinical information is there to support the biological plausibility and how was the statistical analysis undertaken?

The following subgroup analyses were conducted:

- Patients aged above or below 65 years of age
- Grade of disease at baseline.

Subgroup analysis by age was conducted to explore whether the benefits of more intensive therapy differ in elderly patients who may have additional comorbidity and more limited ability to benefit from treatment. The cut-off of 65 was chosen as it divides the analysed population approximately in half (48.9% of patients in CLL4 eligible for analysis and used in the model were aged ≥ 65). Furthermore, the German CLL studies (1;12) used the age of 65 as a cut-off between 'younger' and 'elderly' patients.

Disease stage at baseline is a strong predictor of survival and hence is likely to affect capacity to benefit from therapy (7).

Subgroup analysis was conducted using the patient level data from the CLL4 study. Confidence intervals were generated for subgroups using probabilistic sensitivity analysis and non-parametric bootstrapping.

77. Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

The CLL4 study and other current research consider the role of genetic assays in identifying patients at high risk of rapid disease progression. These data are not available for all the CLL4 patients and we were therefore not able to explore these factors at this stage. In addition, these assays are not yet used in routine practice. Subsequent research into the implications of allowing treatment to be guided by these markers would be appropriate as data continue to emerge.

Previous analyses have found the cost-effectiveness of oral fludarabine, in the second-line treatment of CLL, to be better than that of the iv (33). This is a logical conclusion given that the oral formulation is associated with less administration costs than iv and has been shown to have similar efficacy (33;90;100;101). The difference between iv and oral fludarabine was not considered in this analysis as a meaningful comparison could not be made between patients in CLL4 receiving each formulation because:

- a) In the CLL4 study, patients were not randomised to either oral or iv to allow a valid comparison.
- b) CLL4 opened in 1999, which was 2 years before the availability of oral fludarabine, but by the end of recruitment in 2004 91% of patients were receiving treatment from the oral formulation. Between 1999 and 2004 the profile of patients entered into CLL4 changed. This was because older patients and those with a poorer prognosis were entered when patients were able to receive the oral therapy. This led to a fall in the response rates seen in the study, which was mirrored by a fall in the response rates in the patients receiving chlorambucil (see Table 31) (74;102).

Table 31 : CR/nPR Rates in CLL4 by Year

	1999/2000	2001/2002	2003/2004
Chlorambucil (n=327)	33%	30%	22%
Fludarabine (n=173)	45%	47%	37%
FC (n=173)	68%	56%	63%

It should be noted that because the base case analysis draws both its effectiveness and cost data from the CLL4 patient-level data, any variability in effectiveness and costs between iv / oral fludarabine is accounted for.

To test the impact of the entry criteria on the reported results a sensitivity analysis considers the CLL4 cohort split into subgroups by Binet stage, ie. A progressive, B or C. However, it was not possible to consider the subgroup difference between patients with Binet stage B (as recruited in to CLL4) and those with Binet stage B with disease-related symptoms (as specified within the licence for fludarabine) as the CLL4 CRF only recorded whether patients were Stage A progressive, stage B or stage C. Expert opinion was that this difference would not make a meaningful difference.

78. At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation on initiation of first-line therapy and leave on death. There is no difference between treatment arms in the way the data are handled on exit and entry.

3.2.4. Comparator technology

79. What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the information provided in Section X of your submission.

The comparator therapy is chlorambucil. This is currently the most widely used drug (+/- prednisolone) for the first-line treatment of this patient group (8) (61% projected patients) in the NHS and is the comparator in the CLL4 study (See section 1.1). Fludarabine monotherapy and FC are the next most widely used first-line treatments in the UK, representing 16% and 8% of projected treated patients respectively (8).

3.2.5. Study perspective

80. Did the perspective reflect NICE's Reference Case? If not, how and why did it differ?

The analysis considers costs to the NHS and health benefits to patients. No information was available on costs relating to Personal and Social Services (PSS) and therefore these costs were not included in the analysis.

81. What time horizon was used in the analysis and what was the justification for this choice?

A time horizon of 260 twenty-eight day cycles (approximately 20 years) was used in the model.

This is appropriate because:

- i) CLL is an incurable disease with a mean age of diagnosis of 64 and a median survival of 10 years. The majority of patients have died within the time horizon of the model.
- ii) Therapy naïve CLL patients receiving chemotherapy typically relapse after a period of time and may go on to receive second-line therapy and often third-line or 'salvage' treatments. The response to, and choice of, subsequent therapy is in part driven by prior treatment. A lifetime model allows us to consider not only the first-line treatment but the expected effect this has on subsequent therapy.

3.2.6. Framework

- **Model-based evaluations**

82. Please provide the following.

- **Description of the model type.**
- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

- **A list of all variables that includes their value, range (distribution) and source.**
- **A separate list of all assumptions and a justification for each assumption.**

Description of the Model

The model is a Markov model with 260 cycles, each of 28 days, to give a time horizon of approximately 20 years. The model divides treatment into a maximum of three “lines” of chemotherapy, followed by final disease progression and death. The choice of therapies and structure of the model was informed by current guidelines, consultation with clinical experts, and the design of the CLL4 study (see Key Assumptions and question 86). A schematic of the model depicting the states and directions of travel is provided in Figure 3.

Patient pathway through the model

The model structure for patients treated at first-line with chlorambucil, fludarabine monotherapy or FC is as follows:

Patients enter the model on initiation of first-line treatment. They remain in this state for the period of time for which their first-line chemotherapy continues.

Patients are then divided between those who have a response of 12 months or more and patients who do not achieve this level of response. (This distinction is made because the CLL4 protocol and guidelines indicate that patients with a duration of response of 12 months or longer are eligible for re-treatment with the same agent as was originally used.)

Among patients who achieve a response of 12 months or longer (“responders”), the following path is followed after first-line treatment ends:

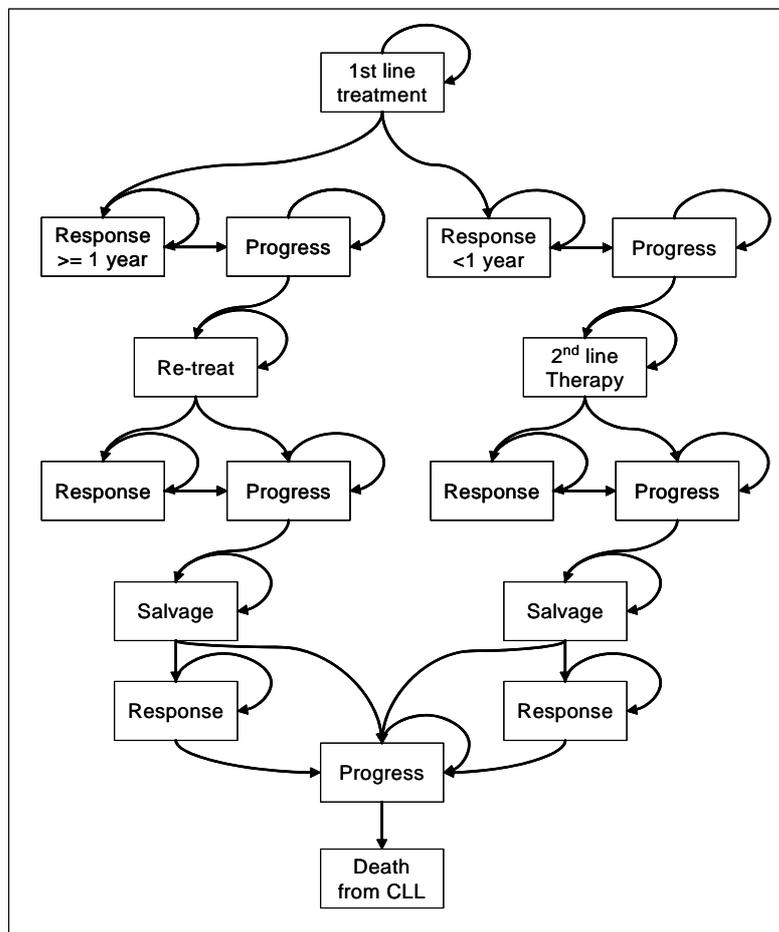
- Patients remain in a “response” state for a number of cycles. Patients then experience disease progression and move into a “progress” state.
- After a period of time in the “progress” state, patients receive their second chemotherapy. In accordance with the CLL4 protocol, these patients are re-treated with the agent that was used for their original chemotherapy (state “re-treat”).
- Patients remain in the “re-treat” state for a number of cycles determined by the duration of therapy. Patients then move from this state into either a “response” state or go direct to a “progress” state. Those patients that achieve a response remain in the “response” state for a number of cycles before also moving into the “progress” state.
- Third-line (termed salvage) therapy is then initiated. As for second-line therapy patients remain in the therapy stage for a number of cycles and then may either respond or progress. Responders spend a number of cycles in the response state before experiencing progression.
- The model assumes that, after remaining in the “progression” state following their third-line of therapy, patients will ultimately die from their CLL.

Patients who do not achieve at least 12 months duration of response follow a similar path to the "responders", but the second-line treatment received is not a repeat of the first-line therapy given.

Background mortality

Patients may transition to death at any time, in addition to death following progression after salvage therapy (not shown in schematic). Non-CLL mortality used was the unweighted average of males and females:
 (http://www.gad.gov.uk/Life_Tables/Interim_Life_Tables.htm)

Figure 3: Schematic of model



NB:

- 1) The mixture of treatments used for the 'Salvage' state is the same for all treatment arms.
- 2) The 'Response' state in this model is comparable with the 'progression-free' or 'remission' states described in previous models (eg, Hancock et al) (5)

Variables in the Model

The variables required to populate the model are:

- The therapies to be included at each line for each of the three treatment options, including first-line treatment and subsequent treatments.
- The length of time spent receiving each chemotherapy
- The likelihood of achieving a response of at least 12 month's duration at first-line, or the overall response rate for subsequent treatments
- The time spent in the response state for each treatment
- The time from progression to subsequent treatment (progression is defined as 'relapse' in the CLL study protocol, for description see Table 17: Study endpoints from CLL4)
- The amount of time spent between final progression and death from CLL
- Non-CLL mortality
- The cost and utility value associated with each state.

The variables used in the model are presented in Table 32, Table 33, Table 34 and Table 35.

Table 32: Treatments used: 1st line and subsequent treatment strategies

Strategy name	F 1st line	CLB 1st line	FC 1st line
Therapy used as:			
First-line	Fludarabine	Chlorambucil	FC
Re-treatment for responders	Fludarabine	Chlorambucil	FC
2nd Treatment	FC	Fludarabine	CHOP
Salvage	Mixed*	Mixed*	Mixed*

FC = combination therapy with fludarabine and cyclophosphamide

*A combination of therapies identified in the literature that have been used to treat fludarabine-refractory or relapsed patients (for details see question 97).

Table 33: Inputs: first-line treatment

Initial treatment	Fludarabine	Chlorambucil	FC	Source
Cycles received, median	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	CLL4 patient level data
Cycles received, mean	5.3	6.8	4.6	
Response rate (%)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
Time in response state (months)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	
Cost per cycle of chemotherapy (£)	1060	188	779	CLL4 audit (Appendix 9)

Table 34: Inputs: Subsequent treatments

Variable	Treatment	Value	Source
Response rate	F re-treatment	74%	Keating, Blood 92(4):1165-71
Response rate	C re-treatment	35%	Montserrat, Cancer 56:2369-75
Response rate	FC re-treatment	<i>AIC information removed</i>	Assumed equal to 1st line (no data)
Response rate	FC after F	54%	Pooled analysis of O'Brien JCO 19:1414-20; Keating, Blood 92(4):1165-71 (21;91)
Response rate	F after C	68%	Johnson; Lancet 347 (25):1432 ff; (71) Catovsky, (103)
Response rate	CHOP after FC	39%	Leporrier, Blood 98 (8): 2319 ff (77)
Response rate	Salvage	22%	Keating, Leukemia and Lymphoma 43(9):1755-762 (104)
DOR (months)	All re-treatment		Assumed equal to 1st line (no data)
DOR (months)	FC after F	20	O'Brien JCO 19:1414-20, (21)
DOR (months)	F after C	10.7	Johnson; Lancet 347 (25):1432 ff, (71)
DOR (months)	CHOP after FC	5.9	Johnson; Lancet 347 (25):1432 ff, uses CAP as approximation for CHOP, (71)
DOR (months)	Salvage	18	Keating, Leukemia and Lymphoma 43(9):1755-762 (104)
Cost per patient	F after C	3714	NICE second-line appraisal
Cost per cycle	FC after F	779	Assumed equal to 1st line (no data identified)
Cost per patient	CHOP after FC	2886	NICE second-line appraisal (105)
Cost per patient	Salvage	3241	Hutchinson et al 3rd line therapy (113 episodes) (106)

Table 35: Inputs: other

Parameter	Value	Source
Time between progression and treatment (months, median) (applied to first, second and salvage therapy lines)	<i>AIC information removed</i>	CLL4 patient level data
Cost per month not actively treated (£)	85.96	CLL4 audit (Appendix 9)
Utility values		
Receiving treatment	0.74	Doorduijn (107)
In response	0.80	Median of values available in the literature (see Q.99)
Progressive disease	0.60	Median of values available in the literature (see Q.99)

Assumptions in the model

Overall survival

The CLL4 dataset found that patients treated with FC at first-line experienced longer progression-free survival than patients receiving chlorambucil. However, at this stage of follow-up expert advice has indicated that we should assume for the model that overall survival with F, FC or chlorambucil are equal because the data are not sufficiently mature to show any differences. Therefore, the base case model took a conservative approach and assumed that overall survival was the same for all groups. In order to model this it was necessary that the time from first progression to death was shorter in patients who have received F or FC at first-line than it was with those who received chlorambucil. The model handled this by assuming that any gain in median progression-free survival associated with F or FC was offset by an equal decrease in median survival after final progression.

Progression through states and mortality

The model assumed that patients will progress through all lines of therapy before dying as a consequence of their CLL. Non-CLL related mortality does however occur throughout the model. Non-CLL mortality used was UK age specific all-cause mortality (http://www.gad.gov.uk/Life_Tables/Interim_Life_Tables.htm).

Response to re-treatment with the same therapy in responders

One paper was identified in the literature that reported a response rate for re-treatment with fludarabine (91), which found a response rate of 74%. One paper was identified in the literature that reported a response rate for re-treatment with chlorambucil (108), which found a response rate of 35%. No papers were identified that reported response rates for re-treatment with FC. We therefore assumed in the base case model that response on re-treatment with FC was the same as that on initial treatment. As these estimates are based

on limited data they are varied in sensitivity analyses.

Second-line treatment

Current BCSH guidelines indicate that on failure of chlorambucil, fludarabine, FC or CHOP should be considered. In the base case our model assumed that fludarabine would be used as this is recommended by NICE and is the most widely used second-line therapy after chlorambucil (8). We did consider the effect of chlorambucil failures moving to FC in a sensitivity analysis.

Patients failing fludarabine first-line are assumed to receive FC in the model. Since FC is the most active treatment in the first-line setting it was considered appropriate to use after fludarabine which is the next most active therapy.

The BCSH guidelines do not indicate a specific treatment on relapse after responding to FC at first-line. Therefore, on the advice of experts, and following the CLL4 protocol, we assumed patients would receive CHOP following FC failure.

Salvage therapy

The mix of 'salvage' therapies was assumed to be the same for all patients reaching this stage in the model, regardless of their prior therapies.

Disutility associated with side effects of treatment

The QoL decrement associated with treatment in the model was the same for all treatments received, as no significant differences between treatment arms were found in CLL4 (15;16) (see questions 95 and 101). This assumption was tested in the sensitivity analysis.

83. Why was this particular type of model used?

A Markov model was chosen to simulate the transitions of a hypothetical cohort of CLL patients from the point at which they present for a first CLL treatment until death. A Markov model represents a convenient way of modelling chronic disease where patients pass through a series of well defined and mutually exclusive health states.

84. What was the justification for the chosen structure/how was disease progression represented?

The four main health states in the model include: 1) receiving treatment, 2) in response to treatment, ie. progression-free, 3) having disease which is progressing, and 4) death. These seek to represent the main stages of the disease whilst providing the necessary flexibility to model the different treatment strategies and undertake the sensitivity analysis.

CLL is an incurable disease of elderly patients that can be controlled but not, in general, cured by chemotherapy. Chemotherapeutic agents have the ability to induce progression-free intervals but none has been shown to increase overall survival, which may be extended for patients with early stage disease. Relapse after treatment is expected and patients will experience a sequence of different therapies before death. It appeared consistent with this disease pathway to have a model which:

- Followed patients from decision to treat until death
- Included the costs and benefits of subsequent treatments as well as initial therapy
- Considered treatment to be a sequence of options in which prior chemotherapy influences suitability for subsequent treatment.

85. Is this consistent with a coherent and currently accepted theory of disease progression?

The analysis was consistent with current BCSH guidelines for patients with CLL in whom transplant is not appropriate.

86. What were the sources of information used to develop and inform the structure of the model?

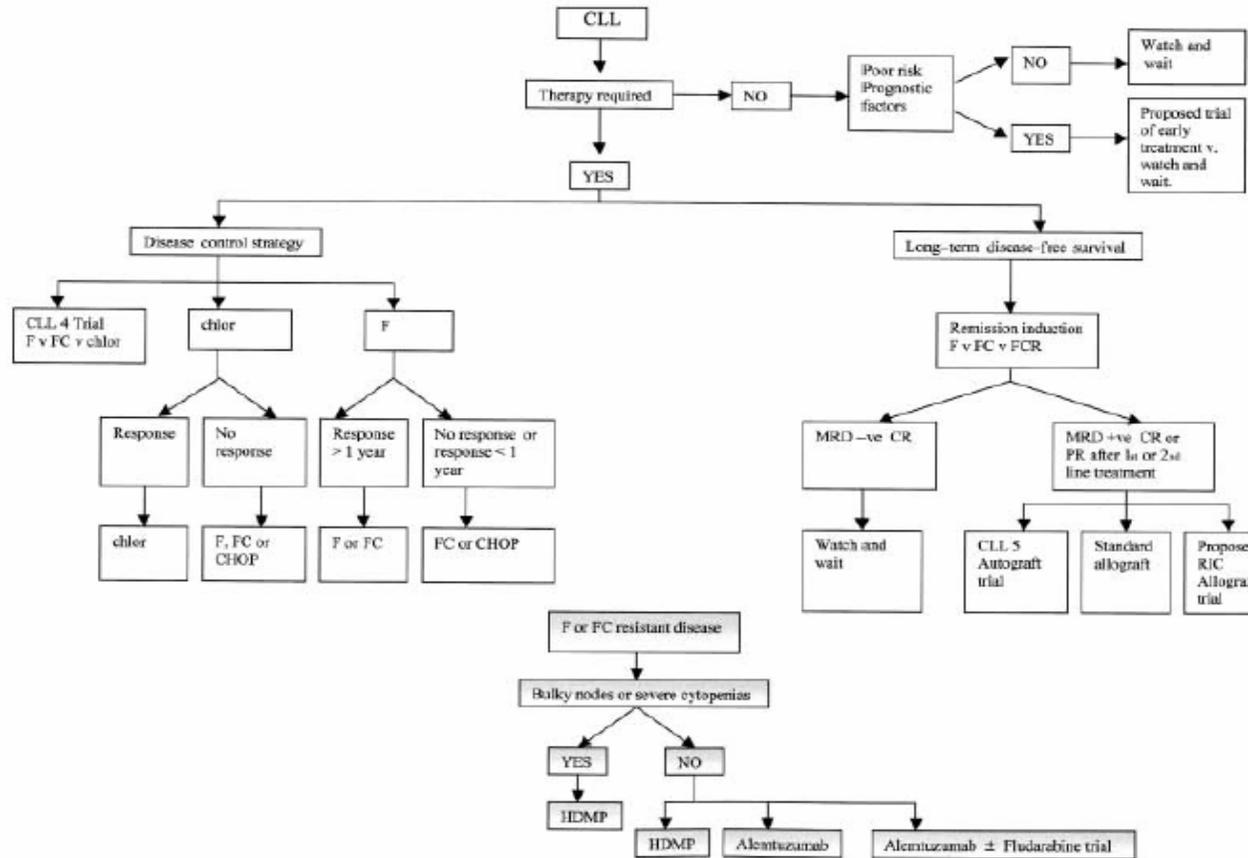
The BCSH guidelines on the diagnosis and management of chronic lymphocytic leukaemia (7) include a treatment algorithm (Figure 4). In these guidelines, patients with CLL are initially divided between those for whom therapy is or is not required. For around 20% of patients where therapy is required, transplantation is an option with the goal of achieving long-term progression-free survival. The modelling analysis described in this document relates to patients for whom therapy is required but who are not eligible for transplant.

As enrolment in to the CLL4 study is the recommended treatment in the BCSH guidelines, the protocol for CLL4 was also used to inform the model design. Features of the CLL4 protocol relevant to the model design include:

- Random allocation of patients to chlorambucil, fludarabine or FC at baseline;
- Instruction that for patients who relapse after a response lasting one year or longer, the initial therapy given may be repeated provided it was well tolerated and without major toxicity.

It is noted that enrolment into CLL4 is now closed and that, pending the results of CLL4, new guidelines will be issued.

The BCSH guidelines were also used to inform the subsequent treatments considered in the model (with the advice of experts on what to use after FC has been used first-line).



Source: British J Haematology; (7)

87. What other structures/measures of disease progression could have been used to inform the structure of the model? Why were they rejected?

Simpler model structures that do not consider the impact of subsequent treatments have been used in previous evaluations (5;17). However, as CLL is an incurable disease whereby patients will receive several lines of chemotherapy, it was considered more appropriate to model over the patient's lifetime from initiation of treatment until death.

The assumed second-line and subsequent treatments offered to patients were consistent with BCSH guidelines. However, as the decision problem was focused on first-line treatment, we simplified the model by not modelling specific treatments in the salvage setting. The BCSH guidelines specify that HDMP (high-dose methylprednisolone) and alemtuzumab may be indicated for fludarabine or FC resistant disease, depending on symptom severity or the presence of bulky disease. In the base case model, data from a single large data series of 147 patients who were refractory to fludarabine or Fludara-containing regimens were used (104). In this study patients received 7 categories of treatment ranging from purine analogues in alkylator combination to 'miscellaneous lymphoma combinations'. As a sensitivity analysis a search was conducted to identify all published studies reporting response data in heavily pre-treated 'salvage' CLL patients; a weighted average of response rates and durations of response was then calculated and used in the model (see question 97).

To capture all treatment options and possible patient pathways would have involved making many assumptions on the proportions of patients moving from one particular therapy to the next. In the absence of any satisfactory data to inform this approach, and to avoid over complication of the model, we simplified the choice of specific treatments according to the guidelines and expert opinion as described below:

- We simplified the number of options in the model by not modelling the option of patients who fail first-line treatment with chlorambucil progressing to receive CHOP.
- For patients who respond to fludarabine at first-line, re-treatment with fludarabine monotherapy and FC are both consistent with BCSH guidelines. Our model used fludarabine monotherapy, as this follows the CLL4 protocol.
- Patients failing fludarabine first-line are assumed to receive FC in the model as this is the most active first-line therapy and is consistent with the BCSH guidelines. However, CHOP could also have been considered as this also consistent with BCSH guidelines.

Overall survival was not used as an outcome measure in this model because survival data from the CLL4 study are not sufficiently mature to show a survival gain associated with fludarabine or FC over chlorambucil.

88. Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model was designed to provide a comprehensive description of the relevant aspects of the disease progression from start of treatment until death. These aspects were validated with expert clinical opinion.

89. For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

Each cycle is 28 days long. This duration was chosen as the time required to conduct one full cycle of treatment. Patients receiving chemotherapy receive differing numbers of chemotherapy cycles according to regimen and response. A cycle length of 28 days allows this to be accurately reflected in the model.

90. If appropriate, was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was not used in the model. Given the large number of cycles and the short cycle length in the model it is likely that any inaccuracy introduced due to no half-cycle correction is small.

91. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and why are they justified? In particular what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The CLL4 trial data were used to populate the first-line treatment in the model. Data were available from CLL4 on when patients progressed or received re-treatment.

Although follow-up of patients from the CLL4 trial continues, adequate data are not yet available to populate the parts of the model relating to second-line or subsequent treatments given, response to second-line therapy or to mortality. Clinical outcomes from this stage onwards were based on clinical guidelines and efficacy data from published literature as described in section 3.2.7; questions 97 and 82. Cost data for second-line treatment were based on the previous NICE appraisal of fludarabine (105) and costs for salvage treatments were based on the literature (106).

Because the CLL4 data are not currently mature enough to estimate survival differences the model assumes that higher response rates and longer progression-free survival with fludarabine and with FC will not translate into extended overall survival. In the base case the model assumes that patients treated with FC and F will experience more rapid subsequent mortality and hence that the effectiveness difference observed will be progressively lost over time. This assumption is subject to sensitivity analysis.

- **Non-model-based economic evaluations**

- Was the evaluation based on patient-level data from a clinical trial or trials?

The economic analysis was based on patient-level clinical data from CLL4 for first-line treatment and response, and modelled data from a review of the literature for second-line and subsequent treatments (see section 3.2.7, question 97).

The cost data for first-line treatment were based on a subset of the CLL4 patients (see section 3.2.9). The costs of second-line treatments were based on the existing NICE technology appraisal of fludarabine (33) and the costs of third-line treatments were based on a published paper (106).

Quality of life was measured directly in CLL4 using a descriptive instrument (EORTC QLQC-30) and utility estimates were obtained from the literature (see section 3.2.8).

- Provide details of the clinical trial, including the rationale for its selection.

The CLL4 study compared chlorambucil, fludarabine monotherapy and FC therapy in the management of patients with previously untreated CLL at Binet stage B, C or A with progressive features. The study was conducted primarily in the UK and ceased recruitment in late 2004: follow-up continues. The results of the CLL4 study are reported in sections 2.3 and 2.5 (Summary details of RCTs & Results of the comparative RCTs) and a description of the study is presented at the end of section 2.4 (Critical Appraisal).

The CLL4 study was selected as a basis for this analysis because:

- It is the largest study of chlorambucil, fludarabine and FC so far conducted in previously untreated CLL;
- The only study to directly compare all three treatments within the same RCT
- The study was conducted predominantly in the UK and so is likely to be relevant to the population of England and Wales;
- Data were available from a resource use audit of a subgroup of the CLL4 patients to allow detailed costing to be conducted;
- Patient-level data from the study were made available to us to allow us to develop a detailed model of the consequences of treatment.

- Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Of 783 patients enrolled entered in CLL4, 6 were excluded before randomisation (11), and a further 57 (See Table 19) were excluded from the analysis as no treatment was received; treatment received was not the same as that randomised; or no data were available to allow us to determine whether treatment was in fact received. These patients are

described in the description of the CLL4 trial (See clinical section and Table 19: Drop outs and missing data in the patient level data).

Among patients who are known to have had received their randomised treatment, the amount of missing efficacy data was very small (0.4% of the sample). Formal imputation was not performed and a complete case analysis was conducted.

Follow-up of the CLL4 study continues and the majority of patients are still alive. Survival data are therefore censored for the majority of included patients.

- Were relevant data collected for all patients in the trial? If data were collected for a subgroup of patients in the trial, how were the data extrapolated to a full trial sample?

The effectiveness analysis was conducted using all patients for whom sufficient data were available.

A detailed micro costing analysis was conducted on a subgroup audit of 113 patients enrolled in the CLL4 study. Detailed data were collected on chemotherapy received, physician and hospital visits associated with chemotherapy and with adverse events, scans and tests performed and concomitant medicines received. Individual patient costs were calculated by multiplying resource use by UK unit costs.

The cost data were extrapolated to the full sample by the following method: The mean number of cycles of treatment received in the audit in the chlorambucil, fludarabine and FC arms were *AIC information removed* and *AIC information removed* cycles and in the whole modelled dataset *AIC information removed*, and *AIC information removed* cycles per patient respectively. To correct for this difference a regression analysis was conducted in the audit dataset to estimate per patient cost as a function of the number of cycles of each chemotherapy received. The findings of this analysis were used to estimate cost per cycle of treatment for the wider patient group.

The cost audit is summarised in section 3.2.9 and described in full in appendix 9.

3.2.7. Evidence

1. Clinical evidence

Where relevant, answers to the following questions should be derived from and consistent with, the clinical evidence section of the submission. Cross references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

92. How was the baseline risk of disease progression estimated (also state which treatment strategy represents the baseline)?

Chlorambucil was the baseline treatment strategy, and was compared with fludarabine monotherapy and with FC therapy. Since observed patient-level data from the CLL4 dataset were used to populate the model there was no need to estimate a risk of disease progression.

93. How were the relative risks of disease progression estimated?

Relative rates of disease progression were taken from the first-line CLL4 patient-level data for chlorambucil, fludarabine and FC.

When patients were censored or had started second-line treatment a Markov process was developed to simulate the likely clinical pathway for these patients after they were no longer observed. The structure and inputs for this Markov process are described in question 82 and the methodology for obtaining the clinical response data is summarised in question 97.

94. Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The observed patient-level data from CLL4 were sufficient to establish the response rate for the three therapies. Progression-free survival (PFS) was estimated by assuming that the risk of progression after censoring was the same as that in the observed period. The model subsequently estimated the number of cycles patients spent in each of the model states. As no evidence currently exists of a difference in overall survival between treatments, we assumed that any gain in PFS associated with fludarabine or FC in comparison to chlorambucil, would be offset by more rapid progression later on (see question 82: Key Assumptions).

Quality adjusted life years were estimated by multiplying the proportion of randomised patients in each state in each time period by a utility estimate for that state (see section 3.2.8 for description of health state valuation).

95. Were the health effects of adverse events associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

A significant difference in QoL was not found between the different treatments in CLL4 (15;16). This indicates that any potential differences in the type of adverse events associated with each therapy do not, when taken together, result in a substantially different overall impact on QoL. Therefore, in the base case analysis the same utility value is used for all patients during treatment. However, it was observed that during the first three months of therapy with fludarabine and FC there was a trend towards lower QoL which was not observed in the chlorambucil patients (15); the effect of accounting for this was explored in a sensitivity analysis (see section 3.4.2).

96. Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Personal consultation on the general model structure was sought from Professor D Catovsky (Lead Investigator of the CLL4 study) and Professor P Hillmen (Chairman of the CLL Trials sub-group of the NCRI [National Cancer Research Institute]). The main areas where expert opinion was utilised were:

1. The generalisability of the CLL4 study population to the licensed indications for fludarabine and FC
2. Advice on how to model overall survival
3. Assumptions on re-treatment rates and suggestions on ranges of sensitivity analyses
4. Advice on the proportion of patients continuing to receive chlorambucil in the event that FC became the recommended first-line treatment for CLL.

Specific points where expert opinion has been used to inform the economic evaluation are referenced throughout this submission. No formal elicitation methods were required or used. Advice on interpretation of the QoL data collected in CLL4 was provided by M Else of The Institute of Cancer Research.

97. What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

No data were available about the response of the CLL4 patients to second-line and subsequent therapy. The resulting assumptions were therefore made:

Response to second-line therapy

The choice of second-line therapy will be influenced by the choice and response to initial treatment. It is known from previous reviews of the literature (109) that many published studies of second-line treatments contain confounding factors in the study population, such as a variety of prior treatments or more than one line of prior treatment.

Patients who received chlorambucil as their first-line therapy and had a response

(progression-free survival) \geq 1 year were re-treated in the model but those whose response was $<$ 1 year were assumed to receive fludarabine as their second-line treatment. The authors and experts were not aware of any significant new studies investigating the second-line use of fludarabine in recent years (the focus of research has been on first-line use) and therefore the pivotal data supporting the existing NICE Technology Appraisal were used as the source of effectiveness. These data, published by Johnson et al, are for patients with a mean of 1.2 prior therapies and exclude prior exposure to anthracycline-containing regimens; overall response rate was 48% (71). These data were validated by a more recent single arm study using fludarabine oral, where patients with a mean number of 2 prior therapies exhibited a 51.3% overall response rate (100).

Patients who received fludarabine as their first-line therapy and had a response (progression-free survival) \geq 1 year were re-treated in the model but those whose response was $<$ 1 year were assumed to receive FC as their second-line treatment. As with fludarabine monotherapy, there was very little data on the use of FC in this setting since the focus of research is on its use as a first-line therapy. One study was identified in the literature that reported response to FC in patients that were refractory to fludarabine with or without alkylating agents; the response rate was 38% in this poor prognosis group (21).

Patients who received FC as their first-line therapy and had a response (progression-free survival) \geq 1 year were re-treated in the model but those whose response was $<$ 1 year were assumed to receive CHOP as their second-line treatment. At the time of the NICE TA of fludarabine in second-line CLL in 2001 (33) there were no data on the use of CHOP in second-line CLL. Since then there has been one study published (77) that, although principally designed to investigate first-line treatments, included a cross-over group of fludarabine to CHOP. This study was therefore used as source for response rates for CHOP following FC.

Response to salvage therapy

In contrast to the use of fludarabine and FC as second-line treatment we were informed by the experts that there were many studies investigating new agents such as alemtuzumab in salvage patients, ie. those refractory to fludarabine and fludarabine-containing regimens. To inform the modelling of this patient group we therefore undertook a literature search to identify response data. The search involved screening papers and abstracts identified through interrogation of the PUBMED, American Society of Hematology (ASH) (2003-2005) and American Society of Clinical Oncology (ASCO) (2003-2005) databases.

Search terms used were 'relapsed' or 'refractory' 'CLL' with 'fludarabine', 'alemtuzumab', 'rituximab', 'CHOP', 'cladribine', 'cyclophosphamide', or 'CAP'.

Study inclusion criteria were:

- Clinical trial of therapeutic agent or combination of therapeutic agents - excluding transplantation and splenectomy

- Published after 1995 (Pubmed search limit)
- Included patients with fludarabine-refractory or relapsed CLL
- Evaluation of efficacy or effectiveness comprised at least one of the following outcomes - response rate /duration of response
- Studies based on marketed products (products commercially available in the UK and used to treat CLL but not necessarily licensed for CLL, eg rituximab) as at February 2006.

No randomised-controlled studies were identified in this specific patient population. The large majority of the published trials are phase II studies, many with a dose-escalation design. In addition, most studies have heterogeneous study populations.

Papers were excluded for the following reasons:

- No separate data/analysis for fludarabine-refractory subgroup
- Treatment initiated for patients with specific conditions such as Richter's syndrome or autoimmune haemolytic anaemia
- Dose-escalation studies, with the exception of the studies where a given dose level accounted for at least 90% of all included patients or when separate outcome analysis was provided for each dose level
- Studies involving patients previously treated with CAMPATH or rituximab
- Studies where the treatment did not reflect the usual practice in EU.

A total of 56 articles were identified and 39 papers / abstracts were selected for inclusion in the review and estimation of response rates in the salvage setting (See appendix 10). Of these studies, one was considered as appropriate for the base case analysis as it was the largest and patients had received a median of 3 prior regimens (104). However, it did not contain a large proportion of patients treated with alemtuzumab and therefore a sensitivity analysis was undertaken using a pooled analysis of all 39 studies.

3.2.8. Measurement and valuation of health

98. Which health benefits were measured and how was this undertaken?

The main health benefit assessed was Quality Adjusted Life Years (QALYs). QALYs were calculated by estimating the difference in utility associated with progressive disease and patients experiencing a response. The proportion of patients experiencing a response, combined with the duration of that response, compared to those who did not respond or progressed after an initial response, gave us the expected utility gain associated with a therapy.

The previous NICE Technology Appraisal of fludarabine measured the health benefit of treatment in terms of the 'cost per year in remission' (33). In order to explore if the results of this current analysis, using the more encompassing QALY approach, were driven by the method or the new data, we undertook a simple analysis using cost per year in remission.

99. Which health benefits were valued? How and why were these values selected? What other values could have been used instead?

Overview

Utility is estimated according to the three main states in the model: 1) receiving treatment, 2) in response, and 3) progressive disease.

The quality of life data from the CLL4 study were generated from a descriptive instrument (EORTC-QLQ-C30) and, as such, did not provide preference-based utility data that could be entered directly into the model. An open and comprehensive search was therefore undertaken to identify appropriate data. The literature search uncovered a handful of articles. Applying criteria relating to methodological robustness and data applicability, utility estimates are taken from two papers: 1) Doorduijn et al (107), and 2) Hancock et al (5). In the base case, the model uses the baseline value cited in Doorduijn et al for patients "receiving initial treatment" (0.74). For the "in response" and "progressive disease" health states values from Hancock et al are applied (0.8 and 0.6, respectively). All values are varied in the sensitivity analysis

Methods

Quality of life was measured in the CLL4 study using the EORTC QLQ-C30 (version 2.0). This instrument was administered at the time of starting chemotherapy (baseline), at 3 months, at 6 months, at 12 months and annually thereafter. No statistically significant difference between groups was reported in mean quality of life values (15;16). However, a significant difference was found in the change in quality of life over baseline between patients according to response status (see Table 36).

Table 36: QoL findings from CLL4 study

Response status	N	EORTC – CRC 30 Global QoL		
		Baseline	12 month	Change from baseline
Complete response / nodular PR	181	67	72	+5
Partial response	152	65	69	+4
No response / progressive disease	66	66	60	-6

The quality of life data from CLL4 were generated from a descriptive instrument and therefore did not provide preference-based utility data that could be entered directly into the model. A search was therefore undertaken to investigate if appropriate data were

available in the literature. In anticipation of there being very little available data the search was left intentionally wide and terms were:

1. QUALITY-OF-LIFE
2. EQ5D
3. EORTC ADJ QLQ-C30
4. QLQ-C30
5. EUROQOL
6. (Quality ADJ of ADJ Life)
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. CHRONIC-LYMPHATIC-LEUKEMIA#.DE OR B-CELL- LEUKEMIA#.DE.
9. CLL.TI,AB.
10. CHRONIC ADJ LYMPHOCYTIC ADJ (LEUKEMIA OR LEUKAEMIA).TI,AB.
11. (8 OR 9 OR 10).TI,AB.
12. LYMPHOMA#.W..DE.
13. LYMPHOMA
14. (12 OR 13).TI,AB.
15. 11 OR 14
16. 15 AND 7

A schematic of the search strategy is shown in Figure 5. The search identified 418 hits which were screened at the title stage and any article that was not obviously 'quality of life', 'CLL' or 'lymphoma' related was rejected (eg. neurological malignancies and AIDS related to lymphomas).

The remaining 90 abstracts were then reviewed to see if they specifically mentioned quality of life as a measure being studied or reported, which resulted in 40 abstracts. 30 abstracts were rejected (see appendix 10), leaving 10 papers for review. Of the 10 papers reviewed two had been identified in the clinical search (90;110). Three papers relevant to QoL in CLL, which we were already aware of but were not found in this search, are also included in Table 37 (5;15-17).

Figure 5: Quality of Life in CLL and Lymphoma search strategy

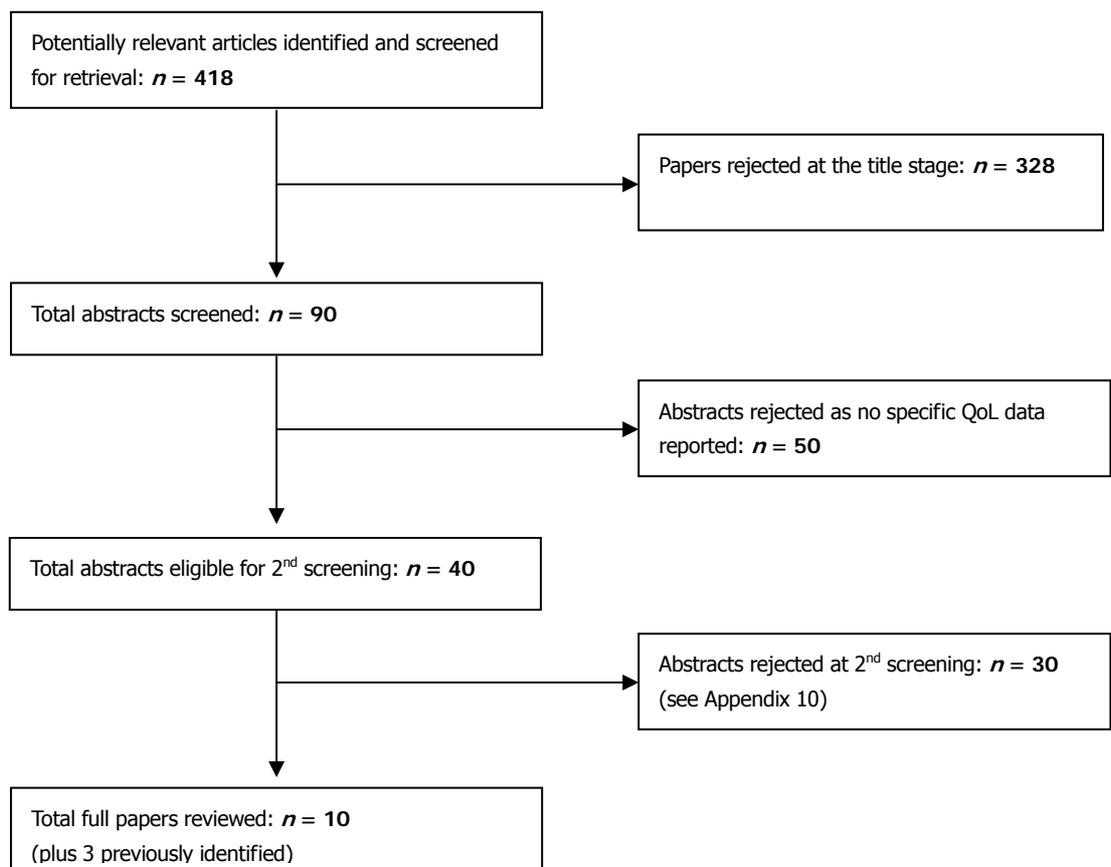


Table 37: Quality of Life Papers Reviewed

Author	Title	Comment
Best et al 1995 (17)	Fludarabine in the treatment of chronic lymphocytic leukaemia	Included utility estimates – (also identified in economic search)
Doorduyn et al 2005 (107)	Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy	Included QLQ C-30 and EQ-5D although patient population was not CLL
Else et al 2005 (15;16)	Quality of Life in the LRF CLL4 Trial (abstract / poster)	Included QLC-C30 data (CLL4 QoL previously identified in clinical search)
Goor et al 2005 (111)	Economic assessment on the management of chronic lymphocytic leukemia	Economic review that mentions QoL. No new data (did not appear in earlier search on cost-effectiveness as was added to database after search)
Hancock et al 2002 (5)	Fludarabine as first line therapy for chronic lymphocytic leukaemia	Included utility estimates (also identified in earlier economic search)
Holzner et al 2001 (99)	Quality of life measurement in oncology - A matter of the assessment instrument?	Included baseline QLQ-C30 score for CLL patients
Holzner et al 2004 (112)	Quality of life of patients with chronic lymphocytic leukemia: Results of a longitudinal investigation over 1 yr	Included baseline QLQ-C30 score for CLL patients
Hyde et al 2002 (110)	Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: A technology assessment	Investigated cost-effectiveness of fludarabine in second-line CLL. A review of previous studies to inform the NICE appraisal of fludarabine against CHOP. No new QoL data presented
Klasa et al 2002 (113)	Randomized phase III study of fludarabine phosphate versus cyclophosphamide, vincristine, and prednisone in patients with recurrent low-grade non-Hodgkin's lymphoma previously treated with an alkylating agent or alkylator-containing regimen	No details of QLQ-C30 scores reported
Molica 2005 (27)	Quality of life in chronic lymphocytic leukemia: A neglected issue.	Review with no specific values reported
Redaelli et al 2003 (97)	The burden and outcomes associated with four leukemias: AML, ALL, CLL and CML	Review with no additional values to those reported in other papers
Rossi et al 2004(90)	Efficacy and safety of oral fludarabine phosphate in previously untreated patients with chronic lymphocytic leukemia	Reported that with oral fludarabine there is no negative impact on QoL as measured with the QLQ-C30
Stephens et al 2005 (95)	Chronic lymphocytic leukemia: Economic burden and quality of life: Literature review	Review with no additional values to those reported in other papers

No new studies (ie. additional to those previously found in the clinical and economic searches (5;17) [Hancock et al 2002, Best et al 1995]) reporting utility estimates in CLL were identified. One of the recent reviews (95) (Stephens et al) confirmed our findings in that they identified only 8 articles and concluded that, 'The literature on the quality of life

of CLL patients is very limited'. Two studies by Holzner et al (99;112) (Holzner 2001 and 2004) reported a mean global quality of life score (Measured with the EORTC QLQ-C30) in CLL that was very close to the baseline value reported in CLL4 (64.9 [from Holzner 2001 & 2004] vs 65.5 [mean baseline from CLL4]). The Holzner papers confirmed that the baseline QLQ-C30 values seen in CLL4 were reasonable but did not help us any further in estimating corresponding utility values from CLL4.

Table 38: Selected results from Doorduijn et al, patients with low or low-intermediate NHL at baseline

However, a key paper was found that described a recent study in the Netherlands, which reported the impact of chemotherapy on quality of life using both the EORTC QLQ-C30 and EQ5D in patients with Diffuse large B-Cell NHL (107) (Doorduijn 2005). HRQoL results from Doorduijn et al are presented in Table 38.

	Utility measured by EQ-5D (mean)	QLQ-C30 Global QoL (mean)
Baseline (n=63)	0.74	65
Change from baseline, patients progression-free at 10 months (n=31)	+0.04	+7
Change from baseline, patients at progression (n=13)	-0.24	-18
At progression – progression-free	0.28	25

Patients in the Doorduijn study were divided into those with low or low-intermediate aaPI (age-adjusted International Prognostic Index) and high-intermediate or high aaPI. The mean age of all the patients (n=128) was higher than those in CLL4 (72 v 64) and there were less males (56% vs 74%). In the group with low or low-intermediate aaPI NHL this study reported mean utility at baseline of 0.74, that mean utility among those progression-free at one year had increased by 0.04 over baseline, and that utility at progression had fallen by 0.24 from baseline. The mean QLQ-C30 global QoL measure was found to be 65 at baseline (on a scale of 1 to 100), to have increased by 7 points over baseline among those progression-free at one year and to have fallen by 18 points from baseline among patients assessed at progression.

In comparison, baseline QoL measured by QLQ-C30 in the groups in the CLL4 study ranged between 65 and 67 points. Change over baseline to 12 months in patients reported to be responders was an increase in 4 points in patients with a partial response and 5 points in patients experiencing complete response. Unfortunately, no measure in CLL4 is directly comparable to the assessment "at progression" in the study by Doorduijn et al so direct mapping between the CLL4 and Doorduijn studies was not possible. However, the Doorduijn study does suggest that a 0.28 difference in utility between progression and progression-free states can be experienced in elderly (65-84 years) patients with a haematological malignancy.

A key driver of cost-effectiveness in the model is the difference in utility between response and progression. The Doorduijn cohort appears similar to the CLL4 population in terms of baseline QLQ-C30 global health score, and Doorduijn is also the only published source of utility measures generated from patients (using the EQ-5D) that we are aware of. In the absence of published baseline utility data in CLL this has been used as a proxy for patients with CLL at baseline in the economic model. The Doorduijn cohort is however for patients with diffuse large B Cell NHL and are therefore not truly reflective of CLL. For this reason the utility values from Hancock et al are used for the "response" and "progression" states. Using the Hancock values was felt appropriate since these are the median of the three options. These values are tested in the sensitivity analysis.

Table 39: Utility estimates from UK studies

Source	Hancock et al (5)	Best et al (17)	Doorduijn et al (107)	Model base case
Base line	-	-	0.74	0.74
Utility value response	0.8	0.96	0.78	0.80
Utility value, progressive / active disease	0.6	0.81	0.50	0.60
Difference	0.2	0.15	0.28	0.20

100. Were health benefits measured and valued in a manner that was consistent with NICE's Reference Case? If not, which approach was used?

Data providing direct assessment of utility in CLL patients using a validated preference based instrument, as recommended in the reference case, were not available. After a review of the literature, the most appropriate utility data, for establishing a baseline value, appear to be those generated in the Doorduijn et al study. These data are based on EQ-5D responses collected from patients who are elderly, suffering from a lymphoproliferative malignancy and who have a similar Global EORTC QLQ-C30 score at baseline to those in CLL4. To obtain utility data for the states of response to therapy and progressive disease we had to refer to previous estimates used in cost-effectiveness analyses. Sensitivity analysis explores the range of available utility estimates.

101. Which possible (dis)health benefits were excluded from the evaluation (for example, adverse events of treatment)?

Possible survival benefit was excluded because data are not yet mature enough to show a survival gain associated with fludarabine or FC over chlorambucil. Treatment specific disutility has not been considered in the base case as no significant differences between arms in quality of life have been found in the CLL4 study. The published QoL data from CLL4 suggest that any change in quality of life over baseline during the treated period is small.

The base case model allows for a small drop in quality of life during the treatment period (first 3 months) reflecting treatment related toxicity. However, in the CLL4 study it was found that there was no such drop in the chlorambucil arm (although the difference between chlorambucil and fludarabine and FC was not significant) (15). Therefore the impact of removing any utility decrement associated with chlorambucil during the treatment phase was considered in a sensitivity analysis.

102. If health benefits were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health benefits were expressed in QALYs.

3.2.9. Resource identification, measurement and valuation

103. What resources were included in the evaluation (the list should be comprehensive and as disaggregated as possible)?

The following data points were considered.

Chemotherapy

Drugs used; Cycles, route of administration and dose given; Inpatient days, out-patient and day-case visits for administration and follow up; Reasons for dose change and course of treatment less than 3 cycles

Monitoring

Laboratory tests; Biopsies; X-rays/MRIs/scans; Other tests

Medications for prophylaxis

Antibiotics (divided between cheap, medium, and expensive medicines); G-CSF (Growth colony stimulating factor); Blood products; Antivirals (IV and oral); Antiemetics (IV and oral); Vaccines; Other medication

Surgery

Any CLL related surgery

Resource usage of serious adverse events related to chemotherapy

Occurrence; WHO Grade; Relation to therapy; Duration/outcome; Treatment (drugs / visits / setting / tests)

Follow-up

Hospital contacts; investigations and medications related to CLL after the end of treatment.

104. How were the resources measured?

Medical resource use data were collected from a sample of 113 patients included in the CLL4 study. Data were abstracted from patients' medical records from their date of inclusion into the CLL4 study until the earliest of: i) death, ii) initiation of second-line chemotherapy treatment, or iii) the day of data abstraction. To maximise sample size, patients whose treatment was continuing at the time of data collection were included in the study. (Further details can be found in appendix 9).

105. Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

The resources were measured from a sample of 113 patients from the CLL4 study, the baseline and risks of disease progression were measured from 720 patients from the CLL4 study. The patients in the audit were broadly similar to those in the CLL4 study as a whole in terms of age, gender and Binet staging.

The mean number of cycles of treatment received in the audit in the chlorambucil, fludarabine and FC arms were *AIC information removed* and *AIC information removed* cycles and in the whole modelled dataset *AIC information removed*, and *AIC information removed* cycles per patient respectively. To correct for this difference a regression analysis was conducted in the audit dataset to estimate per patient cost as a function of the number of cycles of each chemotherapy received. The findings of this analysis were used to estimate cost per cycle of treatment for the wider patient group.

106. What source(s) of information were used to value the resources?

Unit costs for tests and hospitalisations were taken from standard UK sources in 2003 prices. NHS Reference costs 2003 were used for hospital contacts and the BNF and prescription cost analysis database (114) was used to estimate medication costs. A full list of unit costs used is available in the audit study report (See appendix 9).

The costs of treatment for second-line patients were based on the existing NICE technology appraisal for fludarabine and CHOP in second-line CLL.

The costs of treatment for salvage treatments were based on a large audit of patient notes (113 observed treatment episodes) in low-grade NHL. Although these data were not in CLL they did provide accurate resource and cost data on many different treatments in the third-line to sixth-line setting (106).

107. What is the (anticipated) acquisition cost excluding VAT of the intervention(s)?

Fludarabine phosphate –
1x 50 mg vial = £156.00
15 tablet pack (10mg) = £279.00
20 tablet pack (10mg) £372.00

Cyclophosphamide –
500-mg vial = £2.88
1-g vial = £5.04
20 tablet pack 50 mg = £2.12

Source: BNF 50, September 2005

108. Were the resources measured and valued in a manner consistent with the Reference Case? If not, how and why do the approaches differ?

The costs included in the model were direct costs to the NHS.

109. Were resource values indexed to the current price year?

The audit was carried out in 2004 and costs were expressed in 2003 prices. Average costs were indexed to 2004/2005 prices using the draft of the HCHS (Hospital and Community Health Services) index reported in the 2005 PSSRU (Personal Social Services Research Unit) (115).

110. Provide details and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Resource measurement was based substantially on the CLL audit described above. Full details of the methods are provided in the audit report (see appendix 9) but briefly the following costing assumptions were made:

Out-patient visits

The average unit cost of outpatient attendance in a haematology department was chosen as the unit cost for outpatient visits. NHS reference costs provided unit costs for the first and follow up outpatient attendances. In this analysis, the first outpatient visit in the treatment period was assumed to be first attendance and the remaining visits to be follow up attendances.

Day case costs

The HRG costs report costs for day cases as a separate category of admission. The day case cost reported for "S03: Malignant Disorders of Lymphatic or Haematological Systems w/o cc" is £344. However, the NHS costing manual stated that this relates to a finished consultant episode, and hence may include anything from a single day case admission to a planned series of regular admissions over an extended period.

Of the patients included in the costing, 31 patients reported a total of 191 day case attendances, which is around 6 days per patient. We considered the resulting cost of a day case attendance (around £56) to be unrealistic as this is lower than the cost of an outpatient follow-up appointment. We therefore made an estimate, applying the day case cost of £344 to each cycle in which one or more day case visits were reported. We believe

that this estimate gives a more precise estimate of costs in this patient group. The NHS costing manual notes that the costs of chemotherapy for haematological malignancy will be included in subsequent versions of the HRG costing.

In-patient costs

The inpatient unit cost was estimated as the weighted average of two HRG groups for elective and not elective inpatient stay. These groups were: Malignant Disorders of Lymphatic or Haematological Systems with complications and Malignant Disorders of Lymphatic or Haematological Systems without complications.

Sensitivity analysis conducted in the analysis of the audit identified three main cost uncertainties in the analysis: the use of G-CSF in the audit patients; the unit cost of day case visits; and the incidence of adverse events. The model assumes that the utilisation of these resources in the audit population is an appropriate approximation of typical use in the UK.

3.3. *Analysis of data*

3.3.1. Time preferences

111. Were costs and health benefits discounted at the rates specified in NICE's Reference Case?
Costs and health benefits were discounted at 3.5% in the base case analysis.

3.3.2. Non-linearity

112. Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

A probabilistic sensitivity analysis was performed, including variation in response rates to therapy, duration of response, quality of life and cost inputs.

Distributions around response rate and duration for first-line therapy were generated by non-parametric bootstrap replications from the CLL4 data set.

Response rates and duration for other therapies in the model were extracted from the literature identified in our review. The list of distributions is in the table below. The model required us to estimate response rates and duration for the following treatments:

- CLB re-treatment after initial successful treatment with CLB
- F re-treatment after initial successful treatment with F
- FC re-treatment after initial successful treatment with FC

- F treatment after unsuccessful treatment with CLB
- FC treatment after unsuccessful treatment with F
- CHOP treatment after initial successful treatment with FC
- Salvage treatment.

Response rates were allocated a beta distribution using the number of responders and the sample size reported in identified papers. Where more than one paper was identified that reported response rates for a particular treatment the number of responders and non-responders in suitable papers were pooled.

Where the literature review identified no paper that reported response rates for a particular treatment, the response rate and distribution for the most similar identified patient group was used. These substitutions are noted below.

Duration of response was allocated a lognormal distribution, populated from the literature review for each treatment as follows:

- If a confidence interval or standard error was reported for the treatment in any paper, a lognormal distribution was created to replicate the measure of uncertainty reported
- If a duration of response could be identified but no measure of variability was reported, a lognormal distribution with a 95% confidence interval of an arbitrary +/-30% from the median duration of response was created
- As with response rates, where duration of response could not be identified in the literature for the treatment, the distribution for the most similar identified treatment was used.

Variation in the utility inputs considered three variables: the utility value of patients in response; the loss of utility associated with receiving treatment and the loss of utility associated with progressive disease.

For the utility value of patients in response three estimates were identified in the literature. We created a triangular distribution between the extreme estimates and using the median value as the central estimate.

Three estimates of the utility loss associated with progressive disease could be derived for published sources: a triangular distribution was also used.

Only one estimate of the utility loss associated with treatment was identified (18) – this value was varied by an arbitrary +/- 30%.

All the cost sources used in the base case also reported some measure of variability (standard error or standard deviation). Lognormal distributions were constructed using the measures reported.

Distributions and sources used in the PSA are shown in Table 40.

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Table 40: Distributions used in probabilistic sensitivity analysis

Variable	Treatment	Distribution	Point	P1	P2	Source
Response rate	F first treatment	N/A	<i>AIC information removed</i>			Bootstrap
Response rate	FC first treatment	N/A				Bootstrap
Response rate	CLB first treatment	N/A				Bootstrap
DOR (months)	F first treatment	N/A				Bootstrap
DOR (months)	FC first treatment	N/A				Bootstrap
DOR (months)	CLB first treatment	N/A				Bootstrap
Response rate	F re-treatment	BETA	74%	26	35	Keating, Blood 92(4):1165-71; P1 = responders; P2 = patients (91)
			<i>AIC information removed</i>			Assumed equal to first treatment - no data identified
Response rate	FC re-treatment	N/A				
Response rate	CLB re-treatment	BETA	35%	6	17	Montserrat Cancer 56:2369-75; P1 = responders; P2 = patients (108)
DOR (months)	F re-treatment	N/A	<i>AIC information removed</i>			Assumed equal to first treatment - no data identified
DOR (months)	FC re-treatment	N/A				Assumed equal to first treatment - no data identified
DOR (months)	CLB re-treatment	N/A				Assumed equal to first treatment - no data identified
Response rate	FC after F	BETA	54%	22	41	Pooled analysis from Keating, Blood 92(4):1165-71 (91) & O'Brien JCO 19:1414-20; P1 = responders; P2 = patients (21)
Response rate	F after CLB	BETA	68%	86	126	Pooled analysis from French; Lancet 347 (25):1432 ff (71) Catovsky, P1= responders; P2 = patients (103)
Response rate	CHOP after FC	BETA	39%	12	31	Leporrier, Blood 98 (8): 2319 ff; P1 = responders; P2 = patients (77)
Response rate	Salvage	BETA	22%	32	147	Keating, Leukemia and Lymphoma 43(9):1755-762; P1 = responders; P2 = patients (104)
DOR (months)	FC after F	LNN	20	14	26	O'Brien JCO 19:1414-20; P1, P2 = 95% confidence limits (21)
DOR (months)	F after CLB	LNN	10.65	8.9	15.1	French; Lancet 347 (25):1432 ff; assumes 95% CI is +/- 1.96 * STDEV from mean (71)
DOR (months)	CHOP after FC	LNN	5.88	1.8	18.6	French; Lancet 347 (25):1432 ff; assumes 95% CI is +/- 1.96 * STDEV from mean, CAP as approximation for CHOP; P1, P2 = 95% confidence limits (71)
DOR (months)	Salvage	LNN	18	12.6	23.4	Keating, Leukemia and Lymphoma 43(9):1755-762; (104) P1, P2 = 95% confidence limits
QOL	QOL in response	TRIG	0.80	0.78	0.96	Doorduijn (107); Hancock (5); Best. P1= lower limit; P2 = upper limit (17)
QOL	QOL decrease: response – treat	TRIG	0.06	0.04	0.08	Doorduijn (+/- 30%) P1= lower limit; P2 = upper limit (107)
QOL	QOL decrease: response – relapse	TRIG	0.2	0.15	0.28	Doorduijn (107); Hancock (5); Best. P1= lower limit; P2 = upper limit (17)
Cost per cycle	F first treat	LNN	1060	139		CLL4 audit; P1 = standard error
Cost per cycle	FC first treat	LNN	779	113		CLL4 audit; P1 = standard error
Cost per cycle	CLB first treat	LNN	188	67		CLL4 audit; P1 = standard error
Cost per cycle	All					Assumed equal to 1st line (no data)
Cost per patient	F after CLB	LNN	3714	802		From 2nd line audit, F oral; P1 = standard error
Cost per cycle	FC after F	LNN				Assumed equal to 1st line (no data)
Cost per patient	CHOP after FC	LNN	2886	1241		From 2nd line audit, CHOP; P1 = standard error
Cost per patient	Salvage	LNN	3241	811		Hutchinson et al 3rd line therapy (113 episodes) ; P1 = standard error (106)

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LNN = Lognormal; TRIG = triangular; P1 = first parameter; P2 = second parameter; DOR = Duration of response

3.3.3. Statistical analysis

113. How were rates or probabilities based on intervals transformed into (transition) probabilities?

For first-line treatments transition probabilities were estimated directly from the patient level data. The risk of disease progression was calculated for patients in response after each therapy. The number of patients who were known to have progressed or died was divided by the total number of cycles in which patients were observed in response.

Transition probabilities for second and subsequent lines of treatment were estimated from published median values, assuming a constant relative risk of transition out of a state. If median time spent in a state is t , periods will be consistent with a per period risk of transition out of the state of $0.5^{(1/t)}$.

114. Is there evidence that (transition) probabilities should vary over time for the condition at hand? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

At the time of the analysis the evidence on the rate of progression is immature and the evidence has not demonstrated variation in transition probabilities over time. In particular, relatively few progressions have taken place in the FC arm and evidence is insufficient to explore whether the rate of transition will vary over time. Sensitivity analysis has been conducted to address uncertainty around transition probabilities.

3.3.4. Validity

115. Describe the measures that have been taken to validate and check the model.

The structure and key assumptions in the model have been validated with two experts in the treatment of CLL: Professor D Catovsky (Lead Investigator of the CLL4 study) and Professor P Hillmen (Chairman of the CLL Trials sub-group of the NCRI). See question 96 for details on the specific assumptions.

Numeric values in the model were checked by an experienced modeller not involved in the construction or analyses.

3.4. Results

3.4.1. Base-case result and PSA

116. What was the base-case result (e.g. costs, QALYs and incremental cost per QALY) and was it based on PSA?

Table 41: Base case cost and effectiveness findings (cohort of 1,000)

Treatment strategy	Costs	Outcomes (QALYs)
CLB 1st line	£11,659,803	5,096
F 1st line	£17,590,562	5,399
FC 1st line	£13,657,485	5,864

Table 42: Comparisons between therapies

Incremental	Costs	Outcomes (QALYs)	C/E ratio
F 1st line vs CLB 1st line	£ 5,930,759	302	£ 19,613
FC 1st line vs CLB 1st line	£ 1,997,683	768	£ 2,602
FC 1st line vs F 1st line	-£ 3,933,077	465	Dominant

In the base case treatment with fludarabine instead of chlorambucil increased costs per 1,000 patients by around £5.9m and increased QALYs by 302, at an incremental cost per QALY gained of £19,613.

Treatment with FC instead of chlorambucil would increase costs per 1,000 patients by around £2.0m and increased QALYs by 768, at an incremental cost per QALY gained of £2,602.

In comparison with fludarabine monotherapy, FC was associated with better outcomes and lower costs, and hence FC dominated fludarabine.

Table 43: PSA findings: costs and outcomes

	Costs	Outcomes	
C	£ 11,659,803	5096	
95% CI	(£9511, £12554)	(4.65, 6.42)	
F	17591	5.40	
95% CI	(£14859, £19420)	(4.86, 6.74)	
FC	13657	5.86	
95% CI	(£11772, £15209)	(5.26, 7.3)	
Incremental	Costs	Outcomes	C/E ratio
F vs C	5931	0.30	19613
95% CI	(£3631, £8895)	(-0.19, 0.69)	(£-141953, £285706)
FC vs C	1998	0.77	2602
95% CI	(£365, £4739)	(0.22, 1.33)	(£608, £9294)
FC vs F	-3933	0.47	-8452
95% CI	(£-6399, £-1179)	(-0.13, 1.17)	(£-53398, £33567)

Scatterplots of the incremental cost and QALY gain per patient treated with fludarabine compared to chlorambucil and with FC compared to chlorambucil are shown in the charts below (See question 117: Figure 6 and Figure 7).

117. Please provide cost-effectiveness acceptability curves and scatterplots on cost-effectiveness quadrants.

Figure 6: Incremental costs and outcomes per 1,000 patients
Fludarabine compared to chlorambucil

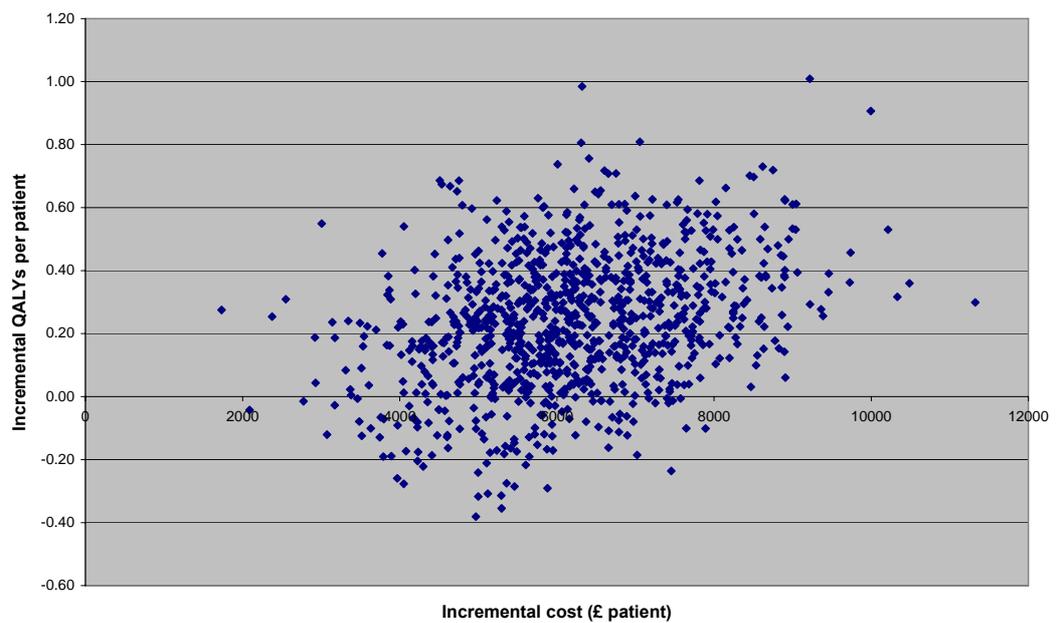
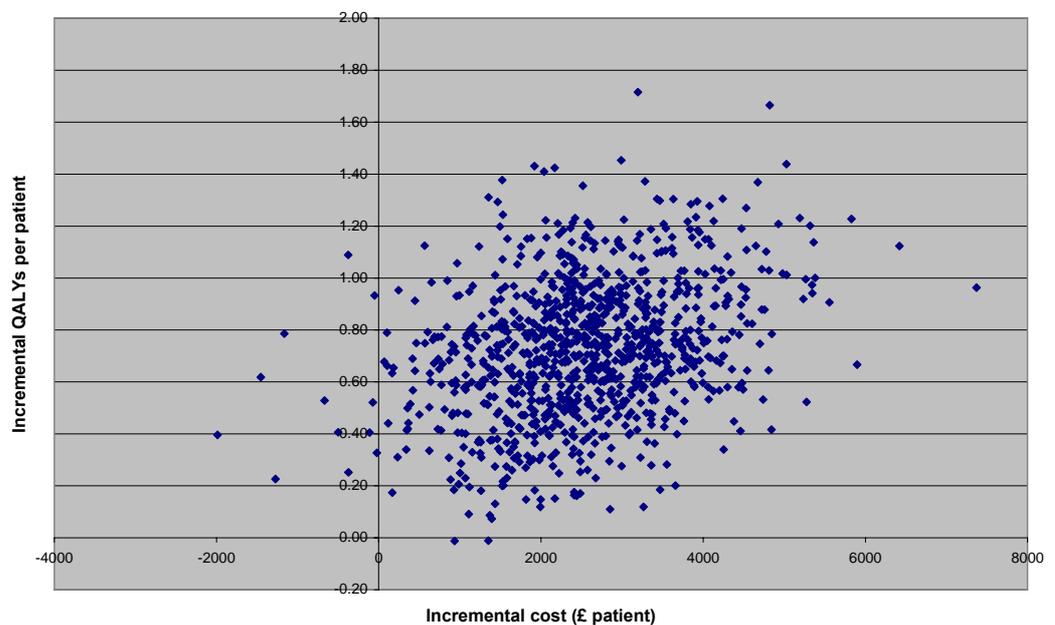
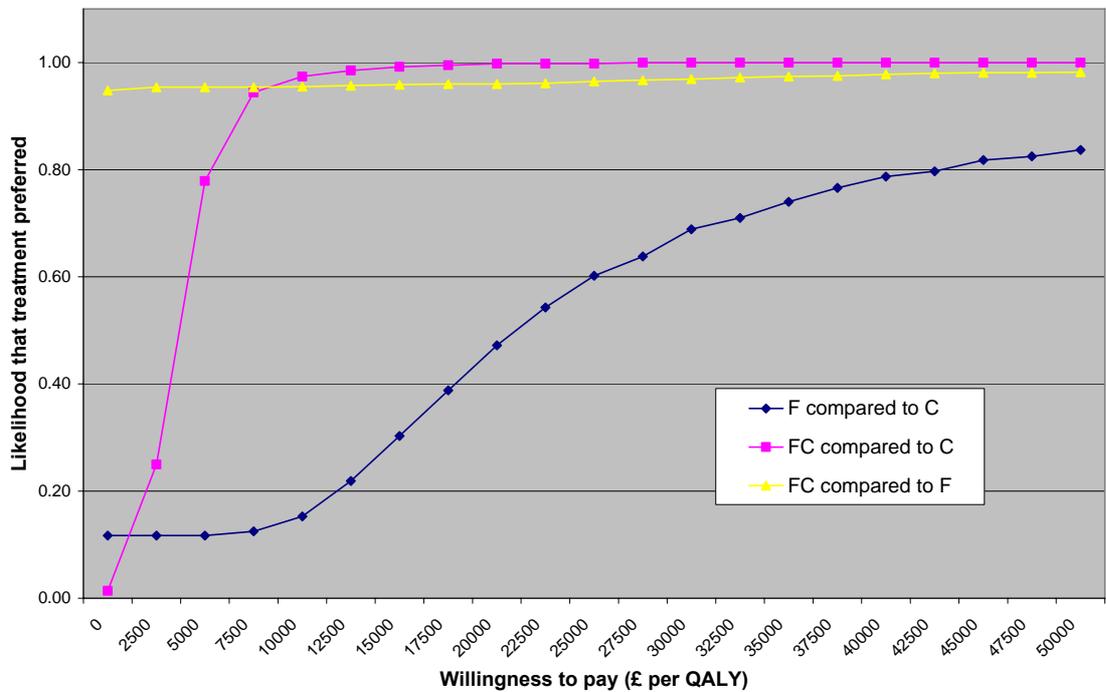


Figure 7 Incremental costs and outcomes per 1,000 patients
FC compared to chlorambucil



A cost-effectiveness acceptability curve was calculated, showing the estimated likelihood that fludarabine will be preferred to chlorambucil; FC preferred to chlorambucil and FC preferred to fludarabine at different levels of willingness to pay for a QALY gained. The CEAC indicates that the model found a high degree of confidence that the cost per QALY gained comparing FC with C is below £10,000. The CEAC indicates less confidence in the cost-effectiveness finding for F compared to C. At a willingness to pay of £50,000 per QALY the likelihood that F will be preferred to C was estimated to be around 83%.

Figure 8: Cost-effectiveness acceptability curve



118. Were results reported for different subgroups of patients? If so, what were the results for them?

The following subgroup analyses were conducted:

Patients aged above or below 65 years of age

Subgroup analysis by age was conducted to explore whether the benefits of more intensive therapy differ in elderly patients who may have additional comorbidity and more limited ability to benefit from treatment. The cut-off of 65 was chosen as it divides the analysed population approximately in half (48.9% of patients in CLL4 eligible for analysis and used in the model were aged ≥ 65). Furthermore, the German CLL studies (1;12) used the age of 65 as a cut-off between 'younger' and 'elderly' patients.

The results of the subgroup analysis by age are shown in Table 44 and Table 45.

Although the changes are not substantive compared to the baseline ICERs it is interesting to note that fludarabine is more cost effective in the older patients, yet FC is more cost-effective in the younger patients. We investigated differences in response rates, progression-free survival and breakdown by stage to see if these explained the finding but there was no apparent reason. Given that the difference between fludarabine and chlorambucil goes in one direction and the difference between FC and chlorambucil goes in the opposite direction we can only attribute the finding to sample size: the progression-free data for FC are in particular not based on large numbers as many of these patients have yet to progress after response.

Table 44: Subgroup analysis for fludarabine patients by age (cohort 1,000)

	Fludarabine		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Age ≥ 65	£ 15,514,002	4720	£ 10,032,495	4394	£ 16,830
Age ≤ 64	£ 19,715,259	6160	£ 13,504,339	5929	£ 26,833

Table 45: Subgroup analysis for FC patients by age (cohort 1,000)

	Fludarabine + cyclophosphamide		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Age ≥ 65	£ 11,340,879	4828	£ 10,032,495	4394	£ 3,021
Age ≤ 64	£ 16,425,248	7164	£ 13,504,339	5929	£ 2,365

Grade of disease at baseline

Disease stage at baseline is a strong predictor of survival and hence is likely to affect capacity to benefit from therapy (7). We therefore undertook a separate analysis that considered each Binet stage. The results of the analyses are shown in Table 46 and Table 47.

Analysis by Binet stage showed a consistent trend for lower overall costs and QALYs gained for stage C patients, which would be expected if these patients are both sicker and older and therefore less likely to live as long as younger fitter patients. Relative to the base case findings, fludarabine compared to chlorambucil became more cost-effective in Stage A+ and Stage B patients whereas FC compared to chlorambucil became less cost effective in Stage A+ and remained virtually the same in Stage B. As with the difference observed in analysis by age group, no particular reason for these changes could be identified.

Table 46: Subgroup analysis by Binet stage at baseline (cohort 1,000)
 Fludarabine relative to chlorambucil

	Fludarabine		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Binet Stage A+	£ 18,748,861	5826	£ 11,945,319	5406	£ 16,215
Binet Stage B	£ 18,907,354	5967	£ 11,974,946	5239	£ 9,526
Binet Stage C	£ 14,469,658	4139	£ 10,972,752	4636	Dominated

Table 47: Subgroup analysis by Binet stage at baseline
 FC relative to chlorambucil

	Fludarabine + cyclophosphamide		Chlorambucil		ICER
	Costs	QALYs	Costs	QALYs	
Binet Stage A+	£ 12,604,990	5508	£ 11,945,319	5406	£ 6,463
Binet Stage B	£ 14,693,166	6381	£ 11,974,946	5239	£ 2,380
Binet Stage C	£ 12,982,361	5423	£ 10,972,752	4636	£ 2,556

Table 48: Subgroup analysis: number of patients in each subgroup

N	Fludarabine	Fludarabine + cyclophosphamide	Chlorambucil
Age ≥65	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
Age < 65	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>
Binet Stage A+	43	46	90
Binet Stage B	87	85	157
Binet Stage C	49	55	108

3.4.2. One-way/multiway sensitivity analysis

Sensitivity analysis should be conducted over a plausible range of prices for technologies whose final price/acquisition cost has not been confirmed.

119. Which variables were subject to sensitivity analysis?

Sensitivity analysis considered uncertainty around treatments used, input parameters, and analytic choices.

Treatments used

An additional analysis ("FCR") considered the impact of assuming that patients who do not respond to FC at first-line receive a second-line of chemotherapy with FCR before proceeding to salvage treatment. A second analysis ("C-FC") considered the use of FC instead of F as second-line therapy after patients fail chlorambucil monotherapy.

Table 49: Treatments used in the base case and sensitivity analysis

Strategy name	Base Case			Sensitivity Analysis	
	F 1st line	CLB 1st line	FC 1st line	Analysis "FCR"	Analysis "C-FC"
Therapy used as:					
First-line	Fludarabine	Chlorambucil	FC	FC	Chlorambucil
Re-treatment for responders	Fludarabine	Chlorambucil	FC	FC	Chlorambucil
2nd Treatment	FC	Fludarabine	CHOP	FCR	FC
Salvage	Mixed*	Mixed*	Mixed*	Mixed*	Mixed*

FC = combination therapy with fludarabine and cyclophosphamide

FCR = combination therapy with fludarabine, cyclophosphamide and rituximab

*A combination of therapies identified in the literature that have been used to treat fludarabine refractory or relapsed patients (for details see question 97)

Input parameters

The following parameters were varied: Efficacy data for first-line treatments, efficacy for subsequent treatments, utility values, and overall survival.

Efficacy of first-line treatments

Table 50: Weighted average overall response rates in other first-line CLL studies

The efficacy data from the CLL4 study were replaced by a pooled analysis of data available from the other CLL studies.

Source	Fludarabine		FC		Chlorambucil	
	n	OR (%)	n	OR (%)	n	OR (%)
Eichhorst 2006 (1)	182	83	180	94		
Eichhorst 2005 (12)	92	85.7				
Flinn 2004 (13)	121	49.6	125	70		
Karlsson 2004 (14)	45	67			47	57
Rai 2000 (9)	170	63			181	37
Spriano 2000 (10)	69	71			73	71
Weighted average		70.1		84.2		48.4

Efficacy of subsequent treatments

Table 51: Response rates with second line therapy – sensitivity analysis

The efficacy of re-treatment, second-line treatments and of salvage treatment was varied between the limits of 95% confidence intervals derived from the underlying studies.

Parameter	Base case	Limits tested
Response rate: FC after F	54%	39%, 68%
Response rate: F after CLB	68%	60%, 76%
Response rate: CHOP after FC	39%	23%, 56%
Response rate: F re-treatment	74%	58%, 86%
Response rate: CLB re-treatment	35%	16%, 59%
Response rate: FC re-treatment	<i>AIC information removed</i>	<i>AIC information removed</i>
Response rate: Salvage	22%	16%, 29%

* 95% CI estimated by bootstrapping response rate for 1st line treatment in CLL4 dataset

An additional sensitivity analysis estimated the rate and duration of response with salvage therapy by pooling all the studies identified in the review of salvage treatments, which gave an estimated response rate of 43% and a response duration of 8.3 months.

Estimated response rates on re-treatment were based on very limited data. A sensitivity analysis explored the effect of assuming response rates on re-treatment to be equal to first line treatment.

Utility Values

Utility values (for the progressive disease and response states) in the base case were replaced by other values identified in the literature, namely the estimates used by Best et al (17) and those observed by (107) Doorduijn et al.

Progression free survival and effect on overall survival

An analysis was conducted to explore the potential relationship between progression free survival and overall survival. Consistent evidence was identified that patients treated with FC or with fludarabine will experience longer progression free survival than patients treated with chlorambucil. However no evidence is yet available to demonstrate a significant difference in overall survival. On the advice of our clinical experts, and to be consistent with the current evidence, the base case of the model assumes that progression free survival differs between treatments but that there is no difference in overall survival between treatments.

To include both of these findings it is necessary for patients treated with FC and with fludarabine to experience a shorter period from first progression to death than patients treated with chlorambucil. In the base case model 100% of the extension in progression free survival seen with fludarabine and with FC is offset by a shorter period from first progression to death. We tested this assumption by reference to the literature.

Rai and colleagues is the only study of fludarabine therapy at first-line identified in the literature review that reported both progression free and overall survival (9). In this study first-line treatment with fludarabine instead of chlorambucil resulted in an increase in median progression free survival of 6 months (from 14 to 20 months, $p < 0.001$). This study reported an increase in median overall survival from 56 months with chlorambucil to 66 months with fludarabine ($p = ns$). We calculated that the period from first progression to death was therefore increased from 42 months with chlorambucil to 46 months with fludarabine (p value not known). See Table 52

Table 52: Median progression free survival and overall survival in Rai et al

Treatment	Fludarabine	Chlorambucil	Difference	
N	170	181		
Median PFS (months)	20	14	+6 months	$P < 0.001$
Overall survival (months)	66	56	+ 10 months	$P = ns$
Time from progression to death (months) ^a	46	42	+ 4 months	Not known

^a Source: calculated by subtracting median PFS from median overall survival

In the Rai study the increase in progression free survival of +6 months observed in the fludarabine arm was not associated with a decrease in time from progression to death (as is the case in our base case model) but instead it was associated with an increase in time from progression to death of +4 months (p value not known). Therefore, in the sensitivity analysis we tested the possibility that the time from final progression to death was the same in all three groups as opposed to the base case where we had shortened the time from progression to death in the fludarabine and FC arms so that overall survival was consistent between treatments. This was a conservative approach, since in the Rai study it had been shown that the time from final progression to death was longer with fludarabine than with chlorambucil.

Utility decrement during treatment

In the base case the model assumes that there is a small decrease in average quality of life among patients while they receive chemotherapy, possibly reflecting toxicity. The QoL data from the CLL4 study (15;16) suggest that quality of life falls from baseline to month 3 with fludarabine and FC therapy but not with chlorambucil, although the differences are very small and do not achieve statistical significance. Therefore a sensitivity analysis explored the possibility that chlorambucil therapy is not associated with this fall in quality of life, due to less frequent toxicity in patients treated with chlorambucil.

Analytic framework

Timeframe

Previous economic analyses have adopted shorter timeframes (5) (Hancock et al 2002) and we explored time horizons for the analysis ranging from 5 to 20 years.

Discount rate

We explored the implications of varying the discount rates for costs and benefits between 0 and 6% compared to the base case rate of 3.5%.

Cost per month / year in remission

To test the influence of the model methodology on the estimated cost per QALY we conducted a much simpler analysis, similar to that conducted by NICE for the appraisal of fludarabine in second-line treatment of CLL. This simpler analysis estimated the cost per month in remission and cost per QALY as follows:

- The response rate for FC, F and CLB was taken from the CLL4 study
- The estimated cost of treatment is calculated by multiplying cost per cycle by the mean number of cycles, both taken from the model
- The median duration of response was estimated from the CLL4 study
- The base case estimate of the utility difference between response and progression was

used to estimate QALY gain.

120. What were the main findings of the sensitivity analysis?

See Table 54: Findings of one-way sensitivity tests

121. Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

Structural uncertainty was investigated by considering the effect of using alternative treatment pathways, namely: We considered the effect of introducing rituximab (as FCR) following the failure of FC and also the effect of using FC in place of fludarabine after the failure of chlorambucil. With reference to Table 49: Treatments used in the base case and sensitivity analysis, it can be seen that introducing rituximab has the effect of doubling the ICER for FC over chlorambucil from £2,602 to £5,777. This is driven by the increased cost associated with rituximab. However, the incremental ratio remains well below accepted thresholds. Compared to chlorambucil followed by fludarabine, introducing FC after chlorambucil results in a small decrease in costs and a slight increase in QALYs gained; therefore there is only a modest impact on the ICER, compared to baseline, indicating that the decision on whether to use fludarabine or FC after chlorambucil need not be made on economic factors.

We also considered the effect of using a much simpler model structure that considered cost per month / year in remission. The results of this analysis are shown in Table 53.

The incremental cost per month / year in remission of using fludarabine and FC in place of chlorambucil are £621 / £7,452 and £67 / £804 respectively. These are within the range that might be expected given that the incremental cost per year in remission for fludarabine compared to CHOP in the second-line setting was found by NICE to be £2,700 (33).

The incremental costs per QALY for fludarabine and FC, compared to chlorambucil, are higher in this simple analysis as it only considers the gain associated with first-line treatment. However, the relative increase and difference between the treatments is consistent with the complex model that accounts for subsequent treatments; this would indicate that it is the underlying benefits in the clinical data that are driving the results as opposed to the modelling method employed.

Table 53: Cost per month in remission analysis

Arm	Chlorambucil	Fludarabine	FC	Notes
Cost of first line treatment				
Cycles, mean	6.85	5.26	4.61	CLL4 – Patient level data
Cost per cycle (£)	188	1060	779	CLL4 audit appendix 9
Cost per patient (£)	1290	5572	3591	Cost * cycles
Cost per patient, increase over chlorambucil (£)		4283	2302	
Time in response gained				
Response rate (%)				CLL4 – Patient level data
Median DOR (months)	<i>AIC information removed</i>	<i>AIC information removed</i>	<i>AIC information removed</i>	Estimated from CLL4
Expected time in remission (months)				Response rate * DOR
Time in remission, gain over chlorambucil (months)		6.9	34.4	
QALY per patient, gain over chlorambucil		0.11	0.57	Assuming 0.2 QoL gain associated with remission
Incremental cost-effectiveness estimates				
Cost per month in remission, vs chlorambucil (£)		621	67	Incremental cost / Incremental months in remission
Cost per QALY, vs chlorambucil (£ per QALY)		£37,250	£4,020	Assuming 0.2 QoL gain associated with remission

Table 54: Findings of one-way sensitivity tests

Sensitivity tests	Fludarabine		Chlorambucil		FC		F - CLB	FC-CLB
	Costs	QALYs	Costs	QALYs	Costs	QALYs	C/E ratio	C/E ratio
Base case	£17,590,562	5399	£11,659,803	5096	£13,657,485	5864	£19,613	£2,602
FC followed by FCR	£17,590,562	5399	£11,659,803	5096	£16,559,966	5944	£19,613	£5,777
CLB followed by FC	£17,590,562	5399	£11,342,252	5157	£13,657,485	5864	£25,892	£3,276
Re-treat if response \geq 6 months	£17,631,601	5341	£11,411,810	5011	£13,792,354	5871	£18,836	£2,770
Response rates at 1 st line from literature	£19,965,370	6035	£11,235,413	4950	£16,037,850	6966	£8,050	£2,383
F re-treat: response rate upper limit	£17,658,799	5486	£11,659,803	5096	£13,657,485	5864	£15,372	£2,602
F re-treat: response rate lower limit	£17,500,835	5283	£11,659,803	5096	£13,657,485	5864	£31,258	£2,602
CLB re-treat: response rate upper limit	£17,590,562	5399	£11,760,638	5225	£13,657,485	5864	£33,648	£2,970
CLB re-treat: response rate lower limit	£17,590,562	5399	£11,578,458	4992	£13,657,485	5864	£14,788	£2,385
FC re-treat: response rate upper limit	£17,590,562	5399	£11,659,803	5096	£13,701,080	5916	£19,613	£2,489
FC re-treat: response rate lower limit	£17,590,562	5399	£11,659,803	5096	£13,614,202	5812	£19,613	£2,731
FC after F: response rate upper limit	£17,628,615	5441	£11,659,803	5096	£13,657,485	5864	£17,333	£2,602
FC after F: response rate lower limit	£17,551,669	5356	£11,659,803	5096	£13,657,485	5864	£22,705	£2,602
F after CLB: response rate upper limit	£17,590,562	5399	£11,672,786	5111	£13,657,485	5864	£20,554	£2,635
F after CLB: response rate lower limit	£17,590,562	5399	£11,645,968	5081	£13,657,485	5864	£18,705	£2,569
CHOP after FC: response rate upper limit	£17,590,562	5399	£11,659,803	5096	£13,662,925	5869	£19,613	£2,591
CHOP after FC: response rate lower limit	£17,590,562	5399	£11,659,803	5096	£13,652,543	5859	£19,613	£2,612
Salvage: response rate upper limit	£17,639,926	5441	£11,718,254	5147	£13,693,739	5893	£20,145	£2,649
Salvage: response rate lower limit	£17,551,183	5365	£11,613,174	5055	£13,628,565	5841	£19,209	£2,567
Salvage data from pooled studies	£17,565,263	5376	£11,628,977	5068	£13,639,416	5849	£19,295	£2,575
Response rates on re-treatment equal first line	£17,600,056	5411	£11,796,880	5272	£13,657,485	5864	£41,727	£3,142

Table continued over

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Table 54: Findings of one-way sensitivity tests (continued)

Sensitivity tests	Fludarabine		Chlorambucil		FC		F-CLB	FC-CLB
	Costs	QALYs	Costs	QALYs	Costs	QALYs	C/E ratio	C/E ratio
Base case	£17,590,562	5399	£11,659,803	5096	£13,657,485	5864	£19,613	£2,602
Utility values from Doorduijn	£17,590,562	5025	£11,659,803	4656	£13,657,485	5632	£16,040	£2,046
Utility values from Wessex	£17,590,562	6740	£11,659,803	6460	£13,657,485	7135	£21,175	£2,962
No utility decrement during chlorambucil treatment	£17,590,562	5399	£11,659,803	5151	£13,657,485	5864	£23,927	£2,801
Removing rapid 'progression to death time' for fludarabine and making equal to chlorambucil	£17,833,286	5540	£11,659,803	5096	£14,479,804	6342	£13,918	£2,263
Time horizon 5 years	£12,607,123	3187	£7,771,150	3166	£8,572,225	3168	£227,255	£379,930
Time horizon 10 years	£16,270,783	4733	£10,702,549	4565	£11,826,875	4855	£33,113	£3,868
Time horizon 15 years	£17,338,768	5265	£11,480,251	4994	£13,190,023	5605	£21,570	£2,797
Discount rates: cost 0%; outcomes 6%	£19,748,014	4873	£13,380,577	4630	£15,886,345	5221	£26,179	£4,243
Discount rates: cost 0%; outcomes 0%	£19,748,014	6360	£13,380,577	5940	£15,886,345	7075	£15,162	£2,207
Discount rates: cost 6%; outcomes 6%	£16,395,936	4873	£10,696,744	4630	£12,473,140	5221	£23,431	£3,008
Discount rates: cost 6%; outcomes 0%	£16,395,936	6360	£10,696,744	5940	£12,473,140	7075	£13,571	£1,565

3.4.3. Interpretation of economic evidence (300 word maximum)

122. Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ and why should the results in the submission be given more credence than those in the published literature?

Only two published economic evaluations were identified that reported on the cost-effectiveness of fludarabine as a first-line therapy for the treatment of CLL. The WMHTAC report published in 2002 estimated that on average, over three years, the incremental cost per QALY ratio of fludarabine compared to chlorambucil was £48,000. (5).

An earlier economic evaluation published in 1995 by the DEC (Development & Evaluation Committee) of the South and West Regional Health Authority was also identified (17). The cost-effectiveness of IV fludarabine was compared to chlorambucil plus prednisone. Fludarabine was found to result in an increase in time free of progressive disease after treatment but at an increased cost, which is consistent with our findings. However, the effectiveness data used in this analysis were not from an RCT, as there were none available at the time, and the basis of the utility estimates was not clear from the report. Taken together, these issues make it difficult to draw more meaningful comparisons between the DEC report and the current evaluation.

The model presented in this submission is based on a prospective, randomised, multi-centre, comparative trial. Data were collected on effectiveness of fludarabine, chlorambucil, and FC used as first-line therapy in UK patients. The costs were based on an audit of a sample from the trial and these included adverse events. Based on a review of the literature, this model also considered the costs and consequences of subsequent lines of chemotherapy and followed patients until death. The results from the model should be given more credence than those in the published literature as:

- The first-line data are based on patient-level data for both costs and effects
- It is based on current practice using the most up-to-date clinical guidelines for the UK
- Treatment sequelae are considered over a lifetime framework.

123. Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The model is based on patients in the CLL4 trial, which are broadly consistent with those of the licensed indication. The main differences between the licensed indication and patients entered into CLL4 were that patients with non-progressive Binet stage B disease could enter the trial and that patients with hepatic impairment were excluded from CLL4. Expert opinion was that this would not significantly affect the applicability of this analysis to patients who would normally be treated for first-line CLL.

We were advised that CLL4 may have included a lower proportion of elderly patients than the general CLL4 population treated with first-line chemotherapy. This was because these elderly patients may have been too frail to be treated with fludarabine and therefore could not take the risk of randomisation to anything other than chlorambucil. This potentially increases the applicability of the analysis as these patients will, because of their condition, continue to be treated with chlorambucil and not be considered in the decision problem of whether to use fludarabine or FC.

Fludarabine is also indicated and currently used for the second-line treatment of CLL. This indication has been subject to previous NICE appraisal (33). Fludarabine monotherapy is unlikely to be used second-line if it has previously been used first-line, either as a monotherapy or in combination with cyclophosphamide. It may however, be used second-line following chlorambucil; these patients have been considered in the current analysis both as a monotherapy following chlorambucil in the case and as FC following chlorambucil in a sensitivity analysis.

Fludarabine is used experimentally in other neoplastic diseases but currently has no licensed indications other than for the treatment of CLL.

124. What are the main strengths and weaknesses of the evaluation? How should these affect the interpretation of the results?

The main strengths of the evaluation are that the analysis uses patient level data from the largest RCT yet conducted in the UK to inform patient events; that the study considered subsequent therapy to explore the likely lifetime consequences of first-line treatment; and that the patients and analyses are relevant to the UK setting as the CLL4 study was conducted largely in the UK.

The main weaknesses of the study are: follow-up available to first-line therapy is insufficient to demonstrate a difference in overall survival and the lack of good quality utility data in patients with CLL.

The model suggests that the improvement in response rate with FC over chlorambucil is such that FC is likely to be highly cost-effective if progression-free survival continues to develop as observed in the CLL4 study. This finding seems robust subject to plausible variation in inputs and follow up of ongoing studies continues.

The model suggests that the cost-effectiveness of fludarabine monotherapy compared to chlorambucil is dependent on the quality of life of patients who respond to therapy, but that fludarabine monotherapy will be cost-effective if improvements in progression-free survival translate into improvements in overall survival.

125. What further analyses could be undertaken to enhance the robustness/completeness of the results?

The most important analysis that can be undertaken to improve the robustness of the results is to include the patient level data from CLL4 from second-line randomisation. These data are currently not complete, as many patients are still in their first-line response, but once the data are available they will replace the assumptions on subsequent therapies we have had to make based on the literature from other studies and expert opinion.

4. Budget Impact

Objective

A budget impact calculation was conducted to determine the potential impact on NHS expenditure of more widespread uptake of FC in future years.

Methods

IMS data were used to derive the number of patients relevant for this analysis. We extracted the number of patients treated in 2005 with a diagnosis of CLL, receiving their first chemotherapy with chlorambucil, chlorambucil in combination with prednisolone, or with fludarabine containing regimens. The treatments are consistent with management of patients with CLL who are not eligible for transplant in the BCSH guidelines. The total number of new patients requiring first-line treatment each year was modelled as a constant.

Although incidence of diagnosed CLL has increased in recent years, we are aware of no evidence that treated prevalence is increasing. This is consistent with increased diagnosis of patients with Stage A disease, for whom treatment is not required.

Two scenarios were compared: "No change" and "FC recommended". In the "No change" scenario, we assumed that the number of patients receiving treatment with each agent remains constant over time at the same rate as in 2005.

In the "FC recommended" scenario, we assume that an increased number of patients receive FC. We assume that patients currently receiving chlorambucil, with or without a steroid, or fludarabine with or without cyclophosphamide, might be eligible for FC treatment. Of eligible patients, we assumed that 80% might receive FC combination (expert opinion was that up to 20% patients eligible for FC will be too frail or elderly to tolerate fludarabine), with 15% continuing to receive chlorambucil and 5% fludarabine (Table 55).

Table 55: Estimated number of treated patients, England and Wales

Therapy	2005 MAT Q3		Patients 2007	
	Patients (n)	Patients (%)	No change	FC recommended
Chlorambucil	1,982	72%	1,982	277 (10%)
FC	516	19%	516	2,215 (80%)
Fludarabine	271	10%	271	277 (10%)
Potentially eligible for FC	2,769	100%	2,769	2,769 (100%)
Other / unclassified*	462		462	
TOTAL	3,231		3,231	3,231

* The IMS data showed that 14% of patients were treated with a mixture of other therapies such as pentostatin (5%), cladribine (3%) or were unclassified (2%). It was assumed that the proportion of patients receiving unlicensed or experimental therapies will continue regardless of any decisions on the main therapies of chlorambucil, fludarabine and FC.

Table 56: Mean cost per patient starting first-line treatment by year since start of treatment

The per patient cost of treatment for each year since the start of therapy was extracted from the model for each strategy of starting first-line treatment with fludarabine, chlorambucil and FC. These costs are shown in Table 56.

Time since start of treatment	Cost per patient		
	F	Chl	FC
Year 1	£6,959	£2,404	£4,697
Year 2	£1,335	£1,554	£1,017
Year 3	£1,588	£1,465	£993
Year 4	£1,485	£1,316	£965
Year 5	£1,339	£1,110	£972

The expected cost of managing patients treated at first-line for CLL starting in 2007 was calculated as the number of patients starting treatment in 2007 multiplied by expected costs of treatment in year 1.

In 2008 the expected cost was new treatment in 2008 plus the cost of the second year of treatment of patients who begin treatment in 2007. Costs in subsequent years are built up in a similar manner.

Results

Expected expenditure in each year is shown in Table 57 and Table 58 below.

Table 57: Estimated cost per year: "No change" scenario

No. in arm	271	1982	516	
%	9.8%	71.6%	18.6%	
Year	F	ChI	FC	Total
2007	£1,885,847	£4,764,566	£2,423,715	£9,074,128
2008	£2,247,623	£7,843,839	£2,948,690	£13,040,153
2009	£2,678,059	£10,747,078	£3,461,170	£16,886,307
2010	£3,080,471	£13,356,057	£3,959,205	£20,395,733
2011	£3,443,286	£15,556,581	£4,460,845	£23,460,712

*NB: Although these percentages sum to 100 they represent the 85% (2,769 out of 3,231) of total first-line patients in England & Wales who are not treated with 'other' unclassified and experimental regimens

Table 58: Estimated cost per year: "FC recommended" scenario

No. in arm	138	415	2215	
%	5.0%	15.0%	80.0%	
Year	F	ChI	FC	Total
2007	£963,452	£998,467	£10,405,067	£12,366,986
2008	£1,148,278	£1,643,763	£12,658,796	£15,450,838
2009	£1,368,182	£2,252,169	£14,858,881	£18,479,232
2010	£1,573,769	£2,798,909	£16,996,958	£21,369,636
2011	£1,759,125	£3,260,053	£19,150,512	£24,169,691

*NB: Although these percentages sum to 100 they represent the 85% (2,769 out of 3,231) of total first-line patients in England & Wales who are not treated with 'other' unclassified and experimental regimens

The analysis suggests that switching patients from current management to the "FC recommended" scenario would increase costs in the first year by around £3.3m, but that lower costs of subsequent treatment with FC treated patients within this timeframe mean that the budget impact in year 5 would be negligible (annual expenditure in year 5 estimated to be £24.2 vs £23.5 m).

Summary

CLL is a common cancer and the number of patients starting treatment in any given year is estimated to be over 3,000. This analysis compared continuation of current treatment practice with a scenario in which FC use was substantially increased and found an increase in NHS expenditure in the first one-two years, but that this change would be modest by year 5.

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