NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegaspargase for treating acute lymphoblastic leukaemia

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pegaspargase for treating acute lymphoblastic leukaemia [ID863]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pegaspargase for treating acute lymphoblastic leukaemia

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Is there sufficient evidence available to assume equal effectiveness between pegaspargase, native E. coli derived asparaginase and Erwinia-derived asparaginase in the paediatric or adult populations?
- How generalisable are the results from the trials to clinical practice? The UKALL protocols form the basis of current clinical practice in England, with pegaspargase being administered at a dose of 1,000 IU/m^2. This is lower than all of the comparative evidence available for pegaspargase (2,500 IU/m^2) and that recommended in the Summary of product characteristics.

Cost effectiveness

- Is treatment sequencing a valid approach to modelling? The ERG commented that the comparison of pegaspargase followed by Erwinia derived asparaginase versus Erwinia derived asparaginase followed by pegaspargase does not inform the decision at hand, that is should pegaspargase be recommended for routine use within the NHS.
- Does the company's economic model reflect clinical practice in England?
  - In the model the paediatric population received 1 course of treatment at the maintenance and 2 courses at the delayed intensification treatment periods. The ERG stated that in the most recent paediatric treatment protocols specify only 1 course of treatment at the maintenance and delayed intensification treatment periods.
  - The model used a rate of 6 doses of E.coli derived asparaginase or Erwinia derived asparaginase for each dose of pegaspargase but the ERG considered that 4 doses was a better estimate.
- Is it appropriate to use the rates of hypersensitivity to reflect the proportion of patients who require a treatment switch as a result of hypersensitivity?
  - With respect to the hypersensitivity to native E. coli derived asparaginase, the ERG agreed with the company that 20% can be considered as a reliable and conservative estimate. However, there is no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinia derived asparaginase also reflect the proportion of patients who require a treatment switch. Based on alternative data sources which explicitly report the rate of treatment switching, the ERG used 13.2% and 9% for pegaspargase and Erwiniaderived asparaginase, respectively, in the ERG base case.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of pegaspargase within its marketing authorisation for treating acute lymphoblastic leukaemia.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with acute lymphoblastic leukaemia (ALL)	Newly diagnosed people with ALL	As the use of asparaginase in the UK is driven by the UKALL protocols, the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort, as per the protocols. Patients who experience a relapse or are older than 65 would have regimens that do not include pegaspargase The submission therefore meets the scope in that it considers patients of relevance to decision-makers in the NHS.	The patient population described in the final scope are: “People with acute lymphoblastic leukaemia”. This is in line with the patient population described in the licence indication for pegaspargase: "Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients".
Int.	Pegaspargase plus standard chemotherapy	As per scope	N/A	The intervention described in the company submission matches the intervention described in the final scope: pegaspargase plus standard chemotherapy. However, the dose used in the economic model is not the recommended dose.
Com.	Non-pegylated forms of:	As per scope	Asparaginase treatment will be	The comparators are in line with

	• Escherichia coli-derived L-asparaginase plus standard chemotherapy • Erwinia chrysanthemi-derived L-asparaginase (crisantaspase) plus standard chemotherapy	Treatment sequences modelled: 1. Pegaspargase >> Erwinia-derived asparaginase 2. Native E. coli-derived asparaginase >> Erwinia-derived asparaginase 3. Erwinia-derived asparaginase >> Pegaspargase 4. Erwinia-derived asparaginase >> Native E. coli-derived asparaginase	given as part of 1st line ALL treatment, and in cases of hypersensitivity reactions, a switch to an alternative (2nd line) asparaginase will be necessary. Although the licence for pegaspargase does not preclude its use as a 2nd line asparaginase therapy there is not currently a clinical scenario in the UK in which pegaspargase would be used in this setting, since patients would not receive native E. coli- or Erwinia-derived asparaginase as a 1st line asparaginase. In addition, with the availability of Erwinia-derived asparaginase, patients experiencing hypersensitivity to pegylated or native E. coli enzyme would in practice no longer be switched to the other E. coli enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinia-derived enzyme following hypersensitivity to pegaspargase A further complication in this field is that native E. coli-derived asparaginase is not licensed for use in the UK. Unavailability in the	the final NICE scope

			United States has seen it removed from United States treatment guidelines (NCCN 2015). Erwinia derived asparaginase is licensed in the UK and, although the wording of its indication does not limit its use to a specific line of asparaginase therapy, the product is only positioned in treatment protocols as a 2nd line asparaginase. Hence, with this context in mind, the current standard of care treatment pathway in the UK is pegaspargase 1st line followed by Erwinia-derived enzyme in cases of hypersensitivity, and this treatment sequence has been modelled. Although not currently part of UK clinical practice and unrealistic given the current unavailability of native E. coli enzyme and the 2nd line positioning of Erwinia, alternative switching scenarios of native to Erwinia, Erwinia to pegylated, and Erwinia to native could be clinically possible, and are also modelled.	
Out.	The outcome measures to be considered include:	As per scope except for progression-free survival which wasn't included	Event free survival was used in many studies and this outcome will incorporate progression free	All outcomes in the scope are included in the company submission, except for

	• Overall survival • Progression-free survival • Treatment response rates • Event-free survival • Asparaginase activity • Adverse effects of treatment • Health-related quality of life		survival. In addition, there are a large amount of patients, especially paediatric patients, who are cured and as such do not progress	progression-free survival which wasn't reported in any of the included studies. Instead, event free survival was used in many studies and this outcome incorporates progression free survival according to the company.

2 The technology and the treatment pathway

2.1 Pegaspargase (Oncaspar, Baxalta) is a polyethylene glycol conjugate of Escherichia coli derived L-asparaginase. L- asparaginase is an enzyme that hydrolyses asparagine (an amino acid) leading to cell death. Pegaspargase received its marketing authorisation in January 2016. It is given intravenously. In September 2008, pegylated L-asparaginase was granted orphan status by the European Medicines Agency for the treatment of ALL.

2.2 The specific treatment regimens, drug selection, dosages, and treatment duration differ depending on patient age (adults and younger patients), and among different subtypes of ALL, but multi-agent chemotherapy is generally used and treatment is grouped into three main phases:

- **Remission/Induction**: The aim of treatment is to clear as many leukaemic cells as possible and achieve bone marrow remission (less than 5% blasts). Drugs used in this phase include vincristine, corticosteroid (e.g. prednisone), cyclophosphamide, anthracyclines (e.g. doxorubicin), and asparaginase (3 types are available: native E coli derived asparaginase, Erwinia derived asparaginse and pegaspargase).
- **Intensification/consolidation**: The aim of treatment is to irradiate residual disease. Drugs used during this phase are cytarabine, methotrexate and 6-mercaptopurine.
- **Maintenance**. The aim of treatment is to prevent disease relapse. Drugs used during this phase are 6-mercaptopurine, methotrexate, corticosteroids, and vincristine.

2.3 Treatment decisions also take into account patient's disease risk category:

- **Low-risk ALL**: Aged between age 1 and 10 years, less than 50,000 white blood cells per cubic millimetre (mm^3) of blood when

diagnosed, leukaemia cells with chromosome changes that respond well to treatment, negative central nervous system status (low amount of leukemic cells in spinal fluid), rapid early response to induction treatment.

- **High-risk ALL**: Aged less than age one or older than ten years, more than 50,000 white blood cells/mm^3 of blood when diagnosed, positive CNS status (high amount of leukemic cells in spinal fluid) leukemia cells with chromosome changes that are more difficult to treat (mixed-lineage leukaemia gene rearrangement).
- **Very high-risk ALL**: Patient also has leukaemia cells that have parts of chromosome 9 and chromosome 22 fused together (Philadelphia chromosome) or leukaemia cells which have too few chromosomes (hypodiploid).
- **Standard risk ALL**: patient does not share any features with the low-risk or high-risk groups.

2.4 According to the company, pegaspargase has been included in NHS England baseline commissioning since April 2013. In addition, pegaspargase has been the first line asparaginase in UK practice mandated since 2003, being adopted in UKALL protocols for children, adolescents and young adults (UKALL 2003, which completed enrolment in 2010; UKALL 2011) and for adults (UKALL14). The company stated as such although the marketing authorisation for pegaspargase does not preclude its use as a second line asparaginase therapy, there is not currently a clinical scenario in which pegaspargase would be used as a second line asparaginase therapy, since patients would not receive native E. coli-or Erwinia derived asparaginase as a first line asparaginase. The company highlighted that UKALL protocols have seen clinicians adopt pegaspargase at a dose of 1,000 IU/m^2 lower than the summary of product characteristics recommended dose of 2,000-2,500 IU/m^2.

2.5 The treatment pathway for pegaspargase for the treatment of ALL is shown in figure 1.and the treatment protocols for UKALL 2003,

UKALL2011 and UKALL14 are shown below. For further details of UKALL 2003, UKALL2011 and UKALL14, see sections 4.4, 4.13-21, 4.35-4.40.

Table2: Treatment protocol UKALL2003

Risk category	Standard	Low	Intermediate	High
Induction (3-5 weeks)	2 doses 1,000 IU/m^2	2 doses at 1,000 IU/m^2	2 doses at 1,000 IU/m^2	2 doses 1,000 IU/m^2
Consolidation (4-9 weeks)	-	-	-	-
Interim maintenance phase 1 (8 weeks)	-	-	-	2 doses at 1,000 IU/m^2
Interim maintenance phase 2 (8 weeks)	-	-	-	2 doses at 1,000 IU/m^2
Delayed intensification phase 1 (8 weeks)	1 dose at 1,000 IU/m^2	1 dose at 1,000 IU/m^2	1 dose at 1,000 IU/m^2	3 doses at 1,000 IU/m^2
Delayed intensification phase 2 (8 weeks)	1 dose at 1,000 IU/m^2	-	1 dose at 1,000 IU/m^2	3 doses at 1,000 IU/m^2

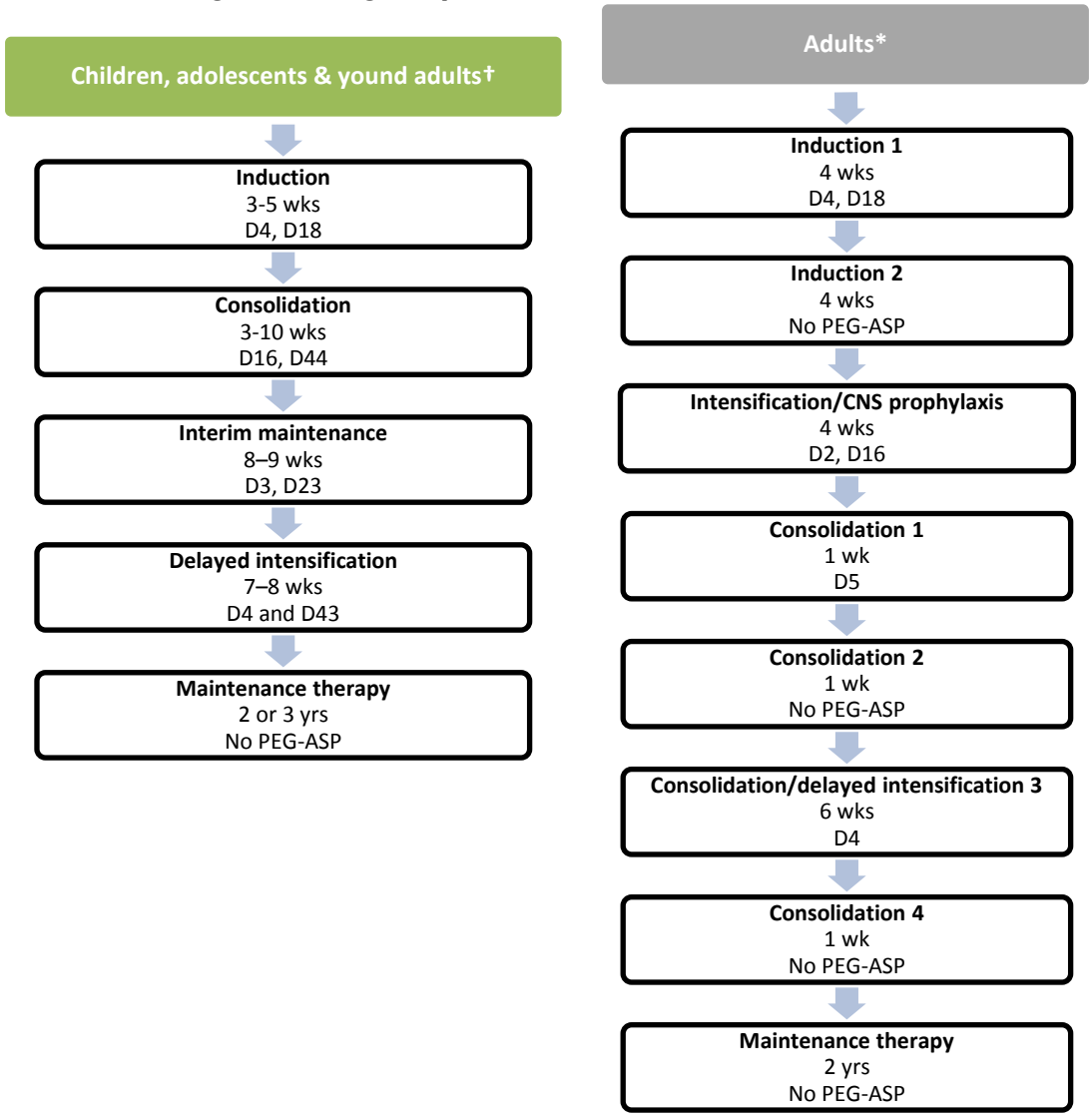
Table 3: Treatment protocol UKALL2011

Risk category	Standard	Slow early response*	High risk cytogenetics**	High
Induction phase 1 (4 weeks)	2 doses at 1,000 IU/m^2	1 dose () at 1,000 IU/m^2	1 dose at 1,000 IU/m^2	2 doses at 1,000 IU/m^2
Consolidation (3-10 weeks)	-	2 doses at 1,000 IU/m^2	2 doses at 1,000 IU/m^2	-
Interim maintenance phase 1 (8 -9 weeks)	-	2 doses at 1,000 IU/m^2	2 doses at 1,000 IU/m^2	-
Delayed intensification phase 1 (7 -8 weeks)	1 dose on day 4 at 1,000 IU/m^2	1 dose at 1,000 IU/m^2	2 doses at 1,000 IU/m^2	1 dose at 1,000 IU/m^2
*Defined on the basis of minimal residual disease following induction therapy; ** or Downs syndrome				

Trial protocol UKALL2014

- Two induction phases (4 weeks each): 1,000 IU/m^2 IV pegaspargase on days 4 and 18 of first induction phase.
- Intensification/CNS prophylaxis (4 weeks): 1,000 IU/m^2 IV pegaspargase on days 2 and 16.
- Two consolidation phases (Cycle 1 and 2; 1 week each): 1,000 IU/m^2 IV pegaspargase on day 5 of first consolidation phase
- Consolidation/delayed intensification (Cycle 3; 6 weeks): 1,000 IU/m^2 IV pegaspargase on day 4 of cycle 3.
- Consolidation (Cycle 4; 1 week)
- Maintenance (2 years).

Figure 1. Treatment Algorithm for pegaspargase (Source: Company submission Figure 1, Page 34).



Abbreviations: D, days; PEG-ASP, pegaspargase; wks, weeks
Source: CS, page 34; derived from UKALL 2011 and UKALL 14 protocols.
Wks represent overall length of treatment phase. D represents day of phase on which pegaspargase is administered. Pegaspargase is not administered in some treatment phases as denoted by "No PEG-ASP".
Pegaspargase dose 1,000 IU/m^2 throughout.
†In UKALL 2011 duration of treatment phases and total number of pegaspargase doses in each phase vary depending on which of three regimens that patients are assigned to, based on MRD risk. The total number of pegaspargase doses varies between three and seven between regimens.
*In UKALL 14, patients receive between three and six pegaspargase doses depending on their age and whether or not they have had a transplant.

Table 4 Technology

	Pegaspargase	Native E.coli derived L-asparaginase	Erwinia chrysanthemi-derived L-asparaginase
Marketing authorisation	Acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.	N/A	Used in combination with other anti-neoplastic agents to treat acute lymphoblastic leukaemia
Administration method	Either intermuscular or intravenous infusion	Intravenous infusion	Intravenous injection or by intramuscular or subcutaneous injection.
Cost	£1296.19 per vial Costs are based on a dose of 1,000 IU/m^2 which is used in clinical practice, which equates to 1 vial of pegaspargase per dose. Although the SmPC recommended dose is higher (2,000-2,500 IU/m^2), 1 vial would be used per treatment administration	£70.87 per vial The mean intravenous daily dose in children and adults in the monotherapy is 200 U per kg body weight (BW) or 6000 U per m^2 body surface area (BSA)	£613.00 per vial For all patients the usual dose is 6,000 Units/m^2 body surface area (200 Units/kg of body weight), three times a week for three weeks.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The clinical experts agreed that pegaspargase is the standard treatment for acute lymphoblastic leukaemia in clinical practice. A clinical expert stated that currently paediatric and adult patients with newly diagnosed acute lymphoblastic leukaemia are primarily treated in the context of a clinical trial.

3.2 The patient expert explained that whilst improving survival is the most important outcome for patients, any treatment that improved quality of life by reducing side effects or other aspects of the patient experience would be highly valued by patients. The patient experts explained that pegaspargase requires fewer injections than other types of asparaginase which has a positive impact on patient's quality of life.

3.3 Comments received from patient groups stated that a diagnosis of acute lymphoblastic leukaemia greatly affects patients and their family and friends. Therefore access to effective treatments which improve patient quality of life is of particular importance.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company carried out 2 systematic reviews to identify key clinical evidence in two populations:

- Children and young people newly diagnosed with ALL who received pegaspargase as an initial (first line) treatment (hereby referred to as paediatric population).
- Children and adults with ALL (no age criteria) who were treated with native E coli-derived asparaginase, Erwinia derived asparaginase or pegaspargase at any stage in the treatment pathway (hereby referred to as adult population).

4.2 The evidence presented in the company's submission focussed on 2 studies (CCG-1962 and UKALL 2003). CCG-1962 was a multicentre randomised controlled trial comparing pegaspargase with native E coli derived asparaginase. UKALL 2003 was a single arm multicentre trial of pegaspargase.

4.3 CCG-1962 included 118 patients (aged 1-9 years) with newly-diagnosed with ALL were randomised to receive either pegaspargase (2,500 IU/m^2 intramuscular [IM] on day 3 of induction and each D1

phase) or native asparaginase (6,000 IU/m^2 IM 3 times per week, for 9 doses in induction, and 6 doses in each DI phase). Treatment duration for girls and boys was 2 and 3 years, respectively. There was a greater proportion of people in the pegaspargase group aged 1-2 years (34% versus 19%) and people with a blood platelet count at diagnosis of less than 50,000 (51% versus 34%) than the placebo group. The company stated that none of these factors or any other risk factors were statistically significantly different between the treatment arms (for further details of the baseline patient characteristics, see table 10, page 57 of the company submission). The primary outcome measure in CCG-1962 was incidence of high-titre asparaginase antibodies in DI no.1. Secondary outcomes included event free survival (events included: induction death, no induction response, relapses at any site, and second malignant neoplasm). For further details see Table 8, page 48 of the company submission.

4.4 UKALL 2003 included 3,207 children and young adults (aged 1-24 years) with ALL representing 97% of the eligible patient population with ALL aged 1-24 years in the UK and Ireland. All patients in the trial were treated with 1,000 IU/m^2 IM per dose of pegaspargase and between 4 and 12 doses depending on their clinical risk classification following induction. Patients classified with low risk minimal residual disease were randomised to receive either standard treatment (2 D1 cycles; n=260) or reduced treatment (1 D1 cycle; n=260). Patients classified with high risk minimal residual disease were randomised to receive either standard treatment (2 D1 cycles) or augmented treatment (n=267). Treatment duration for females and males was 2 years and 3 years, respectively, from the start of interim maintenance. MRD, minimal residual disease. The company stated that no difference was observed in the characteristics of minimum residual disease low-risk or high-risk patients who did and did not undergo randomisation. There were no statistically significant differences

between the randomised arms in either of the minimum residual disease risk groups. For further details see table 11, pages 59-60 of the company submission. The primary outcomes were event free survival (defined as time to relapse, secondary tumour or death) and overall survival (defined as time to death). For further details of the outcome measures see Tables 8, page 48 of the company submission.

4.5 The company also provided supportive evidence for the paediatric population. This included 3 trials which compared pegaspargase with native E coli derived asparaginase: CCG-1961, DFC1-91-01, and DFC ALL 05-001. In all 3 trials patients were to receive either pegaspargase (2,500 IU/m^2 IM or Intravenous [IV]) or native E. coli derived asparaginase (25,000 IU/m^2 IM).

- CCG-1961 included 2078 children and young adults (up to 21 years of age) with newly diagnosed high risk ALL. The primary outcomes were event-free survival and overall survival (for further details of the study, see Table 4.5, page 43 of the ERG report).
- DFC1-91-01 included 377 children and young adults (aged 1-18 years) with newly diagnosed standard risk (n=137) or high risk (n=240) ALL. The primary outcome was event-free survival at 5 years (for further details of the study, see Table 4.9, page 50 of the ERG report).
- DFC ALL 05-001 included 463 children and young adults (aged 1-18 years) with newly diagnosed ALL who had achieved complete remission. The primary outcome was safety (For further details of the study, see Table 4.10, page 551-52 of the ERG report). For details of all the supportive evidence provided by the company, see pages 74-103 of the company submission.

4.6 The clinical evidence for the adult population came from 3 trials (Douer 2007, Douer 2014 and Wetzler 2007).

- Douer (2007) was a prospective, non-randomised study in adults aged 17–55 years with newly diagnosed ALL. Patients were treated with pegaspargase at a dose of 2,000 IU/m^2 administered by intravenous infusion at the induction phase of treatment. The aim of the study was to assess the pharmacodynamics and safety of intravenous pegaspargase and outcomes assessed included response.
- Douer (2014) was a prospective, non-randomised study in adults aged 18–57 years with newly diagnosed ALL. Patients were treated with pegaspargase at a dose of 2,000 IU/m^2 administered by intravenous infusion at an induction phase 1 and 2, intensification phase 1 and 2 and delayed re-induction 1 and 2 of treatment. The aim of the study was to assess pharmacokinetics and safety of intravenous pegaspargase. Outcomes assessed included complete response, overall survival and disease free survival.
- Wetzler (2007) was a prospective, non-randomised study in adults with ALL who did and did not achieve asparagine depletion following treatment with pegaspargase. Patients were treated with 2,000 IU/m^2 of pegaspargase administered by intravenous infusion at an induction and intensification phase of treatment. Outcomes assessed included complete response, overall survival and disease free survival. For further details of the studies, see pages 104-107 of the company submission.

ERG comments

4.7 The ERG was satisfied that all relevant studies were included in the company submission.

4.8 The ERG stated that it disagreed with the company that CCG-1962 and UKALL2003 were the most important trials to assess the clinical effectiveness of pegaspargase.

- The ERG did not consider CCG-1962 to be key to this appraisal because the trial population were young children aged between 1

and 9 years of age which is only a small proportion of the population eligible for treatment with pegaspargase. However the ERG noted that it was the only head to head study which compared pegaspargase with E.coli derived asparaginase in patients with newly diagnosed ALL who were treated from induction.

- The ERG had concerns about the CCG-1962 trial. It noted that the trial had a small sample size which equated to 59 patients in each treatment arm. The ERG considered CCG-1962 to be of poor quality. It considered the randomisation process was unclear and treatment allocation concealment was unclear which could result in a high risk of bias, particularly as the trial design was an open label study.
- The ERG had concerns about the UKALL 2003. It considered it to have limited relevance for this NICE appraisal because it did not include a relevant comparator.

4.9 The ERG identified 7 RCTs in the company's searches which it considered relevant for this NICE appraisal. Five RCTs compared pegaspargase with E. coli derived asparaginase, and 2 RCTs comparing E. coli derived asparaginase with Erwinia derived asparaginase.

- Four of the 5 RCTs which compared pegaspargase with native E. coli derived asparaginase (CCG-1961, CCG-1962, DFCI-91-01 and DFCI ALL 05-001) were presented in the company's submission. The fifth RCT identified by the ERG was the DFCI ALL 05-01trial which included children and young adults (aged 1-18 years) with newly diagnosed standard risk ALL who achieved complete response during induction. For further details, see table 4.2 page 35 of the ERG report.
- The 2 RCTs which compared native E. coli derived asparaginase with Erwinia derived asparaginase were the DFCI-95-01 and EORTC CLG 58881 trials. DFCI-95-01 included children and young adults (aged 0-18 years) with newly diagnosed standard risk or high

risk ALL. The study compared E. coli derived asparaginase 25000 IU/m^2/week IM with Erwinia derived asparaginase 25000 IU/m^2/week IM during the Intensification phase. EORTC CLG 58881 included children and young adults (aged 0-18 years) with newly diagnosed standard, intermediate or high risk ALL. The study compared E. coli derived asparaginase 10000 IU/m^2 /twice weekly IV with Erwinia derived asparaginase 1000 IU/m^2/twice weekly IV. For further details, see table 4.2 page 35 of the ERG report.

Clinical trial results

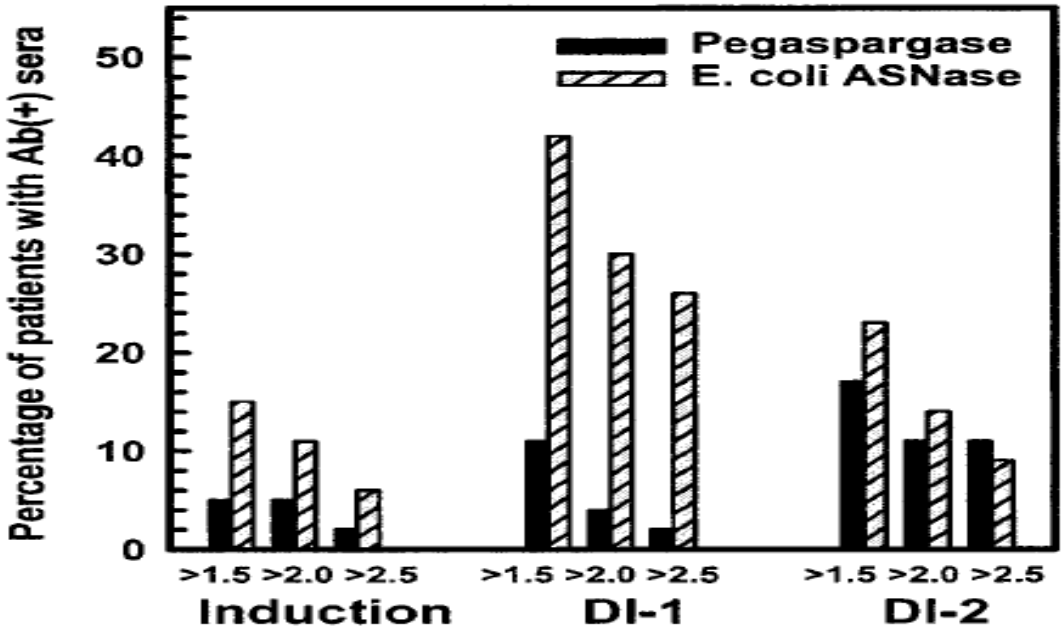
Paediatric population

CGC-1962

Immunogenicity

4.10 The primary endpoint of CCG-1962 was to establish whether the incidence of high-titre anti-asparaginase antibodies in children treated with pegaspargase was decreased by at least 50% in DI no. 1 compared with those treated with native asparaginase. A secondary endpoint was to establish whether the same decrease occurred in DI no. 2. There was a statistically significantly lower proportion of patients with high levels (antibody ratio ≥2.5) of blood anti-asparaginase antibodies at the delayed intensification first stage (D1-1) of the treatment pathway in the pegaspargase group compared with the native E. coli derived asparaginase group (2% vs. 26%, p=0.001). There was no statistically significantly lower proportion of patients with high levels (antibody ratio ≥2.5) of blood anti-asparaginase antibodies at induction or delayed intensification second stage (D1-2) of the treatment pathway in the pegaspargase group compared with the E. coli derived asparaginase group. See Figure 2 for further details.

Figure 2: Proportion of patients with anti-asparaginase antibodies at each stage of the treatment pathway in CGC-1962 (source figure 5, page 62 of the company submission).



4.11 Antibody ratios measured during induction and during DI no. 2 cycles of treatment did not significantly differ between the pegylated or native asparaginase treatment arms (Table 5).

Table 5: Asparaginase antibody formulation in CCG-1962 (source Table 13, page 63 company submission)

Chemotherapy phase	Native asparaginase mean ratio† ± SEM (n)	pegaspargase mean ratio† ± SEM (n)	p-value
Induction	2.3 ± 0.9 (47)	1.3 ± 0.2 (41)	NS
DI no. 1	3.0 ± 0.7 (43)	1.9 ± 0.8 (47)	p=0.01‡
DI no. 2	2.1 ± 0.6 (45)	2.1 ± 0.8 (45)	NS

Abbreviations: DI, delayed intensification; NS, not significant; SEM, standard error of the mean.

† Calculated as the ratio of antibody over negative control, ‡ Wilcoxon 2-sample test

Event free survival

4.12 In CCG-1962 there was no statistically significant improvement in event-free survival measured at 3 years with pegaspargase compared with E. coli derived asparaginase. Updated analysis at 5 and 7 years showed improvement in event-free survival with pegaspargase compared with E. coli derived asparaginase, but the results were not statistically significant (see table 6).

Table 6: Event free survival at 3, 5, and 7 years in CCG-1962 (source Table 17, page 65 of the company submission)

Event free survival	Native E. coli asparaginase % (95% CI)	Pegaspargase % (95% CI)
3-year EFS†	79 (68–90) [78]	83 (73–93) [85]
5-year EFS†	73 (61–85)	78 (67–88)
7-year EFS†	66 (52–80)	75 (63–87)

Abbreviations: CI, confidence interval; EFS, event-free survival; SmPC, summary of product characteristics.
† All EFS data are sourced from the Oncaspar® SmPC; 3 year data presented by Avramis et al are shown in square brackets.

UKALL 2003

Event-free survival

4.13 **All patients**: Event-free survival measured at the end of the trial 5 years follow- up (October 2011) was 87.2% (95% C.I 85.8 to 88.6). The event-free survival measured at a further 2 years follow-up (October 2013) was 87.3% (95% C.I 86.1 to 88.5). For further details see table 18 and figures 7 and 8, pages 66-68 of the company submission.

4.14 **Minimal residual disease Low risk**: Event-free survival at the end of the trial 5 years follow- up (October 2011) was 95.5% (95% C.I 92.8 to 98.2) in patients with low risk ALL. There was a 1% non-statistically significant difference in event free survival between the patients receiving reduced and standard treatment with low risk ALL. For

further details see table 19 and figure 9, pages 68-9 of the company submission. .

4.15 **Minimal residual disease High risk**: Event-free survival at the end of the extended trial follow- up (October 2013) there was a statistically significant difference in event free survival between the patients receiving standard treatment and augmented treatment with high risk ALL (OR=0.61, 95% C.I 0.39 to 0.98, p=0.04). For further details see table 20, and figure 10, pages 70-71 of the company submission.

Overall survival

4.16 **All patients:** Overall survival measured at 5 years follow- up (October 2011) was 91.5% (95% C.I 90. To 92.7). Overall survival measured at a further 2 years follow-up (October 2013) was 91.63% (95% C.I 90.6 to 92.6). For further details see table 18 and figures 7 and 8, pages 66-68 of the company submission.

4.17 **Minimal residual disease Low risk:** At the end of the extended trial follow-up (October 2013) there was a non- statistically significant difference in overall survival between the patients receiving standard treatment and augmented treatment with low risk ALL (OR=0.67, 95% C.I. 0.19 to 2.30, p=0.53). For further details see table 19 and figure 9, pages 68-9 of the company submission.

4.18 **Minimal residual disease High risk:** Overall survival at the end of the extended trial follow- up (October 2013) there was a non-statistically significant difference in overall survival between the patients receiving standard treatment and augmented treatment with high risk ALL (OR=0.67, 95% C.I. 0.38 to 1.17, p=0.16). For further details see table 20, and figure 10, pages 70-71 of the company submission.

Relapse risk

4.19 **All patients:** The cumulative risk of relapse measured at 5 years follow- up (October 2011) was 8.85% (95% C.I 7.8 to 10.0). The cumulative risk of relapse measured at a further 2 years follow-up (October 2013) was 8.8% (95% C.I 7.8 to 9.8). For further details see page 71 of the company submission.

4.20 **Minimal residual disease Low risk:** At 5 years follow- up (October 2011) there was a non- statistically significant difference in the cumulative risk of relapse between the patients receiving standard treatment and augmented treatment with low risk ALL (OR=0.55, 95% CI 0.21 to 1.43, p=0.23). For further details see page 71of the company submission.

4.21 **Minimal residual disease High risk:** At 5 years follow- up (October 2011) there was a statistically significant difference in the cumulative risk of relapse between the patients receiving standard treatment and augmented treatment with high risk ALL (OR=0.55, 95% C.I. 0.33 to 0.94, p=0.03). For further details see page 71 of the company submission.

Results from supporting studies for the paediatric population (identified by the company and ERG)

Table 7: Summary of the results from the supporting trials of the paediatric populations (source Table 4.16, page 58 of the ERG report)

Pegaspargase versus E. coli asparaginase				
Study	Population Age (years)	Pegaspargase %	E.coli %	Difference %
Event free survival at 5 years				
CCG-1961	1 to 21	81.2 (SD 2.4)	71.7 (SD 2.7)	9.5
CCG-1961	16 to 21	81.8 (SD 5.4)	66.9 (SD 6.7)	14.9
DFCI-91-01	1 to ≤18	78.0 (SD 4.0)	84.0 (SD 4.0%)	6.0
DFCI-ALL 05-001	1 to18	90.0 (95% C.I 86.0 to 94.0)	89.0 95% C.I 85.0 to 93.0)	1.0
Overall survival at 5 years				
CCG-1961	1 to 21	88.7 (SD 1.9)	83.4 (SD 2.2)	5.3
CCG-1961	16 to 21	83.2 (SD 6.8)	75.6 (SD 7.7)	0.9
DFCI-ALL 05-001	1 to 18	96.0 (95% C.I 93.0 to 98.0)	94.0 (95% C.I 89.0 to 96.0)	2.0
E. coli asparaginase versus Erwinia asparaginase				
Study	Population Age (years)	Erwinia %	E.coli %	Difference %
Event free survival at 10 years				
DFCI-95-01	0 to 18	75.2 (SE 3.8)	84.6 (SE 3.4)	0.4
Event survival at 6 years				
EORTC-CLG 58881	0 to 18	59.8 (SE 2.6)	73.4 (SE 2.0)	6.0
Overall survival at 10 years				
DFCI-95-01	0 to 18	75.2 (SE 3.8)	84.4 (SE 3.4)	9.2
Overall survival at 6 years				
EORTC-CLG 58881	0 to 18	75.1 (SE 2.3)	83.9 (SE 2.0)	8.8

Adult population

Douer 2007

4.22 The primary endpoint of the Douer (2007) study was to establish the remission rate in adults who received pegaspargase. Secondary endpoints were to establish the rate of asparagine depletion and level

of blood anti-asparaginase antibodies. After 1 intravenous dose of pegaspargase, 96% of patients had complete remission. All of the patients in the study had complete asparagine depletion 2 hours after the first dose of pegaspargase, and 1 patient developed anti-asparaginase antibodies.

Douer 2014

4.23 The primary endpoint of the Douer (2014) study was to establish the remission rate in adults who received pegaspargase. Secondary endpoints were disease free survival and overall survival. After the first induction phase of treatment, 96% of patients had complete remission. The rates of disease free survival and overall survival were 58% and 51% respectively after 7 years follow-up.

Wetzler (2007)

4.24 The primary endpoint of the Wetzler (2007) study was to compare the disease free survival and overall survival in adult patients who had received pegaspargase and had asparagine depletion compared with those without asparagine depletion. The secondary endpoint was to establish the level of blood anti-asparaginase antibodies after treatment with pegaspargase. After the induction and intensification phase of treatment, the patient group without asparagine depletion had a statistically significantly lower rate of disease free survival (HR 2.21, 95% C.I 1.19 to 4.13, p=0.012) and overall survival (HR 2.37, 95% C.I 1.38 to 4.09). There was a statistically significantly lower rate of anti-asparaginase antibodies in the group which had asparagine depletion compared with the group which did not achieve asparagine depletion (9.5% versus 31.8%, p=0.012).

ERG comments

4.25 The ERG stated that overall it agreed with the company that there was no evidence to conclude that there was a difference in the clinical effectiveness of pegaspargase and E.Coli derived asparaginase.

However, the ERG stated that it was unclear whether this was because of a lack of evidence or lack of a difference in effect. None of the included RCTs were powered to assess equivalence and it was not possible to pool results from different studies.

4.26 The ERG highlighted that it was important to note that the UKALL protocols use a dose of 1,000 IU/m^2 for pegaspargase. However, the summary of product characteristics (SmPC) recommended dose is higher (2,000-2,500 IU/m^2). Moreover, there is no comparative evidence for this lower dose of pegaspargase versus other types of asparaginase. All trials comparing pegaspargase with E. coli derived asparaginase compared 2,500 IU/m^2 pegaspargase with 6,000 IU/m^2 E. coli derived asparaginase. In addition, there are no studies that provide a head-to-head comparison of pegaspargase used at 1,000 IU/m^2 and 2,500 IU/m^2 doses.

4.27 The ERG noted that none of the studies in the adult population included a control group. The ERG considered that these studies provided no evidence for the relative effectiveness of pegaspargase compared with other asparaginases.

Meta-analyses

4.28 The company reported the result of a meta-analysis of 39 studies.in the paediatric population.

[redacted] For further details, see pages 108-126 of the company submission.

Indirect Treatment comparison

4.29 [redacted] For further details, see page 127 of the company submission.

ERG comments

4.30 The ERG [redacted].

Adverse effects of treatment

4.31 The company reported the results of 5 studies (CG162, UKALL 2003, Douer 2007, Douer 2014, Wetzler 2014) comparing pegaspargase with E. coli derived asparaginase. None of the studies showed a statistically significant difference in adverse events profiles between treatments.

4.32 The company reported the results of 2 studies (DFCI-95-01, EORTC CLG 58881) that it had identified which compared equal doses of E. coli derived asparaginase with Erwinia derived asparaginase. Both studies showed that Erwinia derived asparaginase was associated with a lower incidence of toxicity than native E. coli derived asparaginase.

ERG comments

4.33 The ERG noted the results of these studies, but did not provide further comment.

On-going studies

4.34 The company provided details of 2 ongoing studies: UKALL 2011(in children, adolescents and young adults) and UKALL14 (adult patients).

4.35 UKALL 2011 opened in April 2012, is ongoing, and enrolling patients newly diagnosed with ALL aged 1-24 years. Enrolment closes in April 2018. Patients will receive, as a component of multi-agent chemotherapy, and on the basis of National Cancer Institute (NCI) risk and MRD assessment, between three and seven doses of pegaspargase (1,000 IU/m^2 IM). Asparaginase will be spread over the course of one of three increasing-intensity treatment regimens (Regimen A-C), adopted from the UKALL 2003 study protocol, consisting of some or all of the phases listed below. The duration of treatment phases and number of pegaspargase doses received depends on which of the three regimens the patient is assigned to, according to risk. NCI standard-and high-risk patients receive three doses (Regimen A or B). Patients with slow early response on the basis of MRD following induction therapy, patients with high-risk cytogenetics, and patients with Down syndrome with slow early response receive seven doses (Regimen C).

- Induction (3-5 weeks): 1,000 IU/m^2 IM pegaspargase on days 4 (regimen A & B) and 18 (All regimens).
- Consolidation (3-10 weeks): 1,000 IU/m^2 IM pegaspargase on days 16 and 44 (Regimen C only).
- Interim maintenance (8-9 weeks): 1,000 IU/m^2 IM pegaspargase on days 3 and 23 (Regimen C only).
- Delayed intensification (7-8 weeks): 1,000 IU/m^2 IM pegaspargase on days 4 (All regimens) and 43 (regimen C only).
- Maintenance therapy (2 or 3 years from the start of interim maintenance for girls and boys, respectively).

4.36 The aim of UKALL 2011 is to assess whether further refinement of MRD-based risk stratification and treatment regimen improves survival while reducing the overall burden of therapy in children and young adults with ALL. The primary outcomes being measured in UKALL 2011 include bone marrow/central nervous system relapse and toxicity, and secondary outcomes include rate of remission,

event-free survival, overall survival, quality of life, and treatment-related mortality and morbidity.

4.37 UKALL14 investigates the efficacy and toxicity of pegaspargase in a solely adult ALL population. Adult patients aged 25-65 years newly diagnosed with ALL may be considered for enrolment in Study UKALL14 which opened in December 2010 and closes in December 2016. It is anticipated that UKALL14 will enrol 720 adult patients currently accounting for approximately 85% of all eligible adult patients with ALL.

4.38 Depending on patient age and transplant eligibility, patients will receive a minimum of three and maximum of six doses of pegaspargase (1,000 IU/m^2 intravenous [IV]) over the course of the treatment regimen that consists of:

- Two induction phases (4 weeks each): 1,000 IU/m^2 IV pegaspargase on days 4 and 18 of first induction phase.
- Intensification/CNS prophylaxis (4 weeks): 1,000 IU/m^2 IV pegaspargase on days 2 and 16.
- Two consolidation phases (Cycle 1 and 2; 1 week each): 1,000 IU/m^2 IV pegaspargase on day 5 of first consolidation phase.
- Consolidation/delayed intensification (Cycle 3; 6 weeks): 1,000 IU/m^2 IV pegaspargase on day 4 of cycle 3.
- Consolidation (Cycle 4; 1 week).
- Maintenance (2 years).

4.39 Following induction, patients in complete remission who have a sibling donor (or are high-risk but with no sibling donor), receive an allograft. Standard-risk patients, ineligible for allograft, continue on multi-agent chemotherapy. Patients aged ≥ 41 years will not receive the pegaspargase dose on day 4 of the first induction phase and Ph+ patients will not receive treatment with pegaspargase.

4.40 The primary outcomes being measured in UKALL14 include event-free survival and toxicity, and secondary outcomes include anti-asparaginase antibodies, overall survival, complete response/remission, minimal residual disease quantification after the first induction phase, and death in complete response.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a de novo model (combination of a decision tree and health state transition Markov model) comparing pegaspargase, E.coli derived asparaginase and Erwinia derived asparaginase for children and young people newly diagnosed with ALL treated with pegaspargase as an initial first line treatment (paediatric population) and adults with ALL treated with pegaspargase at any stage of the treatment pathway (adult population). The decision tree starts at treatment initiation of newly diagnosed ALL patients. As a first step, the decision tree was used to model the patient flow during treatment administration. It took into account the dosing, frequency and potential hypersensitivity of asparaginase in different treatment phases. Parallel to the decision tree, the Markov model was used to account for potential relapse/secondary tumour (R/ST) and death. Furthermore, the Markov model was used to extrapolate beyond the time horizon of the clinical trials (5 years).

5.2 The treatment received in the company's economic model aimed to reflect the different treatment phases in the UKALL2014 and UKALL2003 protocols. The paediatric population received 7 cycles of treatment (induction, consolidation, interim maintenance phase, 1 cycle, delayed intensification phase –1 cycle, interim maintenance phase – 2 cycles, delayed intensification phase -2 cycles and continuation phase –1 cycle). The adult population received 5 cycles of treatment (induction, maintenance and consolidation-1 cycle),

,consolidation 3 cycles, and maintenance 1 cycle) The number of doses of E. coli derived asparaginase and Erwinia derived asparaginase was assumed to be 6 times higher than pegaspargase(6 doses of E. coli derived asparaginase or Erwinia derived asparaginase of per 1 dose of pegaspargase). This assumption was based on the opinion of 2 clinical experts contacted by the company.

5.3 Figure 5.3 on page 71 of the ERG report shows the general structure of the decision tree model. In the decision tree model, patients start with 1 of the 2 asparaginase agents: pegaspargase, E. coli derived asparaginase or Erwinia derived asparaginase. For all 3 asparaginase agents, it was assumed that hypersensitivity occurred after 2 treatment dosages. In case of hypersensitivity, patients switched to a different asparaginase treatment (second line treatment). Otherwise, patients continued the first line treatment for the remaining treatment protocol. During second line treatment, patients may again develop hypersensitivity after 2 dosages and asparaginase treatment was then discontinued. The decision tree followed the treatment protocol. Since the treatment protocol differs between subgroups, separate decision trees were modelled for the following subgroups: paediatric high risk, paediatric intermediate risk, paediatric standard risk, older adults (41 - 65 years) and younger adults (26 - 41 years).

5.4 In the decision tree model, the timing of the hypersensitivity and the subsequent treatment switch differed between treatment options and age and risk groups. First, fewer administrations were required for pegaspargase compared with E. coli and Erwinia derived asparaginase as a result of a preferential half-life. Consequently, hypersensitivity occurred at a later moment in time (later treatment phase) in patients treated with pegaspargase. Furthermore, the dosing schedule of asparaginase depends upon the age and the risk of the patient. This differential dosing schedule also impacts the timing

of the hypersensitivity. Older patients and patients classified as high risk developed hypersensitivity earlier in time.

5.5 The Markov model was different for children and adults. The Markov model for the paediatric population had 3 health states: event-free survival; survival with relapse/secondary tumour and death (overall survival). The model for the adult population had 2 health states: alive and death. A variable cycle length was used during the treatment period because the different treatment phases all had a unique duration. Once the treatment was completed, the Markov model consisted of yearly cycles. A lifetime horizon was applied. The company based the analysis from an NHS and personal social services perspective, and costs and benefits were discounted at an annual rate of 3.5%.The model structures for the paediatric and adult populations are shown in figures 3 and 4 respectively.

Figure 3: Model structure (paediatric population)

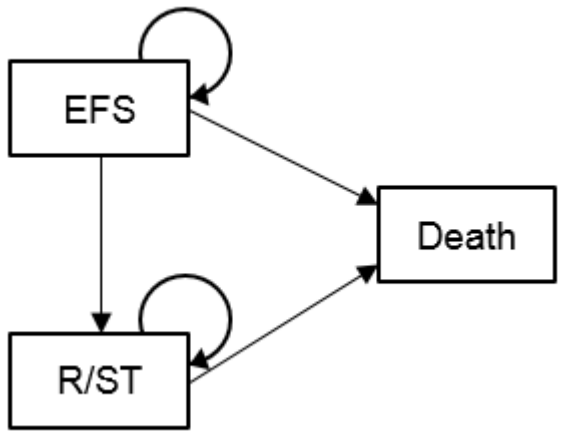
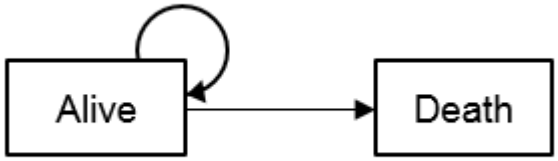


Figure 4: Model structure (adult population)



ERG comments

5.6 The ERG considered the structures of the decision tree and Markov models to be appropriate and the combination of the 2 models was well suited for the purpose of the appraisal. The ERG considered it appropriate that the paediatric and adult population were modelled separately.

5.7 The ERG was concerned about the assumption that overall survival was equal to event-free survival in adult patients with ALL. According to the company, this assumption was based upon expert opinion because of a lack of UK evidence. However, the ERG noted that 1 one clinical trial showed some differences between 5 year event-free survival and overall survival in adult patients with ALL (aged 15-59 years). The ERG commented that the study shows a magnitude of a difference that is more or less similar to the difference in event-free survival and overall survival in the paediatric population. Therefore only allowing differences between event-free survival and overall survival in the paediatric population was inconsistent. However, the ERG acknowledged that since the difference between overall survival and event-free survival was quite small, the impact on the ICER was expected to be marginal.

5.8 The ERG was also concerned about the assumption that hypersensitivity only occurred after 2 administrations of asparaginase. The ERG commented that several studies indicated higher rates of hypersensitivity if pegaspargase was administered more frequently.

The ERG stated that although it was expected that it would only marginally impact the ICER, it would better reflect clinical practice to allow the occurrence of hypersensitivity after more than 2 administrations.

Model details

Population

5.9 The paediatric population consisted of patients 25 years of age or less and was spilt into the categories of high, intermediate and low risk ALL. The adult population consisted of patients aged 26 to 65 years of age, spit into the age categories of 40 years or less and 41 years or more. The median age of the model paediatric population was 7.3 years and was 31.2 years for the age category 40 years or less and 52.6 years for the age category 41 years or more. The mean ages used in the model were obtained from the UKALL 2003 trial for the paediatric population and from Cancer Research UK (CRUK) ALL data for the adult population.

Interventions and comparators

5.10 The intervention being evaluated in the model was the use of pegaspargase as first line treatment and Erwinia derived asparaginase as second line treatment for patients developing hypersensitivity to pegaspargase. This treatment sequence was compared with 3 alternative treatment sequences (see Table 8). Although Erwinia derived asparaginase is only used as second line treatment after hypersensitivity to first line asparaginase in current UK practice (UKALL 200319, 20 and UKALL 1416), its use as first line treatment is considered in 2 alternatives because Erwinia derived asparaginase was listed as a comparator in the final scope issued by NICE and its marketing authorisation in the UK is not limited to a specific line of asparaginase treatment. Since the administration of E. coli derived asparaginase after pegaspargase or vice versa was

considered unsuitable because of the risk of cross reactivity and subsequent hypersensitivity, these treatment sequence alternatives have not been modelled.

Table 8: Treatment alternatives in the cost effectiveness analysis (source Table 5.6, page 76 of the ERG report)

	1st line asparaginase	2nd line asparaginase (in case of hypersensitivity
Intervention	pegaspargase	Erwinia
Comparator 1	E coli	Erwinia
Comparator 2	Erwinia	pegaspargase
Comparator 3	Erwinia	E coli

Overall survival and event-free survival

5.11 The proportion of people in each health state of the Markov model was obtained from event free survival and overall survival data from the UKALL 2003 trial. Patients in the event free survival health state were assumed to be cured after 5 years of treatment. A general mortality risk, weighted by patient sex (proportion in each sex category obtained from UKALL 2003) was applied to patients in the event free survival health state. The mortality risk in the relapse/secondary tumour health state was increased to 90% in the model. In the paediatric population, 5-year overall survival was assumed to be 95%, 90% and 80% for the standard risk, intermediate risk and high risk groups, respectively. The 5-year event free survival was assumed to be 90%, 85% and 75% for the standard, intermediate and high risk groups. The survival curves were used to model patient populations transition through their respective health states (see figure 27 on page 157 of the ERG report for further details).

5.12 In the adult population of the event free survival and overall survival were assumed to be same (no survival with relapse/secondary tumour health state). In Adults, 5-year overall survival was assumed to be

40% in ≤40 year group (upper bound of published range) and 30% in the ≥41 year group. For further details see page 80 of the ERG report.

Hypersensitivity

5.13 Hypersensitivity was assumed to only take place after 2 doses of asparaginase. The company explained that the summary of product characteristics for pegasparagase states that hypersensitivity reactions of Grade 2 or higher were seen in ≥20% of the patients. However, this rate had been observed in patients treated with dosages of pegaspargase of 2,000 and 2,500 IU/m^2, while a dosage of 1,000 IU/m^2 is used in current UK clinical practice. Furthermore, some of these studies included patients who received pegaspargase as second line asparaginase following hypersensitivity to E. coli derived asparaginase. The company highlighted that this sequence increases the risk of hypersensitivity to pegaspargase. According to the company, only 1 study is currently available that reports the hypersensitivity rate of first line pegaspargase at a dosage of 1,000 IU/m^2. The study showed that overall, 2% of the patients developed hypersensitivity, with a range of <1% in patients with standard risk and 6% in patients with intermediate risk. The average rate of 2% was used by the Company as an input in the economic model for hypersensitivity both for first and second line pegaspargase treatment. This rate was also validated by clinical experts. For further details see page 81 of the ERG report.

Utility value estimates

5.14 None of the studies identified by the company included a generic measure of health-related quality of life (such as the EQ–5D) which could be used to estimate utility values. Also no studies using EQ–5D for patients with ALL in the UK were identified. Utility value estimates were obtained by using Health Utility Index (HUI) data obtained from a study by Furlong et al (2012) based on US and Canadian ALL

treatment protocols. The relative difference in quality of life estimates between the general UK population with ALL and the ALL patients in Furlong (2012) was applied to published EQ-5D estimates for the general population. A utility decrement of 0.014 was applied to patients experiencing hypersensitivity in the model. This estimate was obtained from the NICE clinical guideline 134 'Anaphylaxis'.

Table 9: Utility decrements in the company model (source Table 40, page 166 of company submission)

Paediatric	Ind. 25%	Cons. 16%	IM 1 12%	DI 1 12%	IM 2 12%	DI 2 12%	Cont. 7%	End week 0%
Adults	Ind. 25%	Int. 25%	Cons. 1 12%	Cons. 3 12%	Maint. 7%	End week 0%		

Abbreviations: Ind., induction; Int., intensification; Cons; consolidation; Cont., continuation; Maint., maintenance; IM, interim maintenance; DI, delayed intensification

5.15 Costs incorporated in the company's model included drug acquisition and administration costs and costs associated with administration of hypersensitivity reactions to treatment. The estimated treatment administration cost of £163 was based on half an hour administration and an hour monitoring by a band 6 nurse. The costs associated with a hypersensitive reaction of £470.00 in the model were obtained from the costing statement 2011 for NICE clinical guideline 134 ' Anaphylaxis'. The company undertook scenario analyses which varied the cost of a hypersensitivity reaction to pegaspargase from £72 (the lowest estimate in NICE clinical guideline 134) to £611 (the highest estimate in NICE clinical guideline 134) No other costs were included in the model.

Table 10: Unit costs associated with the technology in the model (source Table 44, page 175 of the company submission)

Items	Pegaspargase	E.coli asparaginase	Erwinia derived asparaginase
Technology cost	£1296.19 per vial		
		£70.87 per vial	
			£613 per vial
Administration cost	£163.50	£163.50	£163.50

Pegaspargase 3,750 IU vial; native E.coli asparaginase 10,000 IU vial; Erwinia 10,000 IU vial.

ERG comments

5.16 The ERG was concerned that the literature searches used to obtain studies for model inputs and parameters may not have identified all the available studies. The ERG stated that they were concerned that the company use of English language filters and basing the search on clinical effectiveness, which had study design filters may have resulted in the model inputs not being based on the most relevant available evidence.

5.17 The ERG considered it was appropriate that the model was adjusted according to different ALL risk groups and age groups. However the ERG considered that the rationale for defining high, medium and low risk ALL in the paediatric population it was unclear in the company submission. The ERG stated that it appeared that the risk categories had been obtained from the UKALL2003 trial but it noted that a slightly different categorisation had been used in the UKALL2011 trial (see table 5.5 on page 75 of the ERG report for further details of the risk group classification in the 2 studies).

5.18 The ERG also considered it was appropriate that patients aged 65 and older and patients with relapsed disease were not included in the model because asparaginase therapy would not be given to these patients in accordance with standard treatment protocols in clinical practice.

5.19 The ERG doubted whether the median age of the UKALL 2003 trial was more reliable than data from the CRUK since the inclusion of patients in the UKALL 2003 trial had been expanded over time. At the start of the study only patients up to 18 years were eligible, but the upper age limit was increased to 20 years in February 2006 and to 24 years in August 2007. It is therefore possible that the age of the paediatric population was slightly underestimated since older patients were only eligible in the last 5 years. Therefore, in the ERG base-case analysis, the starting age of the paediatric population was considered to be 7.3 years instead of 5 years.

5.20 The ERG agreed with the approach of the company to include all possible relevant comparators although these were currently not standard practice in the UK. By including Erwinia derived asparaginase as first line treatment in the cost effectiveness analysis, it has been possible to assess the cost effectiveness of pegaspargase fist line-followed by Erwinia derived asparaginase second line against all other possible treatment sequences. However, the ERG noted that the comparison of pegaspargase followed by Erwinia derived asparaginase compared with Erwinia derived asparaginase followed by pegaspargase does not inform the decision at hand, that is should pegaspargase be recommended for routine use in the NHS.

5.21 The ERG stated that a key weakness of the model was that there was no evidence on which to assess the relative clinical effectiveness of pegaspargase compared with E.coli derived asparaginase and Erwinia derived asparaginase in the adult population.

5.22 The ERG agreed with the company that there is no evidence to suggest that there is a difference in effectiveness between pegaspargase, E. coli derived asparaginase and Erwinia derived asparaginase. However, the ERG stated that it was unclear whether this was caused by the true absence of differences or a lack of well-powered comparative studies. Since it may be possible that the

effectiveness differs between asparaginase formulations, the ERG considered the assumption of equal effectiveness too simplistic.

5.23 The ERG stated that an important weakness of the model was that there was no evidence on which to assess the relative hypersensitivity rates of pegaspargase compared with E.coli derived asparaginase and Erwinia derived asparaginase for both model populations. The ERG questioned whether all hypersensitivity rates used as input for the cost effectiveness analysis reflected the proportion of patients who required a treatment switch because of hypersensitivity to asparaginase. With respect to the hypersensitivity to native E. coli derived asparaginase, the ERG agreed that 20% can be considered as a reliable and conservative estimate. However, there was no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinia derived asparaginase also reflected the proportion of patients who required a treatment switch. The rate of hypersensitivity to pegaspargase was based on the estimate of hypersensitivity in Vora et al. (2013). However, no definition of that rate had been provided and from the reported information it appeared most reasonable to assume that the reported percentage reflects the proportion of patients with a grade 3 or 4 adverse event. The ERG found another paper reporting hypersensitivity to pegaspargase given at a dosage of 1,000 IU/m^2. In that publication, the proportion of patients with a treatment switch has explicitly been reported and was 13.2%. The ERG has used this estimate in the ERG base case analysis.

Company's base-case results and sensitivity analysis

5.24 The results of the company's base-case analyses are presented in the tables 11-13.

Table 11: Company's base case results for the whole population (source Table 5. 13, page 96 of the ERG report)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.>Erwinia	£7,871	17.3431	—	—	—
Native Asp.>Erwinia	£12,612	17.2926	£4,741	-0.0504	Dominated
Erwinia>Native Asp.	£48,149	17.3396	£40,277	-0.0035	Dominated-
Erwinia>PEG-Asp.	£48,234	17.3477	£40,362	0.0047	£8,627,243

Abbreviations: ASP, asparaginase; ICER, incremental cost-effectiveness ratio; PEG-Asp, pegaspargase; QALYs, quality-adjusted life years

Table 12: Company's base case results for the paediatric population (source Table 5.14, page 97 of the ERG report)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp. >Erwinia	£8,545	22.1294	—	—	—
Native Asp. >Erwinia	£12,352	22.0633	£3,807	-0.0662	Dominated
Erwinia >Native Asp.	£44,781	22.1248	£36,236	-0.0046	Dominated
Erwinia >PEG-Asp.	£44,900	22.1356	£36,355	0.0061	£5,917,762

Abbreviations: ASP, asparaginase; ICER, incremental cost-effectiveness ratio; PEG-Asp, pegaspargase; QALYs, quality-adjusted life years

Table 13: Company's base case results for the adult population (source Table 5.15, page 97 of the ERG report)

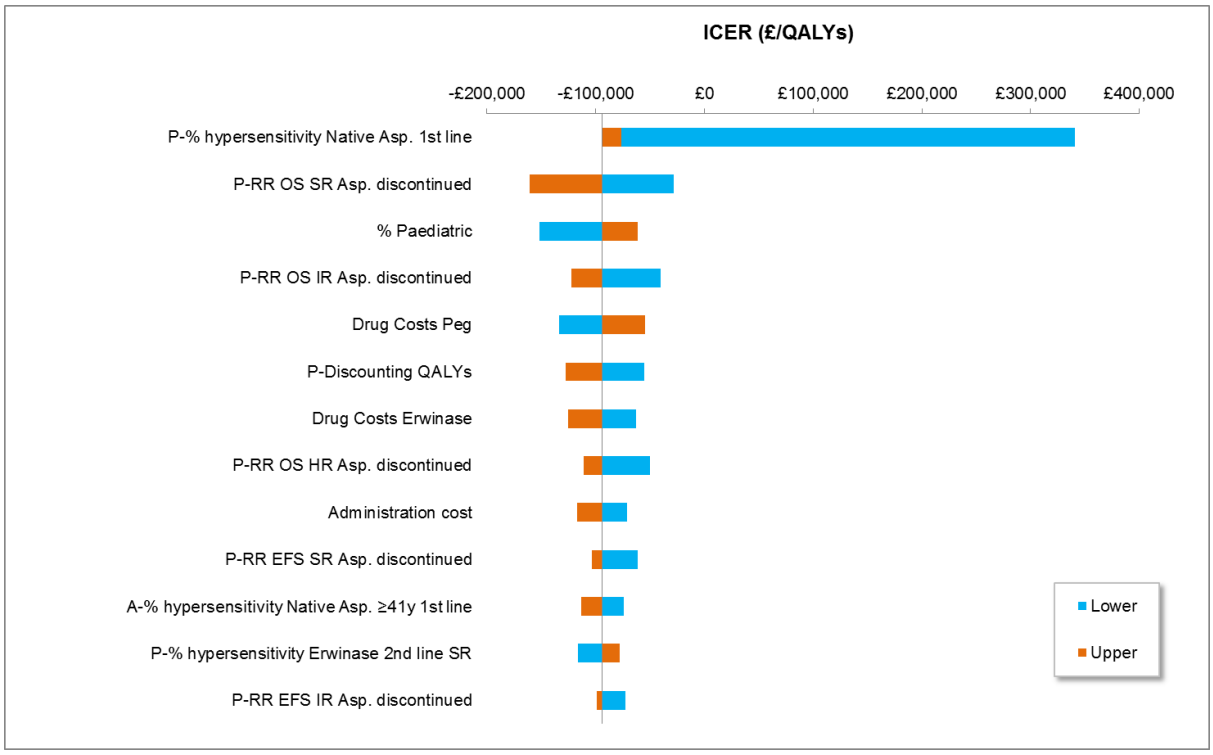
Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp. >Erwinia	£5,913	3.4327	—	—	—
Native Asp. >Erwinia	£13,368	3.4280	£7,455	-0.0047	Dominated
Erwinia. >Native Asp.	£57,936	3.4324	£52,023	-0.0003	Dominated
Erwinia. >PEG-Asp.	£57,922	3.4332	£52,010	0.0004	£123,446,241

Abbreviations: ASP, asparaginase; ICER, incremental cost-effectiveness ratio; PEG-Asp, pegaspargase; QALYs, quality-adjusted life years

5.25 The company's probabilistic sensitivity analysis showed that if the maximum acceptable amount for an additional QALY was £20,000 then pegaspargase would have a 78% probability of being cost effective compared with E. coli derived asparaginase and Erwinia derived asparaginase.

5.26 The company conducted a series of deterministic sensitivity analyses (for further details, see table 51, page 188 of the company submission). The key driver of the cost-effectiveness results was the hypersensitivity rate for 1 first line treatment of E. coli derived asparaginase (see Figure 5 for the results of the company's sensitivity analyses).

Figure 5: Results of the company's sensitivity analyses (source Figure 5.10, page 102 of the company submission)



ERG comments

5.27 The ERG stated that the assumptions around the clinical effectiveness model inputs were the main drivers of the company's cost effectiveness estimates, and specifically the hypersensitivity rate for first line treatment of E. coli derived asparaginase for the paediatric population. The ERG noted that the difference in costs between pegaspargase first line and *E.* coli derived asparaginase first line was primarily a result of the higher administration costs of E. coli derived asparaginase as it is more frequently administered in the model. The ERG noted that the higher costs for the alternatives with Erwinia derived asparaginase as first line treatment were mainly caused by

the higher technology costs (90% of the total incremental costs). See table 5.16 on page 98 of the ERG report for further details.

5.28 The ERG noted that the company's deterministic sensitivity analysis showed that the cost effectiveness estimates remained constant when most of the model parameters were changed. The ERG noted that the ICERs varied significantly when the hypersensitivity rate for first line treatment with *E.* coli derived asparaginase was varied. The ERG noted that when the hypersensitivity rate was set to 0%, that is less than the 2% base rate used for pegaspargase, there was no longer an increase but rather a decrease in the QALY for pegaspargase.

5.29 The ERG concluded that the cost effectiveness estimates from the model appear credible if the following assumptions were assumed reasonable:

- Event-free survival and overall survival are the same for all formulations in the adult population.
- Only the hypersensitivity rate differs per treatment.
- Pegaspargase followed by Erwinia derived asparaginase was marginally more clinically effective than other treatments in the paediatric population.

ERG exploratory analyses

5.30 The ERG defined a new base case analysis (see Table 14). The ERG's base case included the following amendments:

- Correction of errors in the model (for further details, see pages 105-106 of the ERG report) :
  - Correction of the risk distribution in paediatric patients.
  - Correction of background mortality.
  - Correction of some number of administrations in case of hypersensitive.

- Adjustments to the company's model (for further details, see pages 106-108 of the ERG report):
  - Used mean instead of the median age in the paediatric population
  - No second interim maintenance and delayed intensification treatment courses.
  - Using a hypersensitivity rate for pegaspargase based on the Vora study and based on the percentage of patients switching asparaginase treatment.
  - Using the same risk of hypersensitivity to Erwinia derived asparaginase for first and second line treatment and based on the percentage of patients switching asparaginase treatment.
  - Using model overall survival and event free survival estimates based on published evidence.
  - Allow the overall survival and event free survival of the different formulation to vary independently in the probabilistic sensitivity analysis.
  - Change the relative reduction in mortality for patients who discontinue asparaginase treatment because of hypersensitivity to 2 different formulations.
  - Change the mortality risk for patients in the R/ST state.
  - Estimating the event-free survival in the PSA dependent on overall survival.
  - Change the timing of the different treatment phases.
  - Change the standard errors used in the PSA.

5.31 The impact on the company's ICER of the individual ERG amendments are provided in Table 15. The ERG commented that changes in the hypersensitivity rate for pegaspargase and Erwinia derived asparaginase and a larger reduction in overall survival and event-free survival in case of asparaginase treatment had the largest impact on the ICER.

Table 14: ERG's deterministic base-case analysis (sourceTable 5.20, page 109 of the ERG report)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp. >Erwinia	**£7,329**	**17.5787**	—	—	—
Native Asp. >Erwinia	£11,083	17.5607	-£3,754	0.0179	Dominated
Erwinia >PEG-Asp.	£35,513	17.5787	-£28,184	0.0000	Dominated
Erwinia >Native Asp.	£35,447	17.5608	-£28,118	0.0179	Dominated

Abbreviations: ASP, asparaginase; ICER, incremental cost-effectiveness ratio; PEG-Asp, pegaspargase; QALYs, quality-adjusted life years

5.32 The ERG's probabilistic sensitivity analysis showed that if the maximum acceptable amount for an additional QALY was £20,000 then pegaspargase would have a 50% probability of being cost effective compared with *E.* coli asparaginase and Erwinia derived asparaginase. For further details of the ERG's probabilistic sensitivity analysis, see figure 5.11 and pages 108-109 of the ERG report.

ERG scenario analyses

5.33 The ERG also carried out a series of scenario analyses (see table 16 for the results of the scenario analysis, and see pages 110-111 of the ERG report for further details of each of the scenarios). .

- **Scenario 1:** Using a pegaspargase dose of 25,00IU/m^2
- **Scenario 2:** Best-case scenario with better event-free survival and overall survival for pegaspargase.
- **Scenario 3**: Worst-case scenario with worse event-free survival for pegaspargase.
- **Scenario 4**: Utility values based on an algorithm to map HUI3 on EQ-5D rather than using the Furlong study.
- **Scenario 5:** Change utility decrement for patients in the R/ST health state.

- **Scenario 6:** Apply 4 doses of native E.Coli asparaginase or Erwinia derived asparaginase for each dose of pegaspargase.

Table 15: Results of the ERG's amendments to the company's model (source ERG report table 6.1 page 116)

	PEGF. >Erw vs E.Coli . >Erw			PEG. > Erw vs Erw. >PEG			PEG. >Erw vs Erw. >Ecoli		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Company Base-case	**-£4,741**	**0.050**	**PEG dominant**	**-40,362**	**-0.005**	**£8,627,245 (SW)**	**-40,277**	**0.003**	**PEG dominant**
Corrections in the model	-£4,384	0.051	PEG dominant	-37,218	-0.005	£7,921,590 (SW)	-37,142	0.004	PEG dominant
Mean age for paediatric population	-£4,741	0.050	PEG dominant	-40,362	-0.005	£8,718,463 (SW)	-40,277	0.003	PEG dominant
No second interim maintenance and delayed intensification course + correction timing treatment	-£3,980	0.050	PEG dominant	-32,768	-0.005	£ 6,996,189 (SW)	-32,705	0.003	PEG dominant
Hypersensitivity rate pegaspargase 13.2%	-£3,096	0.019	PEG dominant	-38,688	-0.031	£1,249,290 (SW)	-38,632	-0.028	£1,385,524 (SW)
Hypersensitivity rate Erwinia 9%	-£7,022	0.012	PEG dominant	-39,048	0.000*	PEG dominant	-38,920	0.012	PEG dominant
OS estimates based upon evidence from UKALL2003 trial	-£4,741	0.052	PEG dominant	-40,362	-0.005	£8,314,504 (SW)	-40,277	0.004	PEG dominant
EFS estimates based upon evidence from UKALL2003 trial	-£4,750	0.051	PEG dominant	-40,451	-0.005	£8,548,844 (SW)	-40,366	0.004	PEG dominant
Reduction OS and EFS in case of discontinuation asparaginase = 19%	-£4,741	0.192	PEG dominant	-40,363	-0.018	£2,260,256 (SW)	-40,278	0.013	PEG dominant
Yearly mortality rate in the R/ST state = 35%	-£4,741	0.049	PEG dominant	-40,362	-0.005	£8,941,672 (SW)	-40,277	0.003	PEG dominant
ERG Base-case	-£3,754	0.018	PEG dominant	-28,184	0.000**	£2,492,445,178 (SW)	-28,118	0.018	PEG dominant

Table 16: Results of the ERG scenario analyses (source: ERG report table 5.21, page 112)

	Pegaspargase. >Erwinia vs native E coli. >Erwinia			Pegaspargase. >Erwinia vs Erwinia. >Pegaspargase			Pegaspargase. >Erwinia vs Erwinia. >native E. coli		
Scenario	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	IC
Base Case	**-£4,099**	**0.02**	**Dominant**	**-£28,526**	**0.01**	**Dominant**	**-£28,462**	**0.02**	**Domi**
Oncaspar Dose per SmPC (2500)	-£3,306	0.02	Dominant	-£27,842	0.01	Dominant	-£27,670	0.02	Domi
Best case scenario	-£4,039	1.45	Dominant	-£28,309	1.45	Dominant	-£28,244	1.45	Domi
Worst case scenario	-£4,141	-0.86	£4,810 (SW)	-£28,626	-0.87	£32,907 (SW)	-£28,562	-0.86	£33 (
Utilities based on Mapping	-£4,099	0.02	Dominant	-£28,526	0.01	Dominant	-£28,462	0.02	Domi
Utility R/ST state 68% reduction	-£4,099	0.02	Dominant	-£28,526	0.01	Dominant	-£28,462	0.02	Domi
4 doses E. coli or Erwinia for each dose PEG	£739	0.02	£36,499 (NE)	-£17,213	0.01	Dominant	-£17,155	0.02	Domi

NE = North-east quadrant, PEG = Pegaspargase, SW = South-west quadrant

6 Equality issues

6.1 The company stated that access to pegaspargase for children and young people was an important equality issue.

7 Authors

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with input from the Lead Team (Gail Coster, Rachel Elliot and Judith Wardle).

Appendix A: European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003789/WC500200737.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pegaspargase for treating acute lymphoblastic leukaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pegaspargase within its marketing authorisation for treating acute lymphoblastic leukaemia.

Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood.

ALL is most common in children, adolescent and young adults, with 65% of cases diagnosed in people aged under 25 years A second increase in incidence is observed in people aged over 60 years. In England, 536 people were diagnosed with ALL in 2011 and 202 people died from ALL in 2012.[1]

The aim of treatment in ALL is to achieve a cure. Treatment can take up to 3 years to complete and is generally divided into 3 phases; induction, consolidation and maintenance. The choice of treatment can depend on the phase. There is currently no NICE guidance for treating ALL. During induction, newly diagnosed ALL is generally treated with chemotherapy combinations including prednisone, vincristine, anthracycline and L-asparaginase. During the consolidation phase, intensified chemotherapy is used, which may include high dose methotrexate with mercaptopurine, L-asparaginase, or a repeat of the induction therapy. During the maintenance phase low dose chemotherapy is used, which typically consists of weekly methotrexate and daily mercaptopurine for an extended period of time to prevent relapse.

The technology

Pegaspargase (Oncaspar, Baxalta) is a polyethylene glycol conjugate of *Escherichia coli* derived L-asparaginase. L- asparaginase is an enzyme that hydrolyses asparagine (an amino acid) leading to cell death. The polyethylene glycol conjugation of L-asparaginase is expected to extend its duration of activity, increase bioavailability and improve tolerability. It is given intramuscularly or intravenously.

Pegaspargase does not currently have a marketing authorisation in the UK for ALL. It has received a a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) ‘as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients'.

Intervention(s)	Pegaspargase plus standard chemotherapy
Population(s)	People with acute lymphoblastic leukaemia
Comparators	Non-pegylated forms of: • *Escherichia coli* derived L-asparaginase plus standard chemotherapy • *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • treatment response rates • event-free survival • asparaginase activity • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Guidelines: ‘Improving outcomes in children and young people with

and NICE Pathways	cancer' (August 2005) Cancer Service Guideline, Review proposal date: June 2016 'Improving outcomes in haematological cancers' (October 2003) Cancer Service Guideline Review proposal date: September 2019 Related Quality Standards: 'Children and young people with cancer' (February 2014) NICE quality standard 55 Review date TBC Related NICE Pathways: 'Blood and bone marrow cancers' (June 2015) NICE pathway http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	Specialist cancer services for children and young people, Chapter 106, 'Manual for prescribed services'. November 2012. http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14 http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

Cancer Research UK (2014) Acute lymphoblastic leukaemia (ALL) statistics, Accessed December 2015

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pegaspargase for treating acute lymphoblastic leukaemia [ID863]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Baxalta (pegaspargase) Patient/carer groups • Action for Sick Children • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • Childhood Cancer Parents Alliance • Children with Cancer UK • Children's Cancer and Leukaemia Group • Chronic Lymphocytic Leukaemia Support Association • CLIC Sargent • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • National Children's Bureau • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Teenage Cancer Trust • Together for Short Lives	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Medac GmbH (*Escherechia coli* derived L-asparaginase) • Porton Biopharma (formerly Public Health England) (*Erwinia chrysanthemi* derived L-asparaginase [crisantaspase]) Relevant research groups • Cochrane Haematological Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research

Consultees	**Commentators (no right to submit or appeal)**
• Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society for Haematology • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiography • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society Others • Department of Health • NHS England • NHS Lincolnshire West CCG • NHS Mansfield & Ashfield CCG • Welsh Government	Associated Public Health Groups • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Pegaspargase for treating acute lymphoblastic leukaemia [ID863]

Company evidence submission

3rd March 2016

FULL

File name	Version	Contains confidential information	Date
Baxalta Pegaspargase in ALL STA	**1**	**Yes**	**3 March 2016**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukaemia
AYA	Adults and young adults
BM	Bone marrow
BNF	British National Formulary
CCG	Children's Cancer Group
CEAC	Cost-effectiveness acceptability curve
CMA	Cost minimisation analysis
CNS	Central nervous system
CR	Complete response/remission
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DI	Delayed intensification
DI no. 1	Delayed intensification cycle number 1
DI no. 2	Delayed intensification cycle number 2
DT	Decision tree
EFS	Event-free survival
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
HPLC	High-performance liquid chromatography
HR	High-risk
HRQL	Health-related quality of life
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IR	Intermediate-risk
IU	International unit
IV	Intravenous
MA	Marketing authorisation
MRD	Minimal residual disease
M1	Bone marrow status <5% lymphoblasts
M2	Bone marrow status 5–25% lymphoblasts

M3	Bone marrow status >25% lymphoblasts
N/A	Not applicable
NCI	National Cancer Institute
NHS	National Health Service
NS	Not significant
OS	Overall survival
PCR	Polymerase chain reaction
PEG-ASP	Pegaspargase
Ph+/–	Philadelphia chromosome positive/negative
QALY(s)	Quality adjusted life year(s)
R/ST	Relapse/secondary tumour
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SCT	Stem cell transplant
SEM	Standard error of the mean
SR	Standard-risk
WBC	White blood cell

1 Executive summary

ALL is an acute, rapidly progressing, and life-threatening form of cancer involving lymphocyte-producing cells called lymphoblasts. ALL is rare, with an average of 744 new cases of ALL diagnosed in the UK between 2011 and 2013 (644 in patients aged <65 years), accounting for 0.2% of all new cancer diagnoses, and 9% of all new leukaemia diagnoses (1). Incidence is strongly related to age with 54% of ALL cases in the UK being diagnosed in children aged 0–14 years (2011–2013 data) (1). In the paediatric and young adult population (0–25 years), the median and weighted mean age is 5 years and 7.3 years, respectively (1, 2).

Treatment for ALL is complex, involving administration of multiple chemotherapeutic agents across multiple treatment phases, including remission induction, intensification/consolidation and continuation/maintenance. ALL treatment in the UK has been driven for several decades by UKALL protocols and the evolution of treatment regimens within these protocols has resulted in improvements in patient prognosis: five-year EFS improved from 35% in 1972 to 87% in 2010 among patients aged 1–24 years (2-4). For adult patients treated in the UKALL programme, the improvement has been less dramatic but nonetheless apparent with each successive study over a 35 year period (5).

Asparaginase, a bacterial-derived enzyme that depletes circulating asparagine on which leukaemic cells depend (6), is recognised as one of the most valuable drugs in the multi-agent treatment of ALL (7). Historically native E. coli-derived asparaginase was the standard of care 1st line asparaginase, but is highly immunogenic, leading to the production of antiasparaginase antibodies (8), and inducing treatment-limiting hypersensitivity reactions in 20–40% of patients (2). An alternative, Erwinia-derived asparaginase, has lower rates of treatment-switching hypersensitivity reactions (6% (9)), but both native E. coli- and Erwinia-derived asparaginases have arduous injection profiles, with regular injections (3 times weekly) (8, 10), which if given intramuscularly can be painful and cause bruising.

Pegaspargase, in which the immunogenicity of the native enzyme is masked by conjugation with a polyethylene glycol group, has equivalent long term outcomes (EFS, OS) to native E. coli asparaginase (11). However, it elicits fewer hypersensitivity reactions that would necessitate an asparaginase treatment switch (2% (2)) and has a more favourable injection profile with fewer injections (2-4, 12) and, in adults, allowing intravenous administration (12). In the paediatric population, who generally receive intramuscular injections, this may reduce the pain burden, while in adults who are prone to thromobocytopoenia and thus bruise easily, intravenous administration would be of benefit (expert opinion).

Given the benefits of pegaspargase, and with native E. coli asparaginase not licensed (nor listed in the BNF), the clinical community in the UK recognised the need to utilise pegaspargase as the asparaginase of choice for ALL treatment. Although UK marketing authorisation was only granted in January 2016, pegaspargase has been the standard of care 1st line asparaginase in UK practice since 2003, being adopted in UKALL protocols for children, adolescents and young adults (since 2003: UKALL 2003, UKALL 2011) and for adults (since 2010: UKALL14). By contrast the use of Erwinia-derived asparaginase

in these protocols is limited to 2nd line asparaginase use in the case of hypersensitivity experienced with the pegylated enzyme (3, 12).

The UKALL protocols have seen clinicians adopt pegaspargase at a dose of 1,000 IU/m^2, lower than the SmPC recommended dose of 2,000–2,500 IU/m^2. UKALL 2003 (2, 4) provides favourable long term outcomes and safety evidence at this reduced dose for more than 3,200 children and young adult ALL patients treated between 2003 and 2011, accounting for more than 97% of the eligible ALL population over that time (3). This data has provided the clinical community with confidence to continue to use 1,000 IU/m^2 pegaspargase as the standard of care in the ongoing UKALL 2011 paediatric protocol and adopt it in the adult UKALL14 protocol. This submission considers the use of pegaspargase according to these protocols as these reflect current practice and are of most relevance to the NHS.

NHS England included pegaspargase in baseline commissioning in April 2013 (13). Given the clinical community's recognition of the value of pegaspargase to both the NHS and patients, it would be detrimental to patient care should this no longer be available, as well as potentially jeopardise the treatment of ALL patients in the ongoing UKALL protocols (as outlined in the NICE scoping comments).

1.1 *Statement of the decision problem*

The objective of this technology appraisal is to evaluate the clinical- and cost-effectiveness of pegaspargase according to its licensed indication, allowing for its use as a component of antineoplastic combination therapy in ALL in paediatric, adolescent and young adult (AYA) patients, and adult patients.

The NICE decision problem is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with ALL	Newly diagnosed people with ALL	As the use of asparaginase in the UK is driven by the UKALL protocols, the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort, as per the protocols described in Section 3.6. Patients who experience a relapse or are older than 65 would have regimens that do not include pegaspargase (14). Our submission therefore meets the scope in that it considers patients of relevance to decision-makers in the NHS.
Intervention	Pegaspargase plus standard chemotherapy	As per scope	NA
Comparator(s)	Non-pegylated forms of: • Escherichia coli-derived L-asparaginase plus standard chemotherapy • Erwinia chrysanthemi-derived L-asparaginase (crisantaspase) plus standard chemotherapy	As per scope Treatment sequences modelled: 1. Pegaspargase >> Erwinia-derived asparaginase 2. Native E. coli-derived asparaginase >> Erwinia-derived asparaginase 3. Erwinia-derived asparaginase >> Pegaspargase 4. Erwinia-derived asparaginase >> Native E. coli-derived asparaginase	Asparaginase treatment will be given as part of 1st line ALL treatment, and in cases of hypersensitivity reactions, a switch to an alternative (2nd line) asparaginase will be necessary. Although the licence for pegaspargase does not preclude its use as a 2nd line asparaginase therapy there is not currently a clinical scenario in the UK in which pegaspargase would be used in this setting, since patients would not receive native E. coli- or Erwinia-derived asparaginase as a 1st line asparaginase. In addition, with the availability of Erwinia-derived asparaginase, patients experiencing hypersensitivity to pegylated or native E. coli enzyme would in practice no longer be switched to the other E. coli enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinia-derived enzyme following hypersensitivity to pegaspargase (3, 12). A further complication in this field is that native E. coli-derived asparaginase is not licensed for use in the UK. Unavailability in the United States has seen it removed from United States treatment guidelines (NCCN 2015) (15).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Erwinia derived asparaginase is licensed in the UK and, although the wording of its indication does not limit its use to a specific line of asparaginase therapy (10), the product is only positioned in treatment protocols as a 2nd line asparaginase (3, 7, 12, 16). Hence, with this context in mind, the current standard of care treatment pathway in the UK is pegaspargase 1st line followed by Erwinia-derived enzyme in cases of hypersensitivity, and this treatment sequence has been modelled. Although not currently part of UK clinical practice and unrealistic given the current unavailability of native E. coli enzyme and the 2nd line positioning of Erwinia, alternative switching scenarios of native to Erwinia, Erwinia to pegylated, and Erwinia to native could be clinically possible, and are also modelled.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Treatment response rates • Event-free survival • Asparaginase activity • Adverse effects of treatment • Health-related quality of life	As per scope except for progression-free survival which wasn't included	Event free survival was used in many studies and this outcome will incorporate progression free survival. In addition, there are a large amount of patients, especially paediatric patients, who are cured and as such do not progress (2-4).
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes	As per scope In addition, we will present a cost minimisation analysis	Cost minimisation included as we have conservatively assumed equivalence in outcome (OS & EFS) between the asparaginase products, and the entire treatment period lasts around 2-3 years, with all outcomes of interest being observed during this time. A cost minimisation model would, therefore, allow decision-makers to assess the differences over this time

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	NA	NA	NA
Special considerations including issues related to equity or equality	NA	ALL presents primarily in children, adolescents, and young adults, with 74.4% of cases diagnosed in people aged under 25 years (1). Equity of treatment for children and young people with cancer is a concern, as evident from the NICE Quality Standard 55 “Cancer services for children and young people” (17). ALL is also an orphan disease (18). The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (19). Therefore, continued access, where appropriate, to a treatment such as pegaspargase should help to promote equality for both younger patients and those with rarer forms of cancer, especially as pegaspargase has a decreased number of infusions and hypersensitivity reactions than native E. coli-derived or Erwinia-derived asparaginase (8, 20). This is what prompted the NHS to adopt the product into baseline commissioning in 2013 (13). As highlighted in feedback provided by NCRI/RCP/ACP, and Royal College of Pathologists and BSH during NICE scoping, a negative appraisal would also put at risk the ongoing clinical protocols in the UK, which would be detrimental to patient care.	

Abbreviations: ALL, acute lymphoblastic leukaemia; NA, not applicable; NHS, National Health Service.

1.2 *Description of the technology being appraised*

Pegaspargase, a polyethylene glycol conjugate of E. coli-derived L-asparaginase, is a bacterial enzyme that depletes circulating asparagine, an essential amino acid on which leukaemic cells, incapable of synthesising asparagine, depend, leading to cell death.

Pegaspargase received marketing authorisation from the EMA on 14th January 2016 for the treatment of people with newly diagnosed ALL (Table 2). However, it is established as the standard of care asparaginase in the UK; it has been used by clinicians in the UK since 2003 for the treatment of the vast majority of ALL patients according to UKALL protocols (2-4, 12). As such, these protocols form the basis of current clinical practice, with pegaspargase being administered at a dose of 1,000 IU/m^2, lower than that recommended by the SmPC (2,500 IU/m^2). This submission considers the use of pegaspargase according to these protocols as these reflect current practice and are of most relevance to the NHS.

Table 2: Technology being appraised

UK approved name and brand name	Pegaspargase (Oncaspar®) Pegaspargase is currently the only marketed form of pegylated asparaginase available and the evidence base available for pegylated asparaginase is specific to pegaspargase
Marketing authorisation/CE mark status	Pegaspargase received EMA marketing authorisation on 14th January 2016 for use in the treatment of people with newly diagnosed ALL
Indications and any restriction(s) as described in the summary of product characteristics	Pegaspargase is indicated as a component of antineoplastic combination therapy in ALL in paediatric patients from birth to 18 years, and adult patients Contraindications include hypersensitivity, severe hepatic impairment, history of serious thrombosis, pancreatitis, or serious haemorrhagic event with prior L-asparaginase therapy
Method of administration	**SmPC recommendation** Pegaspargase can be given either by IM injection or IV infusion UK clinical practice: UKALL protocols ***Paediatric and young adult patients*** (UKALL 2003, UKALL 2011) (2, 3) Administered by IM injection ***Adult patients (UKALL14) (12)*** Administered by IV infusion
Doses	**SmPC recommendation** ***Paediatric and young adult patients (≤21 years)*** 2,500 IU/m^2 every 14 days ***Adult patients (>21 years)*** 2,000 IU/m^2 every 14 days **UK clinical practice: UKALL protocols (2, 3, 12)** 1,000 IU/m^2 Dosing frequencies based on the ongoing UKALL protocols, UKALL 2003, UKALL 2011 and UKALL14 demonstrate that in clinical practice dosing frequency depends on the patient's age and phase of treatment in which pegaspargase is given

	(induction, consolidation, intensification etc) and the duration of each phase More detail is provided in Section 3.6 and Section 4.3 for the UKALL 2003 protocol, and in Figure 1 and Section 3.6 for ongoing UKALL 2011 and UKALL14 protocols

Abbreviations: ALL, acute lymphoblastic leukaemia; EMA, European Medicines Agency; IM, intramuscular; IU, international units; IV, intravenous; SmPC, summary of product characteristics; ULN, upper limit of normal.

1.3 *Summary of the clinical effectiveness analysis*

1.3.1 *Efficacy*

Evidence in children, adolescents and young adults

Evidence supporting the use of pegaspargase in 1st line ALL has been accrued over a number of years in a large number of completed and ongoing UK-based and international study protocols, driven by academic collaborations. The majority of data exist in children, adolescents and young adults, consistent with the predominance of new ALL cases in patients aged <25 (1). Evidence for pegaspargase was identified by way of systematic review, of which the pivotal studies presented in this submission are:

- CCG-1962 (11), the only randomised head-to-head comparison of pegylated versus native E. coli-derived asparaginase given from induction (Section 4.3), and
- UKALL 2003 (2, 4), providing evidence for the use of pegaspargase at a dose of 1,000 IU/m^2 in >3,200 children, adolescents and young adults in the UK and Ireland (Section 4.3).

In study CCG-1962 (11) a total of 118 children (aged 1–9 years) newly-diagnosed with ALL were randomised to receive either pegaspargase (2,500 IU/m^2 IM on day 3 of induction and each DI phase) or native asparaginase (6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase).

- EFS rates at three, five, and seven years, respectively, were similar but numerically higher for those treated with pegaspargase (83%, 78%, and 75%) versus those treated with native asparaginase (79%, 73%, and 66%)
- Pegaspargase was also associated with significantly lower immunogenicity, shown by lower mean antibody ratio and rate of high antibody titres during the 1st delayed intensification phase compared with E. coli-derived asparaginase.
- Development of neutralising antibodies is known to lead to a decrease in enzyme activity and consistent with this, high antibody titres were associated with low asparaginase activity in the E. coli arm but not in the pegylated arm. Asparaginase activity considered adequate to deplete asparagine (>0.1 IU/mL) was detected in 95% and 91% of pegaspargase-treated patients versus 19% and 22% of E. coli asparaginase-treated patients during the first and second delayed intensification phases of treatment.

Systematic review identified a total of 39 studies which provided data on pegaspargase or E. coli-derived asparaginase in 1st line ALL treatment in children/adolescents/young

adults. [redacted] as described in Section **Error! Reference source not found.**.

The evidence base for pegaspargase is considerably enhanced by, and is potentially unique as a result of the UKALL protocols (UKALL 2003 complete, UKALL 2011 and UKALL14 recruiting and ongoing), which since 2003 have seen the vast majority of newly diagnosed ALL patients in the UK and Ireland treated exclusively with pegaspargase as the standard of care 1st line asparaginase.

UKALL 2003 (2, 4) enrolled a total of 3,207 children and young adult patients aged 1–24 years, representing 97% of the eligible ALL patient population aged 1–24 years in the UK and Ireland (2-4). All patients received treatment with pegaspargase (1,000 IU/m^2 per dose, 4–12 doses) as part of one of three escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. Among all patients enrolled in UKALL 2003:

- five-year EFS was 87.3%
- five-year OS was 91.6%.
- five-year cumulative risk of relapse was 8.8%

When comparing the long term outcomes of EFS and OS from UKALL 2003 with those from CCG-1962, as well as pooled estimates generated from the wider evidence base, the UKALL regimens, at a dose of 1,000 IU/m^2, provide numerically superior outcomes to any other study. The use of this reduced dose is therefore supported by a robust and substantial evidence base, and has provided the clinical community with confidence in its continued use in UKALL 2011 in paediatric and young adult patients, and in UKALL14 in adult patients, respectively.

Evidence in adults

Although evidence for adults is limited relative to that in the younger population, three studies were identified that support the use of pegaspargase in older adult populations (age range: 17–71 years). Douer et al (21, 22), demonstrated that adult patients (up to the age of 57 years), newly diagnosed with ALL, have an excellent chance of achieving remission (96%) when treated with up to six 2,000 IU/m^2 doses of pegaspargase beginning in induction. In CALGB 9511 (23) effective asparagine depletion was shown to be feasible as part of an intensive multi-agent therapeutic regimen and that effective asparagine depletion was associated with improved outcomes (HR for OS: 2.37, 95% CI 1.38–4.09, p=0.002).

Upcoming data from UKALL14 (12) will provide evidence supporting the use of the reduced dose of 1,000 IU/m^2.

Evidence versus Erwinia-derived asparaginase

There is no evidence available that Baxalta are aware of that would enable a direct comparison of pegaspargase with Erwinia-derived asparaginase. In studies comparing native E. coli asparaginase and Erwinia-derived asparaginase, long term outcomes are significantly worse for the Erwinia enzyme, but at doses that are lower than are now used in practice (See Appendix 4: Duval 2002 (24), Moghrabi 2007/Silverman 2010 (9, 20); 10,000 IU/m^2 twice weekly or 25,000 IU/m^2 weekly vs 60,000 IU/m^2 weekly in UKALL protocols (3)). Experts validated the assumption that, given the limitations of the evidence, pegaspargase, E. coli asparaginase and Erwinia-derived asparaginase could be assumed to be equivalent for OS and EFS.

1.3.2 *Safety*

Based on available safety data submitted to the EMA for marketing authorisation (EPAR, Appendix 1), it was concluded that the treatment of ALL patients with pegaspargase at doses of 2,000 to 2,500 IU/m^2 is considered to be well tolerated and the toxicities manageable. The data from UKALL 2003 (and the subsequent data that will come from UKALL 2011 and UKALL14) are the most appropriate data in relation to the safety profile of pegaspargase. Current data from the >3,000 patients treated in UKALL 2003 support the overall observations of the EMA, with the authors concluding that the toxic effects attributable to pegaspargase were similar to or lower than those they have seen reported in the literature with the native form.

A key concern with the use of all asparaginase-containing products is the development of antibodies to the enzyme that can result in hypersensitivity reactions which would necessitate a switch to an alternative asparaginase formulation. Vora et al, in their publication of the UKALL 2003 protocol suggest that hypersensitivity rates of 20-40% are to be expected for native E. coli-derived asparaginase (2). Reported hypersensitivity rates are variable but depend on the grade of severity, and when rates eliciting a switch in asparaginase treatment are analysed published rates are observed as high as 75% (25). Concerning the immunologically-distinct Erwinia-derived asparaginase, Moghrabi et al report that when used 1st line, 6% of Erwinia-treated patients develop hypersensitivity reactions resulting in a treatment switch (9). In contrast, and of more relevance to UK clinical practice given the years of use as 1st line standard of care, when >3,000 patients in UKALL 2003 received treatment with pegaspargase at the reduced dose of 1,000 IU/m^2, hypersensitivity reactions were experienced by only 2% of patients across the entire study (n=54/3,126) (2, 4).

1.4 *Summary of the cost-effectiveness analysis*

The main strength of the evaluation is that it is relevant to UK decision-makers as the model reflects the current standard of care for UK patients in both the paediatric and adult populations, and also uses associated UK-specific data, where available.

The main limitations are in the lack of head-to-head data, especially in the adult population. Key inputs were also validated by experts in the different specialties to ensure the values used were reflective of UK experience, especially as the regimens differ from other countries, so the data transferability could be questioned.

Some values are also very variable in the data reported, and we have been conservative in our use of the data (e.g. the rate of hypersensitivity for the native product has an upper reported limit of hypersensitivity of 76%, but we used a UK-referenced upper bound of 40% in our model, and the lower reference case amount of 20%. These figures were validated by both adult and paediatric experts.

The base case demonstrated that pegaspargase used 1st line dominated or was more cost effective than all the other interventions modelled. In order to evaluate the uncertainty, we also undertook extensive sensitivity analyses, as per Section 5.8. This showed the results of the model are robust in the face of uncertainty in both the parameter inputs, as well as the structural assumptions required to construct the model. All scenarios indicated that Pegaspargase – Erwinase is cost-effective at the £20,000 willingness to pay threshold.

This should be considered alongside the benefits to patients in terms of the reduced rate of hypersensitive reactions and reduced number of administrations to a predominantly paediatric population, who experience anxiety and pain. In addition, when asked on the dosing equivalence of native asparaginase or Erwinase, the expert advised that every intravenous infusion of pegaspargase is replaced by six IM injections of either native E.coli enzyme or Erwinase. They stated that the adult population was prone to thrombocytopoenia, and thus commonly experience pain and bruising when having an injection.

An assumption is that pegaspargase, native asparaginase and Erwinase are equivalent in terms of OS and EFS, and because all the outcomes of interest are experienced during the treatment phase, a cost minimisation analysis (CMA) is an alternative modelling methodology that can be used to represent the decision problem, as this demonstrates the actual impact on the NHS. The decision tree and Markov model are also used in the CMA. This resulted in a cost saving of £354 per patient, and further demonstrates the cost benefits of continued use of pegaspargase 1st line in the NHS, as well as the continued use in ongoing trials in both paediatric and adult patient populations (UKALL11 & UKALL14), which will lead to further data in the disease area.

Table 3 Incremental cost-effectiveness results

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.>Erwinase	£7,871	17.3431	—	—	—
Native Asp.>Erwinase	£12,612	17.2926	-£4,741	0.0504	-£94,029
Erwinase>Native Asp.	£48,149	17.3396	-£40,277	0.0035	-£11,541,184
Erwinase>PEG-Asp.	£48,234	17.3477	-£40,362	-0.0047	£8,627,243

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

2 The technology

2.1 *Description of the technology*

Brand name: Oncaspar®

UK approved name: Pegaspargase

Therapeutic class: antineoplastic and immunomodulating agents

Mechanism of action: L-asparaginase is a bacterial enzyme that catalyses the hydrolysis of asparagine, an essential amino acid for lymphoblastic leukaemic tumour cells (26). Whereas normal cells are able to synthesise asparagine, tumour cells are dependent on circulating asparagine for fundamental cell processes (27). Depletion of circulating asparagine by L-asparaginase activity results in the death of leukaemic cells (28).

Pegylation of native L-asparaginase, where polyethylene glycol is bound to L-asparaginase, reduces the immunogenicity of the enzyme and therefore the risk of hypersensitivity reactions, and increases the circulating half-life of the enzyme compared with native L-asparaginase, meaning less frequent administrations are required (29).

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Marketing authorisation/CE marking*

Following European Medicines Agency (EMA) assessment the European Commission granted marketing authorisation for pegaspargase (Oncaspar®) for the treatment of acute lymphoblastic leukaemia (ALL) on 14th January 2016.

2.2.2 *Indication in the UK*

Pegaspargase is indicated as a component of antineoplastic combination therapy in ALL in paediatric patients from birth to 18 years, and adult patients.

This submission only considers pegaspargase use in newly-diagnosed ALL patients. Current use of asparaginase in the NHS is in the newly-diagnosed setting for patients <65 years (UKALL 2011 & UKALL14). Relapsed and older patients do not routinely receive pegaspargase and were therefore not considered a part of this submission, as they would not be relevant for the NHS decision-maker.

2.2.3 *Restrictions or contraindications*

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1.
- Severe hepatic impairment (bilirubin>3 times upper limit of normal [ULN]; transaminases >10 times ULN).
- History of serious thrombosis with prior L-asparaginase therapy.

- History of pancreatitis, including that related to previous asparaginase therapy
- History of serious haemorrhagic events with prior L-asparaginase therapy

Special warning and precautions for use

- Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out an accelerated reduction of asparaginase activity.
- Low asparaginase activity levels are often accompanied by the appearance of antiasparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. Expert advice should first be sought.
- Hypersensitivity reactions to pegaspargase, e.g. life threatening anaphylaxis, can occur during the therapy. As a routine precautionary measure the patient should be monitored for an hour after administration, having resuscitation equipment and other means required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids etc.). Pegaspargase should be discontinued in patients with serious allergic reactions (see SmPC Sections 4.3 and 4.8). Depending on the severity of the symptoms, administration of antihistamines, corticosteroids and possibly circulation stabilising medical product is indicated as counter measure.
- Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving pegaspargase. Pegaspargase should be discontinued in patients with serious thrombotic events.
- Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur in patients receiving pegaspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment; particularly when other medicinal products with coagulation inhibiting effects such as acetylsalicylic acid and nonsteroidal anti-inflammatory medicinal products are used simultaneously (see SmPC Section 4.5).
- Regular monitoring of the coagulation profile is necessary. Fibrinogen can be regarded as a parameter of the pro and anti-coagulatory system. When there is a marked drop in fibrinogen or Anti-thrombinIII deficiency, consider targeted substitution (e.g. fresh frozen plasma).
- Pegaspargase may possess immunosuppressive activity. It is therefore possible that use of this medicinal product promotes infections in patients.
- Combination therapy with pegaspargase can result in severe hepatic toxicity and central nervous system toxicity.
- Caution is required when pegaspargase is given in combination with other hepatotoxic substances, especially if there is pre-existing hepatic impairment. In this case, patients should be monitored for liver impairment.
- In the presence of symptoms of hyperammonemia (e.g. nausea, vomiting, lethargy, irritation), ammonia levels should be monitored closely.
- Safety and efficacy in Philadelphia chromosome positive (Ph+) patients has not been established. A possible increased risk of hepatotoxicity when combining

imatinib with L-asparaginase therapy should be taken into account prior deciding to use pegaspargase in this patient population.

- The decrease in the number of circulating lymphoblasts is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely.
- There have been reported adverse reactions of pancreatitis. Patients should be informed of the characteristic symptom of pancreatitis that, if left untreated, could become fatal: persistent abdominal pain that could be severe, which may radiate to the back. If pancreatitis is suspected, pegaspargase should be discontinued; if pancreatitis is confirmed, pegaspargase should not be restarted. Appropriate investigations (e.g. ultrasound) should therefore be performed up to four months after termination of pegaspargase therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended. Disturbances of exocrine pancreatic function can result in diarrhoea.
- Serum amylase measurements should be carried out frequently to identify early signs of inflammation of the pancreas.
- In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.
- Blood and urine glucose levels should be monitored during treatment with pegaspargase as they may rise.
- Effective contraception must be used during treatment and for at least 6 months after pegaspargase discontinuation. Since an indirect interaction between components of the oral contraception and pegaspargase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation (see SmPC Sections 4.5 and 4.6).
- This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

2.2.4 *SmPC/Information for use and assessment report*

SmPC and EPAR are provided in Appendix 1.

2.2.5 *Main issues discussed by regulatory authorities*

The Committee for Medicinal Products for Human Use, based on their review of data on quality, safety, and efficacy of pegaspargase (Oncaspar®), concluded that the benefit/risk was favourable in ALL. The marketing authorisation approval is subject to the following conditions:

- The medicinal product is subject to restricted medical prescription (to be administered in a hospital setting by an experienced physician/healthcare professional).
- Oncaspar® is subject to additional monitoring. Health professionals are asked to report any suspected adverse reactions.

- The marketing authorisation holder shall submit the first periodic safety update report for pegaspargase within six months following authorisation.
- The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed risk management plan presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the risk management plan. An updated risk management plan should be submitted:
    - At the request of the EMA.
    - Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile, or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- The marketing authorisation holder shall complete:
    - Post-authorisation efficacy study: in order to further define the efficacy and safety of pegaspargase in patients with newly diagnosed ALL, the marketing authorisation holder should submit the results of Study CAALL-F01, a prospective multicentre cohort study evaluating pegaspargase used in the 1st line treatment of children and adolescents with ALL along with multi-agent chemotherapy. The clinical study report (CSR) should be submitted by December 2025. This study will be undertaken in France.
    - Post-authorisation efficacy study: in order to further define the efficacy and safety of pegaspargase in adult patients with ALL, the marketing authorisation holder should submit the results of a multicentre, open label, single arm, Phase II trial evaluating the efficacy and toxicity of treatment regimens including pegaspargase in adults (aged 18–60) with newly diagnosed Philadelphia chromosome negative ALL. The CSR should be submitted by December 2018 (STPI 10). This is a legacy trial, so has not been prompted by the MA process.
    - Both of the above studies have similar patient populations (in terms of newly diagnosed patient populations of similar age groups) to protcols currently being used in the UK (UKALL 2011 & UKALL14). Due to the differing regimens used in other countries, the UKALL studies are of the most relevance to local decision-makers.

2.2.6 *Anticipated date of availability in the UK*

Pegaspargase is already available in the UK and has been used for treating the vast majority of patients with ALL for over a decade. Since 2003 it has been the standard of care asparaginase, being administered as the 1st line asparaginase as a part of multi-agent chemotherapy in the UKALL programme of clinical protocols (UKALL 2003 (2, 4), UKALL 2011 (3), UKALL14 (12)).

Recognising the value of pegaspargase and to overcome the inequity of “postcode prescribing”, the clinical community sought to have pegaspargase included in the National Health Service (NHS) England baseline commissioning, which was effective from April 2013 (13).

2.2.7 *Regulatory approval outside the UK*

Pegaspargase was originally developed in the late 1980s and obtained marketing authorisation in the United States as a 2nd line asparaginase in ALL following the development of hypersensitivity to native E. coli-derived L-asparaginase. In Europe, pegaspargase was authorised (also in 1994) in Germany for the same indication, with a second European authorisation being obtained in Poland in 2008.

In addition, pegaspargase gained marketing authorisation (MA) as a 1st line asparaginase in the United States in 2006. Although pegaspargase has not had marketing authorisation as a 1st line asparaginase in the European Union until now, it is funded in Belgium and Italy, and as described in Section 2.2.6, since April 2013 has formally been included in NHS England baseline commissioning. The applications for reimbursed status in these countries were made by the clinical community in the countries concerned without involvement by the sponsoring company.

Marketing authorisation was granted on 14th January 2016 in the 28 European Union member states plus Iceland, Norway, and Liechtenstein via the centralised process.

2.2.8 *Ongoing HTAs in the rest of the UK*

Submission to the Scottish Medicines Consortium is currently scheduled for the 2nd of May 2016.

2.3 *Administration and costs of the technology*

UK clinical practice: UKALL protocols

Since 2003 pegaspargase has been used in UK clinical practice as the 1st line standard of care asparaginase for ALL patients based on the UKALL protocols – UKALL 2003 (Patients <25 years of age; completed), UKALL 2011 (Patients <25 years of age; ongoing) and UKALL14 (Patients 25–65 years of age; ongoing).

Differences do exist between SmPC recommendations and UKALL protocols on such things as dose (2,500 international unit [IU]/m^2 or 2,000 IU/m^2 depending on age vs 1,000 IU/m^2 for all ages) and dosing frequency (every 2 weeks vs. variable frequency depending on the specific phase of treatment in which pegaspargase is administered).

The use of pegaspargase at the reduced dose and UKALL specified dosing frequency is currently supported by clinical efficacy and safety data from >3,000 children, adolescents and young adults from UKALL 2003 (see Section 4.3 for further detail). The evidence for the reduced dose demonstrates no loss of efficacy and a broadly comparable safety profile to the SmPC recommended dose. Further evidence in children, adolescents and young adults, and in adults, will become available at this lower dose from UKALL 2011 and UKALL14, respectively (See Section 3.6). UKALL 2011 and UKALL14 are enrolling patients until April 2018 and December 2016, respectively.

The vast majority of patients with ALL in the UK have been treated using these UKALL protocols, and as such the UKALL specified treatment protocols are the most relevant to this submission. Information is provided in Table 4 which reflects both the SmPC recommendations and UKALL clinical practice protocols.

Table 4: Costs of the technology being appraised

	Information	Source
Pharmaceutical formulation	Provided as a clear, colourless solution for injection/infusion One vial of 5 ml solution contains 3,750 Units	SmPC
Acquisition cost (excluding VAT)†	£1296.19 per vial	
Method of administration	**SmPC recommendation** Can be given by intramuscular injection or intravenous infusion. For smaller volumes, the preferred route of administration is intramuscular. When given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If higher volume is given, the dose should be divided and given at several injection sites. Intravenous infusion is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution together with an already running infusion. **UK clinical practice: UKALL protocols** ***Paediatric and young adult patients (UKALL 2003, UKALL 2011)*** Administered intramuscularly ***Adult patients (UKALL14)*** Administered intravenously	SmPC
Doses	**SmPC recommendations** ***Paediatric and young adult patients ≤21 years:*** The recommended dose in patients with a body surface area ≥0.6 m^2 and who are ≤21 years of age is 2,500 IU (equivalent to 3.3 ml)/m^2 body surface area every 14 days. Children with a body surface area <0.6 m^2 should receive 82.5 IU (equivalent to 0.1 ml)/kg body weight every 14 days. ***Adult patients >21 years:*** Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2,000 IU/m^2 every 14 days. **UK clinical practice: UKALL protocols** ***All patients:*** 1,000 IU/m^2	SmPC UKALL 2003 (2) UKALL 2011 protocol (3) UKALL14 protocol (12)
Dosing frequency	**SmPC recommendation** Every 14 days **UK clinical practice: UKALL protocols** Dosing frequencies based on the ongoing UKALL protocols, UKALL 2003, UKALL 2011 and UKALL14 demonstrate that in clinical practice dosing frequency depends on the phase of treatment in which pegaspargase is given (induction, consolidation, intensification etc) and the duration of each phase. More detail is provided in Section 3.6 and 4.3 for the UKALL	SmPC UKALL 2003 (2) UKALL 2011 protocol (3) UKALL14 protocol

	Information	Source
	2003 protocol, and in Figure 1 and Section 3.6 for ongoing UKALL 2011 and UKALL14 protocols	(12)
Average length of a course of treatment	As per individual UKALL treatment protocols for paediatric, child, adolescent, young adult, and adult patients e.g. In UKALL 2011, for all patients, overall treatment will last for exactly 2 years from the start of interim maintenance for female patients and 3 years from the start of interim maintenance for male patients.	UKALL 2003 (2) UKALL 2011 protocol (3) UKALL14 protocol (12)
Average cost of a course of treatment	**Paediatric and young adult patients:** Between £5,144 and £15,246 for intermediate/standard-risk and high risk patients, respectively, who complete pegaspargase treatment (no hypersensitivity) as per UKALL 2003 protocol (see Section 3.6) **Adult patients:** Between £6,034 and £7,544 for adults ≥41 years and ≤40 years, respectively, who complete pegaspargase treatment (no hypersensitivity) as per UKALL14 protocol and do not undergo transplant (see Section 3.6) Costs are based on a dose of 1,000 IU/m^2 which is used in clinical practice, which equates to 1 vial of pegaspargase per dose. Although the SmPC recommended dose is higher (2,000-2,500 IU/m^2), 1 vial would be used per treatment administration	UKALL 2003 (2) UKALL14 protocol (12)
Anticipated average interval between courses of treatments	NA. See dosing frequency above	
Anticipated number of repeat courses of treatments	NA. See dosing frequency above	
Dose adjustments	No dose adjustment is recommended in the SmPC. However, patients experiencing a hypersensitivity will switch to Erwinase, per the current protocols	SmPC
Anticipated care setting	Pegaspargase should be prescribed and administered by physicians and health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available, which is common for all forms of asparaginase. Due to co-morbidities and a generally poor health state, most adult ALL patients receive their chemotherapy as a hospital inpatient Most paediatric ALL patients receive induction therapy as an inpatient and their subsequent treatment phases as day case patients	SmPC Expert opinion

Abbreviations: NA, not applicable; SmPC, summary of product characteristics.
† List price.

2.3.1 *Patient access scheme*

A patient access scheme (PAS) is not being submitted.

2.4 *Changes in service provision and management*

2.4.1 *Additional test/investigations*

Pegaspargase is already the current standard of care for treating ALL in the NHS. No additional tests or investigations are required for pegaspargase beyond those that are already part of current clinical practice

2.4.2 *Main resource use to the NHS associated with the technology*

Pegaspargase is administered intramuscularly or intravenously over a period of up to 1–2 hours, and should be prescribed and administered by physicians and health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available (see SmPC).

In UK clinical practice, the aim is to deliver treatment without admitting the patient to hospital. Paediatric patients are generally admitted for the induction phase, but with the aim of discharging them as soon as possible, often during the induction phase (Expert opinion). This means that subsequent treatment phases (consolidation, intensification and maintenance doses) are delivered in a day case setting. By contrast, adult patients generally receive the majority or all of their treatment in an inpatient setting (Expert opinion).

Pegaspargase requires only one dose for every six doses of native E. coli-derived asparaginase or Erwinia-derived asparaginase, and as such is much less resource intensive than these alternatives (8, 10).

2.4.3 *Additional infrastructure requirements*

Pegaspargase is the current standard of care and is well-established in the NHS for the treatment of patients with ALL. As such, no additional NHS infrastructure is required to accommodate pegaspargase.

As highlighted in feedback provided by NCRI/RCP/ACP and Royal College of Pathologists and BSH during NICE scoping, a negative recommendation for pegaspargase as 1st line asparaginase could lead to removal from baseline commissioning, potentially disrupting the current UKALL protocols and leading to a subsequent detrimental effect on patient care in the UK.

2.4.4 *Patient monitoring requirements*

Pegaspargase is already the current standard of care in the NHS for patients with ALL. As such, patient monitoring requirements will be unchanged.

Specific monitoring requirements for pegaspargase, as specified in the SmPC are described in Section 2.2.3.

Monitoring requirements for pegaspargase are consistent with those of native E. coli-derived and Erwinia-derived asparaginase.

2.4.5 *Need for concomitant therapies*

No concomitant medications are specified in the marketing authorisation or used in the key clinical trials.

2.5 *Innovation*

Yes, we believe this technology to be innovative as it has become the standard of care 1st line asparaginase treatment of patients with ALL of all ages. Asparaginase is recognised as one of the most valuable drugs in the treatment of ALL (7). Although, until recently, pegaspargase has not had marketing authorisation in the UK, the value of this product as 1st line asparaginase treatment for patients with ALL has been recognised in the clinical community for over a decade. It has been the 1st line asparaginase of choice in UK clinical practice since 2003 with the vast majority of ALL patients receiving treatment under the UKALL protocols (UKALL 2003, UKALL 2011, UKALL14). In addition, in April 2013 pegaspargase was formally included in baseline commissioning by NHS England, meaning that it is routinely funded (13). This application was made by the clinical community without involvement of the manufacturer to overcome the inequity of "postcode prescribing" at the time.

Reimbursement decisions in the absence of marketing authorisation as a 1st line asparaginase have also been made in Belgium and Italy, and a large number of completed and ongoing academically led treatment protocols outside of the UK also now employ pegaspargase in 1st line use (AIEOP-BFM ALL-2009, ALL-MB 2008, CO-ALL-08-09, DCOG ALL-11, GMALL 07/2003, HOVON 100 ALL /EORTC 06083, IntReALL SR 2010, MC-PEGASP.1/Adults, GIMEMA LAL 1913, NOPHO ALL2008).

As outlined in the scoping meeting for this appraisal, an eminent clinician commented that patient care would be detrimentally affected should pegaspargase no longer be available. As a result, clinicians would be required to adopt an E. coli-derived native asparaginase (that is not licensed and not listed in the BNF) or Erwinase. Native asparaginase has been shown to have a higher rate of hypersensitivity and requires an increased number of administrations (8, 20); this is important for the paediatric population given the demonstrated increased anxiety associated with more frequent injections (30). Furthermore, many adult ALL patients have thrombocytopenia and are thus prone to bleeding and bruising following intramuscular administration of native asparaginase. Pegaspargase overcomes this complication as it may be administered via intravenous infusion, and requires only one dose versus six for native asparaginase or erwinase (Expert opinion).

3 Health condition and position of the technology in the treatment pathway

3.1 *Disease overview*

ALL, also known as acute lymphocytic leukaemia or acute lymphoid leukaemia is an acute, rapidly progressing, and life-threatening form of cancer involving lymphocyte-producing cells called lymphoblasts. ALL is classified primarily by the type of lymphocyte affected – B-cell or T-cell – with the majority of patients affected by B-cell ALL (31).

Between 2011 and 2013, an average of 744 new cases of ALL were diagnosed in the UK (crude incidence rate 1 per 100,000 males and 1 per 100,000 females), accounting for 0.2% of all new cancer diagnoses in the UK, and 9% of all new leukaemia diagnoses (1). The incidence of ALL is strongly correlated with age; in the UK between 2011 and 2013 an average of 54% of ALL cases were diagnosed in children aged 0–14 years (1). Age-specific incidence rates are highest in infants aged 0–4 years and drop sharply through childhood, adolescence, and young adulthood, reaching their lowest point at age 30–34 in males and 35–39 in females. A total of 644 new cases of ALL were diagnosed in patients aged 65 years or younger (1).

The symptoms of ALL result from the over-production and accumulation in the blood and bone marrow (BM) of leukaemic lymphoblast cells, and the subsequent disruption in the production of normal blood cells. Children with ALL may experience an insidious or explosive course of disease before diagnosis, whereas adults present more uniformly with rapid-onset disease. Common symptoms of ALL include anaemia, fatigue, frequent fever and infection, easy bruising and bleeding, and enlarged lymph nodes, liver and/or spleen (32). Young children may present with resistance to walking due to bone pain resulting from BM expansion and leukaemic cell bone infiltration, and central nervous system (CNS) involvement may manifest as headaches, nausea/vomiting, and cranial nerve palsies.

A wide range of factors influence prognosis in ALL including patient characteristics, leukaemic cell characteristics and response to initial therapy. Age is the most important prognostic factor, and a continuous decrease in survival is observed with increasing age from children to elderly patients (33). Increasing lymphoblast cell counts at diagnosis also confer a poorer outcome (34), particularly among patients with ALL affecting B-cell precursor cells. Chromosomal abnormalities in ALL result in biological differences in the disease which affect prognosis.

Response to initial induction chemotherapy is another important prognostic factor. Minimal residual disease (MRD) assessments provide a sensitive measure of early treatment response and are frequently used to determine whether patients require further induction therapy (35). More than 90% of patients who have persistent MRD after chemotherapy experience a clinical relapse despite continued chemotherapy, with a median time to relapse of 4–5 months (36).

3.2 *Burden to patients, carers and society*

The symptom burden is high in ALL patients. The most common presenting signs and symptoms in children diagnosed with ALL are lymphadenopathy (70%), hepatosplenomegaly (59–66%), fatigue (63%), and bleeding (43%) (37). Over one third of patients may present with a limp, bone pain, arthralgia or refusal to walk due to leukemia infiltration of the periosteum, bone or joint, or to the expansion of the marrow cavity by leukemia cells (38). Of adults with ALL, 79%, 55%, and 49% of patients report lack of energy, difficulty sleeping and pain, respectively, with half of them rating their impact as moderate to very severe in intensity (39).

Short-term impacts during treatment for ALL include long hospitalisations, school absences, broken friendships, alopecia, nausea and vomiting, mouth ulcers, weight gain and mood alterations (40). Skeletal abnormalities, occurring as a result of treatment of

ALL with steroids, are commonly seen in children and adolescents with ALL, with their effects ranging from mild pain through to disabling osteonecrosis (41). Affecting any or multiple joints but most commonly the hip and knee, 15–20% of children and young adults with ALL experience disabling symptoms, requiring in some cases surgical intervention including replacement of the affected joint (41).

The psychological burden is also substantial; in an evaluation of the parental-reported emotional and behavioural functioning of children newly diagnosed with ALL, up to 29% of children with ALL were found to be in the at-risk/clinical range for depression and anxiety at 1-12 months and at 1 month, respectively, after diagnosis, compared with a healthy population (15%, $p<0.05$ for both comparisons) (42).

Assessment of health-related quality of life (HRQL) in children with ALL using health utilities index (HUI) 2 and HUI3 demonstrates important deficits experienced during active treatment (0.2 quality-adjusted life years [QALYs]) compared with the general population (43). Disability was most evident in mobility/ambulation, emotion, self-care, and pain, and the severity of this disability was seen to reduce over the course of treatment and after treatment had finished; severe deficits were experienced during initial treatment (induction of remission of disease), reflecting the combined effects of disease and treatment, while only mild non-significant deficits compared with the healthy population were seen within the 2 years post-treatment (43).

The burden of ALL can be far-reaching, particularly given that the disease presents primarily in younger patients. Carers, such as family members, often have to deal with numerous stressful events, and commonly suffer psychological, behavioural, and physical disruption to their daily lives and their health (44).

While ALL affects a relatively small proportion of the population, the costs associated with its management are substantial. In England in 2014, there were 26,438 admissions for ALL, resulting in 41,046 bed days (ICD10 code C91.0) (45). The associated cost-burden relating to ALL admissions is estimated to be in excess of £23.6 million (HRG codes PM40 and SA24) (46).

3.3 *Clinical pathway of care*

Treatment of ALL represents one of the most complex and intensive programs in cancer therapy (15). The specific treatment regimens, drug selection, dosages, and treatment duration will vary depending on patient age (adults and younger patients), and among different subtypes of ALL, but the basic principles are similar. Multi-agent chemotherapy is generally used and treatment is grouped into three main phases:

1) remission-induction
2) intensification/consolidation
3) continuation/maintenance

Prophylactic treatment is also directed to the CNS early in the clinical course to prevent relapse attributable to leukaemic cells sequestered in this site (15).

Induction therapy is aimed at clearing as many leukaemic cells as possible and thus achieving bone marrow remission (<5% blasts) (15). Drugs used during induction

typically include vincristine, corticosteroid (e.g. prednisone), cyclophosphamide, anthracyclines (e.g. doxorubicin), and asparaginase (available in three different forms, see Section 3.3.1) (15). During the consolidation or intensification phase, cytarabine, methotrexate and 6-mercaptopurine are often added with the aim of eradicating residual disease (15). Maintenance therapy aims to prevent disease relapse and generally includes 6-mercaptopurine, methotrexate, corticosteroids, and vincristine (15).

In adult patients, allogeneic transplant is currently the treatment of choice for eligible adults in first complete remission. At present, a group of adults with ALL in whom the risk of relapse is less than the risk of sibling allogeneic SCT cannot be defined. Accordingly, the UKALL14 study continues to propose sibling allogeneic SCT for every eligible patient where a sibling donor is available. Patients who receive a transplant cease to receive asparaginase (12).

3.3.1 *Asparaginase therapy*

Asparaginase is recognised as one of the most valuable drugs in the treatment of ALL (7). It is used during the induction and consolidation phases (15), and works by depleting circulating exogenous asparagine on which leukaemic cells, incapable of synthesising endogenous asparagine, depend, leading to leukaemic cell death (6).

There are three different forms of asparaginase: native E. coli-derived asparaginase, native Erwinia-derived asparaginase (Erwinase) or a form of the E. coli-derived asparaginase which has been modified by pegylation (pegaspargase).

Historically, native E. coli-derived asparaginase was used as the 1st line asparaginase treatment for patients with ALL. However, this form is highly immunogenic leading to the production of antiasparaginase antibodies in 45–75% of patients, and frequently would lead to hypersensitivity reactions that limit treatment effectiveness (8, 20). A switch to pegaspargase – for which pegylation masks the immunogenic characteristics of the native enzyme – or Erwinia-derived enzyme – which is immunologically distinct from the E. coli-derived enzyme – would then have been necessary.

Pegaspargase was originally used as a 2nd line asparaginase in the late 1980s and the product was subsequently licensed in 1994 in the United States and Germany, and in 2008 in Poland for 2nd line use. The pegylated enzyme then gained marketing authorisation for 1st line asparaginase use in the United States in 2006, and the European Union licence was approved in January 2016. However, the value of this product as a 1st line asparaginase was recognised well before this in the clinical community in the UK and internationally, with the UK, Belgium and Italy reimbursing the product, and a large number of completed and ongoing academically led treatment protocols employing pegaspargase as a 1st line asparaginase, including the UK UKALL protocols.

Pegaspargase is now the standard of care 1st line asparaginase therapy, with the majority of ALL patients in the UK receiving this treatment as part of the UKALL protocols or, if not enrolled, receiving treatment based on the protocol, with treatment reimbursed by baseline commissioning. As such although the licence for pegaspargase does not preclude its use as a 2nd line asparaginase therapy there is not currently a clinical scenario in which pegaspargase would be used as a 2nd line asparaginase therapy, since

patients would not receive native E. coli- or Erwinia-derived asparaginase as a 1st line asparaginase.

In addition, with the availability of Erwinia-derived asparaginase, patients experiencing hypersensitivity to pegylated or native E. coli enzyme would in practice no longer be switched to the other E. coli enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinia-derived enzyme following hypersensitivity to pegaspargase (3, 12).

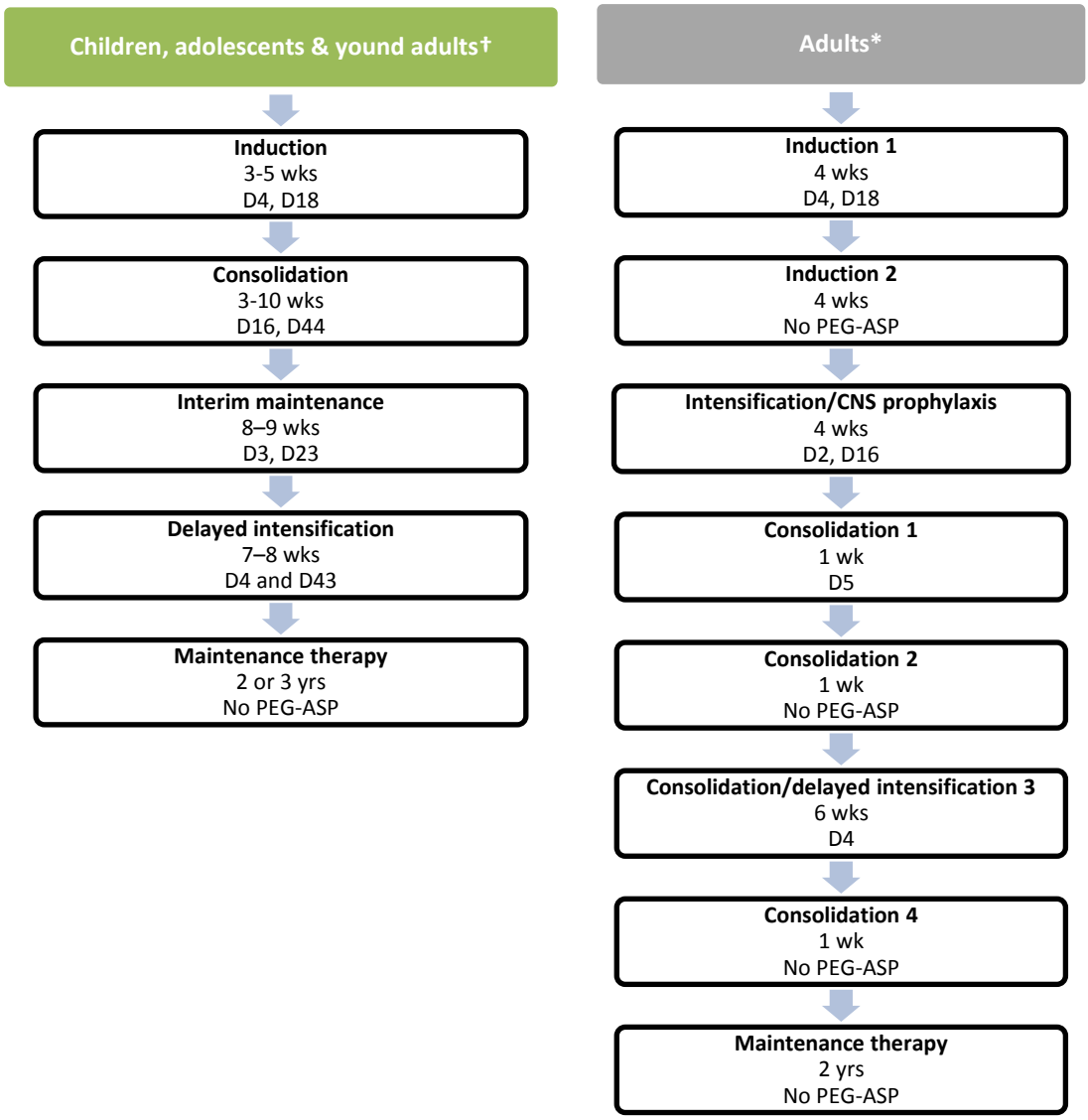
A further complication in this field is that native E. coli-derived asparaginase is not licensed for use in the UK and is not listed in the BNF. Similarly, unavailability in the United States has seen it removed from United States treatment guidelines (NCCN 2015) (15).

Erwinia derived asparaginase is licensed in the UK and, although the wording of its indication does not limit its use to a specific line of asparaginase therapy (10), the product is only positioned in treatment protocols as a 2nd line asparaginase (3, 7, 12, 16).

Hence, with this context in mind, the current standard of care treatment pathway in the UK is pegaspargase 1st line followed by Erwinia-derived enzyme in cases of hypersensitivity. Although not currently part of UK clinical practice and unrealistic given the current unavailability of native E. coli enzyme and the 2nd line positioning of Erwinia, alternative switching scenarios of native E. coli enzyme to Erwinia, Erwinia to pegylated enzyme and Erwinia to native E. coli enzyme could be clinically possible.

An overview of the treatment algorithms for pegaspargase use in clinical practice as detailed in the UKALL protocols is provided in Figure 1. These algorithms demonstrate how pegaspargase is used in a number of different phases of treatment and how this differs between paediatric/young adult and adult patients.

Figure 1: Overview algorithms for pegaspargase use in clinical practice



Abbreviations: D, days; PEG-ASP, pegaspargase; wks, weeks
Source: derived from UKALL 2011 and UKALL14 protocols (3, 12).
Wks represent overall length of treatment phase. D represents day of phase on which pegaspargase is administered. Pegaspargase is not administered in some treatment phases as denoted by "No PEG-ASP". Pegaspargase dose 1,000 IU/m^2 throughout.
†In UKALL 2011 duration of treatment phases and total number of pegaspargase doses in each phase vary depending on which of three regimens that patients are assigned to, based on MRD risk. The total number of pegaspargase doses varies between three and seven between regimens.
*In UKALL14, patients receive between three and six pegaspargase doses depending on their age and whether or not they have had a transplant.

3.4 *Life expectancy*

The prognosis for paediatric and young adult patients with ALL has improved dramatically over several decades with advances in treatment. For patients in the UK treated under the numerous UKALL protocols there has been a stepwise improvement in prognosis from a 5-year event-free survival (EFS) of 35% in 1972 to 80% in 2003 (3).

For adult patients treated in the UKALL program the improvement has been less dramatic but nonetheless apparent with each successive study over a 35 year period (5).

The latest data from the UKALL program (UKALL 2003 (2), see Section 4.3 for further details), in which pegaspargase was incorporated into the treatment algorithm as the 1st line asparaginase for the first time, shows a further improvement, with a 5-year EFS of 87% reported for patients ≤24 years of age.

The latest estimate of 5-year survival in the UK for all patients with ALL is 64.7%[a] based on data from the Haematological Malignancy Research Network (47). Further data from Cancer Research UK demonstrate the poorer prognosis for older patients with a gradual reduction in survival observed with increasing age:

- 90% in patients aged below 14 years (48)
- 66% among patients aged 15–24 years (48)
- 40% among patients aged 25–64 years (48)
- 15% among patients aged 65 years or older (48)

In September 2008, pegylated L-asparaginase was granted orphan status by the European Commission for the treatment of ALL; at the time of designation, ALL affected approximately 0.7 in 10,000 people in the European Union, below the threshold for orphan designation of 5 people per 10,000 (18). Data relating specifically to the incidence of ALL in England and Wales shows that there were 529 and 40 new cases of ALL diagnosed in 2012, respectively (crude incidence rate 1.0 and 1.3 per 100,000, respectively) (49).

3.5 *Relevant NICE guidance, pathways or commissioning guides*

Currently there are no NICE guidelines or pathways for the treatment of ALL. The NICE pathway on blood and bone marrow cancers does cover leukaemia but does not specifically include any information on ALL. NHS England included pegaspargase in baseline commissioning in April 2013 (13).

3.6 *Clinical guidelines*

ALL treatment in the UK has been and continues to be driven by the UKALL protocols which date back to the 1970s (3). Since 2003 pegaspargase has been the 1st-line asparaginase mandated in UKALL protocols with the vast majority of ALL patients receiving treatment according to these protocol treatment algorithms: 97% of eligible patients aged <25 years were treated according to UKALL 2003 (3) which completed enrolment in 2010, and the majority of children, adolescents and adults will continue to be treated according to the ongoing UKALL 2011 and UKALL14 protocols.

Information relating to each of the three UKALL protocols is provided below.

[a] Based on B- and T-lymphoblastic leukaemia (47).

Children, adolescents and young adults: UKALL 2003

UKALL 2003 (2, 4) enrolled patients aged 1-<25 years between October 2003 and June 2011, accounting for 97% of all eligible patients in the UK and Ireland. According to the UKALL 2003 protocol (described in greater detail in Section 4.3), patients were stratified and allocated to one of three increasing-intensity treatment regimens based on their clinical risk status as determined by age, white blood cell (WBC) count at diagnosis, and treatment response at day 8 and 15 of induction. In addition, eligible patients were stratified and entered into treatment intensification and reduction randomisations according to their MRD status at the end of induction and week 11.

Treatment phases consisted of:

- an induction phase (4–5 weeks)
- consolidation and CNS-directed therapy (4–9 weeks)
- one/two interim maintenance phases (8 weeks each)
- one/two delayed intensification phases (8 weeks each)
- continuation therapy

Patients received one of three escalating-intensity treatment regimens (designated Regimen A, B, and C, respectively) depending on their clinical risk grouping. As a component of multi-agent chemotherapy, all patients received pegaspargase (1,000 IU/m^2 intramuscular [IM]) throughout treatment across different phases of treatment.

- Clinical standard-risk (regimen A) and intermediate-risk (regimen B) patients received four doses (two in induction and one in each delayed intensification phase), and clinical high-risk patients (regimen C) received 12 doses (two in induction, two in each interim maintenance phase, and three in each delayed intensification phase).
- MRD low-risk patients were randomised to receive standard regimen A or B as above or reduced treatment comprising only one delayed intensification cycle, and hence only three pegaspargase.
- MRD high-risk patients randomised to receive standard regimen A or C (4 doses) or augmented treatment with Regimen C (12 doses).

In the interim between UKALL 2003 finishing recruitment and UKALL 2011 commencing, presenting ALL patients aged 1-<25 years received treatment according to a set of interim treatment guidelines (16) in which the treatment regimens from UKALL 2003, in terms of pegaspargase dosing, were adopted.

Children, adolescents and young adults: UKALL 2011

UKALL 2011 (3) opened in April 2012, is ongoing, and enrolling patients newly diagnosed with ALL aged 1–24 years. Enrolment closes in April 2018.

Patients will receive, as a component of multi-agent chemotherapy, and on the basis of National Cancer Institute (NCI) risk and MRD assessment, between three and seven

doses of pegaspargase (1,000 IU/m^2 IM). Asparaginase will be spread over the course of one of three increasing-intensity treatment regimens (Regimen A–C), adopted from the UKALL 2003 study protocol, consisting of some or all of the phases listed below. The duration of treatment phases and number of pegaspargase doses received depends on which of the three regimens the patient is assigned to, according to risk. NCI standard- and high-risk patients receive three doses (Regimen A or B). Patients with slow early response on the basis of MRD following induction therapy, patients with high-risk cytogenetics, and Down syndrome patients with slow early response receive seven doses (Regimen C)

- Induction (3–5 weeks): 1,000 IU/m^2 IM pegaspargase on days 4 (regimen A & B) and 18 (All regimens)
- Consolidation (3–10 weeks): 1,000 IU/m^2 IM pegaspargase on days 16 and 44 (Regimen C only)
- Interim maintenance (8–9 weeks): 1,000 IU/m^2 IM pegaspargase on days 3 and 23 (Regimen C only)
- Delayed intensification (7–8 weeks): 1,000 IU/m^2 IM pegaspargase on days 4 (All regimens) and 43 (regimen C only)
- Maintenance therapy (2 or 3 years from the start of interim maintenance for girls and boys, respectively)

The aim of UKALL 2011 is to assess whether further refinement of MRD-based risk stratification and treatment regimen improves survival while reducing the overall burden of therapy in children and young adults with ALL.

The primary outcomes being measured in UKALL 2011 include BM/CNS relapse and toxicity, and secondary outcomes include rate of remission, event-free survival (EFS), overall survival (OS), quality of life, and treatment-related mortality and morbidity.

Adult patients: UKALL14

UKALL14 (12) is the first large-scale study investigating the efficacy and toxicity of pegaspargase in a solely adult ALL patient population. Adult patients aged 25–65 years newly diagnosed with ALL may be considered for enrolment in Study UKALL14 (12) which opened in December 2010 and closes in December 2016. It is anticipated that UKALL14 will enrol 720 adult patients currently accounting for approximately 85% of all eligible adult ALL patients.

Depending on patient age and transplant eligibility, patients will receive a minimum of three and maximum of six doses of pegaspargase (1,000 IU/m^2 intravenous [IV]) over the course of the treatment regimen that consists of:

- Two induction phases (4 weeks each): 1,000 IU/m^2 IV pegaspargase on days 4 and 18 of first induction phase
- Intensification/CNS prophylaxis (4 weeks): 1,000 IU/m^2 IV pegaspargase on days 2 and 16

- Two consolidation phases (Cycle 1 and 2; 1 week each): 1,000 IU/m^2 IV pegaspargase on day 5 of first consolidation phase
- Consolidation/delayed intensification (Cycle 3; 6 weeks): 1,000 IU/m^2 IV pegaspargase on day 4 of cycle 3
- Consolidation (Cycle 4; 1 week)
- Maintenance (2 years)

Following induction, patients in complete remission who have a sibling donor (or are high-risk but with no sibling donor), receive an allograft. Standard-risk patients, ineligible for allograft, continue on multi-agent chemotherapy

Patients aged ≥41 years will not receive the pegaspargase dose on day 4 of the first induction phase and Ph+ patients will not receive treatment with pegaspargase.

The primary outcomes being measured in UKALL14 include EFS and toxicity, and secondary outcomes include anti-asparaginase antibodies, OS, complete response/remission (CR), MRD quantification after the first induction phase, and death in CR.

3.7 *Issues relating to current clinical practice*

Within the context of a complex, multi-agent chemotherapy regimen, the main clinical practice issues related specifically to the asparaginase component of chemotherapy are discussed below.

Frequency of administration

Native E. coli-derived L-asparaginase and native Erwinia-derived L-asparaginase have shorter half-lives than pegaspargase (26–30 hours and 16 hours, respectively versus 5.5–7 days) (8). Thus to maintain the depletion of asparagine crucial to chemotherapeutic activity, the two native products require much more frequent administration than pegaspargase (three times weekly versus once every 2–4 weeks) (8, 10). For every one dose of pegaspargase, six doses of either native asparaginase or Erwinase are stipulated/ required based on half-life differences.

Method of administration

Asparaginase formulations can be administered either intravenously or intramuscularly. For intramuscular administration, the number of injections may be very high in larger patients, especially as the volume should be split to achieve an acceptable intramuscular distribution. In addition, intramuscular injections can be painful and this may be of particular concern for children in whom intravenous injections are not generally considered appropriate (3). By reducing the frequency of IM injections required and the option of delivering intravenously with pegaspargase versus other asparaginase formulations, the pain and anxiety burden that patients experience could be reduced; a study comparing weekly intramuscular asparaginase with bi-weekly intravenous pegaspargase demonstrated a reduction in patient reported and parent-proxy-reported anxiety (30, 50).

Hypersensitivity

A key concern with the use of asparaginase is the development of hypersensitivity reactions necessitating a switch to an alternative asparaginase formulation. Symptoms of hypersensitivity range in severity from mild reactions to very severe symptoms including systemic anaphylaxis (51).

Rates of Grade 3 or higher hypersensitivity reactions to native asparaginase vary across studies but are in the range of 0–13% (see Table 29 and Appendix 4). When milder allergic reactions are taken into consideration, however, the rates of hypersensitivity reactions to native asparaginase are much higher. Bowman et al reported 13% Grade 3 or higher hypersensitivity, but 25% incidence of any grade hypersensitivity (COG P9906 (52)), while Wacker et al reported 8% Grade 4 hypersensitivity, but 76% incidence of hypersensitivity leading to a switch in asparaginase formulation (POG 8602 (25)).

The SmPC for Oncaspar® states that hypersensitivity reactions of Grade 2 or higher are seen in ≥20% of patients treated with pegaspargase. This rate appears high but should be interpreted in the context that SmPC data was based on patients treated with the recommended dose of 2,000 to 2,500 IU/m^2 and includes some patients treated with 2nd line pegaspargase following hypersensitivity to native E. coli enzyme, a scenario known to increase the risk of hypersensitivity to pegaspargase (53-55).

In contrast, and of more relevance to UK clinical practice, when used in >3,000 patients in UKALL 2003 at the reduced dose of 1,000 IU/m^2 hypersensitivity reactions were experienced by only 2% of patients across the entire study treated with between 4 and 12 doses of pegaspargase (n=54/3,126).

Limited data was identified in the systematic review for Erwinia-derived asparaginase as a 1st line asparaginase and none comparing with pegaspargase; Moghrabi et al report that when used 1st line, 6% of Erwinia-treated patients develop hypersensitivity resulting in a treatment switch to native asparaginase (9). Note that a lower dose of Erwinase than is used effectively in clinical practice today was administered in the Moghrabi study, but the reported hypersensitivity rates were broadly consistent with the SmPC for Erwinia that reports hypersensitivity in the 1–10% range (9, 10).

When hypersensitivity reactions occur early in treatment, therapeutic delays are often generated, which can compromise the aims of therapy and necessitate a treatment switch (7). Hypersensitivities also impact the patient's quality of life, especially where a treatment delay occurs (See Section 5.3.3).

In the absence of pegaspargase, treatment costs have been shown to increase by an estimated 180% when a patient develops hypersensitivity to native E. coli-derived L-asparaginase since a switch to the much more expensive Erwinia-derived L-asparaginase becomes necessary (56).

Conclusion

Pegaspargase thus addresses the main issues encountered with native E. coli-derived and Erwinia-derived asparaginases. Pegylation of native E. coli-derived L-asparaginase, where polyethylene glycol is bound to L-asparaginase, reduces the immunogenicity of the enzyme and therefore the risk of hypersensitivity reactions, and increases the

circulating half-life of the enzyme compared with that of native L-asparaginase, meaning less frequent administrations are required (29).

3.8 *Equality*

ALL presents primarily in children, adolescents, and young adults, with 74.4% of cases diagnosed in people aged under 25 years (1). Equity of treatment for children and young people with cancer is a concern, as evident from the NICE Quality Standard 55 “Cancer services for children and young people” (17). ALL is also an orphan disease (18). The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (19). Therefore, continued access, where appropriate, to a treatment such as pegaspargase should help to promote equality for both younger patients and those with rarer forms of cancer, especially as pegaspargase has a decreased number of infusions and hypersensitivity reactions than native E. coli-derived or Erwinia-derived L-asparaginase (8, 20).

4 Clinical effectiveness

4.1 *Identification and selection of relevant studies*

Two systematic reviews were conducted to inform the clinical evidence base for pegaspargase and relevant comparators.

Systematic review 1 was designed to specifically identify evidence to allow a comparison of pegaspargase and native E. coli-derived for 1st line treatment of ALL in newly diagnosed children and adolescents. This search was conducted in August 2015

A subsequent systematic review (Systematic review 2) was conducted to broaden the search to identify evidence for pegaspargase, native E. coli-derived asparaginase, and Erwinia-derived asparaginase, irrespective of age group and line of treatment. This search was conducted in 31st January 2016.

4.1.1 *Systematic review 1: 1st line treatment of ALL in children and adolescents*

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of pegaspargase in 1st line treatment of ALL in newly diagnosed paediatric and adolescent patients. The specific objectives of the systematic review were:

- to evaluate efficacy and safety of pegaspargase when used as 1st line therapy in ALL
- to assess the efficacy and safety of pegaspargase compared to native asparaginase when they are used in 1st line ALL treatment.

4.1.1.1 Search strategy

Searches were conducted in Medline, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects), ClinicalTrials.gov, and the International Clinical Trials Registry Platform. These searches were supplemented by hand searching congress and society websites over the last three years.

Full details of the search strategy are provided in Appendix 2.

4.1.1.2 Study selection

Inclusion and exclusion selection criteria are shown in Table 5. In view of the planned network meta-analysis (See Section **Error! Reference source not found.**), if any studies assessing specific chemotherapy protocols that did not contain asparaginase would have been needed to complete the evidence network, these studies were to be searched for post-hoc and reported with the rest of the studies.

Table 5: Eligibility criteria used in search strategy

	Inclusion criteria
Population	Paediatric and/or adolescent patients with ALL
Interventions & comparators	1st line treatment for ALL Pegaspargase or native E. coli-derived asparaginase
Outcomes	The search did not initially restrict to any outcome to allow for identification of all possible reported outcomes
Study design	Case reports & editorials were excluded
Language restrictions	Only English, French & German extracted

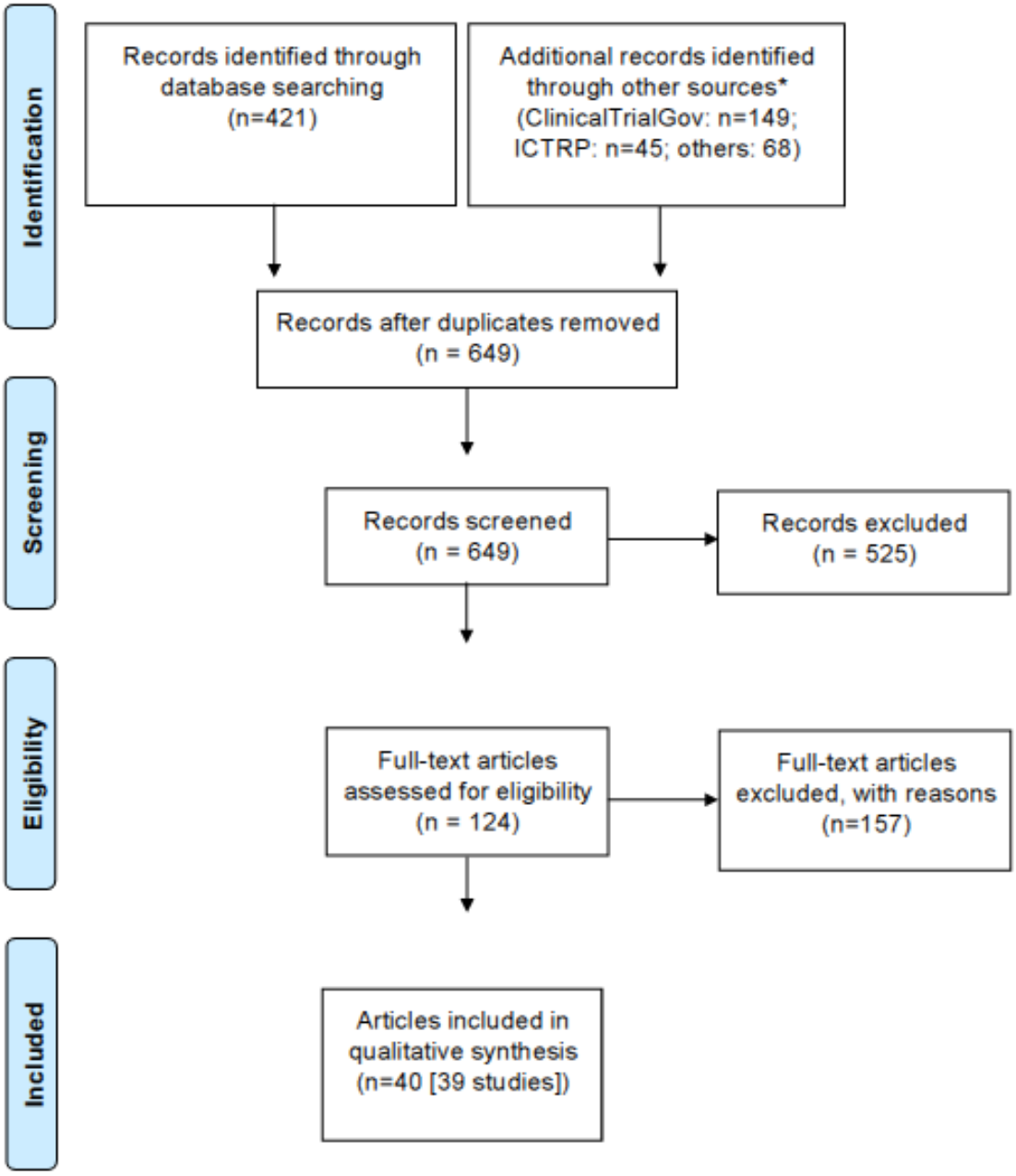
Abbreviations: ALL, acute lymphoblastic leukaemia; RCT, randomised controlled trial.

Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion.

Following assessment and exclusion of studies based on title, abstract and full text, 39 studies (40 publications) were included in the final data set. Twenty three publications reported data on pegaspargase (some of which also included data for native E. coli asparaginase), and are listed in Table 7 (2, 4, 11, 20, 50, 53-55, 57-71). Nineteen publications reported additional studies that included native E. coli asparaginase data and are listed in Table 30 (9, 20, 24, 25, 52, 68, 72-84). Silverman 2010 (20) and Gökbuget, 2013 (68) report data from more than one study, hence their inclusion in both lists.

The systematic review schematic is shown in Figure 2.

Figure 2: Schematic for the systematic review of clinical evidence



A full list of excluded studies is provided in Appendix 2.

4.1.2 *Systematic review 2: Treatment of ALL in all patients*

A second systematic review was conducted to comprehensively update the first systematic review. The objectives were the same as in the first review (see Section 4.1.1).

4.1.2.1 Search strategy

Searches were conducted in Medline, Cochrane Library (Cochrane Database of Searches were conducted in Medline, EMBASE, the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects) and EBM Reviews.

Full details of the search strategy are provided in Appendix 2.

4.1.2.2 Study selection

Inclusion and exclusion selection criteria are shown in Table 6. In view of the planned network meta-analysis (see Section **Error! Reference source not found.**), if any studies assessing specific chemotherapy protocols that did not contain asparaginase would have been needed to complete the evidence network, these studies were to be searched for post-hoc and reported with the rest of the studies.

Table 6: Eligibility criteria used in search strategy

	Inclusion/exclusion criteria
Population	Patients with ALL
Interventions & comparators	Patients with ALL who have received any type of the following asparaginase as part of a chemotherapeutic protocol: • Main intervention: Pegylated L-asparaginase derived from *Escherichia coli* • Clinical comparator: 'Native' (non-pegylated) L-asparaginase derived from *Escherichia coli* • Clinical comparator: Crisantaspase (Erwinase) derived from *Erwinia chrysanthemi* Studies not directly evaluating the clinical effectiveness or the safety/tolerability profile of at least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patients, were excluded
Outcomes	The search did not initially restrict to any outcome to allow for identification of all possible reported outcomes
Study design	Comments, editorials, systematic reviews or reviews were excluded
Language restrictions	English language publications only

Abbreviations: ALL, acute lymphoblastic leukaemia; ASP, asparaginase; PEG-ASP, pegaspargase; RCT, randomised controlled trial.

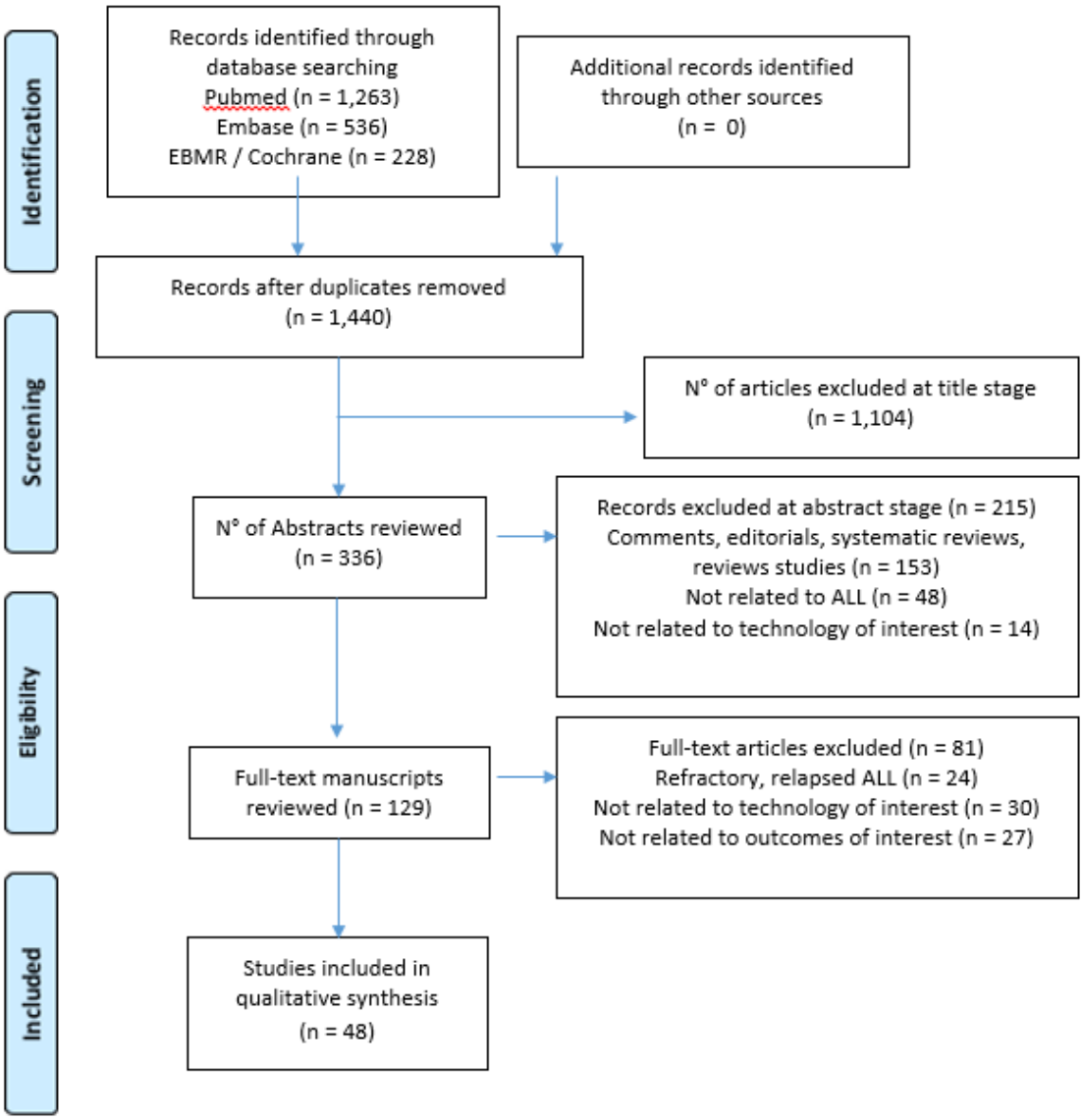
Studies identified were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion.

In addition to those studies found by systematic review 1, the second systematic review identified a further five publications providing pegaspargase data (Table 7). Two publications (Place 2015 (30) and Merryman 2012 (85)) were additional publications for studies previously identified (DFCI 05-001 and DFCI 05-01). Three additional publications were identified for studies exclusively in adult patients (21-23).

Systematic review 2 also identified four additional studies providing data on Erwinia-derived asparaginase (86-89).

The schematic for systematic review 2 is shown in Figure 3.

Figure 3: Schematic for systematic review 2 of clinical evidence



A full list of excluded studies is provided in Appendix 2.

4.2 *List of relevant studies*

For clarity all studies providing pegaspargase data, whether randomised or non-randomised are listed in this section (Table 7).

Pivotal studies

CCG-1962 and UKALL 2003 are pivotal studies providing evidence for the 1st line use of pegaspargase in children, adolescents and young adults with ALL, and are described in detail in Section 4.3 to 4.7.

- CCG-1962 is the only trial available that provides direct randomised comparative evidence for pegylated versus E. coli-derived asparaginase when given during the induction phase of treatment, and treatment continued through subsequent phases with the randomly assigned asparaginase.

- UKALL 2003, although not providing comparative evidence versus other asparaginases, does provide pivotal evidence for the use of pegaspargase in UK and Ireland clinical practice. The enrolled population of >3,200 patients represents 97% of the eligible ALL population in the UK and Ireland aged 1-<25 years (3).

Supporting studies

Numerous other studies assessing pegaspargase in 1st line therapy were identified by the systematic review, based on the eligibility criteria defined in Table 5, including those that supported the marketing authorisation application. These include randomised studies, in which pegaspargase was directly compared with another asparaginase or where patients were randomised to variations of treatment protocols which included pegaspargase. Non-randomised studies also provide relevant evidence supporting pegaspargase. All studies supporting 1st line use are listed in Table 7 and are described further in Section 4.8.1.

Evidence supporting the use of pegaspargase in adults is more limited than the evidence base in paediatric/young adult patients. Non-randomised data from three studies is summarised in Section 4.8.2. There is an ongoing study in the adult (25–65 years of age) population (UKALL14) that will provide more data on this patient population in the future (12).

Table 7: List of relevant studies investigating pegaspargase

Trial no. (acronym)	Population	Asparaginase(s) assessed	Primary study ref(s)
RCTs			
CCG-1962	Children (1-9 years) with standard-risk ALL	PEG-ASP E. coli ASP	Avramis, 2002 (11)
UKALL 2003	Consecutive children and young adults (aged 1–24 years) with ALL	PEG-ASP	Vora, 2013 (2) Vora, 2014 (4)
CCG-1961	Patients 16 to 21 years old (young adults) with high risk ALL	PEG-ASP E. coli ASP	Seibel 2008 (55) Nachman 2009 (57) Panosyan 2004 (58)
DFCI-91-01	Children (aged 0-18 years) with newly diagnosed ALL (excluding mature B-cell ALL)	PEG-ASP E. coli ASP	Silverman, 2001 (59)
DFCI ALL 05-001	Patients with newly diagnosed ALL aged 1-18 years who achieved complete remission	PEG-ASP E. coli ASP	Place, 2015 (30) Silverman, 2013 (50)
DFCI-87-01	Newly diagnosed ALL	PEG-ASP E. coli ASP Erwinia ASP	Silverman 2010 (20)

Trial no. (acronym)	Population	Asparaginase(s) assessed	Primary study ref(s)
DFCI ALL 05-01	Children and adolescents (1-18 yrs) with newly diagnosed ALL who achieved CR during induction	PEG-ASP E. coli ASP	Merryman 2010 (60) Merryman, 2012 (85) Silverman, 2011 (61)
AALL07P4	Newly diagnosed HR B-cell ALL	PEG-ASP (Carba)	Angiolillo, 2014 (62)
COG AALL0232	Children and young adults (1-30 yrs) with newly diagnosed ALL	PEG-ASP	Larsen, 2011 (63) Larsen, 2012 (64)
COG AALL0331	Children with SR (age 1-9.99 yrs and initial WBC <50,000/µl) B-cell precursor (B-ALL)	PEG-ASP	Maloney, 2013 (65)
NOPHO ALL2008 (NCT00819351)	Children aged 1–17 years, with Philadelphia chromosome negative B-cell precursor including Downs syndrome, T-cell, or bi-lineage ALL	PEG-ASP	Henriksen, 2015 (66)
POG 9006	Children with high risk B-Precursor ALL	PEG-ASP E. coli ASP	Lauer, 2001 (53)
POG 9406	Newly diagnosed high risk ALL in patients aged between 10 and 30 years of age	PEG-ASP E. coli ASP	Tower, 2014 (54)
Non-RCTs			
CCG-1961m/CCG-1991	Children up to 14 years old with newly diagnosed ALL	PEG-ASP	Jastaniah, 2015 (67)
GMALL 07/03	AYAs aged 15-35 years with ALL	PEG-ASP	Gokbuget, 2013 (68)
MDACC BFM augmented	Newly diagnosed patients aged 12-40 yrs with de novo Philadelphia chromosome negative ALL	PEG-ASP	Rytting, 2013 (69)
INTERFANT-06	De novo ALL patients (children)	PEG-ASP	Van der Sluis, 2013 (70)
CoALL 08-09	Newly diagnosed acute B-progenitor or T-cell leukaemia	PEG-ASP	Escherich, 2013 (71)
Adult data			
NR	Newly diagnosed ALL in adults up to 55 years of age	PEG-ASP	Douer, 2007 (21)
NCT00184041	Newly diagnosed ALL in adults up to 57 years of age	PEG-ASP	Douer, 2014 (22)
CALGB 9511	Untreated ALL or acute undifferentiated leukaemia in adults (age range not specified)	PEG-ASP	Wetzler, 2007 (23)

Abbreviations: ALL, acute lymphoblastic leukaemia; BM, bone marrow; Carba, Calaspargase pegol Escherichia coli asparaginase; CR, complete remission; E. coli ASP; native E. coli-derived asparaginase; HR, high-risk; NR, not reported; PEG-ASP, pegaspargase; SR, standard risk.

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Comparative summary of RCT methodology*

Methodologies of the pivotal RCTs are summarised in Table 8.

Table 8: Comparative summary of methodology of CCG-1962 and UKALL 2003

Trial no. (acronym)	CCG-1962	UKALL 2003
Study objective	To assess the efficacy and safety of native versus pegaspargase as part of induction and two DI chemotherapy phases in the treatment of children newly diagnosed with standard-risk ALL	To assess the relative efficacy of reduced, standard, and augmented intensity regimens, adjusted on the basis of MRD risk status, in the treatment of children and young adults with low-risk ALL
Trial design	Multicentre, randomised, open-label, Phase III	Multicentre, randomised, open-label
Method of randomisation	Randomised 1:1 (method of randomisation not stated)	Randomisation (1:1) occurred at day 28 following induction therapy, and was via telephone call to the central trials unit, using computer randomisation. Only clinical standard- and intermediate-risk patients were eligible for randomisation (see below). Randomisation was stratified by: • Day 29 MRD result (low-risk, high-risk) • Gender (male, female) • Age (<10 years, ≥10 years) • WBC count at diagnosis (<50×10^9/L, ≥50×10^9/L)
Method of blinding (care provider, patient and outcome assessor)	N/A, the study was open-label	N/A, the study was open-label
Eligibility criteria for participants	Standard-risk ALL; aged 1–9 years; WBC counts ≤50,000 µL; patients were eligible with massive lymphadenopathy, massive splenomegaly, large mediastinal mass, concurrent CNS, or testicular leukaemia	Children and young adults aged 1–24 years with ALL. Patients with mature B-cell ALL were not eligible. Patients with Philadelphia chromosome-positive ALL were transferred to other protocols once their Philadelphia chromosome status was known
Settings and locations where the data were collected	8 CCG centres in the US (children's hospitals and clinics)	45 centres in the UK and Ireland
Duration of study	Treatment duration for girls and boys was 2 and 3 years, respectively Patients were enrolled between May 1997 and November 1998	Treatment duration for females and males was 2 years and 3 years, respectively, from the start of interim maintenance Patients were enrolled between October 2003 and June 2011
Trial drugs	Treatment consisted of:	Treatment consisted of:

Trial no. (acronym)	CCG-1962	UKALL 2003
	• 4 weeks of induction • 4 weeks of consolidation • Two 8-week interim maintenance phases • Two 8-week DI phases, and • Maintenance therapy At the start of induction, patients were randomly assigned to receive either: • Pegaspargase 2,500 IU/m^2 IM on day 3 of induction and each DI phase, OR • Native asparaginase 6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase (For full details of all drugs administered throughout the trial see Appendix 3)	• Induction (4 weeks) • Consolidation (4-9 weeks) • Two interim maintenance phases (8 weeks) • Two DI phases (7 weeks) • Continuation therapy Patients received one of three escalating-intensity treatment regimens (designated Regimen A, B, and C, respectively) depending on their clinical risk grouping (see below). Each regimen included treatment with pegaspargase 1,000 IU/m^2 IM. All regimens included two doses at induction, on days 4 and 18. Regimen A and B also included a single dose at DI no.1 and DI no.2 (both day 4). Regimen C included two doses at consolidation (day 16 and 44), interim maintenance no.1 and no.2 (both day 3 and 23), and DI no.1 and no.2 (both day 5 and 43). Regimens are described in full detail in Appendix 3. <u>Clinical risk classification</u> To determine their treatment pathway, following induction therapy, patients were categorised into one of three clinical risk of relapse categories on the basis of NCI criteria, cytogenetics, and early response to induction:[†] • Clinical standard-risk (proceed to MRD assessment) • Clinical intermediate-risk (proceed to MRD assessment) • Clinical high-risk (assigned to Regimen C) <u>MRD assessment</u> Clinical standard-risk and clinical intermediate-risk patients were eligible for MRD assessment and stratification:[‡] • MRD low-risk (proceed to randomisation) • MRD high-risk (proceed to randomisation) • MRD indeterminate-risk (Regimen A if clinical standard-risk; Regimen B if clinical intermediate-risk)

Trial no. (acronym)	CCG-1962	UKALL 2003
		Randomisation MRD low-risk patients were randomly assigned to receive either: • Reduced treatment (Regimen A if clinical standard-risk, Regimen B if clinical intermediate-risk, but with only one DI cycle in both cases) • Standard treatment (Regimen A if clinical standard-risk, Regimen B if clinical intermediate risk) MRD high-risk patients were randomly assigned to receive either: • Standard treatment (Regimen A if clinical standard-risk, Regimen B if clinical intermediate risk) • Augmented treatment (Regimen C)
Permitted and disallowed concomitant medications	Not specified	Not specified
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome: • Incidence of high-titre asparaginase antibodies in DI no. 1 Blood samples were collected on days 0, 7, 14, 21, and 28 of DI no. 1 Asparaginase antibody assays were done by a modified indirect solid-phase ELISA. The assay was done with a computer-controlled instrument from Dynatech Laboratories (Chantilly, VA). An antibody against native E. coli-derived asparaginase was used initially to create a titration curve for both native asparaginase and pegaspargase. Later, the sera from patients who had high-titre antibodies to pegaspargase were used for that enzyme preparation. The titres were compared with the same patient's pretreatment control serum and negative control serum from a healthy volunteer. The assay had excellent linearity, reproducibility, and low detection limits, but the absorbance of control varied between assays. Day-to-day variation was corrected by expression of antibody titres as the ratio of sample over negative control for each assay. In the protocol, high-titre antibody was defined as a ratio of serum antibody to	• EFS, defined as time to relapse, secondary tumour, or death • OS, defined as time to death

Trial no. (acronym)	CCG-1962	UKALL 2003
	the average control value of 2.5. For statistical analyses, we used the highest ratio of 4 post-treatment samples collected from each patient during each asparaginase-containing phase.	
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	<u>Secondary outcomes:</u> • Incidence of high-titre asparaginase antibodies in DI no. 2 • Asparaginase activity, asparaginase protein, and asparaginase levels in serum in induction and DI phases • Asparaginase activity, asparaginase protein, and asparaginase levels in CSF during induction • Response rate - BM status (percentage of lymphoblasts) during induction at day 7, day 14, and end of induction • EFS (events included: induction death, no induction response, relapse at any site, and second malignant neoplasm) Blood samples were collected on days 0, 7, 14, 21, and 28 of induction and DI cycles[§] CSF samples were collected on days 0, 7, and 28 of induction[§] BM aspirates and spinal taps were performed at entry and on day 7 and day 28 of induction. Patients with ≥5% lymphoblasts on day 7 had a further BM aspirate on day 14. BM aspirates were also taken at the end of DI no. 2 and maintenance therapy BM status was defined as follows: M1: <5% lymphoblasts regardless of proportion of mature lymphocytes; M2: 5–25% lymphoblasts; M3: >25% lymphoblasts Asparaginase activity was measured by ammonia produced from asparagine with a Nessler reation. Reacted enzymatic activity solutions were placed in an ELISA plate and the ELISA plate reader was used to read optical density, calculate calibration line, and quantify samples Asparaginase protein was measured by ELISA similar to that used for measuring asparaginase antibodies described above Asparagine levels were measured via	• Cumulative risk of relapse • Treatment-related toxic effects

Trial no. (acronym)	CCG-1962	UKALL 2003
	HPLC in which amino acids were derivatised with PITC.	
Pre-planned subgroups	None	None

Abbreviations: ALL, acute lymphoblastic leukaemia; BM, bone marrow; CCG, Children's Cancer Group; CNS, central nervous system; CSF, cerebrospinal fluid; DI, delayed intensification; EFS, event-free survival; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; IM, intramuscular; IU, international unit; MRD, minimal residual disease; N/A, not applicable; NCI, National Cancer Institute; OS, overall survival; PITC, phenylisothiocyanate; WBC, white blood cell.

† Patients were stratified according to initial clinical risk of relapse, on the basis of three metrics: the NCI risk criteria (NCI standard-risk: patients aged <10 years with a WBC count $<50\times10^9$/L; NCI high-risk: patients aged ≥10 years with a WBC $\geq50\times10^9$/L), leukaemia cytogenetics (all patients with a cytogenetic abnormality involving rearrangement of the MLL gene, hypodiploidy [<45 chromosomes], or intrachromosomal amplification of chromosome 21 were classified as clinical high-risk), and early response to induction therapy as assessed by BM morphology on day 8 and 15 of treatment in patients aged <16 years. Patients who had >25% of the marrow made up of blast cells at day 8 (NCI high-risk) or day 15 (NCI standard-risk) were reclassified to the clinical high-risk group irrespective of initial classification and were not eligible for MRD stratification and randomisation.

‡ MRD was measured by a standardised real-time quantitative PCR method for immunoglobulin and T-cell receptor antigen gene rearrangements. Patients with undetectable MRD after induction (day 29) and before interim maintenance were classified as MRD low-risk, as were those with detectable (<0.01%) MRD at the end of induction but undetectable MRD before the start of interim maintenance. Those with ≥0.01% MRD at the end of induction were classified as MRD high-risk. Patients in whom MRD could not be measured because no or poor-quality samples were available and those with persistent disease which was <0.01% MRD before the start of interim maintenance were classified as MRD indeterminate.

§ Some serum and CSF samples were collected within 2 days of each of these induction days. The actual day of sampling was used in all calculations.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Table 9: Summary of statistical analyses

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CCG-1962	No hypothesis was stated. The authors postulate that pegaspargase would cause less antibody formation than native asparaginase in patients with no prior exposure to asparaginase, resulting in more sustained asparaginase enzyme activity and therefore asparagine depletion. The primary endpoint was the incidence of high-titre asparaginase antibodies in DI no. 1.	• Comparisons of induction response rates, antibody ratio levels, and asparaginase activity groupings used exact χ^2 tests that involved global tests of differences and tests for trend (ordering) • For comparisons of actual values for asparaginase antibodies and antibody ratio, the Wilcoxon nonparametric rank test was used • Kaplan-Meier estimates were used for life-table estimation (EFS outcomes), and the log-rank test was used to compare these outcomes. These EFS analyses used intent-to-treat analyses that included all randomly assigned patients. It was acknowledged by the authors that only large differences in EFS between treatments would be detected	Based on the literature assessed by the study authors, it was assumed that 50% of patients treated with native asparaginase would develop antibodies during the first delayed intensification phase. The study was designed to detect a change from 50% to 25% or less in incidence of antibodies, with a power of 80% for a one-sided hypothesis test. This led to a sample requirement of approximately 118 patients, assuming that 10% of patients might not have samples available for testing (because of early relapse or noncompliance).	Not specified.
UKALL 2003	No hypothesis was stated. The authors postulate that children and young adults with clinical standard- or intermediate-risk ALL, who are predicted to	• Categorical variables were compared with standard χ^2 tests • The relationship between sex, age, WBC count, and	• The anticipated total accrual to the study over a six year period was 2,500 patients, of whom it was expected 400 would be eligible for the randomisation of	Patients who died within 35 days of starting treatment or who never achieved remission, or both, were deemed to be induction failures. They were

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	have a low risk of relapse on the basis of rapid clearance of MRD following induction therapy, would benefit from a reduced intensity treatment without adversely affecting EFS. The authors aim was to rule out a 7% reduction in EFS in the MRD low-risk group given one delayed intensification course compared with those given two. The authors also postulate that children and young adults with clinical standard- or intermediate-risk ALL, who have persistent MRD following induction therapy (MRD high-risk), would benefit from augmented post-remission therapy in terms of improved EFS and OS. The primary endpoints were EFS and OS.	immunophenotype, and between those variables and MRD risk group was examined with logistic regression • For time-to-event outcomes, Kaplan-Meier curves were produced and compared with the log-rank method. Only first events were counted – competing events were censored • HR and 95% CIs were calculated as exp[(O-E)/V±1.96/√V], in which O=observed events, E=expected events, and V=variance. • A 95% CI for the difference in five-year EFS for the MRD low-risk group was calculated on the basis that the OR can be estimated by the logarithm of the survival in the reduced-treatment group divided by the logarithm of the survival in the standard group. • Cox regression multivariate analyses were used to test whether effects of prognostic factors were independent, with additional interaction tests and tests of proportional hazards using an interaction with time	the MRD low-risk group • In view of the few relapses expected in the MRD low-risk group, and with a one-sided p-value, the study would have 80% power to detect a reduction in five-year EFS in the group given one DI course from 95% to 88%. The investigators aimed to rule out a 7% reduction in EFS in the group given reduced treatment (one DI course) relative to that given standard treatment (two DI courses) • The proportion of patients in the low-risk group was higher than had been originally anticipated, and because of a shortfall in recruitment to the high-risk group, it was decided to increase the sample size in the low-risk group to narrow CIs of the differences in outcomes between the groups	included in analyses of EFS and OS, but excluded from analyses of relapse or remission death.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		variable for significant factors • All analyses were by intention-to-treat and p-values two-sided		

Abbreviations: ALL, acute lymphoblastic leukaemia; CI, confidence interval; DI, delayed intensification; EFS, event-free survival; HR, hazard ratio; MRD, minimal residual disease; OR, odds ratio; OS, overall survival; RCT, randomised controlled trial; WBC, white blood cell.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

CCG-1962

In CCG-1962, 118 children were enrolled and randomly assigned to receive standard chemotherapy combined with either native E-coli-derived asparaginase (n=59) or pegaspargase (n=59).

On day 14 of induction, four children treated with native asparaginase had a BM status classified as M3 (>25% blasts). On day 28 of induction, one child on pegaspargase had M2 BM (5–25% blasts). As stipulated in the protocol, these patients were taken off the study at the end of induction and treated with a more intensive regimen.

One patient left the country during the maintenance phase and was lost to follow-up. There were 10 children (eight in the pegaspargase arm) who did not receive all required doses of asparaginase during the DI phases (no. 1 or 2) because of toxicity, protocol violation, or parental choice.

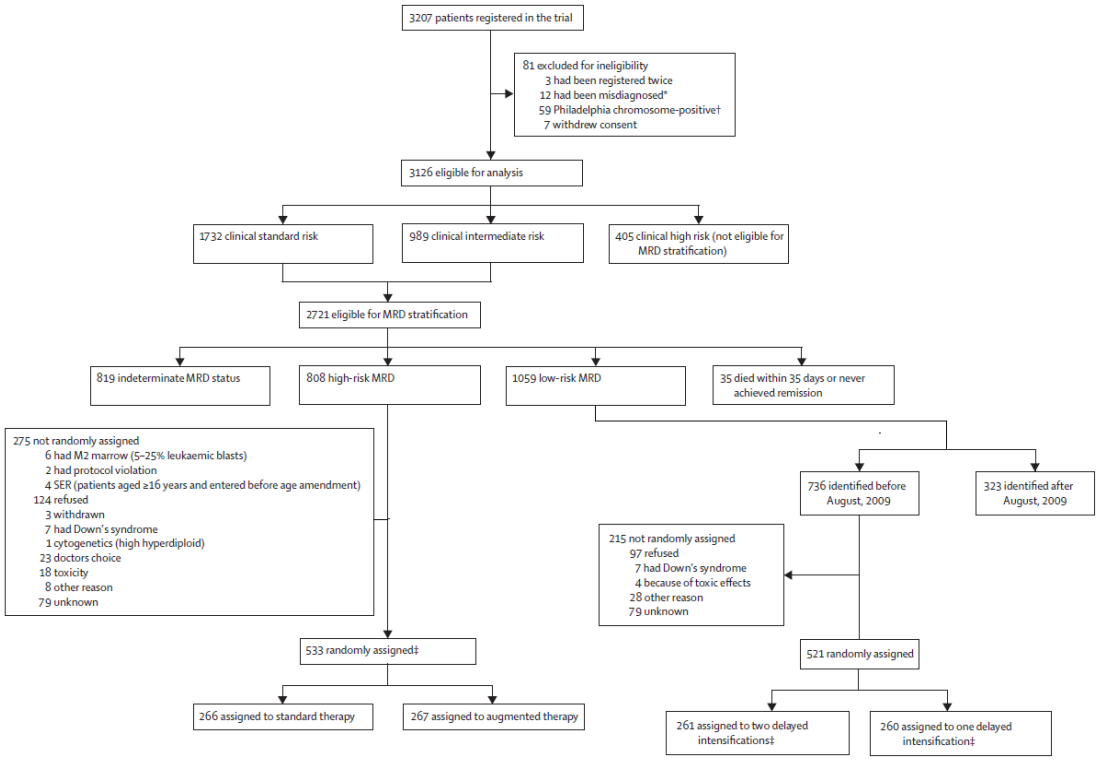
UKALL 2003

A total of 3,207 patients were registered to UKALL 2003. Initial stratification resulted in 1,816 NCI standard-risk and 1,310 NCI high-risk patients. On the basis of cytogenetics and early BM response, 1,732 patients were reclassified as clinical standard-risk, 989 clinical intermediate-risk, and 405 clinical high-risk.

All eligible patients, with the exception of 34 patients who died within 35 days or never achieved remission, were assessed for MRD status after induction and before first interim maintenance. However, clinical high-risk patients were not eligible for MRD stratification and randomisation. Of 2,686 clinical standard- or intermediate-risk patients tested for MRD status, 1,059 (39%) were MRD low-risk, 808 (30%) MRD high-risk, and 819 (30%) MRD indeterminate-risk.

Of 736 eligible MRD low-risk patients, 521 underwent randomisation: 260 to reduced treatment (one delayed intensification cycle), and 261 to standard treatment (two delayed intensification cycles). Of 808 eligible MRD high-risk patients, 533 were randomly assigned: 266 to standard treatment and 267 to augmented treatment. The patient flow in UKALL 2003 is presented in Figure 4.

Figure 4: Patient disposition in UKALL 2003



Abbreviations: MRD, minimal residual disease; SER, slow early response.
* One patient had Burkitt's lymphoma, one T-cell lymphoma, one T-cell non-Hodgkin lymphoma, one mature B-cell acute lymphoblastic leukaemia, two acute myeloid leukaemia, five mixed-phenotype acute leukaemia, and one precursor B non-Hodgkin lymphoma.
† 52 patients were transferred to EsPhALL and seven to another Philadelphia chromosome-positive study protocol.
‡ No patients were lost to follow-up within 1 year or excluded from analysis.

4.5.2 *Baseline characteristics and demographics*

CCG-1962

Patient characteristics at baseline in CCG-1962 are summarised in Table 10. At diagnosis, a higher percentage of patients in the native asparaginase arm were aged 1–2 years, had platelet counts of <50,000 µL, and had CNS 2 (defined as 0–4 cells/µL and at least 1% lymphoblasts). None of these or other risk factors were significantly different between the two treatment arms.

Institutional immunophenotypes found that among 116 patients tested, 103 were CD10+, 107 were CD19+, and two were classified as T lineage (both in the native asparaginase arm). No patients had B-cell leukaemia. In each arm, 2–4 children had massive splenomegaly or hepatomegaly. One patient in each arm had massive lymphadenopathy. No patients had concurrent CNS or testicular leukaemia. Three patients had Down syndrome, two of whom were treated with pegaspargase.

Table 10: Baseline characteristics of participants in CCG-1962

CCG-1962 Baseline characteristics	Native asparaginase n (%)	Pegaspargase n (%)

CCG-1962 Baseline characteristics	Native asparaginase n (%)	Pegaspargase n (%)
Total	59 (100)	59 (100)
Age (years)		
1–2	20 (34)	11 (19)
3–5	18 (30)	26 (44)
6–9	21 (36)	22 (37)
Gender		
Male	33 (56)	31 (53)
Female	26 (44)	28 (47)
Race		
White	39 (66)	38 (64)
Non-white	20 (34)	21 (36)
WBC count at diagnosis		
<20,000	46 (78)	47 (80)
>20,000	13 (22)	12 (20)
CALLA+	53 (90)	50 (85)
Platelet count at diagnosis		
<50,000	30 (51)	20 (34)
50,000–149,000	19 (32)	21 (36)
>150,000	10 (17)	18 (30)
Haemoglobin level		
<8	24 (41)	30 (52)
8–11	29 (49)	22 (38)
>11	6 (10)	6 (10)
CNS disease		
>5 cells/µL, positive cytology	0 (0)	0 (0)
<5 cells/µL, positive cytology	9 (15)	4 (7)
<5 cells/µL, negative cytology	46 (78)	52 (88)
Mediastinal mass <1/3 thoracic diameter	6 (10)	4 (7)
Hepatomegaly, edge below the umbilicus	2 (3)	4 (7)
Splenomegaly, edge below the umbilicus	3 (5)	3 (5)
Lymphadenopathy, massive	1 (2)	1 (2)

Abbreviations: CALLA, common acute lymphoblastic leukaemia antigen; CNS, central nervous system; WBC, white blood cell.

UKALL 2003

Patient characteristics at baseline in UKALL 2003 are summarised in Table 11. No difference was observed in the characteristics of MRD low-risk or high-risk patients who did and did not undergo randomisation. There were no statistically significant differences between the randomised arms in either of the MRD risk groups.

Table 11: Baseline characteristics of participants in UKALL 2003

UKALL 2003 Baseline characteristics	Overall n (%)	MRD low-risk				p-value[†]	MRD high-risk				p-value[‡]
		Eligible for randomisation n (%)	Eligible but not randomised n (%)	Underwent MRD low-risk randomisation			Eligible for randomisation n (%)	Eligible but not randomised n (%)	Underwent MRD high-risk randomisation		
				Reduced treatment (one DI cycle) n (%)	Standard therapy (two DI cycles) n (%)				Standard treatment n (%)	Augmented treatment n (%)	
Total	3,126 (100)	736 (100)	215 (100)	260 (100)	261 (100)		808 (100)	275 (100)	266 (100)	267 (100)	
Age (years)											
Median (IQR)	5 (3–10)	4 (3–8)	5 (3–9)	4 (3–8)	4 (3–8)	0.79	5 (3–11)	6 (3–11)	5 (3–10)	5 (3–10)	0.66
<2	209 (7)	42 (6)	13 (6)	13 (5)	16 (6)	0.61[§]	45 (6)	15 (5)	15 (6)	15 (6)	0.81[¶]
2–9	2,078 (67)	534 (73)	153 (71)	192 (74)	189 (72)		532 (66)	175 (64)	178 (67)	179 (67)	
10–15	610 (20)	127 (17)	36 (17)	46 (18)	45 (17)		131 (16)	49 (18)	38 (14)	44 (17)	
≥16	229 (7)	33 (4)	13 (6)	9 (3)	11 (4)		100 (12)	36 (13)	35 (13)	29 (11)	
Gender						0.31					0.14
Male	1,776 (57)	415 (56)	115 (53)	142 (55)	158 (61)		464 (57)	168 (61)	151 (57)	145 (54)	
Female	1,350 (43)	321 (44)	100 (47)	118 (45)	103 (39)		344 (43)	107 (39)	115 (43)	122 (46)	
WBC count ($\times 10^9$/L)											
Median (IQR)	12 (5–40)	11 (5–31)	12 (5–36)	10 (4–30)	9 (5–28)	0.19	13 (5–33)	12 (4–29)	13 (5–35)	13 (5–36)	0.14
<10	1,407 (45)	360 (49)	99 (46)	127 (49)	134 (51)	0.56[††]	352 (44)	124 (45)	114 (43)	114 (43)	0.79[‡‡]

UKALL 2003 Baseline characteristics	Overall n (%)	MRD low-risk				p-value†	MRD high-risk				p-value‡
		Eligible for randomisation n (%)	Eligible but not randomised n (%)	Underwent MRD low-risk randomisation			Eligible for randomisation n (%)	Eligible but not randomised n (%)	Underwent MRD high-risk randomisation		
				Reduced treatment (one DI cycle) n (%)	Standard therapy (two DI cycles) n (%)				Standard treatment n (%)	Augmented treatment n (%)	
10–19	502 (16)	128 (17)	38 (18)	44 (17)	46 (18)		154 (19)	55 (20)	44 (17)	55 (21)	
20–49	526 (17)	113 (15)	32 (15)	45 (17)	36 (14)		165 (20)	54 (20)	61 (23)	50 (19)	
50–99	315 (10)	75 (10)	28 (13)	24 (9)	23 (9)		61 (8)	17 (6)	25 (9)	19 (7)	
≥100	376 (12)	60 (8)	18 (8)	20 (8)	22 (8)		76 (9)	25 (9)	22 (8)	29 (11)	
Immunophenotype						0.16					1.00§§
B lineage	2,731 (87)	680 (92)	194 (90)	241 (93)	245 (94)		695 (86)	236 (86)	231 (87)	228 (85)	
T lineage	388 (12)	56 (8)	21 (10)	19 (7)	16 (6)		112 (14)	38 (14)	35 (13)	39 (15)	
Not known	7 (<1)	0	0	0	0		1 (<1)	1 (<1)	0	0	
NCI risk group						0.23					0.87
High	1,310 (42)	263 (36)	84 (39)	85 (33)	94 (36)		307 (38)	106 (39)	102 (38)	99 (37)	
Standard	1,816 (58)	473 (64)	131 (61)	175 (67)	167 (64)		501 (62)	169 (62)	164 (62)	168 (63)	

Abbreviations: DI, delayed intensification; IQR, interquartile range; MRD, minimal residual disease; NCI, National Cancer Institute; WBC, white blood cell.
† Comparing eligible MRD low-risk patients who were and were not randomised.
‡ p-value for heterogeneity, comparing those MRD high-risk patients who were randomised versus those who were not.
§ p-value for trend (age groups as ordered categories)=0.51.
¶ p-value for trend=0.42.
†† p-value for trend=0.13.
‡‡ p-value for trend (ordered categories)=0.34.
§§ Excluding “unknown” category.

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 12: Quality assessment results for CCG-1962 and UKALL 2003

	CCG-1962	UKALL 2003
Was randomisation carried out appropriately?	Not clear. Method of randomisation was not stated	Yes. Treatment allocation in both groups was obtained by telephone call to the central trials unit, using computer randomisation
Was the concealment of treatment allocation adequate?	Not clear	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, there were no significant differences in patient characteristics	Yes, there were no significant differences in patient characteristics
Were the care providers, participants and outcome assessors blind to treatment allocation?	Study was open-label	Study was open-label
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Life-table comparisons of EFS outcomes for treatment regimens used intent-to-treat analyses that included all randomly assigned patients	Yes All analyses were by intention-to-treat that included all randomised patients. No patients were lost to follow-up before one year

Abbreviations: EFS, event-free survival; N/A, not applicable; RCT, randomised controlled trial.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 *CCG-1962*

4.7.1.1 Immunogenicity: Antibodies to asparaginase

The primary endpoint of CCG-1962 was to establish whether the incidence of high-titre anti-asparaginase antibodies in children treated with pegaspargase was decreased by at least 50% in DI no. 1 compared with those treated with native asparaginase. A secondary endpoint was to establish whether the same decrease occurred in DI no. 2.

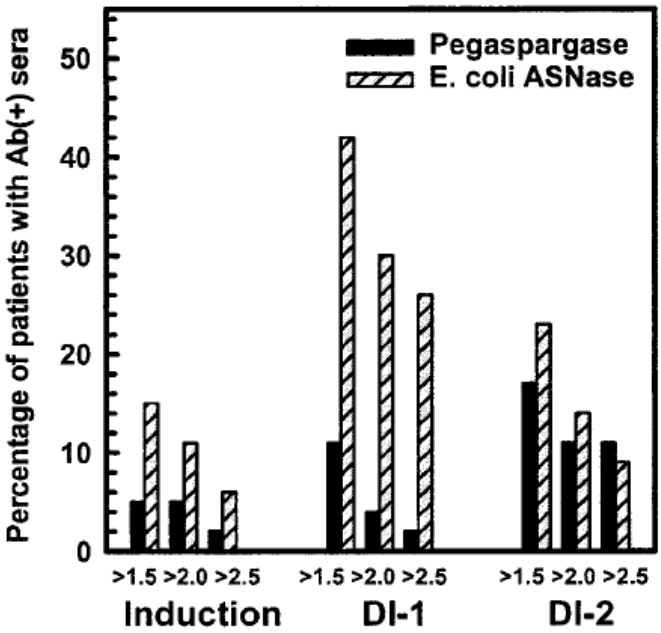
The percentages of children with maximal antibody ratios over negative control of ≥1.5, ≥2.0, and ≥2.5 during induction, DI no. 1, and DI no. 2 treatment cycles are shown in Figure 5.

In DI no. 1, 11 of 43 children (26%) in the native asparaginase treatment arm had high-titre anti-asparaginase antibodies (ratio ≥2.5). Although this percentage was lower than that expected from the existing literature (26% versus 50%), the incidence of such high-titre antibodies was significantly lower in the pegaspargase arm: only 1 of 47 children (2%) in the pegaspargase arm had an antibody ratio ≥2.5 (p=0.001, Wilcoxon test).

The differences between treatments were less apparent during DI no. 2 (p=0.09, Wilcoxon test), and not significant in induction. Irrespective of treatment cycle, comparison of the maximum antibody ratio of each patient showed higher titres among patients treated with native asparaginase than among those treated with pegaspargase (p=0.0009, Wilcoxon test).

Antibody levels tended to decrease between days 7 and 28 of each asparaginase-containing treatment cycle, and were lower in DI no. 2 than DI no. 1.

Figure 5: Percentage of patients with anti-asparaginase antibody ratios over negative control more than 1.5, 2.0, and 2.5 in CCG-1962



Abbreviations: Ab(+), antibody positive; ASNase, asparaginase; DI-1, delayed intensification no. 1; DI-2, delayed intensification no. 2.

In DI no. 1, the mean ± standard error of the mean (SEM) antibody ratio was 1.9 ± 0.8 (n=47) in children treated with pegaspargase and 3.0 ± 0.7 (n=43) in those treated with native asparaginase (p=0.001, Wilcoxon 2-sample test) (Table 13). Antibody ratios measured during induction and during DI no. 2 cycles of treatment did not significantly differ between the pegylated or native asparaginase arms (Table 13).

Table 13: Asparaginase antibody formation in CCG-1962

Chemotherapy phase	Native asparaginase mean ratio† ± SEM (n)	Pegaspargase mean ratio† ± SEM (n)	p-value
Induction	2.3 ± 0.9 (47)	1.3 ± 0.2 (41)	NS
DI no. 1	3.0 ± 0.7 (43)	1.9 ± 0.8 (47)	p=0.001‡
DI no. 2	2.1 ± 0.6 (45)	2.1 ± 0.8 (45)	NS

Abbreviations: DI, delayed intensification; NS, not significant; SEM, standard error of the mean.
† Calculated as the ratio of antibody over negative control.
‡ Wilcoxon 2-sample test.

4.7.1.2 Asparaginase activity

The level of circulating asparaginase considered adequate to achieve depletion of asparagine is 0.1 IU/mL (90). A higher percentage of samples in the pegaspargase arm compared with the native arm, had adequate asparaginase activity at day 21 of DI cycles no. 1 and no. 2 (Table 14).

Table 15 shows the proportions of serum samples, collected 3–14 days following the first dose of asparaginase, in which asparaginase activity was >0.1 IU/mL, and the association with anti-asparaginase antibodies.

More than 89% of samples from patients treated with native asparaginase and more than 95% of samples from those treated with pegaspargase contained levels of asparaginase >0.1 IU/mL when the antibody ratio was low (ratio of anti-asparaginase antibodies over negative control <1.5), across induction and DI no. 1 and no. 2. In contrast, during DI no. 1, only 50% of samples from native asparaginase-treated patients with antibody ratios ≥1.5 had asparaginase activity >0.1 IU/mL (p<0.001 by trend test). This association between high antibody ratios and low asparaginase activity was also observed in DI no. 2 (p=0.01 by trend test) for patients treated with native asparaginase. Among pegaspargase-treated patients, however, fewer samples had elevated antibody ratios, and all samples from patients with antibody ratios ≥1.5 exhibited adequate asparaginase activity >0.1 IU/mL (Table 15).

Table 14: Percentage of samples with adequate asparaginase activity at day 21 of DI no. 1 and DI no. 2 in CCG-1962

Definition of adequate asparaginase activity	Day 21 DI no. 1		Day 21 DI no. 2	
	Native asparaginase (%)	Pegaspargase (%)	Native asparaginase (%)	Pegaspargase (%)
>0.03 IU/mL†	31	95	39	91
>0.1 IU/mL	19	95	22	91

Abbreviations: DI, delayed intensification; IU, international units.
† Based on a 1977 report by Holcenberg and Roberts (91) which estimated that asparaginase activity of 0.03 IU/mL was sufficient for depletion of asparagine to <0.1 μM.

Table 15: Percentage of samples with adequate asparaginase activity (>0.1 IU/mL) during days 3–14 of induction and DI cycles in CCG-1962

Antibody ratio	Induction n/N (%)	DI no. 1 n/N (%)	DI no. 2 n/N (%)
Native asparaginase			
<1.5	79/89 (89)	54/58 (93)	55/59 (93)
1.5–2.0	3/3 (100)	4/8 (50)	6/7 (86)
>2.0	5/8 (63)	10/20 (50)	7/11 (64)
Pegaspargase			
<1.5	95/98 (97)	67/69 (97)	63/65 (95)
1.5–2.0	0/0	5/5 (100)	5/5 (100)
>2.0	3/3 (100)	2/2 (100)	9/9 (100)

Abbreviations: IU, international units.

4.7.1.3 BM status

The results of BM examinations, performed on days 7 and 14 of induction, are presented in Table 16. There was more rapid clearance of lymphoblasts in the pegaspargase arm than in the native asparaginase arm (p=0.05 and 0.015, respectively; χ^2 test with ordering). Twice as many patients in the native asparaginase arm had M3 BM (>25% lymphoblasts) on day 7 than in the pegaspargase arm. All four patients with M3 BM on day 14 were in the native asparaginase arm. One patient in the pegaspargase arm had M2 BM (5–25% lymphoblasts) on day 28.

As of February 2001, seven patients had relapsed in the pegaspargase arm (two BM, three CNS, one combined BM and CNS, and one death after BM relapse), and eight had relapsed in the native asparaginase arm (four BM, four CNS).

Table 16: BM status on days 7 and 14 of induction in CCG-1962

BM status†	Native asparaginase		Pegaspargase	
	Day 7 n (%)	Day 14 n (%)	Day 7 n (%)	Day 14 n (%)
M1 (<5% lymphoblasts)	26 (47)	43‡ (83)	36 (63)	52§ (96%)
M2 (5–25% lymphoblasts)	13 (24)	5 (10)	13 (23%)	2 (4%)
M3 (>25% lymphoblasts)	16 (29)	4 (8)	8 (14%)	0
Total patients	55 (100)	52 (100)	57 (100%)	54 (100%)

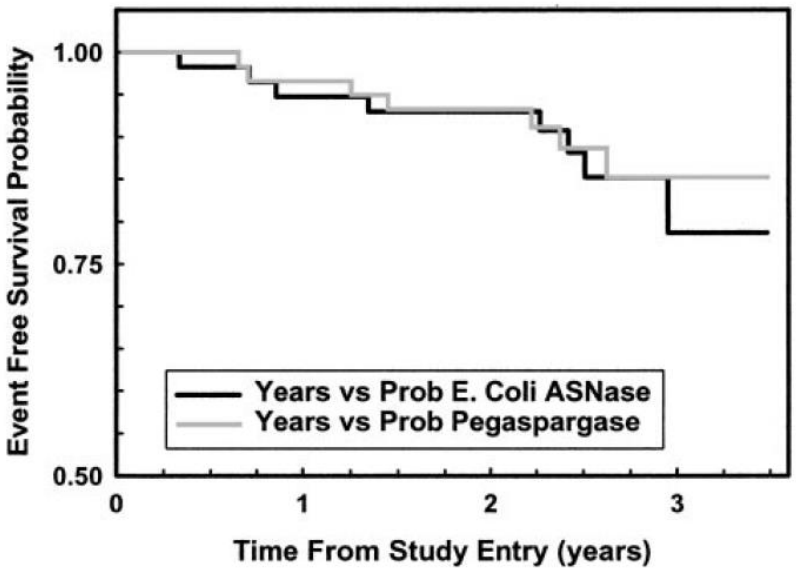
Abbreviations: ALL, acute lymphoblastic leukaemia; BM, bone marrow; M1, <5% lymphoblasts; M2, 5–25% lymphoblasts; M3, >25% lymphoblasts.
† Two patients were excluded from analysis: one had Philadelphia chromosome-positive ALL, and one mistakenly received both asparaginase preparations.
‡ Includes 24 patients with M1 BM on day 7 and day 28 who did not have a BM aspirate on day 14.
§ Includes 34 patients with M1 BM on day 7 and day 28 who did not have a BM aspirate on day 14.

4.7.1.4 EFS

Three-year EFS rates for native and pegaspargase, respectively, were 78% and 85% (p=not significant [NS]) (Figure 6), as reported by Avramis et al (11). An updated analysis presented in the SmPC for pegaspargase (Oncaspar®) reports three-year EFS rates of 79% and 83%. Of the 15 relapses across the two arms, three were in patients taken off the study because of Philadelphia chromosome-positive ALL, parental refusal to have a second DI phase, and pancreatitis preventing asparaginase treatment. Excluding these three patients, the three-year EFS rates for native and pegaspargase were 85% and 88%, respectively (p=NS).

Five-year and seven-year EFS rates were higher in the pegaspargase arm (78 and 75%, respectively) than in the native asparaginase arm (73 and 76%, respectively) (Table 17) (See Oncaspar® SmPC in Appendix 1).

Figure 6: Kaplan-Meier plot of EFS for all randomly assigned patients in CCG-1962



Abbreviations: ASNase, asparaginase; EFS, event-free survival; Prob, probability.
Black line shows data for native asparaginase-treated patients (n=59); grey line shows data for pegaspargase-treated patients (n=59); p=0.773 log-rank.

Table 17: EFS rate at 3, 5, and 7 years in CCG-1962

EFS time point	Native asparaginase % (95% CI)	Pegaspargase % (95% CI)
3-year EFS†	79 (68–90) [78]	83 (73–93) [85]
5-year EFS†	73 (61–85)	78 (67–88)
7-year EFS†	66 (52–80)	75 (63–87)

Abbreviations: CI, confidence interval; EFS, event-free survival; SmPC, summary of product characteristics.
† All EFS data are sourced from the Oncaspar® SmPC (Appendix 1); 3 year data presented by Avramis et al are shown in square brackets (11).

4.7.1.5 Asparaginase levels in serum and CSF

Mean pretreatment serum asparagine levels were 41±4 µM and 55±5 µM for native and pegaspargase treatment arms, respectively. During induction, asparagine levels fell to <3 µM in most patients when asparaginase activity was more than 0.1 IU/mL. In each treatment arm there was a small decrease in asparagine concentration with increased asparaginase activity. At each asparaginase activity, there appeared to be a trend toward lower asparagine concentrations with native asparaginase treatment compared with pegaspargase.

There was no significant difference in cerebrospinal fluid (CSF) asparagine elimination kinetics between the two treatment arms. With native asparaginase treatment, CSF asparagine fell from a median pretreatment level of 2.8 µM to 1.0 µM on day 7 and 0.3 µM on day 28 of induction. With pegaspargase treatment CSF asparagine fell from a median pretreatment level of 2.3 µM to 1.1 µM on day 7 and 0.6 µM on day 28 of induction.

4.7.1.6 Conclusion

CCG-1962 enrolled 118 children newly-diagnosed with standard-risk ALL. Patients were randomly assigned to receive asparaginase as either native E. coli enzyme (n=59; 6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase) or pegaspargase (n=59; 2,500 IU/m^2 IM on day 3 of induction and each DI phase).

Among all randomised patients, EFS at three, five, and seven years was similar between treatment arms: 79%, 73%, and 66%, respectively, in native asparaginase-treated patients, and 83%, 78%, and 75%, respectively, in patients treated with pegaspargase.

However, in DI no. 1, 26% of native asparaginase-treated patients had high-titre anti-asparaginase antibodies compared with 2% of pegaspargase-treated patients. High-titre antibodies were associated with low asparaginase activity in the native asparaginase arm but not in the pegaspargase arm. In addition, patients treated with pegaspargase demonstrated more rapid clearance of lymphoblasts in bone marrow aspirates taken on days 7 and 14 of induction than did patients receiving native asparaginase.

4.7.2 *UKALL 2003*

4.7.2.1 EFS and OS

The primary outcomes of UKALL 2003 were EFS, defined as time to relapse, secondary tumour, or death, and OS, defined as time to death.

All patients

By the end of follow-up on October 31, 2011, among the 3,126 patients enrolled in the study and who were eligible for analysis, the five-year EFS was 87.2% (95% CI 85.8–88.6) and five-year OS 91.5% (95% CI 90.3–92.7) (Table 18; Figure 7).

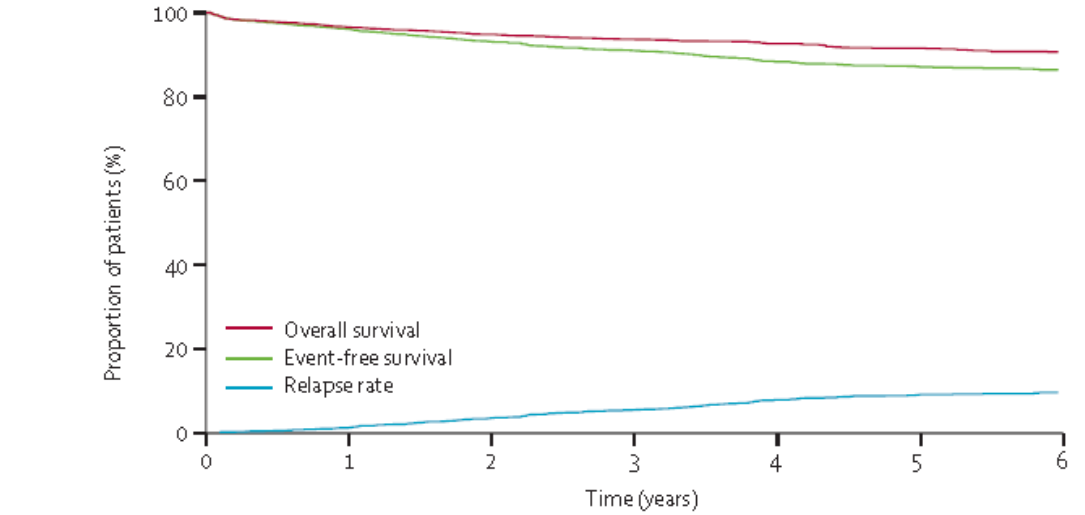
After a further two years of follow-up (to October 31, 2013), the five-year EFS among all enrolled patients remained stable at 87.3% (95% CI 86.1–88.5), and the five-year OS 91.6% (95% CI 90.6–92.6) (Figure 8).

Table 18: Kaplan-Meier estimates for specific events at five years among all patients enrolled in UKALL 2003 (based on follow-up to October 31, 2011)

Event	Number of events†	Actuarial percentage at five years % (95% CI)
Induction failure	34	1.1 (0.7–1.5)
Isolated CNS relapse	44	1.9 (1.3–2.5)
Any CNS relapse	69	3.0 (2.2–3.8)
Non-CNS relapse	123	5.9 (4.7–7.1)
Any BM relapse	140	6.6 (5.4–7.8)
Non-BM relapse	52	2.3 (1.7–2.9)
Relapse	192	8.8 (7.6–10.0)
Secondary tumour	15	0.6 (0.2–1.0)
Death in remission‡	77	2.7 (2.1–3.3)
Any event	318	87.2 (85.8–88.6)§
Death	224	91.5 (90.3–92.7)§

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system.
† Competing events were censored.
‡ Excludes patients who died after development of a secondary tumour.
§ Event-free percentage.

Figure 7: EFS, OS, and relapse, in all patients enrolled in UKALL 2003 (based on follow-up to October 31, 2011)

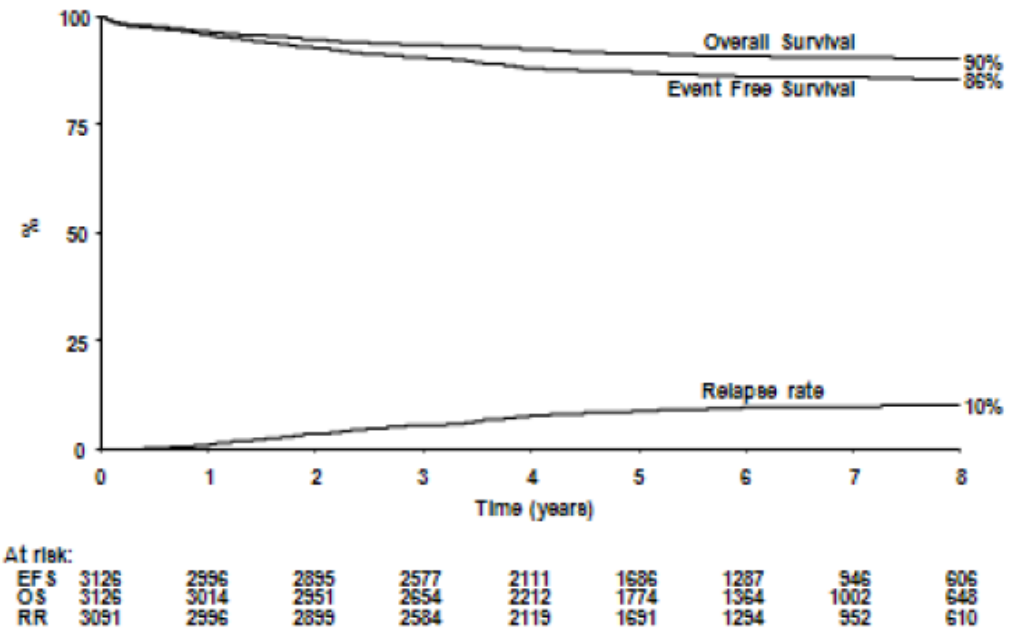


Number at risk

Overall survival	3126	2755	2284	1838	1412	1041	670
Event-free survival	3126	2743	2243	1786	1345	985	630
Relapse	3092	2743	2247	1789	1348	988	634

Abbreviations: EFS, event-free survival; OS, overall survival.

Figure 8: EFS, OS, and relapse in all patients enrolled in UKALL 2003 (based on follow-up to October 31, 2013)



Abbreviations: EFS, event-free survival; OS, overall survival, RR, relapse rate.

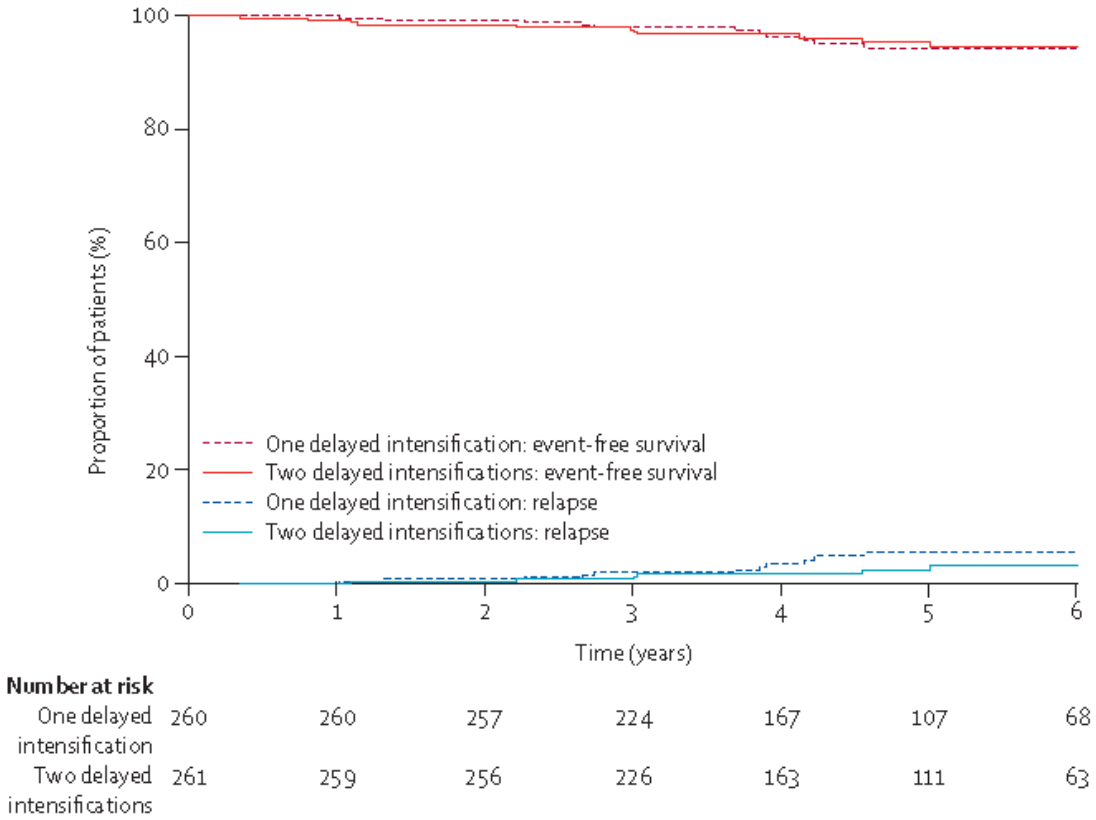
MRD low-risk

Among the population of MRD low-risk patients randomised to either standard treatment (two DI cycles as part of Regimen A or B, depending on clinical risk status) or reduced treatment (only one DI cycle), there was no difference in EFS or OS by the end of follow-up in 2011. Five-year EFS was 95.5% (95% CI 92.8–98.2) with two DI cycles and 94.4% (95% CI 91.1–97.7) with one DI cycle. The difference in five-year EFS between the standard and reduced treatment groups was 1.1% (95% CI -5.6–2.5) meaning that the primary endpoint of the randomisation (to rule out a 7% reduction in EFS) was achieved (Figure 9; Table 19).

By the end of follow-up, OS in the standard treatment group was 98.5% (95% CI 96.9–100.0) and 97.9% (95% CI 95.3–100.0) in the reduced treatment group (unadjusted OR 0.67 [95% CI 0.19–2.30]; p=0.53) (Table 19).

In the group of MRD low-risk patients receiving standard treatment, six of 261 patients relapsed (two isolated marrow, one isolated CNS, two combined marrow and CNS, and one combined marrow and skin), two had secondary tumours, (one acute myeloid leukaemia and one lymphoblastic lymphoma), and three died in remission (one because of respiratory syncytial virus pneumonitis during maintenance treatment [patient with Down syndrome], one veno-occlusive and herpes simplex virus pneumonitis with pulmonary haemorrhage during DI no. 2, and one Gram-negative sepsis during DI no. 1 (Table 19). Among MRD low-risk patients receiving reduced treatment, 11 of 260 patients relapsed (three isolated BM, four isolated CNS, two combined BM and CNS, one testes, and one isolated cervical lymph node) (Table 19).

Figure 9: EFS and relapse in MRD low-risk patients in UKALL 2003 (follow-up to October 31, 2011)



Abbreviations: EFS, event-free survival; MRD, minimal residual disease.

Table 19: Events in MRD low-risk patients in UKALL 2003 (follow-up to October 31, 2011)

Event	Standard treatment (n=261)		Reduced treatment (n=260)		Unadjusted analyses		Adjusted analyses†	
	No. of events	Actuarial %age at five years (95% CI)	No. of events	Actuarial %age at five years (95% CI)	OR for standard treatment group (95% CI)	2-sided p-value	OR for standard treatment group (95% CI)	2-sided p-value
Any event‡	11	4.5 (1.8–7.2)	11	5.6 (2.3–8.9)	1.00 (0.43–2.31)	0.99	1.09 (0.47–2.53)	0.84
Relapse§	6	2.4 (0.2–4.6)	11	5.6 (2.3–8.9)	0.55 (0.21–1.43)	0.23	0.60 (0.23–1.57)	0.30
Remission death	3	1.2 (0–2.6)	0	0	7.40 (0.77–71.04)	0.08	8.39 (0.86–81.61)	0.06
Any death	4	1.5 (0–3.1)	6	2.1 (0–4.3)	0.67 (0.19–2.30)	0.53	0.71 (0.21–2.48)	0.61

Abbreviations: CI, confidence interval; DI, delayed intensification; MRD, minimal residual disease; No. number; OR, odds ratio; WBC, white blood cell.
† Adjusted for the same variables that randomisation was stratified by: age (<10 years vs ≥10 years), gender (male vs female), WBC count (<50×10^9/L vs ≥50×10^9/L).
‡ Includes two secondary tumours.
§ includes relapse in patient who was incorrectly reported as low-risk (allocated to receive two DI cycles).

MRD high-risk

By the end of follow-up on October 31, 2013, EFS was significantly improved among MRD high-risk patients randomised to receive augmented treatment (Regimen C) compared with those receiving standard treatment (Regimen A or B depending on clinical risk status) (OR 0.61 [95% CI 0.39–0.98]; p=0.04) (Table 20). Five-year EFS was 89.6% (95% CI 85.9–93.3) in the augmented treatment group versus 82.8% (95% CI 78.1–87.5) in the standard treatment group (Table 20; Figure 10).

Patients receiving augmented therapy also had a numerically, but not significantly, improved OS (92.9%; 95% CI 89.8–96.0) compared with those receiving standard therapy (88.9% [95% CI 85.0–92.8]; OR 0.67 [95% CI 0.38–1.17]; p=0.16) (Table 20).

Table 20: Events in MRD high-risk patients in UKALL 2003 (follow-up to October 31, 2013)

Event	Standard treatment (n=266)		Augmented treatment (n=267)		Statistics for augmented treatment group	
	No. of events	Actuarial %age at five years (95% CI)	No. of events	Actuarial %age at five years (95% CI)	Unadjusted OR (95% CI)†	p-value
Any relapse	35‡	14.2 (9.7–18.7)	20§	7.5 (4.2–10.8)	0.55 (0.33–0.94)	0.03
Any BM relapse	26	10.5 (6.6–14.4)	11	4.6 (1.9–7.3)	0.42 (0.22–0.81)	0.009
Any non-BM relapse	9	4.1 (1.4–6.8)	9	3.1 (0.9–5.3)	0.95 (0.38–2.39)	0.91
Death during remission	9	3.5 (1.3–5.7)	7	2.7 (0.7–4.7)	0.76 (0.28–2.02)	0.59
EFS¶	44	82.8 (78.1–87.5)	28	89.6 (85.9–93.3)	0.61 (0.39–0.98)	0.04
OS	29	88.9 (85.0–92.8)	20	92.9 (89.8–96.0)	0.67 (0.38–1.17)	0.16

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; EFS, event-free survival; HR, hazard ratio; MRD, minimal residual disease; No., number; OR, odds ratio; OS, overall survival; WBC, white blood cell.

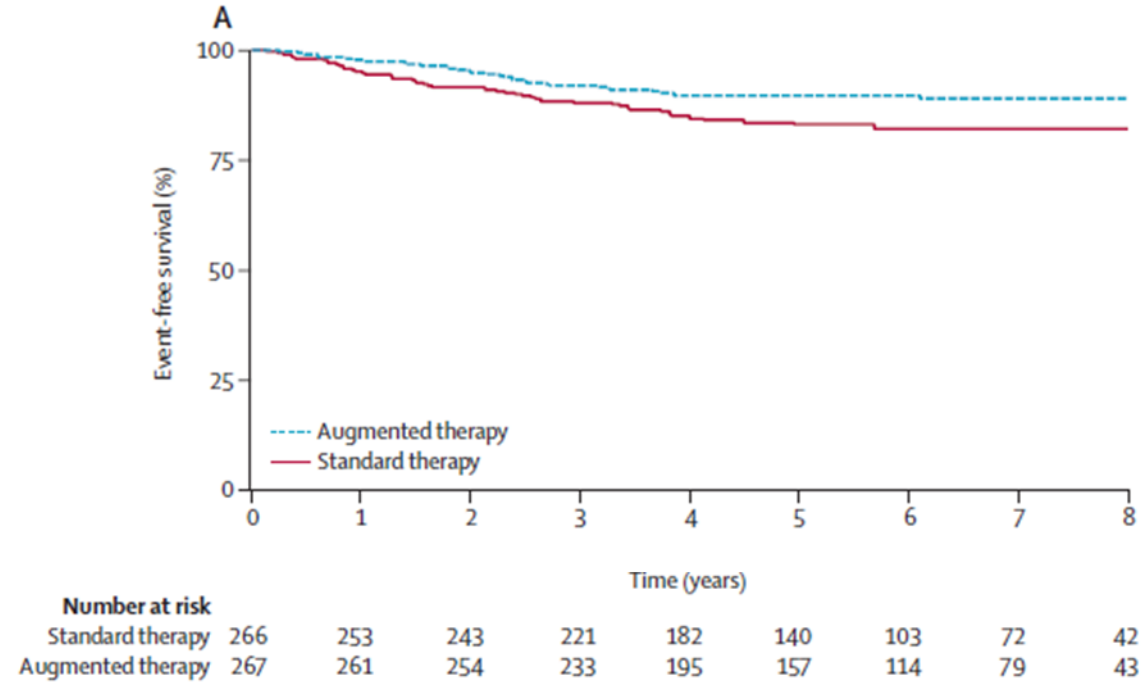
† Randomisation was balanced for age, initial WBC count, and sex. Adjusted analyses for these factors were not materially different. There was no deviation from the proportional hazards assumption in this analysis, so Cox HRs are almost identical to the ORs presented here.

‡ Eight isolated CNS, 19 isolated BM, six combined BM and CNS, one BM and testes, one skin and lymph node.

§ Nine isolated CNS, nine isolated BM, one combined BM and CNS, one marrow and testes.

¶ Includes one secondary tumour occurring in a patient who received augmented treatment.

Figure 10: EFS in MRD high-risk patients in UKALL 2003 (follow-up to October 31, 2013)



Abbreviations: EFS, event-free survival; MRD, minimal residual disease.
44 EFS events occurred in the standard group versus 28 in the augmented treatment group. 35 patients in the standard group had a relapse versus 20 in the augmented treatment group. Numbers at risk apply to both graphs.

4.7.2.2 Cumulative risk of relapse

All patients

By the end of follow-up on October 31, 2011, among the 3,126 patients enrolled in UKALL 2003, the five-year cumulative risk of relapse was 8.8% (95% CI 7.6–10.0) (Table 18; Figure 7).

After a further two years of follow-up (to October 31, 2013), the five-year cumulative risk of relapse among all enrolled patients remained stable at 8.8% (95% CI 7.8–9.8).

MRD low-risk

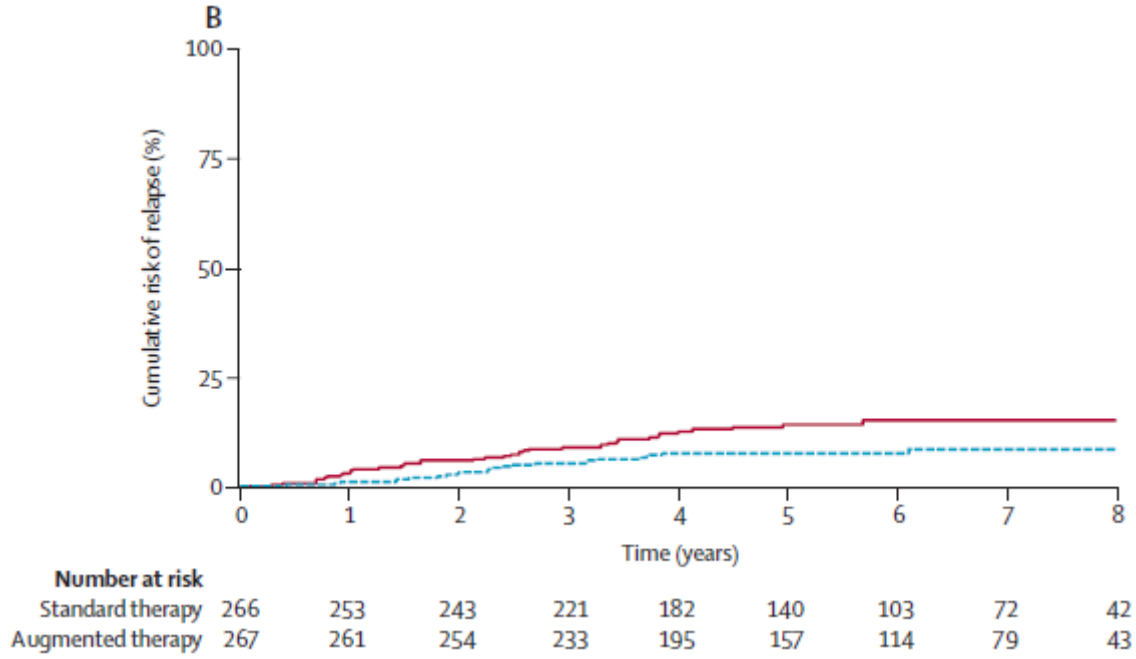
Among MRD low-risk patients randomised to receive either standard or reduced treatment, the five-year cumulative risk of relapse was numerically higher, though not significantly, among patients receiving reduced treatment (5.6% [95% CI 2.3–8.9]) compared with those receiving standard treatment (2.4% [95% CI 0.2–4.6]; unadjusted OR 0.55 [95% CI 0.21–1.43]) (Table 19; Figure 9).

MRD high-risk

The improved five-year EFS seen among MRD high-risk patients receiving augmented treatment compared with those receiving standard treatment (Table 20; Figure 10) was attributable to a decreased risk of any relapse in the augmented treatment group (7.5% [95% CI 4.2–10.8]) compared with the standard treatment group (14.2% [95% CI 9.7–18.7]) (Table 20). The cumulative risk of relapse was lower across the entire duration of follow-up among MRD high-risk patients receiving augmented treatment than those

receiving standard treatment (Figure 11). This reduction in relapse risk was composed mainly of a decrease in the risk of relapse involving the BM in the augmented treatment group (4.6% [95% CI 1.9–7.3]) compared with the standard group (10.5% [95% CI 6.6–14.4]) (Table 20).

Figure 11: Cumulative risk of relapse in MRD high-risk patients in UKALL 2003 (follow-up to October 31, 2013)



35 patients in the standard treatment group had a relapse versus 20 in the augmented treatment group.

Of all prognostic factors, MRD risk status was the single most important determinant of outcome with a five-year cumulative relapse rate of 4.0% (95% CI 2.4–5.6) in MRD low-risk patients versus 15.0% (95% CI 12.3–17.7) in MRD high-risk patients (log-rank p<0.0001). Older age, high WBC count, and T-cell immunophenotype were significantly associated with MRD high-risk status. Excluding MRD indeterminate patients, 106 of 131 relapses (81%) occurred within the MRD high-risk group.

Table 21: Five-year cumulative risk of relapse by prognostic factor and MRD risk status

Prognostic factor	Five-year cumulative risk of relapse (%)	
	MRD low-risk % (95% CI)	MRD high-risk % (95% CI)
Overall	4.0 (2.4–5.6)	15.0 (12.3–17.7)
Age (years)		
<10	3.5 (1.7–5.3)	11.7 (8.6–14.8)
≥10	5.8 (1.7–9.9)	22.7 (16.6–28.8)
WBC count		
<50×10^9/L	4.1 (2.1–6.1)	13.5 (10.4–16.6)
≥50×10^9/L	3.4 (0.7–6.1)	19.6 (13.3–25.9)
Immunophenotype		

Prognostic factor	Five-year cumulative risk of relapse (%)	
	MRD low-risk % (95% CI)	MRD high-risk % (95% CI)
B lineage	3.8 (2.0–5.6)	14.8 (11.7–17.9)
T lineage	5.8 (0.3–11.3)	15.9 (9.0–22.8)
NCI risk group		
High	4.1 (1.6–6.6)	20.3 (15.6–25.0)
Standard	3.9 (1.7–6.1)	10.6 (15.6–25.0)

Abbreviations: CI, confidence interval; MRD, minimal residual disease; NCI, National Cancer Institute; WBC, white blood cell.

4.7.2.3 Conclusion

UKALL 2003 enrolled 3,207 children and young adults (aged 1–24 years) with ALL, accounting for 97% of all eligible patients aged <25 years in the UK and Ireland (3). All patients received treatment with pegaspargase (1,000 IU/m^2 IM per dose, 4–12 doses) as part of one of three possible escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. In addition, MRD low-risk patients were randomised to receive either standard treatment (two DI cycles; n=261) or reduced treatment (only one DI cycle; n=260). Similarly, MRD high-risk patients were randomised to receive either standard treatment (n=266) or augmented treatment (n=267).

Among all patients enrolled in UKALL 2003 and treated with chemotherapy including pegaspargase, the five-year EFS, OS and cumulative risk of relapse were 87.3%, 91.6%, and 8.8%, respectively.

Among MRD low-risk patients, there was no significant difference in five-year EFS between patients on reduced treatment (94.4%) and those on standard treatment (95.5%).

Five-year EFS was 89.6% among MRD high-risk patients receiving augmented treatment compared with 82.8% of those receiving standard treatment. Five-year OS was also higher in the augmented treatment group (92.9%) compared with the standard group (88.9%).

4.8 *Supporting studies providing pegaspargase clinical data*

4.8.1 *Children, adolescents and young adults*

Studies which provide additional evidence on the 1st line use of pegaspargase in children, adolescents and young adults with newly diagnosed ALL were identified by way of systematic review, described previously in Section 4.1 and listed in Section 4.2. All studies are summarised in Table 22 to Table 29, providing information on study methods, asparaginase exposure and specific outcomes measured. Key supporting studies – CCG-1961, DFCI-91-01 and DFCI ALL 05-001 - are also discussed further below.

CCG-1961

In CCG-1961 (55), 2,078 patients up to the age of 21 years with newly diagnosed high risk ALL were enrolled and placed on induction therapy which included native E. coli-derived asparaginase. Following remission, patients were classified as rapid early or slow early responders, and those eligible rapid early responders (n=1,299) were randomised in a 2x2 factorial design to standard or longer duration (3 months longer), and to standard or increased intensity, post-induction intensification. Standard intensity regimens included native asparaginase (6,000 IU/m^2 IM) for 6 doses in delayed intensification, whereas in increased intensity regimens pegaspargase (2,500 IU/m^2 IM) was substituted in for 1 dose and also added to consolidation, interim maintenance and reconsolidation (2, 1 and 1 dose, respectively). Additional chemotherapy agents were also added.

Increased intensity post-induction intensification which included pegylated rather than native asparaginase led to improved EFS (81% vs 72%, p<0.001) and OS (89% vs 83%, p<0.003) at 5 years, demonstrating the overall merits of including pegaspargase in treatment regimens in these patients. However, given the other differences between standard and intense regimens implemented in this study, robust conclusions cannot be drawn as to the relative efficacy of pegaspargase versus native E. coli asparaginase.

This study induced remission using only native and not pegaspargase, and the authors commented that because of the high incidence of allergic reactions to the pegylated enzyme observed following the use of native asparaginase in induction, the protocol for their subsequent high-risk trial dictated that all patients receive pegaspargase in induction and all subsequent phases (55).

DFCI-91-01

In DFCI-91-01 (59) 377 patients aged 0–18 years with newly diagnosed ALL were enrolled. Patients were classified as standard (n=137) or high risk (n=240), and were eligible to undergo five separate randomisations involving steroids pre-induction, asparaginase, 6-mercaptopurine, doxorubicin for high risk patients and cranial radiation. For asparaginase therapy, patients were randomised to either pegaspargase (2,500 IU/m^2 IM bi-weekly for 15 doses) or native E. coli-derived asparaginase (25,000 IU/m^2 IM weekly for 30 doses) during intensification. All patients underwent induction therapy in the absence of asparaginase.

Overall 5-year EFS for all patients was 83%±2%, with no statistical difference between those randomised to pegaspargase (78%±4, n=106) and native E. coli enzyme (84%±4, n=92, p=0.29)[b]. In this study 12% of patients (43/352) received <25 weeks of asparaginase therapy, primarily as a result of asparaginase-related dose limiting toxicity (86%), and this was significantly associated with poorer outcomes compared with those who received at least 26 weeks therapy (73% vs 90%, respectively, p<0.01). Of the patients randomised to pegaspargase, 25% experienced a toxic reaction compared with 36% of E. coli–randomised patients (p=0.09). Pegylated enzyme was also associated with a lower incidence of mild allergic reactions (p=0.02), although there were no differences in the rates of dose-limiting toxicities such as severe allergic reaction (p=0.22), severe pancreatitis (p=0.78), or CNS thrombosis (p=1.00) (59).

DFCI ALL 05-001

The longer half-life of pegaspargase means that less frequent dosing is required than for native E. coli asparaginase, making intravenous administration more feasible. DFCI ALL 05-001 enrolled patients aged 1-18 years with newly diagnosed ALL and aimed to assess efficacy and safety of IV pegaspargase versus IM E. coli-derived asparaginase in an open-label, randomised design (30, 50).

Following induction therapy with pegaspargase, patients who achieved complete remission were randomised to either pegylated enzyme (n=232; 2,500 IU/m^2 15 doses IV, one every 2 weeks) or to native enzyme (n=231; 25,000 IU/m^2 30 doses IM, one per week). Outcomes were similar, with 5-year disease-free survival rates of 90% and 89%, respectively for pegylated and native enzymes (p=0.58). Overall survival rates were 96% and 94%, respectively (n=0.30). Toxicity profiles were also similar with no differences in the overall frequency of asparaginase-related toxicities (28% vs 26% for pegylated and native asparaginase, respectively; p=0·60), or in the frequency of allergy (p=0·36), pancreatitis (p=0·55), or thrombotic or bleeding complications (p=0·26). However, significantly more anxiety was reported by patients and by parent-proxy in the E. coli group (using the PedsQL 3.0 Cancer module quality of life questionnaire) (30, 50).

Overall this study showed that IV pegaspargase and IM native E. coli asparaginase have similar efficacy and safety but IV pegylated enzyme has the advantage of less frequent dosing and a less anxiety provoking route of administration (30, 50).

[b] Pegylated asparaginase was not available in Canada; 127 patients treated in Canadian centres were therefore assigned to receive E. coli asparaginase during intensification.

4.8.1.1 Study design/patient population

Table 22: Study design & patient population: Studies with pegaspargase data

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
Randomised							
CCG-1962	Avramis et al, 2002 (11)	Not specified Enrolment: May 1997-Nov 1998	To evaluate safety, efficacy, and PK of a single IM dose of PEG-ASP instead of multiple IM doses of native E. coli-ASP in each of 3 phases of therapy	- Interventional - Prospective - Randomised at induction - Multicentre - Phase III - Open-label	Children (1-9 years) with standard-risk ALL	SR	Incidence of high-titre ASP antibodies in DI no. 1
UKALL 2003	Vora et al, 2013 (2) Vora et al, 2014 (4)	UK and Ireland Oct 2003-June 2011	To test whether adjustment of treatment intensity according to MRD risk stratification was feasible. This is a randomised comparison of augmented therapy with standard-intensity post-remission therapy in patients with persistent MRD at the end of induction treatment	- Interventional - Prospective - Randomised: MRD low-risk patients were randomly assigned (1:1) to receive one (reduced treatment) or two (standard treatment) delayed intensifications and MRD high-risk patients were randomly assigned (1:1) to standard treatment or an intensive schedule. Randomisation was stratified by MRD result and balancing for sex, age and WBC count at diagnosis. - Multicentre - Open label	Consecutive children and young adults (aged 1–24 years) with ALL MRD low risk (Vora 2013) MRD high-risk patients (Vora 2014)	SR IR MRD low/high risk	EFS OS
CCG-1961	Seibel 2008 (55)	US Enrolment: Sept 1996-May 2002	To determine the relative contributions of length and strength to post-induction intensification (PII)	- Interventional - Prospective - Randomised: to E. coli-ASP (part of standard therapy) vs PEG-ASP (part of increased intensity therapy) (post induction for rapid early responders). For HR patients: 1) to doxorubicin with or without dexrazoxane; 2) to once-daily vs twice-daily cranial radiation - Treatment was stratified between rapid and slow early responders (RER and SER) based on the day 7 bone marrow status (<25% blasts [RER] or >25% blasts [SER]) - Multicentre	Patients 1 to 21 years old with high risk ALL	HR	EFS OS
	Panosyan 2004 (58)		To determine whether the prevalence of Ab formation in the HR ALL patients is a predictor of poor treatment outcome				ASP antibodies ASP activity
	Nachman 2009 (57)		To assess the outcome for young adults with ALL enrolled onto the CCG 1961 study between 1996 and 2002		Patients 16 to 21 years old (young adults) with high risk ALL (subgroup)		EFS OS
DFCI-91-01	Silverman et	US, Canada	To improve outcome while	- Interventional	Children (aged	SR	Not mentioned

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
	al, 2001 (59)	Enrolment: Dec 1991-Dec 1995	minimising toxicity	- Prospective - Randomised: Central randomisation. All patients randomised to: • High-dose IV 6-MP • Standard-dose oral 6-MP during the first year of post-remission therapy Patients underwent 3 additional randomisations: • To native or PEG-ASP • To doxorubicin continuous infusion or to bolus • To once-daily or twice daily cranial radiation • PEG-ASP was not available in Canada: children treated at Canadian institutions (n=127) were directly assigned to receive E. coli-ASP - Multicentre	0-18 years) with newly diagnosed ALL (excluding mature B-cell ALL)	HR Infant HR	
DFCI ALL 05-001	Silverman et al, 2013 (50) Place et al, 2015 (30)[†]	US, Canada Enrolment 2005-2010	To compare the relative toxicity and efficacy of IV PEG-ASP and IM E. coli ASP	- Interventional - Prospective - Randomised: following complete remission at induction with 1 dose PEG-ASP, patients were randomised at post-induction to E. coli-ASP or PEG-ASP - Phase III - Multicentre	Patients with newly diagnosed ALL aged 1-18 years who achieved complete remission following induction	SR HR VHR	Safety
DFCI-87-01	(Silverman 2010 (20))	US 1985–2000	The Silverman article summarises DFCI ALL clinical trials conducted between 1985 and 2000. The protocols in these studies aimed at improving survival rates while minimising acute and late toxicities	- Interventional - Prospective - Randomised: patients randomised to: • 40 mg/m^2 or 4 g/m^2 MTX with leucovorin (induction) • E. coli-ASP, Erwinia or PEG-ASP (induction) - Multicentre	Newly diagnosed ALL	SR HR VHR	Not specified
DFCI ALL 05-01	Merryman et al, 2010 (60) Merryman 2012 (85)	US, Canada Enrolment 2005-2010	To assess toxicity of ASP particularly potential associated myelosuppression in children and adolescents with ALL	- Interventional - Prospective - Randomised: to E. coli-ASP or PEG-ASP at consolidation - Not multicentre	Children and adolescents (1-18 yrs) with newly diagnosed ALL who achieved CR during induction	Standard risk	Not specified
	Silverman et		To compare 2 week IV PEG-ASP			Not	Median NSAA

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
	al, 2011 (61)		with weekly IM E. coli-ASP in terms of toxicity and ASP levels			specified	
AALL07P4	Angiolillo et al, 2014 (62)	US July 2008-Jan 2011	To determine the pharmacokinetic and pharmacodynamic comparability of Carba to PEG-ASP in patients with newly diagnosed high-risk B-cell ALL	- Interventional - Prospective - Randomised: Randomly assigned at a 2:1 ratio to receive Carba 2,100 or 2,500 IU/m^2) vs PEG-ASP 2,500 IU/m^2 - Multicentre - Phase III - Open-label	Newly diagnosed HR B-cell ALL	HR	PK
COG AALL0232	Larsen et al, 2011 (63) Larsen et al, 2012 (64)	Location: Not specified Enrollment: Jan 2004- Jan 2011	To compare high-dose methotrexate (HD-MTX) with Capizzi C-MTX + ASP in children and young adults with HR-ALL	- Interventional - Prospective - Randomised: 2 x 2 factorial design with an augmented intensity BF backbone to: DEX versus PRED during induction; HD-MTX (5gm/m2 biweekly x 4) versus C-MTX/ASP during IM-1 - Phase III	Children and young adults (1-30 yrs) with newly diagnosed ALL	HR	Not specified
COG AALL0331	Maloney et al, 2013 (65)	Enrolment: April 2005-May 2010	To assess the relative value of individual components of intensified post-induction therapy	- Interventional - Prospective - Randomised for SR-Av only: 2 X 2 randomisation at end-induction to standard (SC) vs. intensified consolidation (IC) and standard interim maintenance (IM) / delayed intensification (DI) vs. intensified IM/DI for SR-Av (not Low or High) pts - Phase III	Children with SR (age 1-9.99 yrs and initial WBC <50,000/µl) B-cell precursor (B-ALL)	SR	EFS
NOPHO ALL2008 (NCT00819351)	Henriksen et al, 2015 (66)	Nordic and Baltic countries Enrolment: July 2008 onwards	To describe the clinical aspects of PEG-ASP allergy in children treated according to the NOPHO ALL2008 protocol	- Interventional - Prospective, still ongoing recruitment for complete study at publication - Randomised: on day 30 after induction initiation to two dosages of PEG-ASP. Randomisation only applied to SR and IR groups - Multicentre	Children aged 1–17 years, with Philadelphia chromosome negative B-cell precursor including Downs syndrome, T-cell, or bi-lineage ALL	SR IR HR	
POG 9006	Lauer, 2001 (53)	US Jan 1991-Jan 1994	To compare the efficacy and toxicity of two different intensification	- Interventional - Prospective	Children with high risk B-	HR	CCR

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
			regimens: A (12 early intensive courses of antimetabolite based chemotherapy -intermediate-dose MTX/MP) and B (12 early intensive courses of alternating myelosuppressive, non-cross-resistant combination chemotherapy with MTX/MP + PEG-ASP)	- Randomised: to either PEG-ASP or no ASP at consolidation (1:1) - Multicentre - Phase III	Precursor ALL		
POG 9406	Tower, 2014 (54)	US 1994–1999	Determine the efficacy and toxicity of higher dose vs standard dose IV MTX and pulses of high dose cytosine arabinoside with ASP vs standard dose cytosine arabinoside and teniposide during intensified continuation therapy for higher risk pediatric B-precursor ALL	- Interventional - Prospective - Randomised: in a 2 × 2 factorial design to: MTX 1 gm/m^2 (Regimens A/B) vs 2.5 gm/m^2 (Regimens C/D); Teniposide/ara-C (Regimens A/C) vs high dose ara-C/ASP (Regimens B/D) Patients with t(4;11) or t(9;22) were excluded from randomisation and were assigned to Regimen A. Patients with Down syndrome were randomised to receive only Regimens A or B (lower MTX dosing). - Phase III	Newly diagnosed high risk ALL in patients aged between 10 and 30 years of age	HR	Not specified
Non-randomised							
CCG-1961m/CCG-1991	Jastaniah et al, 2015 (67)	Saudi Arabia Jan 2001-Dec 2007	To identify causes of variability in outcomes in children with ALL treated in a resource-rich developing country	- Observational - Retrospective - Not randomised - No multicentre	Children up to 14 years old with newly diagnosed ALL	SR, HR	Not specified
GMALL 07/03	Gokbuget et al, 2013 (68)	Germany Start date April 2003	To assess efficacy and safety of pediatric derived protocol GMALL 05/93 and 07/03	Interventional - Prospective - Not randomised - Multicentre - Open-label	AYAs aged 15-35 years with ALL	HR/VHR, SR	Not specified
MDACC BFM augmented	Rytting et al, 2013 (69)	USA Enrolment: not specified	To compare ABFM therapy in patients aged 12-40 to historical HYPER CVAD regimen	- Interventional - Prospective - Case control study - Single centre	Newly diagnosed patients aged 12-40 yrs with de novo Philadelphia chromosome	Not specified	Not specified

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
					negative ALL		
INTERFANT-06	Van der Sluis, 2013 (70)	The Netherlands and Germany Recruitment: July 2009-May 2010	To show that the ASP dose regimen used in the INTERFANT-06 protocol is safe in infants, provides sufficient ASP activity during induction treatment and leads to complete asparagine depletion in serum for the desired time period	- Interventional - Prospective - Not randomised (single arm) - Multicentre	De novo ALL patients (children)	SR IR HR	Not specified
CoALL 08-09	Escherich, 2013 (71)	Germany Enrollment Oct 2011-Dec 2011	To assess the safety and efficacy on the front-line application of clofarabine in combination with PEG-ASP in high risk B-progenitor as well as T-ALL patients, who received this combination in a prospective phase II trial at the beginning of the consolidation therapy within the CoALL 08-09 protocol	- Interventional - Prospective - Not randomised (stratified): Based on clinical parameters: Patients with high risk of relapse based on MRD at the end of induction were stratified to receive the combination of clofarabine and PEG-ASP at the beginning of consolidation. All other patients received the standard HIDAc in combination with PEG-ASP - Multicentre - Phase II	Newly diagnosed acute B-progenitor or T-cell Leukemia	Risk of relapse based on MRD: this level was used to stratify patients into treatment arms	Safety

Abbreviations: ABFM, augmented Berlin-Frankfurt-Münster; ALL, acute lymphoblastic leukemia; AP, acute pancreatitis; ara-C, cytosine arabinoside; ASP, asparaginase; AUC, area under the curve; AYA, adolescents and young adults; BFM, Berlin-Frankfurt-Münster; Carba, Calaspargase pegol Escherichia coli asparaginase; C-MTX, Capizzi methotrexate; CCR, continuous complete remission; CR, complete remission; CVAD, cyclophosphamide, vincristine, adriamycin, and dexamethasone; DEX, dexamethasone; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; EFS , event-free survival; HD-MTX, High-dose methotrexate; HR SCT, high risk stem cell transplant; HR, high risk; HR-ALL, acute lymphoblastic leukemia; HR-chemo, high risk chemotherapy; IC, intensified consolidation; IM, intensified maintenance; IM, intramuscular; IR, intermediate risk; IV, intravenous; LR, low risk; MP, mercaptopurine; MRD, minimal residual disease; MTX/MP, methotrexate/mercaptopurine; NSAA, nadir serum asparaginase activity; OS, overall survival; PEG-ASP, pegaspargase; PK, pharmacokinetics; PRED, prednisone; RER, rapid early responders; SAA, Serum asparaginase activity; SC, standard consolidation; SER, slow early reponders; SR, standard risk; SR-Av, standard risk average; US, United States; VHR, very high risk; WBC, white blood cells.

† Place et al, 2015 (30) was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates presented in Section 4.10.

4.8.1.2 Exposure to asparaginase

Table 23: Exposure to asparaginase: Studies with pegaspargase data

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
Randomised						
CCG-1962	Avramis et al, 2002 (11)	- Induction: 4 weeks - Consolidation: 4 weeks - Interim maintenance: 2 x 8-week phases - DI: 2 x 8-week phases - Maintenance therapy	Randomisation at induction phase - Induction: E. coli-ASP vs PEG-ASP (R) - Consolidation: no ASP - Interim maintenance 1 & 2: no ASP - Delayed intensification 1 & 2: E. coli-ASP vs PEG-ASP (as in induction) - Maintenance: no ASP	- PEG-ASP - E. coli-ASP	- PEG-ASP: 2,500 IU/m^2 - E. coli-ASP: 6,000 IU/m^2	IM
UKALL 2003	Vora et al, 2013 (2) Vora et al, 2014 (4)	- Induction - Consolidation - Interim maintenance treatment - Delayed intensification - Continuing therapy	- Induction: PEG-ASP (UK protocol) (all) - Consolidation: Regimen A: No ASP Regimen B: No ASP Regimen C: PEG-ASP - Interim maintenance treatment: Regimen A or B: No ASP Regimen C: PEG-ASP - Delayed intensification: Regimen A or B: PEG-ASP Regimen C: PEG-ASP - Continuing therapy: no ASP (all)	PEG-ASP	PEG-ASP: 1,000 U/m^2	IM
CCG-1961	Nachman 2009 (57) Panosyan 2004 (58) Seibel 2008 (55)	**Standard therapy** - Induction - Consolidation - Interim maintenance - Delayed intensification - Reconsolidation - Maintenance **Increased intensity therapy** - Induction - Consolidation	**Standard therapy** - Induction: E. coli-ASP (all) - Consolidation: No ASP - Interim maintenance: No ASP - Delayed intensification: E. coli-ASP (all) - Reconsolidation: No ASP - Maintenance: No ASP **Increased intensity therapy** - Induction: E. coli-ASP (all) - Consolidation: PEG-ASP (all)	- E. coli-ASP - PEG-ASP	- E. coli-ASP: 6,000 IU/m^2 - PEG-ASP: 2,500 IU/m^2 - if allergy: Erwinia: 6,000 IU/m^2	IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
		- Interim maintenance - Delayed intensification - Reconsolidation - Interim maintenance 2 - Delayed intensification 2 - Maintenance 2	- Interim maintenance: PEG-ASP (all) - Delayed intensification: PEG-ASP (all) - Reconsolidation: PEG-ASP (all) - Interim maintenance 2: PEG-ASP (all) - Delayed intensification 2: PEG-ASP (all) - Maintenance 2: PEG-ASP (all)			
DFCI-91-01	Silverman et al, 2001 (59)	- Investigational window (3 days) - Induction (4 weeks) - CNS therapy (3 weeks) - Intensification (30 weeks) - Continuation (until 2 years of CCR)	- Investigational window: no ASP - Induction: no ASP (all) - CNS therapy: no ASP (all) - Intensification: PEG-ASP vs E. coli-ASP (R) - Continuation: no ASP (all) In addition to ASP randomisation: - CNS therapy randomisation - Intensification with/without doxotrubicine for HR	- PEG-ASP - E. coli-ASP	- PEG-ASP: 2,500 IU/m^2 - E. coli-ASP: 25,000 IU/m^2	IM
DFCI ALL 05-001	Silverman et al, 2013 (50) Place et al, 2015 (30)[†]	- Induction - Consolidation - CNS intensification (Timing of CNS phase dependent on risk stratification) - Continuation	Randomisation at post-induction - Induction: PEG-ASP - CNS intensification (SR/HR) or consolidation (VHR): E. coli-ASP vs IV PEG-ASP (R) - Continuation	- PEG-ASP - E. coli-ASP	- E. coli ASP: 25,000 IU/m^2 weekly (30 doses) - PEG-ASP: IV 2,500 IU/m^2 every 2 wks (15 doses)	- IV (PEG-ASP) - IM (E. coli-ASP)
DFCI-87-01	Silverman 2010 (20)	- Remission Induction - CNS-directed treatment - Intensification - Continuation	Randomisation at induction - Induction: E. coli, Erwinia or PEG-ASP 1 dose (R) - CNS therapy: none - Intensification: E. coli-ASP (all) - Continuation: no ASP	- PEG-ASP - E. coli-ASP - Erwinia ASP	E. coli: 25,000 IU/m^2/week (intensification) Induction doses not specified	IM (E. coli ASP)
DFCI ALL 05-01	Merryman et al, 2010 Silverman et al, 2011 (61)	- Induction - Consolidation - CNS therapy - Reinduction - Maintenance	Randomisation at consolidation - Induction: PEG-ASP - Consolidation: E. coli-ASP vs PEG-ASP (R) - CNS therapy: E. coli-ASP vs PEG-ASP - Reinduction: not specified (all) Maintenance: no ASP (all)	- E. coli-ASP - PEG-ASP	- E. coli-ASP: weekly IM as 25,000 IU/m^2 - PEG-ASP: every 2-wk as 2,500 IU/m^2	- IM (E. coli-ASP) - IV (PEG-ASP)
AALL07P4	Angiolillo et al,	- Induction	Randomisation at induction	Carba	- PEG-ASP:	IV

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
	2014 (62)	- Extended induction - Consolidation - Interim maintenance - Delayed intensification - Maintenance	- Induction: PEG-ASP vs Carba (R) - Extended induction: PEG-ASP vs Carba - Consolidation: PEG-ASP vs Carba - Interim maintenance: PEG-ASP vs Carba - Delayed intensification: PEG-ASP vs Carba - Maintenance: no ASP	PEG-ASP	2,500 IU/m^2 - Carba: 2,500 or 2,100 IU/m^2	
COG AALL0232	Larsen et al, 2011 (63) Larsen et al, 2012 (64)	- Induction - Extended induction - Consolidation - Interim maintenance - Delayed intensification - Maintenance	- Induction: PEG-ASP - Extended induction therapy (only for patients with M2 disease or M1 disease with over 1% MRD): PEG-ASP - Consolidation: PEG-ASP - Interim maintenance: • Arm DC: PEG-ASP on days 2 and 22 • Arm DH: No ASP • Arm PC: PEG-ASP on days 2 and 22 • Arm PH: No ASP - Delayed intensification(s): PEG-ASP - After delayed intensification I: • SER patients proceed to interim maintenance II and delayed intensification II • RER patients proceed directly to maintenance - Interim maintenance II: PEG-ASP - Delayed intensification II: same as delayed intensification I - Maintenance therapy: no ASP	PEG-ASP	Not specified	IM
COG AALL0331	Maloney et al, 2013 (65)	- Induction - Consolidation - Interim maintenance - Delayed intensification - Maintenance	- Induction: 3 drug induction - PEG-ASP (all) - Consolidation: standard consolidation (no ASP) vs. intensified consolidation (PEG-ASP) - randomisation for SR-Av patients only (Low or High non randomly assigned) - Interim maintenance & Delayed intensification (until 2008 only): standard interim maintenance & delayed intensification (PEG-ASP) vs. intensified maintenance (PEG-ASP)/intensified DI (PEG-ASP) - Randomisation for SR-Av patients only (Low or High non randomly assigned) - Maintenance	PEG-ASP	PEG-ASP: 2,500 U/m^2	IM
NOPHO	Henriksen et al,	- Induction	For SR & IR	PEG-ASP (two	Post-induction:	IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
ALL2008 (NCT00819351)	2015 (66)	- Consolidation - Delayed intensification - Maintenance - Intensification	- Induction: PEG-ASP (all) - Consolidation: PEG-ASP every 2 vs every 6 wks (R) - Delayed intensification: same as in consolidation. If allergy, Erwinase (all) - Maintenance: same as in delayed intensification (all) For HR – no randomisation: PEG-ASP at all tx phases	dose regimens)	PEG-ASP 1,000 IU/m^2	
POG 9006	Lauer, 2001 (53)	- Induction - Consolidation - Reinduction - Maintenance	- Induction: E. coli-ASP (all) - Consolidation: PEG-ASP vs no ASP (R) - Reinduction: not specified - Maintenance: no ASP (all)	- E. coli ASP - PEG-ASP	- E. coli-ASP: 6,,000 IU/m^2 - PEG-ASP: 2,500 IU/m^2	IM
POG 9406	Tower, 2014 (54)	- Induction - Intensification - Maintenance - Randomisations	- Induction: E. coli-ASP (all) - Intensification: 4 regimens with 3 drug combinations (R) • Regimen A: PEG-ASP at drug pair 3 • Regimen B: PEG-ASP at drug pairs 2 & 3 • Regimen C: PEG-ASP at drug pair 3 • Regimen D: PEG-ASP at drug pairs 2 & 3 - Maintenance: no ASP - Randomisations: • Regimens A & B: MTX 1 gm/m^2 • Regimens C & D: MTX 2.5 gm/m^2 • Regimens A & C: teniposide/ara-C • Regimens B & D: high dose ara-C/ASP	- E. coli-ASP - PEG-ASP	- E. coli-ASP: 6,000 IU/m^2 - PEG-ASP (drug pair 3): 2,500 IU/m^2 - PEG-ASP (drug pair 2): 1,000 IU/m^2	IM
Non-randomised						
CCG-1961m/CCG-1991	Jastaniah et al, 2015 (67)	- Induction - Consolidation - Interim maintenance 1 & 2 - Delayed intensification 1 & 2 - Maintenance	**CCG-1961 (SR patients)** - Induction: PEG-ASP - Consolidation: no ASP - Interim maintenance 1 & 2: No ASP - Delayed intensification 1 & 2: PEG-ASP - Maintenance: No ASP **CCG 1991 (HR patients)** - Induction: PEG-ASP - Consolidation: PEG-ASP	PEG-ASP	PEG-ASP: 2500 U/m^2	IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
			- Interim maintenance 1 & 2: PEG-ASP - Delayed intensification 1 & 2: PEG-ASP - Maintenance: No ASP			
GMALL 07/03	Gokbuget et al, 2013 (68)	- Induction - Consolidation - Maintenance: intensified or conventional maintenance	GMALL 07/03: - Induction: PEG-ASP - Consolidation: PEG-ASP - Maintenance: individualised treatment stratified according to relapse risk with stem cell transplantation for patients with high and very high risk of relapse.	- GMALL 07/03: PEG-ASP	- Study 07: PEG-ASP: 2,500 IU/m2	Not specified
MDACC BFM augmented	Rytting et al, 2013 (69)	Based on ClinicalTrials.Gov: - Induction - Consolidation - Maintenance	- Induction: PEG-ASP - Consolidation: PEG-ASP - Maintenance: no ASP	PEG-ASP	- Not specified	IV
INTERFANT-06	Van der Sluis, 2013 (70)	- Remission induction - Consolidation - Reinduction - Maintenance	- Remission induction: E. coli-ASP (all) - Consolidation: PEG-ASP (all) - Reinduction: PEG-ASP (all) - Maintenance: none	- E. coli-ASP - PEG-ASP	10,000 U/m2/day	Infusion
CoALL 08-09	Escherich, 2013 (71)	- Induction - Consolidation - Reinduction - Maintenance	- Induction: no ASP (all) - Consolidation: PEG-ASP + clorafabine vs PEG-ASP + cytarabine (R) - Reinduction: no ASP (all) - Maintenance: no ASP (all)	- PEG-ASP	- 2,500 IU/m2	- IV

Abbreviations: ASP, asparaginase; Carba, Calaspargase pegol Escherichia coli asparaginase; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; MRD, minimal residual disease; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.

† Place et al, 2015 (30) was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates.

4.8.1.3 Efficacy outcomes

EFS and OS

Table 24: EFS and OS: Studies with pegaspargase data

Study	Citation	EFS				OS			
		Definition	E. coli ASP	PEG-ASP	No ASP	Definition	E. coli ASP	PEG-ASP	No Asp
Randomised									
CCG-1962	Avramis et al, 2002 (11)	Time from study registration until first event (induction death, no induction response, relapse at any site, and second malignant neoplasm)	At 3 yrs: 79% [68, 90] † At 5 yrs: 73% [61; 85] † At 7 yrs: 66 [52; 80] †	At 3 yrs: 83% [73; 93] † At 5 yrs: 78% [67; 88] † At 7 yrs: 75% [63; 87] †		No OS data			
UKALL 2003	Vora et al, 2014 (4)	Time from diagnosis to relapse, secondary tumour or death		5-year EFS: Standard (1 DI): 82.8% [78.1-87.5] Augmented (2 DI): 89.6% [85.9-93.3]		Time from diagnosis to death		5 year Augmented therapy: 92.9% [89.8-96.0] Standard therapy: 88.9% [85.0-92.8] Augmented vs standard OR=0.67 [0.38-1.17]; p=0.16	
	Vora et al, 2013 (2)	Time to relapse, secondary tumour, or death		5-year EFS: • All patients (n=3126): 87.2% [85.8–88.6] • One DI (n=260): 94.4% [91.1–97.7] • Two DI (n=261): 95.5% [92.8–98.2] • MRD low risk (n=1090): 94.2% (92.4-96.0) • MRD high risk		Not specified		5 year All patients in trial (n=3126): 91.5% [90.3–92.7] Augmented therapy (n=260): 97.9% [95.7–100.0] Standard therapy (n=261): 98.5% [96.9–100] Augmented vs standard: OR=0.67	

Study	Citation	EFS				OS			
		Definition	E. coli ASP	PEG-ASP	No ASP	Definition	E. coli ASP	PEG-ASP	No Asp
				(n=1037): 79.8% (76.9-82.7) • NCI SR – MRD HR: 85.8% [82.1-89.5] • NCI SR – MRD low risk: 94.0% [91.6-96.4] • NCI HR – MRD HR: 72.8% [67.9-77.7] • NCI HR – MRD low risk: 94.7% [92.0-97.4]			[0.19–2.30]; p=0.53	
CCG-1961	Nachman 2009 (57)	EFS was defined as time from randomisation to first event (induction failure, induction death, relapse at any site, death in remission, or a second malignant neoplasm, whichever occurred first). Patients who had not had an event were censored at the time of the last contact	E. coli ASP (induction and post-induction) 5-year Young adult RER SPII: 66.9%±6.7%	E. coli ASP (induction) & PEG-ASP (post-induction) 5 year • Young adults: 71.5%±3.6% • Young adult RER IPII: 81.8%±5.4% • Young adult RER 1 DI: 71.1% • Young adult RER 2 DI: 77.1% • Young adult SER (IPII): 70.7%±7.3%		Not specified	5 year Young adults RER (n=76): 75.6±7.7%		
	Seibel 2008 (55)	As per Nachman 2009	5-year • SPII: 71.7%±2.7% • Age 1-9 years SPII: 70.8%±4.2%, P .009; • Age ≥10 yrs SPII: 72.3±3.5%	5-year • IPII: 81.2%±2.4% • Age 1-9 years IPII: 82.1%±4.0% • Age ≥10 yrs IPII: 80.4%±2.9		Not specified	5 year E. coli-ASP only (n=649): 83.4±2.2% Pooled ASP (E. coli Asp only + E. coli ASP/PEG-ASP; n=1299):	5 year E. coli-ASP (induction only) and PEG-ASP (post induction) (n=650): 88.7±1.9%	

Study	Citation	EFS				OS			
		Definition	E. coli ASP	PEG-ASP	No ASP	Definition	E. coli ASP	PEG-ASP	No Asp
							84.7%±1.5%		
DFCI-91-01	Silverman et al, 2001 (59)	EFS: the time from complete remission to the first outcome event	E. coli-ASP at consolidation At 5 yrs: 84±4% (p=0.29)	PEG-ASP at consolidation At 5 yrs: 78±4%			Only pooled ASP data available (E. coli and PEG-ASP)		
DFCI ALL 05-001	Silverman et al, 2013 (50) Place et al, 2015 (30)‡	EFS: time from diagnosis to 1st outcome event (induction failure, induction death, death during remission, second malignant neoplasm, or relapse)‡	4 yr: 90% (n=208)	4 yr: 92% (n=213; p=0.31)		OS: calculated from the time of diagnosis to death from any cause‡	5 yr‡: 94% (89–96)	5 yr‡: 96% (93–98)	
DFCI-87-01	Silverman 2010 (20)	Not specified	Only reports data pooled across all ASP formulations (E. coli, PEG and Erwinia)			Only reports data pooled across all ASP formulations (E. coli, PEG and Erwinia)			
AALL07P4	Angiolillo et al, 2014 (62)	Not specified		3-year EFS • PEG-ASP (n=54): 85.1±5.0% • Carba low (n=69): 75.3±5.2% • Carba high: (n=42) 85.7±5.4% (p=0.33)		Not specified (data from Data on file)		3 year PEG-ASP (n=54): 92.4±3.7% [Carba low (n=69): 84.1±4.5% Carba high (n=42): 90.5±4.5%]	
COG AALL0232	Larsen et al, 2011 (63)	Not specified		5 yrs EFS: • C-MTX/ASP (N=1,217): 75.4 ± 3.6% (p=0.006)	5 yrs EFS: • HD-MTX (N=1,209): 82±3.4%	Not specified		5 year AYA (n=501): 79.8% Younger patients (n=2073): 88.4% (HR)	
COG AALL0232	Larsen et al, 2012 (64)	Not specified		5-yr EFS: • AYA: 68.0% • Younger patients: 80.9%					

Study	Citation	EFS				OS			
		Definition	E. coli ASP	PEG-ASP	No ASP	Definition	E. coli ASP	PEG-ASP	No Asp
COG AALL0331	Maloney et al, 2013 (65)	EFS was defined as time before induction to event (not fully specified)		5 y EFS: •All patients (n=5192): 89±0.6% • SR Low (n=1857): 95% • SR-High: 85% • SR Av with MRD >0.01-<0.1% (172): 77%		Not specified		5 year All patients (n=5192): 96±0.4% SR high (n=636): 94±1% SR low (n=1857): 99±0.3% SR av (n=1500): 96±0.7%	
POG 9006	Lauer, 2001 (53)	Time from induction to failure: difference with CCR: induction failures are included in the EFS		0-1 yrs: 93.5±1.6% 1-2 yrs: 84.1±2.3% 2-3 yrs: 76.2±2.7% 3-4 yrs: 69.4±3.1% 4-5 yrs: 65.3±3.7% 5-6 yrs: 63.0±5.1%	0-1 yrs: 86.8±2.2% 1-2 yrs: 77.2±2.7% 2-3 yrs: 67.6±3.0% 3-4 yrs: 61.6±3.3% 4-5 yrs: 59.3±4.0% 5-6 yrs :58.1±5.6%	No OS data			
POG 9406	Tower, 2014 (54)	No EFS data				OS is defined as the time from complete remission to the date of death or date last seen for those who did not experience an event	5 year 80.4±1.4% (n=784) Only OS data for E. coli ASP at induction and PEG ASP at consolidation		
Non-randomised									
CCG-1961m/CCG-1991	Jastaniah et al, 2015 (67)	EFS: the time from diagnosis to the date of the first event (i.e., induction failure, relapse at any site, or death from any cause) or last contact date		5 year: 77±2.9% 10 year: 77±2.9%		OS was the interval between diagnosis and the date of last follow-up or death from any cause		5-year: 84.7±2.4% 10-year: 83.1±2.7% (n=219)	
GMALL 07/03	Gokbuget et al, 2013 (68)	No EFS data				Not specified		5 year All patients (n=887): 65%	

Study	Citation	EFS				OS			
		Definition	E. coli ASP	PEG-ASP	No ASP	Definition	E. coli ASP	PEG-ASP	No Asp
								SR (n=452): 74% HR (n=310): 58% VHR (n=124): 55%	
MDACC BFM augmented	Rytting et al, 2013 (69)	No EFS data				Not specified		3 year 75%	

Abbreviations: ABFM, augmented Berlin-Frankfurt-Münster; ALL, acute lymphoblastic leukaemia; AP, acute pancreatitis; ara-C, cytosine arabinoside; ASP, asparaginase; AUC, area under the curve; AYA, adolescents and young adults; BFM, Berlin-Frankfurt-Münster; Carba, Calaspargase pegol Escherichia coli asparaginase; C-MTX, Capizzi methotrexate; CCR, continuous complete remission; CR, complete remission; DEX , dexamethasone; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; EFS, event-free survival; HaR, hazard ratio; HD-MTX, High-dose methotrexate; HR SCT, high risk stem cell transplant; HR, high risk; HR-ALL, acute lymphoblastic leukaemia; HR-chemo, high risk chemotherapy; IC, intensified consolidation; IM, intensified maintenance; IM, intramuscular; IR, intermediate risk; IV, intravenous; LR, low risk; MP, mercaptopurine; MRD, minimal residual disease; MTX/MP, methotrexate/mercaptopurine; NSAA, nadir serum asparaginase activity; OS, overall survival; PEG-ASP, pegaspargase; PK, pharmacokinetics; PRED, prednisone; R, randomised; RER, rapid early responders; SAA, Serum asparaginase activity; SC, standard consolidation; SD, standard deviation; SE, standard error; SER, slow early responders; SR, standard risk; SR-Av, standard risk average; US, United States; VHR, very high risk; WBC, white blood cells.
† EFS data have been taken from the SmPC rather than from Avramis 2002. The latter provides only the point estimate at 3 years and no confidence interval; ‡ Information extracted from Place et al, 2015 (30) which was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates.

DFS and CR

Table 25: DFS and remission: Studies with pegaspargase data

Study	Citation	DFS			Complete remission		
		Timing	Definition	DFS, %±SE	Definition	Endpoint, timing	Result
Randomised							
DFCI-91-01	Silverman et al, 2001 (59)	5-year (SR, HR)	LFS: time from complete remission to relapse	PEG-ASP or E. coli-ASP at intensification All (n=377): 87±2% SR (n=137): 90±3% HR (n=240): 85±2%	Not specified	CR at day 52 after diagnosis	E. coli-ASP or PEG-ASP at intensification CRs: • All: 370/377, 98% • SR: 137/137, 100% • HR: 233/240, 97% CCR at 5 years: • All: 312/377, 82.8% • SR: 117/137, 85.4% • HR: 195/240, 81.3%

Study	Citation	DFS			Complete remission		
		Timing	Definition	DFS, %±SE	Definition	Endpoint, timing	Result
DFCI ALL 05-001	Place et al, 2015 (30) ‡	5 year‡	DFS events were defined as death during remission, second malignant neoplasm, or relapse‡	PEG-ASP 90% (95% CI 86–94) ‡ E. coli ASP 89% (95% CI 85–93) ‡	No data		
COG AALL0232	Larsen et al, 2011 (63) Larsen et al, 2012 (64)	No data	No data	No data	Remission was defined as <5% marrow blasts at end induction	Remission rate at end of induction	PEG-ASP Remission: • AYA: 97.2% • Younger patients: 98.8%; p=0.0134
COG AALL0331	Maloney et al, 2013 (65)	No data	No data	No data	Not specified	CCR rate at 5 years	PEG-ASP 5 y CCR (SE): •SR high (n=636): 85% (2%) •SR Low (n=1857): 95% (0.7%) •SR Av (n=1500): 89% (1.1%) •MRD <0.01% at day 29 (n=1310): 91% (1.2%) •MRD >0.01-<0.1% at day 29 (n=172): 77% (4.5%) •SR Av standard consolidation: 88% (1.6%) •SR Av intensified consolidation: 89.3% (1.5%) •SR Av standard consolidation (MRD <0.01% at day 29): 89% (1.6%) •SR Av standard consolidation (MRD >0.01-<0.1% at day 29): 77% (6.0%) •SR Av intensified consolidation (MRD <0.01% at day 29): 91.5% (1.5%) •SR Av intensified consolidation (MRD >0.01-<0.1% at day 29): 76% (6.0%)
POG 9006	Lauer, 2001 (53)	No data	No data	No data	CCR: time from achievement of a complete remission (end	0-1 yrs 1-2 yrs 2-3 yrs	**PEG-ASP, CCR:** 0-1 yrs: 94.9% (1.4) 1-2 yrs: 85.2% (2.3)

Study	Citation	DFS			Complete remission		
		Timing	Definition	DFS, %±SE	Definition	Endpoint, timing	Result
					induction therapy) to failure (Death, relapse, second malignancy)	3-4 yrs 4-5 yrs 5-6 yrs	2-3 yrs: 77.6 (2.7) 3-4 yrs: 70.6% (3.1) 4-5 yrs: 66.3% (3.7) 5-6 yrs: 63.9% (5.1) **No-ASP, CCR:** 0-1 yrs: 90.4% (1.9) 1-2 yrs: 80.4% (2.6) 2-3 yrs: 70.4 (3.0) 3-4 yrs: 64.0% (3.4) 4-5 yrs: 61.6% (4.1) 5-6 yrs: 60.4% (5.7)
POG 9406	Tower, 2014 (54)	5-year (HR)	Time from complete remission to first event (relapse, second malignancy, or death)	E. coli- ASP at induction and PEG- ASP at consolidation: (n=784): 69±1.6% Regimen A: 68±3.5% Regimen B: 75.5±3.2% Regimen C: 72.7±3.3% Regimen D: 70.7±3.3%	CR was defined as <5% leukemic blasts in a cellular bone marrow and no evidence of leukemia involvement elsewhere	CR at end of induction	CR: 881/905, 97.3%
Non-randomised							
CCG-1961m/CCG-1991	Jastaniah et al, 2015 (67)	5-year 10-year	Time from remission to death from any cause or relapse, whichever occurred first	PEG-ASP 5 year: 81.4±2.7% 10 year: 81.4±2.7%	CR defined as <5% blasts in the BM (M1) by the end of induction	CR rate at end of induction	PEG-ASP Remission for SR & HR: 210/214 (98.1%)
GMALL 07/03	Gokbuget et al, 2013 (68)	No data	No data	No data	Not specified	Remission rate at 5 years	PEG-ASP Study 07: •CR (age 15-35; n=887): 91% •CR (age 15-17; n=53): 94% •CR (age 18-25; n=458): 91% •CR (age 26-35; n=376): 90%
MDACC BFM augmented	Rytting et al, 2013 (69)	No data	No data	No data	Remission was defined as <5% blasts at day 29	Remission at day 15 & 29 CCR at 3 years	PEG-ASP Remission: Day 15: 61/85 (72%)

Study	Citation	DFS			Complete remission		
		Timing	Definition	DFS, %±SE	Definition	Endpoint, timing	Result
							Day 29: 80/85 (94%) 3 year (n=80): 71% (events: n=23)
INTERFANT-06	Van der Sluis, 2013 (70)	No data	No data	No data	CR: <5% leukemic blasts in bone marrow (M1 marrow), no leukemic blasts in peripheral blood or CFS, no other documented extramedullary leukemia	CR at day 33	E. coli-ASP CR: 12/12, 100%

Abbreviations: ASP, asparaginase; Carba, Calaspargase pegol Escherichia coli asparaginase; Av, ; CCR, continuous complete remission; CR, complete remission; DFS, disease-free survival; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; LFS, leukaemia-free survival; MRD, minimal residual disease; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.
‡ Information extracted from Place et al, 2015 (30) which was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates.

Relapse and MRD

Table 26: Relapse and MRD: Studies with pegaspargase data

Study	Citation	Relapse		MRD		
		Timing	Results	Definition	Timing	Results
Randomised						
CCG-1962	Avramis et al, 2002 (11)	FU not provided	E. coli-ASP: n=8/59 (13.56%) PEG-ASP: n=7/59 (11.86%)	No data	No data	No data
UKALL 2003	Vora et al, 2013 (2) Vora et al, 2014 (4)	5 year cumulative risk of relapse	PEG-ASP : Any relapse: Standard: 14.2% (95% CI: 9.7-18.7) Augmented: 7.5% (95% CI: 4.2-10.8) OR=0.55 (95% CI 0.33-0.94), p=0.03	No data	No data	No data
CCG-1961	Nachman 2009 (57)	Median FU: 3.5 years	**E. coli-ASP**	No data	No data	No data

Study	Citation	Relapse		MRD		
		Timing	Results	Definition	Timing	Results
	Panosyan 2004 (58) Seibel 2008 (55)		SPII (n=649) •BM relapse: 12.9% •CNS relapse: 4.9% **PEG-ASP** IPII (n=650) •BM relapse: 7.5% •CNS relapse: 4.5%			
DFCI-91-01	Silverman et al, 2001 (59)	Median FU: 5 years	**E. coli-ASP and PEG-ASP:** Overall relapse •All: 46/377, 12.2% •SR: 16/137, 11.7% •HR: 30/240, 12.5% BM only •All: 31/377, 8.2% •SR: 12/137, 8.8% •HR: 19/240, 7.9% CNS only •All: 4/377, 1.1% •SR: 1/137, 0.7% •HR: 3/240, 1.3%	No data	No data	No data
DFCI ALL 05-001	Silverman et al, 2013 (50) Place et al, 2015 (30) ‡	Unclear. Median follow up 6 years‡	E. coli ASP: n=21/231‡ PEG-ASP: n=20/232‡	MRD was defined as <0.001‡	Day 29‡	PEG-ASP (measured following induction. All pts received PEG-ASP in induction prior to randomisation) MRD: 338/378 (89.4%)‡
AALL07P4	Angiolillo et al, 2014 (62)	No data	No data	MRD was defined as <0.01%, because multivariable analyses found this to be the most important prognostic variable in other COG trials	Day 29	PEG-ASP **MRD (<0.01%) day 29** • PEG-ASP 2,500 IU/m^2: n=36/50 (72%) • Carba 2,500 IU/m^2: n=29/39 (74%) • Carba 2,100 IU/m^2: 36/64 (56%) (p=0.10) **MRD (<0.1%) day 29** • PEG-ASP 2,500 IU/m^2: n=39/50 (78%) • Carba 2,500 IU/m^2: n=33/39 (85%)

Study	Citation	Relapse		MRD		
		Timing	Results	Definition	Timing	Results
						• Carba 2,100 IU/m^2: 44/64 (69%) (p=0.18)
COG AALL0232	Larsen et al, 2011 (63) Larsen et al, 2012 (64)	FU not provided	PEG-ASP Bone marrow relapses: • HD-MTX: 42/120, 3.5% • C-MTX/ASP: 68/1217, 5.6% CNS relapses: • HD-MTX: 68/1209, 5.6% • C-MTX/ASP: 32/1217, 2.6%	No data	No data	No data
COG AALL0331	Maloney et al, 2013 (65)	No data	No data	MRD was defined as <0.01%	Day 29	PEG-ASP MRD <0.01% Day 29 (SR patients): 1310/1500, 87.3%
Non-randomised						
CCG-1961m/CCG-1991	Jastaniah et al, 2015 (67)	FU: 10 years	PEG-ASP During the 10 yr FU: • Relapse rate: 33/219 (15.1% [10.29–19.84]) • BM relapse: 13/219 (5.9%) • CNS relapse: 9/219 (4.1%) • BM & CNS: 9/219 (4.1%) • Testicular: 1/219 (0.5%)	No data	No data	No data
GMALL 07/03	Gokbuget et al, 2013 (68)	No data	No data	MRD was defined as <0.01%	Week 16	PEG-ASP MRD (<0.01%) after consolidation (week 16; n=353): assumed to be 74% NB: the abstract provides data on MRD failure: 26%, with no difference between age groups (MRD >0.01%).
MDACC BFM augmented	Rytting et al, 2013 (69)	No data	No data	MRD was defined as <0.01% blasts by flow cytometry	Day 29 Day 84	MRD (<0.01%) in ABFM: • Day 29 (end of induction): n=46/80 (58%) • Day 84: n=55/80 (69%)
INTERFANT-06	Van der Sluis, 2013 (70)	No data	No data	Not detailed	Day 33	E. coli-ASP MRD negativity at day 33: • 1/10, 10%

Abbreviations: ASP, asparaginase; BM, bone marrow; Carba, Calaspargase pegol escherichia coli asparaginase; CI, confidence interval; C-MTX, Capizzi methotrexate; CNS, central nervous system; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; FU, follow-up; HD-MTX; high dose methotrexate; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; MRD, minimal residual disease; OR, odds ratio; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.
‡ Information extracted from Place et al, 2015 (30) which was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates.

Asparaginase activity

Table 27: NSAA, serum asparagine, CSF asparagine: Studies with pegaspargase data

Study	Citation	NSAA, serum asparagine		CSF asparagine	
		E. coli ASP	PEG-ASP	E. coli ASP	PEG-ASP
Randomised					
CCG-1962	Avramis et al, 2002 (11)	**ASP activity at Day 21** Above 0.03 IU/mL: • DI no 1: 31% • DI no 2: 39% Above 0.1 IU/mL • DI no 1: 19% • DI no 2: 22% **% samples with ASP activity above 0.1 IU/mL by Ab ratio over control:** Below 1.5: • Induction: 79/89 (89%) • DI no 1: 54/58 (93%) • DI no 2: 55/59 (93%) 1.5-2.0: • Induction: 3/3 (100%) • DI no 1: 4/8 (50%) • DI no 2: 6/7 (86%) Above 2.0 • Induction: 5/8 (63%) • DI no 1: 10/20 (50%) • DI no 2: 7/11 (64%)	**ASP activity at Day 21** Above 0.03 IU/mL • DI no 1: 95% • DI no 2: 91% Above 0.1 IU/mL • DI no 1: 95% • DI no 2: 91% **% samples with ASP activity above 0.1 IU/mL by Ab ratio over control:** Below 1.5 • Induction: 95/98 (97%) • DI no 1: 67/69 (97%) • DI no 2: 63/65 (95%) 1.5-2.0 • Induction: 0/0 • DI no 1: 5/5 (100%) • DI no 2: 5/5 (100%) Above 2.0 • Induction: 3/3 (100%) • DI no 1: 2/2 (100%) • DI no 2: 9/9 (100%)	Median levels • Pretreatment: 2.8 mM • Day 7 induction: 1.0 mM • Day 28 induction: 0.3 mM	Median levels • Pretreatment: 2.3 mM • Day 7 induction: 1.1 mM • Day 28 induction: 0.6 mM

Study	Citation	NSAA, serum asparagine		CSF asparagine	
		E. coli ASP	PEG-ASP	E. coli ASP	PEG-ASP
DFCI ALL 05-001	Silverman et al, 2013 (50) Place et al, 2015 (30)‡	Median NSAA at week 11 of consolidation: 0.096 IU/mL % of pts with NSAA ≥0.1 IU/mL at week 11 of consolidation: 106/231 (46%)	Median NSAA at week 11 of consolidation: 0.758 IU/mL (p<0.01 vs E. coli) % of pts with NSAA ≥0.1 IU/mL at week 11 of consolidation: 230/232 (99%) (p<0.01 vs E. coli)	No data	No data
DFCI ALL 05-01	Merryman et al, 2010	Median NSAA (IU/ML) at consolidation wk 5: 0.094 wk 11: 0.094 wk 17: 0.092 wk 23: 0.094 wk 29: 0.095 % pts with NSAA > 0.1 IU/mL at consolidation wk 5 (n=92): 48% wk 11 (n=74): 47% wk 17 (n=86): 47% wk 23 (n=76): 46% wk 29 (n=63): 44%	Median NSAA (IU/ML) at consolidation wk 5: 0.67 wk 11: 0.71 wk 17: 0.76 wk23: 0.70 wk 29: 0.70 % pts with NSAA > 0.1 IU/mL at consolidation wk 5 (n=84): 95% wk 11 (n=70): 97% wk 17 (n=73): 97% wk 23 (n=60): 100% wk 29 (n=68): 100%	No data	No data
	Silverman et al, 2011 (61)			No data	No data
AALL07P4	Angiolillo et al, 2014 (62)	No data	No data	No data	Mean CSF asparagine concentration: At day 4: decrease to approximately 25% to 30% of the pre-induction dose values
Non-randomised					
INTERFANT-06	Van der Sluis, 2013 (70)	ASP activity at day 18 (3 days after 1st ASP infusion) • equal or above 20 U/L: 11/12, 92% • equal or above 50 U/L: 10/12, 83% • equal or above 100 U/L: 9/12, 75% ASP activity at day 25 (3 days after 3rd ASP infusion) • equal or above 20 U/L: 10/12, 83% • equal or above 50 U/L: 10/12, 83%	No data	No data	No data

Study	Citation	NSAA, serum asparagine		CSF asparagine	
		E. coli ASP	PEG-ASP	E. coli ASP	PEG-ASP
		• equal or above 100 U/L: 8/12, 67% ASP activity at day 33 (4 days after 5th ASP infusion) • equal or above 20 U/L: 9/12, 75% • equal or above 50 U/L: 5/12, 42% • equal or above 100 U/L: 1/12, 8% Observed trough serum ASP activities† were ≥20, ≥50, or ≥100 U/L in 86%, 71%, and 51% of all measured samples, respectively. If considering only data from days 18 and 25, the observed trough serum ASP activities were ≥20, ≥50, and ≥100 U/L in 91%, 87%, and 74% of measured samples, respectively. Complete asparagine depletion during induction treatment: • At day 18 (3 days after 1st rASP infusion): 11/11, 100% • At day 25 (3 days after 3rd rASP infusion): 12/12, 100% • At day 33 (4 days after 5th rASP infusion): 11/12, 92% • At day 18, 25 and 33: 11/12, 92%			

Abbreviations: ASP, asparaginase; CSF, cerebrospinal fluid; DI, delayed intensification; NSAA, nadir serum asparaginase activity.
† The trough ASP activity levels on day 33 were considerably lower than those on day 18 and day 25 which was due to the fact that the latter levels were assessed 3 days after the asparaginase infusion while the assessment on day 33 was performed 4 days after the last asparaginase infusion. ‡ Information extracted from Place et al, 2015 (30) which was identified subsequent to systematic review 1. Any data from Place et al has not been included in pooled estimates.

Immunogenicity

Table 28: Immunogenicity: Studies with pegaspargase data

Study	Citation	Definition	E. coli-ASP	Other
Randomised				
CCG-1962	Avramis et al, 2002 (11)	ASP antibody assays were done by a modified indirect solid-phase ELISA. The Day to day variation was corrected by expression of antibody titers as the ratio of sample over negative control for each assay. Titers were compared with the same patient's pretreatment control serum and negative control serum from a healthy volunteer	Maximal ratio of Ab over negative control: Ratio ≥2.5 • DI no 1: 11/43, 25.6% • DI no. 2: similar to PEG-ASP (p=.09, Wilcoxon test) • Induction: similar to PEG-ASP • At any time: 26% Ratio ≥1.5 at any time: >40% Mean: DI no. 1 • 3.0±0.7 (n=43) Induction: • 2.3±0.9 (n=47) DI no 2: • 2.1±0.6 (n=45)	**PEG-ASP** Maximal ratio of Ab over negative control Ratio ≥2.5 • DI no 1: 1/47, 2.1% (P<.001, Wilcoxon test) • DI no. 2: similar to E. coli-ASP • Induction: similar to E. coli-ASP Mean: DI no. 1 • 1.9±0.8 (n=47; p=0.001) Induction: • 1.3±0.2 (n=41; NS) DI no 2: • 2.1±0.8 (n=45; NS).
AALL07P4	Angiolillo et al, 2014 (62)	Immunogenicity assessment included the detection of both binding Abs and neutralizing Abs, determined by a validated direct ELISA and an enzymatic coupled activity assay, respectively	PEG-ASP 2,500: n=4/54, 7.4% Carba 2,500: n=2/42, 4.8% Carba 2,100: n=2/69, 2.9%	–
Non-randomised				
INTERFANT-06	Van der Sluis, 2013 (70)	–	–	E. coli-ASP at induction; PEG-ASP at consolidation and reinduction: n=0/12

Abbreviations: Ab, antibody; ASP, asparaginase; Carba, Calaspargase pegol Escherichia coli asparaginase; DI, delayed intensification; E. coli-ASP, native Escherichia coli-derived asparaginase; ELISA, enzyme linked immunosorbent assay; FD, fixed dose; HR, high risk; ID, individualised dose; IM, intramuscular; IR, intermediate risk; IV, intravenous; MRD, minimal residual disease; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.

4.8.1.4 Safety outcomes

Table 29: Safety: Studies with pegaspargase evidence

Study	Citation	ASP at induction	Relevant treatment phase	Selected grade 3/4 AEs	Grade 3+ allergic reactions	Grade 3+ hyperglycemia	Grade 3+ increases in transaminases	Grade 3+ pancreatitis	Grade 3+ thrombosis
Randomised									
CCG-1962	Avramis et al, 2002 (11)	PEG-ASP	Grade 3+ during induction PEG-ASP	• CNS thrombosis: n=1/59 (1.69%) • Other CNS complications: n=0 • Hyperglycemia: n=3/59 (5.08%) • Abnormal LFT: n=0 • Pancreatitis: n=1/59 (1.69%) • Allergy to ASP: n=0	0/59	3/59 (5.08%)	Abnormal LFT: n=0	1/59 (1.69%)	CNS thrombosis: n=1/59 (1.69%)
		E. coli-ASP	E.Coli ASP	• CNS thrombosis: n=2/59 (3.39%) • Other CNS complications: n=0 • Hyperglycemia: n=1/59 (1.69%) • Abnormal LFT: n=0 • Pancreatitis: n=1/59 (1.69%) • Allergy to ASP: n=0	0/59	1/59 (1.69%)	Abnormal LFT: n=0	1/59 (1.69%)	CNS thrombosis: n=2/59 (3.39%)
		PEG-ASP	Grade 3+ at delayed intensification (phase 1) PEG-ASP	• CNS thrombosis: n=1/54 (1.85%) • Other CNS complications: n=3/54 (5.56%) • Hyperglycemia: n=0 • Abnormal LFT: n=0 • Pancreatitis: n=0 • Allergy to ASP: n=1/54 (1.85%)	n=1/54 (1.85%)	6/54 (11.11%)	Abnormal LFT: n=0	0/54	CNS thrombosis: n=1/54 (1.85%)
		E. coli-ASP	Grade 3+ at	• CNS thrombosis: n=0	0/53	1/53 (1.89%)	Abnormal LFT:	0/53	CNS

Study	Citation	ASP at induction	Relevant treatment phase	Selected grade 3/4 AEs	Grade 3+ allergic reactions	Grade 3+ hyperglycemia	Grade 3+ increases in transaminases	Grade 3+ pancreatitis	Grade 3+ thrombosis
			delayed intensification (phase 1) E. coli-ASP	• Other CNS complications: n=2/53 (3.77%) • Hyperglycemia: n=1/53 (1.89%) • Abnormal LFT: n=2/53 (3.77%) • Pancreatitis: n=0 • Allergy to ASP: n=0			n=2/53 (3.77%)		thrombosis: n=0
		PEG-ASP	Grade 3+ at delayed intensification (phase 2) PEG-ASP	• CNS thrombosis: n=0 • Other CNS complications: n=3/48 (6.25%) • Hyperglycemia: n=0; n=0 • Abnormal LFT: n=0 • Pancreatitis: n=2/48 (4.17%) • Allergy to ASP: n=0	0/48	0	Abnormal LFT: n=0	2/48 (4.17%)	CNS thrombosis: n=0/48
		E. coli-ASP	Grade 3+ at delayed intensification (phase 2) E. coli-ASP	• CNS thrombosis: n=0 • Other CNS complications: n=2/53 (3.77%) • Hyperglycemia: n=1/53 (1.89%) • Abnormal LFT: n=2/53 (3.77%) • Pancreatitis: n=0 • Allergy to ASP: n=0	0/53	1/53 (1.89%)	Abnormal LFT: n=2/53 (3.77%)	0/53	CNS thrombosis: n=0/53
UKALL 2003	Vora et al, 2013 (2) Vora et al, 2014 (4)	PEG-ASP	Grade 3+; phase not specified PEG-ASP	Thrombosis • Standard therapy: 8/266 (3%) • Augmented therapy 9/267 (3%)	No data	No data	No data	No data	Standard therapy: 8/266 (3%) Augmented therapy: 9/267 (3%)
DFCI-91-01	Silverman et al, 2001 (59)	No ASP	Grade 3+ AEs at intensification PEG-ASP & E.	No difference between the 2 preparations in the rates of dose limiting toxicities such	Same for E. coli-ASP and PEG-	No data	No data	Same for E. coli-ASP and PEG-ASP	Same for E. coli-ASP and PEG-ASP

Study	Citation	ASP at induction	Relevant treatment phase	Selected grade 3/4 AEs	Grade 3+ allergic reactions	Grade 3+ hyperglycemia	Grade 3+ increases in transaminases	Grade 3+ pancreatitis	Grade 3+ thrombosis
			coli ASP	as severe allergic reaction (p=0.22), severe pancreatitis (p=0.78), or CNS thrombosis (p=1.00)	ASP (p=0.22)			(p=0.78)	(p=1.00)
AALL07P4	Angiolillo et al, 2014 (62)	PEG-ASP	Grade 3+ during induction PEG-ASP	Pancreatitis: 2/54 (3.7%) Hyperlipidemia: 2/54 (3.7%) Hyperbilirubinemia: 4/54 (7.4%) Hyperglycemia: 8/54 (14.8%)	No data	8/54 (14.8%)	Hyperbilirubinemia: 4/54 (7.4%)	2/54 (3.7%)	No data
			Grade 3+ at delayed intensification (phase I) PEG-ASP	Pancreatitis: 0/38 Hyperlipidemia: 0% Hyperbilirubinemia: 0% Hyperglycemia: 3/38 (7.9%)	No data	3/38 (7.9%)	Hyperbilirubinemia: 0%	0/38	No data
NOPHO ALL2008 (NCT00819351)	Henriksen et al, 2015 (66)	PEG-ASP	Grade 3+ Phase not specified PEG-ASP	Grade 3+ allergic reactions to PEG-ASP: • Anaphylaxis: n=9/615 (1.5%; none leading to death) • Allergic reaction: n=36/615 (5.8%)	36/615 (5.85%)	No data	No data	No data	No data
POG 9006	Lauer, 2001 (53)	E. coli-ASP	Grade 3+ at intensification PEG-ASP or no ASP	Regimen B (PEG-ASP) • Allergic reactions 52/238 (22%) Regimen A (no ASP) • Allergic reactions 2/232 (1%)	52/238 (21.85%)	No data	No data	No data	No data
POG 9406	Tower, 2014 (54)	E. coli-ASP	Grade 3+ postinduction PEG-ASP	• Allergy: 119/784 (15.2%)	119/784 (15.2%)	No data	No data	No data	No data
Non-randomised									
MDACC BFM augmented	Rytting et al, 2013 (69)	PEG-ASP	Grade 3 or 4 Phase not specified PEG-ASP	• Allergy (grade 3 only): 17/85 (20%) • Hyperbilirubinemia: 31/85 (36%)	17/85 (20%)	No data	Hyperbilirubinemia: 31/85 (36%)	9/85 (11%)	No data

Study	Citation	ASP at induction	Relevant treatment phase	Selected grade 3/4 AEs	Grade 3+ allergic reactions	Grade 3+ hyperglycemia	Grade 3+ increases in transaminases	Grade 3+ pancreatitis	Grade 3+ thrombosis
				• Elevated ALT: 28/85 (33%) • Pancreatitis: 9/85 (11%)					
CoALL 08-09	Escherich, 2013 (71)	None	Grade 3+ at consolidation PEG-ASP	Clorafabine/ASP • Elevation of transaminases: 19/42 (45%) • Elevation of bilirubin: n=3/42 HIDAC/PEG-ASP: • Elevation of transaminases: 13/61 (21%) • Elevation of bilirubin: n=0	No data	No data	Elevation of transaminases: Clorafabine/PEG-ASP: 19/42 (45%) HIDAC/PEG-ASP: 13/61 (21%) Elevation of bilirubin Clorafabine/PEG-ASP: n=3/42 (7.1%) HIDAC/PEG-ASP: n=0	No data	No data

Abbreviations: AE, adverse event; ASP, asparaginase; DI, delayed intensification; E. coli-ASP; native Escherichia coli-derived asparaginase.
LFT include increase in transaminases, alkaline phosphatase or bilirubin.

4.8.2 *Older adult patients*

The evidence base presented in previous sections supports the use of pegaspargase (generally at a dose of 2,500 IU/m^2 as per SmPC) in children, adolescents, and young adults, with the maximum age of any enrolled population being 40 years of age. The following three studies provide evidence from older populations with ages ranging from 17 up to 71 years of age, supporting the use of pegaspargase in adult patients at the lower dose of 2,000 IU/m^2 as recommended in the SmPC.

Two sequential studies by Douer et al (21, 22), demonstrated that adult patients (up to the age of 57 years), newly diagnosed with ALL, can be treated safely, achieve a long duration of asparagine depletion, and have an excellent chance of achieving remission (96%) when given up to six 2,000 IU/m^2 doses of pegaspargase beginning in induction.

The CALGB 9511 study (23) provided the basis of the treatment protocol developed for the ongoing UK study in adult ALL patients, UKALL14 (see Section 3.6). UKALL14 will be a pivotal study in the adult population, where pegaspargase will be administered to adults for the first time in a large phase 3 setting (12).

4.8.2.1 Douer, 2007

Citation	Douer et al, 2007 (NCT00184041) (21)
Objectives	To assess pharmacodynamics and safety of intravenous PEG-ASP during remission induction in adult patients (<55 years of age) with newly diagnosed ALL
Design details	Interventional, prospective, non-randomised study in the US. Patients were enrolled between 1995 and 1999.
Treatment phases	• Induction (2×phases of 4 weeks each) • Reinduction (6 weeks) • CNS prophylaxis (4 weeks concurrent to 2nd phase of induction when CR achieved after 1st phase, otherwise administered after 2nd phase of induction)
ASP interventions	• Induction: PEG-ASP (2,000 IU/m^2 IV) • Total number of PEG-ASP doses: 1
Key eligibility criteria	Adults (aged 17–55 years) with newly diagnosed ALL
Outcomes assessed	• Response • PEG-ASP pharmacokinetics • Immunogenicity • Toxicity
Patient details	• n=25 • Median age: 27 years (range: 17–55) • Female/male: 9/16 • Median WBC count at diagnosis: 10.3×10^9/L (range: 1.1–389.0) • 21 patients had precursor B-cell ALL, 3 presented with T-cell ALL, 1 patient wasn't determined • Race: Latino (20%), White (2%), Asian (3%)

Key results	After a single IV dose of PEG-ASP administered during induction: • 96% of adult patients achieved complete remission (24/25 patients, 95% CI 80–99.8%) • Complete asparagine depletion was observed in 100% of patients 2 hours after ASP dose, and in 100%, 81%, and 44% on days 14, 21, and 28, respectively, after ASP dose. Mean peak concentration of ASP was 1 IU/mL and mean ASP elimination half-life 7 days • One patient developed anti-asparaginase antibodies on day 22 after the drug was administered. This was associated with immediate disappearance of PEG-ASP enzyme activity and rebound of serum asparagine, but was not associated with any clinical manifestations of hypersensitivity • PEG-ASP was well-tolerated with few grade 3/4 side effects. Allergic reactions or pancreatitis, the most serious potential side-effect, was not observed after a single-dose of PEG-ASP in any patients. The authors state this complication has been reported in 1–4% of >250 adults and children treated in several PEG-ASP clinical trials and in up to 15% of patients treated with native E. coli-derived asparaginase
Conclusion	In adults aged 55 years or younger, PEG-ASP produces a long duration of asparagine depletion, providing a high chance of complete remission (96%) and a safety profile equivalent to E. coli-derived ASP

Abbreviations: ALL, acute lymphoblastic leukaemia; ASP, asparaginase; CNS, central nervous system; CR, complete response; IU, international units; IV, intravenous; PEG-ASP, pegaspargase; US, United States; WBC, white blood cell.

4.8.2.2 Douer, 2014

Citation	Douer et al, 2014 (NCT00184041) (22)
Objectives	To assess pharmacokinetics and safety of intravenous PEG-ASP in adult patients (aged 18–57 years) with newly diagnosed ALL
Design details	Interventional, prospective, non-randomised study in the US. Patients were enrolled between July 2004 and July 2009
Treatment phases	• Induction (2×phases of 4 weeks each) • Intensification 1 (4 weeks) • Consolidation 1 (9 weeks) • Delayed reinduction (6 weeks) • Intensification 2 (4 weeks) • Consolidation 2 (9 weeks) • Delayed reinduction 2 (6 weeks) • Maintenance (24 months) • CNS prophylaxis concurrent to above treatment phases
ASP interventions	• Induction phase 1 and 2: PEG-ASP 2,000 IU/m^2 IV • Intensification 1 and 2: PEG-ASP 2,000 IU/m^2 IV • Delayed reinduction 1 and 2: PEG-ASP 2,000 IU/m^2 IV • Maximum number of PEG-ASP doses: 6
Key eligibility criteria	Adults (aged 18–57 years) with newly diagnosed ALL (excluding T-cell ALL with BM involvement)
Outcomes assessed	• CR

	• Seven-year DFS • Seven-year OS • PEG-ASP pharmacokinetics • Toxicity
Patient details	• n=51 • Median age: 32 years (range: 18–57) • Female/male: 18/31 • Median WBC count at diagnosis: 11.7×10^9/L (range: 0.8–512.0) • 46 patients had precursor B-cell ALL, 5 presented with T-cell ALL, 11 patients were Ph+ • Race: 42 patients of Latino origin (82%)
Key results	In adult patients treated with up to six PEG-ASP doses during induction, intensification and delayed reinduction, with dosing intervals of >4 weeks: • 96% of adult patients achieved complete remission (49/51 patients) with 48 achieving remission after induction phase one • Seven-year DFS and OS were 58% and 51%, respectively • Mean PEG-ASP half-life was 7.1 days (dose one, induction) and 12.1 days (dose four or six, reinduction) • Most common grade 3/4 PEG-ASP-related toxicities were lengthy hyperbilirubinaemia and transaminitis, occasionally resulting in subsequent treatment delays. All toxicities resolved spontaneously • 45% of patients were able to receive all six doses of PEG-ASP, 61% of patients received ≥ three PEG-ASP doses; in only 20% (n=10) of patients, PEG-ASP was discontinued due to toxicity (pancreatitis n=6; allergy n=3)
Conclusion	The authors concluded that the proposed dose and schedule of PEG-ASP, based on its pharmacokinetics and toxicity profile could be applied for safer adaptation of paediatric ALL patient protocols in adults. It should be noted that the dose used (2,000 IU/m^2) is higher than currently used in practice in the UK (1,000 IU/m^2)

Abbreviations: ALL, acute lymphoblastic leukaemia; ASP, asparaginase; BM, bone marrow; CNS, central nervous system; CR, complete response; DFS, disease-free survival; IU, international units; IV, intravenous; OS, overall survival; PEG-ASP, pegaspargase; Ph+, Philadelphia chromosome positive; US, United States; WBC, white blood cell.

4.8.2.3 Wetzler, 2007

Citation	CALGB 9511 (23)
Objectives	To compare OS and DFS among adult ALL patients who did and did not achieve asparagine depletion following treatment with PEG-ASP
Design details	Interventional, prospective, non-randomised study in the US. Patients were enrolled between July 1995 and December 1997
Treatment phases	• Induction (4 weeks) • Intensification (2×4 week cycles) • CNS prophylaxis and interim maintenance (12 weeks) • Late intensification (8 weeks) • Maintenance (until 24 months after diagnosis)
ASP interventions	• Induction: PEG-ASP 2,000 U/m^2 SC (days 5 and 22) • Intensification (first cycle): PEG-ASP 2,000 U/m^2 SC (days 15 and 43) • Maximum number of PEG-ASP doses: 4

Key eligibility criteria	Adults (age range not specified) with untreated ALL or acute undifferentiated leukaemia (excluding Burkitt-type leukaemia)
Outcomes assessed	• CR • OS • DFS • PEG-ASP pharmacokinetics • Anti-PEG-ASP antibodies • Asparagine depletion

Patient details	• n=104 (samples available from 85 patients)
	• Median age:
	  ○ Depleted group: 32 years (range: 17–70)
	  ○ Non-depleted group: 48 years (range: 22–71)
	• Median WBC count:
	  ○ Depleted group: 7.7×10^9/L (range: 1.0–393.0)
	  ○ Non-depleted group: 8.4×10^9/L (range: 1.0–131.1)
	• B-cell immunophenotype:
	  ○ Depleted group: 34 (68%)
	  ○ Non-depleted group: 16 (32%)
	• T-cell immunophenotype:
	  ○ Depleted group: 11 (92%)
	  ○ Non-depleted group: 1 (8%)

Key results	In adult patients treated with up to four PEG-ASP doses during induction and intensification, with dosing intervals of 17 days in induction and 28 days in intensification: • Patients who did not achieve asparagine depletion had inferior OS compared with those who did (HR 2.37 [95% CI 1.38–4.09]; p=0.002) and inferior DFS (HR 2.21 [95% CI 1.19–4.13]; p=0.012) • After adjusting for age, performance status, WBC count, and karyotype in a proportional hazards model, both the OS and DFS HRs decreased to 1.8 ([95% CI 1.0–3.2]; p=0.056, and 1.8 ([95% CI 0.9–3.6]; p=0.084, respectively) • Anti-PEG-ASP antibodies were detected in 31.8% of patients who did not achieve asparaginase depletion compared with 9.5% of those who did (p=0.012)
Conclusion	This study demonstrated that effective asparagine depletion with PEG-ASP in adults with ALL is feasible as part of an intensive multi-agent therapeutic regimen and asparagine depletion appears associated with improved outcomes

Abbreviations: ALL, acute lymphoblastic leukaemia; CI, confidence interval; CNS, central nervous system; CR, complete response; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; PEG-ASP, pegaspargase; SC, subcutaneous; U, units; WBC, white blood cell.

4.9 *Subgroup analysis*

Not applicable

4.10 *Meta-analysis*

[redacted]

4.10.1 *Studies providing additional evidence (non-pegaspargase studies)*

4.10.1.1 Study design/patient population

Table 30: Study design/patient population: Studies with native E. coli and/or Erwinase asparaginase data

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
Randomised							
AL841	Matsuzaki 1999 (72)	Japan Enrolled: Oct 1984-July 1990	To demonstrate that the protocol AL841 provides good long-term disease control without severe late cardiac dysfunction	- Interventional - Prospective - Randomised: Randomisation at maintenance (1:1) to weekly E. coli-ASP vs no ASP - Multicentre	Standard-risk untreated ALL pediatric patients	SR	Cardiac function to assess cardiac toxicity of daunorubicin
ALL-BFM 90	Schrappe 2000 (73)	Germany, Austria and Switzerland Enrolment: Apr 1990-Mar 1995	To improve outcome in patients with childhood ALL by using a reduced treatment regimen	- Interventional - Prospective - Randomised (only IR group after induction phase) - Multicentre	Children and adolescents (up to 18 years old) with ALL (all risk groups)	SR IR HR	EFS
DCOG ALL-10	Pieters 2008 (74)	Netherlands Jan 2005-Oct 2006	To determine the ratio of the population geometric means of the 72-hour serum concentration vs time curves (AUC) for the first administration of E. coli-ASP and Medac ASP	- Interventional - Prospective - Randomised: 1:1 (randomised to E. coli-ASP or to Medac-ASP at induction) - No multicentre - Phase II - Double blind	Previously untreated ALL		Area under the curve (AUC) of ASP in serum after the first dose
DFCI ALL 00-01	Vrooman 2013 (75)	Not specified Enrolment: 2000-2004	To assess the toxicity and efficacy of dexamethasone and a novel dosing method of E. coli-ASP in children and adolescents with newly diagnosed ALL	- Interventional - Prospective - Randomised: Patients who achieved CR were eligible to 2 randomisations: To dexamethasone or prednisone at intensification and continuation; To fixed dose vs individualised dose of E. coli ASP at intensification	Children and adolescents with newly diagnosed ALL	SR HR	Not specified
DFCI ALL 85-01	Silverman 2010 (20)	US 1985–2000	The article summarises DFCI ALL clinical trials conducted between 1985 and 2000. The protocols in these studies aimed at improving survival rates while minimising acute	- Interventional - Prospective - Randomised: to two different E. coli-ASP doses at investigational window	Newly diagnosed ALL	SR HR VHR	Not specified

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
			and late toxicities	- Multicentre			
DFCI ALL 95-01	Moghrabi 2007 (9) Silverman 2010 (20)	US, Canada Enrolment: Jan 1996-Sept 2000	To reduce therapy-related morbidity without compromising efficacy	- Interventional - Prospective - Randomised: to E. coli-ASP or Erwinia at induction - Multicentre	Children (aged 0-18 years) with newly diagnosed ALL (excluding mature B-cell ALL)	SR HR	Not specified
EORTC CLG 58831, 58832, 58881	Vilmer 2000 (76)	France, Belgium, Portugal 58831/58832: enrolment 1983-1989	58831 (1983-1989): to assess cyclophosphamide in SR patients 58832 (1989-1998): to assess omission of CNS radiotherapy plus methotrexate IV high dose 58881 (1990-1993): to assess the toxicity and efficacy of E. coli-ASP and Erwinia when given at equal dosage & to assess the value of high doses of cytarabine with high doses of methotrexate during the interval therapy, & to assess the advantage of adding Iv 6-mercaptopurin to conventional maintenance therapy	- Interventional: The manuscript reports on 3 randomised trials, but only 58881 trial has ASP results - Prospective - Randomised: Randomisation differed across the 3 studies - Multicentre	Children with ALL under 18 years of age	58831: SR 58832: IR & HR 58881: SR, IR, HR	EFS
EORTC-CLG 58881	Duval 2002 (24)	Belgium, France and Portugal Enrolment: Nov 1990-Oct 1993	Compare toxicity and safety of E. coli-ASP and Erwinia	- Interventional - Prospective - Randomised: Randomisation was done centrally and stratified according to: centre; disease (leukemia versus lymphoma); risk factor ("smaller than" 0.8, 0.8-1.19, "bigger than or equal to" 1.2), and immunophenotype (B versus T lineage) for leukemia patients; and by Murphy stage (stage I-II versus III-IV) for lymphoma patients. Randomisation was not stratified by the presence of t(9;22). Subsequent randomisations were stratified according to treatment arm and initial risk factor or Murphy stage. - Multicentre - Phase III	Children (aged 0-18 years) with acute lymphoblastic leukemia or lymphoblastic lymphoma	SR HR VHR	EFS
GMALL 05/93	Gökbuget, 2013 (68)	Germany Start date April 1993	To assess efficacy and safety of pediatric derived protocol GMALL 05/93 and 07/03	- Interventional - Prospective	Adolescents and Young Adults (AYAs) aged 15-	Not specified	Not specified

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
				- Randomised - Multicentre - Open-label	35 years with ALL		
MB-91 vs BFM 90M protocols	Karachunskiy 2008 (77)	Russia Randomisation Aug 1995-April 2002	To compare the new protocol AL-MB91 with respect to survival as well as toxicity and cost indicators against the control protocol ALL-BFM 90M	- Interventional - Prospective - Randomised: Patients were randomised to be treated according to either protocol ALL-MB 91 or protocol ALL-BFM 90m - Multicentre - Masking unclear although it is stated that randomisation was in a blinded fashion	Newly diagnosed precursor B- or T cell ALL, up to 18 years of age	SR IR HR	EFS OS
POG 8602	Harris 2000 (78)	Not specified May 1987-Jan 1991	To investigate the effectiveness of antimetabolite-based intensification regimens in the treatment of patients with standard prognosis or poor prognosis B-precursor ALL. To compare the EFS of children with pre-B or early pre-B ALL treated with intensification regimens that used IDMTX alone or in combination with ASP or AraC and to analyse the toxicity of these anti-metabolite-based intensification regimens	- Interventional - Prospective - Randomised: Randomisation based on risk level: SR early pre-B: regimen A vs B vs C vs D; Poor prognosis early pre-B: B vs C vs D; Pre-B: B vs C - Multicentre	Children with early pre-B and pre-B ALL	SR	CCR stratified for risk group and phenotype
	Wacker 2007 (25)	Not specified Enrolment: Feb 1986-Jan 1991	To describe the outcomes of a large cohort of children with B-precursor ALL, treated with intensive ASP during consolidation, who switched from E. coli to Erwinia due to a clinical allergic reaction to E. coli ASP	-	Newly diagnosed children 1 to 21 years of age with B-precursor ALL	SR (regimen A) HR (regimen B)	Not specified
POG 8704	Amylon 1999 (79)	Not specified May 1987-Jan 1992	To test the hypothesis that high-dose ASP consolidation therapy improves survival in pediatric patients with T cell ALL and advanced stage lymphoblastic lymphoma	- Interventional - Prospective - Randomised: Randomised to E. coli-ASP or no ASP at consolidation	Patients younger than 21 years with T cell ALL and patients with advanced stage lymphoblastic lymphoma	Not specified	Duration of CCR

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
St Jude Study XI	Yetgin 2003 (80)	Location not stated (Authors from Turkey)	To verify whether HDMP was more effective on blast reduction rate than conventional dose steroid therapy	- Interventional - Initial study was prospective but the manuscript conducts a retrospective assessment - Randomised: Randomisation: standard (group A) or high dose (group B) steroids • Groups A1 & B1: full chemotherapy including 3 doses of ASP • Group A2 & B2: limited chemotherapy and no ASP • Group A3 & B3: only steroid monotherapy Given the timing of the study we assume E. coli-ASP - Multicentre	Newly diagnosed ALL children who had shown remission in the St Jude study	SR HR	Not specified
TCCSG L99-15	Kato 2014 (81)	Not specified April 1999-june 2003	To investigate effectiveness of experimental early intensification with HD-AraC/ASP for children with IR ALL	- Interventional - Prospective - Randomised: At intensification IR patients were randomised to no ASP (standard intensification) or E. coli ASP (experimental intensification - Multicentre	Pediatric ALL but the article only provides data for intermediate-risk patients	IR	Not specified
TPOG-ALL-97 and TPOG-ALL-2002	Liang 2010 (82)	Taiwan 1997-2007	To assess long-term outcome of 1390 children with ALL, treated in two successive clinical trials	- Interventional - Prospective - Randomised: • TPOG-ALL-97 (SR only): to E. coli-ASP or epidoxorubicin (epirubicin as the 3rd drug during remission induction therapy - Multicentre	Children with ALL	SR HR VHR	EFS
Non-randomised							
AIEOP-ALL-87	Paolucci 2001 (83)	Not specified Enrolment: 1987-1991	To evaluate: a) the efficacy of treatment intensification with a fourth drug (daunomycin) in the induction phase and a 3 drug reinduction phase to all risk groups b) the impact of the addition of three doses of intrathecal methotrexate during cranial radiotherapy and extended exposure to weekly high-	- Interventional - Prospective - Not randomised: single arm - Multicentre	Children (age 1 to ≤16 years) with non-B-cell ALL	SR IR HR	Not specified

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
			dose ASP during late intensification in high risk patients				
COG P9906	Bowman 2011 (52)	Not specified Recruitment: Mar 2000-Apr 2003	To test the administration of a modified ABFM regimen in a subgroup of patients with B-precursor ALL at particularly high risk of treatment failure. A further objective of this study was to investigate the prognostic significance of MRD	- Interventional - Prospective - Not randomised - Multicentre	Patients with B precursor ALL	HR	CCR
Jude Study XI (modified)	Treepongkaruna 2009 (84)	Thailand Reviewed registry data from 2000-2006	To determine the incidence, risk factors, clinical data, outcome, and mortality of AP in children with ALL	- Cohort study with a nested case-control study - Retrospective - Not randomised - No multicentre	Paediatric patients with ALL and acute pancreatitis. The control group were without pancreatitis	LR SR HR	Incidence of acute pancreatitis

Abbreviations: ABFM, augmented Berlin-Frankfurt-Münster; ALL, acute lymphoblastic leukemia; AP, acute pancreatitis; ara-C, cytosine arabinoside; ASP, asparaginase; AUC, area under the curve; AYA, adolescents and young adults; BFM, Berlin-Frankfurt-Münster; Carba, Calaspargase pegol Escherichia coli asparaginase; C-MTX, Capizzi methotrexate; CCR, continuous complete remission; CR, complete remission; CVAD, cyclophosphamide, vincristine, adriamycin, and dexamethasone; DEX, dexamethasone; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; EFS , event-free survival; HD-MTX, High-dose methotrexate; HR SCT, high risk stem cell transplant; HR, high risk; HR-ALL, acute lymphoblastic leukemia; HR-chemo, high risk chemotherapy; IC, intensified consolidation; IM, intensified maintenance; IM, intramuscular; IR, intermediate risk; IV, intravenous; LR, low risk; MP, mercaptopurine; MRD, minimal residual disease; MTX/MP, methotrexate/mercaptopurine; NSAA, nadir serum asparaginase activity; OS, overall survival; PEG-ASP, pegaspargase; PK, pharmacokinetics; PRED, prednisone; RER, rapid early responders; SAA, Serum asparaginase activity; SC, standard consolidation; SER, slow early responders; SR, standard risk; SR-Av, standard risk average; US, United States; VHR, very high risk; WBC, white blood cells.

4.10.1.2 Exposure to asparaginase

Table 31: Exposure to asparaginase: Studies with native E. coli and/or Erwinia asparaginase data

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
Randomised						
AL841	Matsuzaki 1999 (72)	- Induction - Consolidation - Reinduction - Maintenance	Randomisation at maintenance - Induction: E. coli-ASP (all) - Consolidation: no ASP (all) - Reinduction: no ASP (all) - Maintenance: E. coli-ASP vs. no ASP (R)	E. coli-ASP	Induction: 10,000 u/m^2/d Maintenance: 32 doses in total; 10,000 u/m^2 q wk x 16 (regimen B)	IM
ALL-BFM 90	Schrappe 2000 (73)	- Induction - Consolidation - Reinduction - Intensive reconsolidation	SR - Induction (protocol IA and IB): ASP (all) - Consolidation (protocol M): no ASP (all) - Reinduction (protocol II): ASP (all) - Maintenance: no ASP IR - Induction (protocol IA and IB): ASP (all) - Consolidation (protocol M/M-A): ASP vs no ASP (R) - Reinduction (protocol II): ASP (all) - Maintenance: no ASP HR - Induction (protocol IA only): ASP (all) - Intensive consolidation (Elements HR1, or HR2 or HR3): ASP - Maintenance: not specified	E. coli-ASP or Erwinia E. coli-ASP became unavailable during the study; patients were switched to Erwinia	•Induction: 10,000 E/m^2/d •Consolidation: 25,000 E/m^2 at day •Reinduction: 10,000 E/m^2/d •Intensive reconsolidation: 25,000 E/m^2 at day	IV and IM
DCOG ALL-10	Pieters 2008 (74)	- Induction - Consolidation - Reinduction - Maintenance	- Induction: recombinant E. coli-ASP vs Medac-ASP (R) - Consolidation: not specified - Reinduction: not specified - Maintenance: not specified	E. coli-ASP Medac-ASP	5000 U/m^2	IV
DFCI ALL 00-01	Vrooman 2013 (75)	- Induction - CNS therapy - Intensification	- induction: E. coli-ASP (all) - CNS therapy: no ASP - intensification: E. coli-ASP fixed dose vs. E. coli-ASP	E. coli-ASP	When fixed dose: 25,000 IU/m^2	IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
		- Continuation	individualised dosing (R) - Continuation: no ASP			
DFCI ALL 85-01	Silverman 2010 (20)	- Remission Induction - CNS-directed treatment - Intensification - Continuation	85-01 - Induction: E. coli-ASP 1 dose (all) - CNS therapy: none - Intensification: E. coli-ASP (all) - Continuation: no ASP	E. coli-ASP	E. coli: 25,000 IU/m^2/week	IM
DFCI ALL 95-01	Moghrabi 2007 (9) Silverman 2010 (20)	- Induction (4 wk) - CNS therapy (3 wk) - Intensification (30 wk) - Continuation (until Month 24)	- Induction: E. coli-ASP vs Erwinia (R) - CNS prevention - Intensification: E. coli-ASP vs Erwinia - Continuation: no ASP (all) In addition to ASP randomisation: - CNS randomisation - Intensification with/without dexrazoxane for HR	- E. coli-ASP - Erwinia	- E. coli-ASP & Erwinia: 25,000 IU/m^2	IM
EORTC CLG 58831, 58832, 58881	Vilmer 2000 (76)	**58831/58832/58881** induction consolidation reinduction maintenance	Protocol 58831/58832 - Induction: E. coli-ASP (all) - Consolidation: E. coli-ASP (all) - Reinduction: E. coli-ASP (all) - Maintenance: no ASP (all) Protocol 58881: - As above but E. coli-ASP vs Erwinia	- 58831/58832: E. coli-ASP - 58881: E. coli-ASP vs Erwinia	- 5883/5883: 5,000 IU/m^2/d - 58881: 10,000 IU/m^2/d	IV
EORTC-CLG 58881	Duval 2002 (24)	- Induction (wk 1-5) - Consolidation (wk 5-9) - Reinduction (wk 1-7) - Maintenance (until Month 24)	- Induction: E. coli-ASP vs. Erwinia (R) - Consolidation: no ASP (all) - Reinduction: E. coli-ASP vs. Erwinia - Maintenance: not specified	- Erwinia - E. coli-ASP	10,000 IU twice weekly	IV
GMALL 05/93	Gökbuget, 2013 (68)	- Induction - Consolidation - Maintenance: intensified or conventional maintenance	GMALL 05/93: - Induction: E. coli-ASP - Maintenance: Intensified or conventional maintenance phase (R) - treatment not further specified	- GMALL 05/93: E. coli-ASP - GMALL 07/03: PEG-ASP		Not specified

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
MB-91 vs BFM 90M protocols	Karachunskiy 2008 (77)	- Induction - Consolidation - Reinduction - Maintenance	**ALL-MB 91 (SR & HR)** - Induction : E. coli-ASP - Consolidation I : E. coli-ASP - Consolidation II : E. coli-ASP - Consolidation III : E. coli-ASP - Maintenance : no ASP **ALL-BFM 90m (SR, IR, HR)** - Induction : E. coli-ASP - Consolidation I : No ASP - Consolidation II : No ASP - Consolidation III : E. coli-ASP - Maintenance : no ASP	E. coli-ASP	10,000 U/m^2	- ALL-MB91: IM - ALL-BFM 90m: IV
POG 8602	Harris 2000 (78)	- Induction - Consolidation - Intensification - Maintenance	- Induction: E. coli-ASP - Consolidation: E. coli-ASP (regimen B) vs cytarabine (no ASP; regimen C)(R) - Intensification: no ASP - Maintenance therapy: no ASP	E. coli-ASP	- Induction: 6,000 U/m^2 - Intensification: 25,000 U/m^2	IM
	Wacker 2007 (25)	- Induction - Consolidation - Maintenance	- Induction: E. coli-ASP (all) - Consolidation: No ASP (regimen A) vs E. coli-ASP (regimen B) vs cytarabine (regimen C) vs intermediate-dose methotrexate plus cytarabine (regimen D) (R) - Maintenance: no ASP (all)	E. coli-ASP (if allergy then Erwinia at the same dose and schedule)	- Induction: 6,000 U/m^2 - Consolidation: 25,000 U/m^2 weekly	IM
POG 8704	Amylon 1999 (79)	- Induction - Consolidation - Maintenance - CNS prophylaxis	- Induction: E. coli-ASP (all) - Consolidation: E. coli-ASP vs no ASP (R) - Maintenance: 3 different protocols with and without E. coli-ASP - CNS prophylaxis: no ASP	E. coli-ASP (Elspar)	- 25,000 IU/m^2 given weekly	IM
St Jude Study XI	Yetgin 2003 (80)	Induction – other phases not detailed	R: standard (group A) or high dose (group B) steroids - Groups A1 & B1: full chemotherapy including 3 doses of ASP - Group A2 & B2: limited chemotherapy and no L-SP - Group A3 & B3: only steroid monotherapy	Assumed to be E. coli-ASP	200 U/kg at days 3, 4, 6, 8, 10, 12, (15, 17, 19)	IV or IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
			Given the timing of the study we assume E. coli-ASP			
TCCSG L99-15	Kato 2014 (81)	- Induction - Intensification 1 - Intensification 2 - Reinduction - Maintenance	- Induction: E-Coli (all) - Intensification 1: E. coli-ASP vs no ASP (R) - Intensification 2: no ASP (all) - Reinduction: E. coli-ASP (all) - Maintenance: no ASP (all)	E. coli-ASP	Not specified	Not specified
TPOG-ALL-97 and TPOG-ALL-2002	Liang 2010 (82)	**TPOG-1997** - Induction (10 weeks) - Consolidation (8 weeks) - Reinduction (7 weeks) - Maintenance (17 weeks) **TPOG-2002** - Induction (5 weeks) - Consolidation (8 weeks) - Reinduction (3 weeks) - Maintenance (120 weeks girls/146 weeks boys)	- Induction: • TPOG-97: E. coli-ASP vs. No (SR - R) & E. coli-ASP (all HR) • TPOG-2002: None (SR) & E. coli-ASP (HR) - Consolidation: no ASP (all) - Reinduction: E. coli-ASP vs epirubicin (R) - Maintenance: not specified	E. coli-ASP	- TPOG-200 : 5,000 IU/m^2 - TPOG-97: 10,000 IU/m^2	- IM
Non-randomised						
AIEOP-ALL-87	Paolucci 2001 (83)	- Induction - Consolidation - Reinduction - Continuation	- Induction: E. coli-ASP (all) - Consolidation: no ASP (all) - Reinduction: No ASP (SR/IR) & E. coli-ASP (HR) - Maintenance: not specified	E. coli-ASP	Induction: 6,000 IU/m^2 Reinduction & continuation: 25,000 mg/m^2	Not specified
COG P9906	Bowman 2011 (52)	- Induction - Consolidation - Interim maintenance - Delayed intensification	- Induction: E. coli-ASP (all) - consolidation: E. coli-ASP (all) - interim maintenance: E. coli-ASP (all) - delayed intensification: E. coli-ASP (all)	E. coli-ASP	- Induction: 10,000 IU/m2 - Consolidation & interim maintenance: 6,000 IU/m2	IM
Jude Study XI (modified)	Treepongkaruna 2009 (84)	- Remission induction - Consolidation - Continuation I - Reinduction - Continuation II	SR/HR - Induction: E. coli-ASP (all) - Consolidation: No ASP - Continuation I: E. coli-ASP - Reinduction I: E. coli-ASP	E. coli-ASP	- 10,000 U/m2 - 25,000 U/m2	Not specified

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
		- Reinduction II - Maintenance	- Continuation II: E. coli-ASP - Reinduction II: E. coli-ASP - Maintenance: No ASP Low risk - Induction: E. coli-ASP (all) - Consolidation: None - Continuation I: None - Reinduction I: E. coli-ASP - Continuation II: None - Reinduction II: E. coli-ASP - Maintenance: No ASP			

Abbreviations: ASP, asparaginase; Carba, Calaspargase pegol Escherichia coli asparaginase; DI, delayed intensification; E. coli-ASP, native Escherichia Coli-derived asparaginase; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; MRD, minimal residual disease; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.

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4.12 *Non-randomised and non-controlled evidence*

For simplicity relevant non-randomised studies providing pegaspargase data are listed in Section 4.1.2, described in Section 4.8. Data from non-randomised studies is also included in meta-analysis described in Section 4.10.

4.13 *Adverse reactions*

4.13.1 *Studies reported in section 4.2*

4.13.1.1 CCG-1962

CCG-1962 was a multicentre, randomised, open-label Phase III study, designed to assess the efficacy and safety of native versus pegaspargase as part of induction and two delayed intensification chemotherapy phases in the treatment of children newly diagnosed with standard-risk ALL.

Patients were randomly assigned to receive asparaginase as either native enzyme (n=59; 6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase) or pegylated enzyme (n=59; 2,500 IU/m^2 IM on day 3 of induction and each DI phase). The methodology of CCG-1962 is described in Sections 4.3.

Grade 3/4 events

Grade 3 and grade 4 toxic events during the asparaginase-containing phases of chemotherapy are summarised in Table 32. There were no toxicity-related deaths in either group. Incidence and type of toxic events were very similar between the pegaspargase and native asparaginase arms. Two patients in each arm experienced CNS thrombosis: three on days 14 to 16 of induction and one on day 22 of DI-1. Patients who developed CNS thrombosis received no further asparaginase. Other CNS complications included seizures (three patients), tremors after cytarabine therapy (one patient), hemiparesis (two patients), mood disorder requiring psychiatric intervention (one patient), motor weakness after intrathecal methotrexate (one patient), and moderate sensory nerve dysfunction (one patient). Pancreatitis occurred in one patient in each treatment arm during induction therapy. Three patients in each arm experienced hyperglycaemia. In the pegaspargase arm, there were two acute allergic reactions to asparaginase during DI-1. One patient had a grade 1 allergic reaction and another grade 3 hives.

Table 32: Patients experiencing grade 3/4 toxicity during asparaginase-containing treatment courses

Adverse event, number of patients	Pegaspargase			Native E. coli asparaginase		
	IND	DI-1	DI-2	IND	DI-1	DI-2
Assessable patients	59	54	48	59	53	53
CNS thrombosis	1	1	-	2	-	-
Other CNS complications†	-	3	3	-	2	2
Life-threatening infections‡	-	1	1	-	-	1
Bacteraemia	1	6	10	6	2	9
Hyperglycaemia	3	-	-	1	1	1
Coagulopathy§	1	-	-	3	-	-
Nausea/vomiting	-	-	-	2	1	-
Abdominal pain	-	-	3	-	-	1
Abnormal LFT¶	-	-	-	-	2	2
Pancreatitis	1	-	2	1	-	-
Mucositis	-	-	1	-	-	-
Gastric ulcer	-	-	1	-	-	-
Haemorrhagic cystitis	-	-	-	-	1	-
Constipation	-	-	1	-	-	-
Diarrhoea	-	-	1	-	-	-
Allergy to asparaginase	-	1	-	-	-	-

Abbreviations: IND, induction; DI, delayed intensification; CNS, central nervous system; LFT, liver function tests.
† Including seizures, tremors, facial palsy, hemiparesis, peripheral neuropathy, and motor weakness.
‡ Septic shock including hypotension and/or requiring intubation.
§ Prolonged partial thromboplastin time or hypofibrinogenemia.
¶ Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase greater than 1.5 times the normal value, or total bilirubin greater than 1.5 times the normal value.

Infectious events

Infectious events were the most common toxic events (Table 33). Bacteraemia was most frequent, with 17 episodes in each arm during induction and the DI courses. Life-threatening infections (defined as septic shock with hypotension or requiring intubation) occurred in two instances in the pegaspargase arm, and one in the native arm. No case of invasive fungal disease was reported.

Table 33: Infectious events during all three asparaginase-containing courses

Events, number of patients (%)	Pegaspargase N=59	Native E. coli asparaginase N=59
Bacteraemia	17 (29)	17 (29)
Life-threatening sepsis	2 (3)	1 (2)
Pneumonia	2 (3)	2 (3)
Varicella zoster virus	5 (8)	1 (2)
Urinary tract infection	0 (0)	3 (5)
Cellulitis/skin infection	2 (3)	1 (2)
Clostridium difficile	3 (5)	2 (3)
Pneumocystis	0 (0)	1 (2)
Fungal stomatitis	0 (0)	1 (2)
Herpes simplex	0 (0)	1 (2)

4.13.1.2 UKALL 2003

UKALL 2003 was an open-label, multicentre study which enrolled 3,207 children and young adults (aged 1–24 years) with ALL, accounting for 88% of all eligible patients aged 1–24 years in the UK and Ireland, between 2003 and 2011 (93). The study assessed the impact of adjusting treatment intensity according to MRD risk stratification. All patients received treatment with pegaspargase (1,000 IU/m^2 IM per dose, 4–12 doses) as part of one of three possible escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. In addition, MRD low-risk patients were randomised to receive either standard treatment (two DI cycles; n=261) or reduced treatment (only one DI cycle; n=260). Similarly, MRD high-risk patients were randomised to receive either standard treatment (n=266) or augmented treatment (n=267).

Details of the methodology of UKALL 2003 are reported in Section 4.3.

Adverse events observed in UKALL 2003 are summarised in Table 34. Clinical high-risk patients experienced more toxic effects (hypersensitivity and pancreatitis) than standard-risk and intermediate-risk patients due to the higher cumulative doses of asparaginase received.

Table 34: Number of patients experiencing specific toxic effects by clinical risk groups

	Total (n=3126)	Clinical standard risk (n=1548)	Clinical intermediate risk (n=909)	Clinical high risk (n=669)	p-value for standard risk vs intermediate risk	p-value for standard/ intermediate risk vs high risk
Any SAE	1101 (35%)	369 (24%)	434 (48%)	298 (45%)	<0.0001	<0.0001
Any infection	490 (16%)	191 (12%)	192 (21%)	107 (16%)	<0.0001	0.80
Fungal infection	110 (4%)	35 (2%)	51 (6%)	24 (3%)	<0.0001	0.91
Seizure	135 (4%)	38 (2%)	46 (5%)	51 (8%)	0.001	<0.0001
Other encephalopathy	110 (4%)	21 (1%)	64 (7%)	25 (4%)	<0.0001	0.73
Asparaginase hypersensitivity	54 (2%)	3 (<1%)	8 (1%)	43 (6%)	0.11	<0.0001
Pancreatitis	50 (2%)	10 (1%)	18 (2%)	22 (3%)	0.003	<0.0001
Avascular necrosis	115 (4%)	8 (1%)	80 (9%)	27 (4%)	<0.0001	0.58
Any thrombosis	85 (3%)	27 (2%)	37 (4%)	21 (3%)	0.0005	0.45
CNS thrombosis	50 (2%)	17 (1%)	22 (2%)	11 (2%)	0.01	0.92
Colitis	47 (2%)	22 (1%)	17 (2%)	8 (1%)	0.39	0.46
Vincristine neurotoxicity	65 (2%)	26 (2%)	22 (2%)	17 (3%)	0.20	0.35
SIADH	11 (<1%)	3 (<1%)	4 (<1%)	4 (1%)	0.227	0.23
Mucositis	41 (1%)	6 (<1%)	8 (1%)	27 (4%)	0.12	<0.0001
Other SAE	280 (9%)	82 (5%)	123 (14%)	75 (11%)	<0.0001	0.02

Abbreviation: CNS, central nervous system; SAE, serious adverse event; SIADH; syndrome of inappropriate antidiuretic hormone secretion.

MRD low-risk

There was no statistically significant difference in the numbers of deaths in remission, serious adverse events (SAEs), and grade 3 or 4 toxic effects in patients on reduced treatment and those on standard treatment (one DI cycle [total three ASP doses] vs. two DI cycles [total four ASP doses]; Table 35).

Table 35: Toxic effects in MRD low-risk patients who underwent randomisation

	One delayed intensification (n=260)	Two delayed intensifications (n=261)	Relative risk for group given two delayed intensifications (95% CI)	Two-sided p-value
Grade 3/4 toxic effect†	189 (73%)	200 (77%)	1.05 (0.95–1.16)	0.30
SAE	70 (27%)	82 (31%)	1.17 (0.89–1.53)	0.26
Cumulative toxicity‡	195 (75%)	204 (78%)	1.04 (0.95–1.15)	0.39

Abbreviation: MRD; minimal residual disease; SAE, serious adverse event.
†Measured with Common Terminology Criteria for Adverse Events. ‡Defined as remission death, grade 3–4 toxic effect, or serious adverse event.

High-risk MRD

Statistically significantly more patients in the augmented therapy group than in the standard therapy group experienced at least one SAE (119/267 [45%] vs 91/266 [34%]; p=0·02) (Table 36). The difference was mostly due to events related to asparaginase (hypersensitivity and pancreatitis) and intravenous methotrexate (mucositis and stomatitis).

Dose reductions during post-remission therapy (below 90% of doses mandated by the protocol) were also more common with regimen A than with regimens B and C. Five patients switched from regimen C to the standard regimen due to toxicity (specifically one prolonged neutropenia, one neurotoxicity, two Capizzi methotrexate-related mucositis and one unknown event).

Table 36: Toxicity by treatment group for high-risk MRD patients

	Standard therapy group (n=266)	Augmented therapy group (n=267)	p-value for augmented vs standard therapy
SAEs			
Any SAE	91 (34%)	119 (45%)	0.02
Infection	44 (17%)	43 (16%)	0.91
Encephalopathy	20 (8%)	33 (12%)	0.06
Asparaginase hypersensitivity	2 (<1%)	18 (7%)	0.0003
Pancreatitis	1 (<1%)	8 (3%)	0.04
Avascular necrosis	16 (6%)	13 (5%)	0.57
Thrombosis	8 (3%)	10 (4%)	0.81
Neuropathy	6 (2%)	6 (2%)	1.00
Mucositis	3 (1%)	11 (4%)	0.05
CTCAE grade 3 or 4 AE			
Any AE	223 (84%)	229 (86%)	0.55
Infection	129 (49%)	115 (43%)	0.22
Haemorrhage	4 (2%)	4 (2%)	1.00

	Standard therapy group (n=266)	Augmented therapy group (n=267)	p-value for augmented vs standard therapy
Thrombosis	8 (3%)	9 (3%)	1.00
Mood	14 (5%)	6 (2%)	0.07
Stomatitis	12 (5%)	48 (18%)	<0.0001
Constipation	3 (1%)	4 (2%)	1.00
Vomiting	9 (3%)	20 (8%)	0.05

Abbreviation: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

4.13.2 *Safety overview*

Based on available safety data submitted to the EMA for marketing authorisation (EPAR, Appendix 1), it was concluded that the treatment of ALL patients with pegaspargase at doses of 2,000 to 2,500 IU/m^2 is considered to be well tolerated and the toxicities manageable, as per the recommendations stated in the SmPC and the risk minimisation measures in the Risk Management Plan.

The adverse effects observed with pegaspargase are consistent with those expected of an asparaginase and the EMA concluded that the safety of pegaspargase does not differ dramatically from native E. coli asparaginase. Overall, the most common adverse reactions of Grade 2 or higher (≥20%) observed with pegaspargase doses of 2,000–2,500 IU/m^2 are hypersensitivity including anaphylactic reaction, febrile neutropenia, anaemia, hyperglycaemia, platelet count decreased, neutrophil count decreased and blood bilirubin increased.

In UK clinical practice pegaspargase has been used for over a decade at a reduced dose of 1,000 IU/m^2 in the UKALLL 2003 protocol (2, 4), and subsequently in ongoing protocols in children, adolescents, and young adults, and adults in UKALL 2011 (3) and UKALL14 (12), respectively. Data from >3,000 patients in UKALL 2003 support the overall observations of the EMA, with the authors concluding that the toxic effects attributable to pegaspargase were similar to or lower than those they have seen reported in the literature with the native form.

A key concern with the use of asparaginase is the development of antibodies to the enzyme that can result in hypersensitivity reactions which would necessitate a switch to an alternative asparaginase formulation. The SmPC for Oncaspar® states that hypersensitivity reactions of Grade 2 or higher are seen in ≥20% of patients treated with pegaspargase. This rate appears high but should be interpreted in the context that SmPC data was based on patients treated with the recommended dose of 2,000 to 2,500 IU/m^2 and includes some patients treated with 2nd line pegaspargase following hypersensitivity to native E. coli enzyme, a scenario known to increase the risk of hypersensitivity to pegaspargase (53-55).

In contrast, and of more relevance to UK clinical practice, when used in >3,000 patients in UKALL 2003 at the reduced dose of 1,000 IU/m^2 hypersensitivity reactions were experienced by only 2% of patients across the entire study treated with between 4 and 12 doses of pegaspargase (n=54/3,126).

Vora et al, in their publication of the UKALL 2003 protocol suggest that hypersensitivity rates of 20-40% are to be expected for native E. coli-derived asparaginase (2). Rates of hypersensitivity reported across studies identified by systematic review are variable and range from 0–13% for native E. coli asparaginase (see Table 29 and Appendix 4), compared with 0–8% for pegaspargase (Table 29), and in some cases no difference between the two preparations (CCG-1962 (11) and DFCI-91-01 (59)). However, these rates reflect only hypersensitivity of Grade 3 or higher, and when milder allergic reactions are also considered, significantly higher rates are observed with the native E. coli enzyme (p=0.02; DFCI-91-01 (59)). In additional studies of native E. coli enzyme Bowman et al report 13% Grade 3 or higher hypersensitivity, but 25% incidence of any grade hypersensitivity (COG P9906 (52)), while Wacker et al report 8% Grade 4 hypersensitivity, but 76% incidence of hypersensitivity leading to a switch in asparaginase formulation (POG 8602 (25)). Vrooman et al (DFCI 00-01 (86)) report 20% of patients developing hypersensitivity that required a switch to Erwinia-derived asparaginase.

Limited data was identified in the systematic review for Erwinia-derived asparaginase as a 1st line asparaginase and none comparing with pegaspargase; Moghrabi et al report that when used 1st line 6% of Erwinia treated patients develop hypersensitivity although at a lower dose than used effectively in clinical practice today (9), but broadly consistent with the SmPC for Erwinia that reports hypersensitivity in the 1–10% range (10). In UK clinical practice, Erwinase is used following hypersensitivity to pegaspargase (2-4, 12).

4.14 *Interpretation of clinical effectiveness and safety evidence*

4.14.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Asparaginase is acknowledged as a fundamental component of treatment regimens for ALL (15). Whereas historically native E. coli-derived asparaginase was used, this form of asparaginase is highly immunogenic, frequently eliciting in patients treatment-limiting hypersensitivity reactions. Pegylation of asparaginase reduces the immunogenicity of the enzyme and therefore the risk of hypersensitivity reactions. Pegylation also increases the enzyme's circulating half-life, enabling less frequent administrations, and making intravenous, as opposed to intramuscular, administration feasible. In the ongoing UKALL14 adult protocol, pegaspargase is administered exclusively intravenously (12).

Native asparaginase is not licensed in the UK, and since 2003, pegaspargase has been the standard of care 1st line asparaginase treatment of paediatric, adolescent, and young adult patients with ALL, with the vast majority of patients in the UK and Ireland receiving treatment according to the UKALL protocols (UKALL 2003, UKALL 2011, UKALL14).

Evidence supporting the use of pegaspargase has been accrued over a number of years, driven by academic and international collaborations, recognising the utility of pegaspargase in chemotherapeutic regimens for ALL.

Evidence in children, adolescents and young adults

Systematic reviews of the literature identified randomised and non-randomised studies providing clinical data for the use of native or pegaspargase in 1st line treatment of ALL in children, adolescents and young adults, with the maximum age of any enrolled patient in the identified studies being 40 years.

The pivotal RCT in this data set is that of Avramis et al, 2002 (CCG-1962), which is the only study identified providing a randomised head-to-head comparison of pegylated versus native E. coli-derived asparaginase given from induction (11).

In study CCG-1962, 118 children (aged 1–9 years) newly-diagnosed with ALL were randomised to receive either pegaspargase (2,500 IU/m^2 IM on day 3 of induction and each DI phase) or native asparaginase (6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase). This study demonstrated the following:

- EFS at three, five, and seven years, respectively, was similar but numerically higher for those treated with pegaspargase (83%, 78%, and 75%) versus those treated with native asparaginase (79%, 73%, and 66%).
- Pegaspargase was associated with more rapid clearance of lymphoblasts in BM aspirates taken during induction than was native asparaginase.
- Immunogenicity of pegaspargase was low as expected, with a significantly lower mean antibody ratio and rate of high antibody titres observed during the first delayed intensification phase (1.9 and 2%) versus 3.0 and 26% for E. coli asparaginase.
- The development of neutralising antibodies is known to lead to a decrease in enzyme activity and consistent with this high antibody titres were associated with low asparaginase activity in the E. coli arm but not in the pegylated arm.
- Asparaginase activity considered adequate to deplete asparagine (>0.1 IU/mL) was detected in 95% and 91% of pegaspargase-treated patients versus 19% and 22% of E. coli asparaginase treated patients during the first and second delayed intensification phases of treatment.

[redacted]

- [redacted].
- [redacted].

A key benefit of pegaspargase is its longer half-life (5.5–7 days) compared with that of native asparaginase (26–30 hours) (8), meaning that to maintain the depletion of

asparagine crucial to chemotherapeutic activity, pegaspargase can be administered at a significantly reduced dosing frequency (SmPC recommends once every 14 days for pegaspargase versus every 2–3 days for native asparaginase (8)). This makes intravenous administration more feasible for pegaspargase as opposed to intramuscular administration. When the impact of this on quality of life was assessed, significantly less anxiety was reported by patients and by parent-proxy treated with pegylated versus native asparaginase (Study DFCI ALL 05-001 (30, 50)).

The evidence base for pegaspargase in the 1st line treatment of ALL is considerably enhanced by, and is potentially unique as a result of the UKALL studies (UKALL 2003, UKALL 2011, UKALL14), which since 2003 have seen the vast majority of newly diagnosed ALL patients in the UK and Ireland treated exclusively with pegaspargase as the 1st line asparaginase according to the UKALL protocols.

UKALL 2003 enrolled a total of 3,207 children and young adult patients aged 1-<25 years, representing 97% of the eligible ALL patient population aged 1–24 years in the UK and Ireland (2-4). In this study, all patients received treatment with pegaspargase (1,000 IU/m^2 per dose, 4–12 doses) as part of one of three possible escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. In addition, MRD low-risk patients were randomised to receive either standard treatment (two DI cycles; n=261) or reduced treatment (only one DI cycle; n=260). Similarly, MRD high-risk patients were randomised to receive either standard treatment (n=266) or augmented treatment (n=267).

Among all patients enrolled in UKALL 2003:

- five-year EFS was 87.3%,
- five-year OS was 91.6%, and
- five-year cumulative risk of relapse was 8.8%, demonstrating the overall utility of pegaspargase in multi-agent chemotherapy for children, adolescents and young adults with ALL.

The UKALL 2003 protocol has also allowed investigators to determine if overall treatment intensity for ALL patients could be modified, according to risk stratification, allowing a more risk-directed approach to therapy, including modification of dosing frequency for pegaspargase. Among MRD low-risk patients, there was no significant difference in five-year EFS or OS among patients on reduced (94.4% and 97.9%, respectively) versus standard treatment (95.5% and 98.5%, respectively), showing that one delayed intensification course rather than two was sufficient in these low risk patients (including a total of three rather than four pegaspargase doses) (2). In contrast, patients with MRD after induction therapy (MRD high-risk patients), may see EFS and OS benefits from receiving augmented treatment (Regimen C: additional therapies added at consolidation, maintenance and delayed intensification phase including eight additional doses of pegaspargase versus Standard therapy, including four doses of pegaspargase [Regimen A or B]) (4).

The vast majority of newly diagnosed patients in the UK and Ireland continue to be treated with pegaspargase as the 1st line asparaginase, with two further ongoing UKALL

studies – UKALL 2011 (3) in children, adolescents, and young adults, and UKALL14 (12) in adults.

Evidence in adults

The predominant evidence base presented in this submission supports the use of pegaspargase in children, adolescents, and young adults. Although evidence for adults is limited relative to that in the younger population, three further studies were identified by systematic review (Systematic review 2) that provide pegaspargase evidence for older adult populations (age range: 17–71 years). Two sequential studies by Douer et al (21, 22), demonstrated that adult patients (up to the age of 57 years), newly diagnosed with ALL, can be treated safely, achieve a long duration of asparagine depletion, and have an excellent chance of achieving remission (96%) when treated with up to six 2,000 IU/m^2 doses of pegaspargase beginning in induction.

A further study, CALGB 9511 (23) demonstrated that effective asparagine depletion with pegaspargase in adults with ALL is feasible as part of an intensive multi-agent therapeutic regimen and that effective asparagine depletion is associated with improved outcomes (HR for OS: 2.37, 95% CI 1.38–4.09, p=0.002 and HR for DFS: 2.21, 95% CI 1.19–4.13, p=0.012). Study CALGB 9511 (23) provided the basis of the treatment protocol developed for the ongoing UK study in adult ALL patients, UKALL14 (12), which currently has enrolled around 85% of eligible adult patient in the UK.

UKALL14 (12), described further in Section 3.6 will be a pivotal study in the adult population, where pegaspargase will be administered to adults for the first time in a large Phase III setting.

Evidence versus Erwinia-derived asparaginase

There is no evidence available that Baxalta are aware of that would enable a direct comparison of pegaspargase with Erwinia-derived asparaginase. Furthermore, the relevance of such a comparison is questionable from a clinical perspective given that pegaspargase is currently the 1st line standard of care, with Erwinia-derived asparaginase, although licensed (10), being positioned in treatment protocols as a 2nd line agent following hypersensitivity reactions to pegaspargase (7, 16).

In studies comparing native E. coli asparaginase and Erwinia-derived asparaginase, long term outcomes are significantly worse for the Erwinia enzyme, but at doses that are lower than are now used in practice (See Appendix 4: Duval 2002 (24), Moghrabi 2007/Silverman 2010 (9, 20); 10,000 IU/m^2 twice weekly or 25,000 IU/m^2 weekly vs 60,000 IU/m^2 weekly in UKALL protocols (3)). Experts validated the assumption that, given the limitations of the evidence, pegaspargase, E. coli asparaginase and Erwinia-derived asparaginase could be assumed to be equivalent for OS and EFS.

Safety profile

Based on available safety data submitted to the EMA for marketing authorisation (EPAR, Appendix 1), it was concluded that the treatment of ALL patients with pegaspargase at doses of 2,000 to 2,500 IU/m^2 is considered to be well tolerated and the toxicities manageable, as per the recommendations stated in the SmPC and the risk minimisation measures in the Risk Management Plan.

The adverse effects observed with pegaspargase are consistent with those expected of an asparaginase and the EMA concluded that the safety of pegaspargase does not differ dramatically from native E. coli asparaginase. Overall, the most common adverse reactions of Grade 2 or higher (≥20%) observed with pegaspargase doses of 2,000–2,500 IU/m^2 are hypersensitivity including anaphylactic reaction, febrile neutropenia, anaemia, hyperglycaemia, platelet count decreased, neutrophil count decreased and blood bilirubin increased.

In UK clinical practice pegaspargase has been used for over a decade at a reduced dose of 1,000 IU/m^2 in the UKALLL 2003 protocol (2, 4), and subsequently in ongoing protocols in children, adolescents, and young adults, and adults in UKALL 2011 (3) and UKALL14 (12), respectively. The data from UKALL 2003 and the subsequent data that will come from the ongoing UKALL 2011 and UKALL14 are the most appropriate data in relation to the safety profile of pegaspargase. Current data from >3,200 patients in UKALL 2003 support the overall observations of the EMA, with the authors concluding that the toxic effects attributable to pegaspargase were similar to or lower than those they have seen reported in the literature with the native form.

A key concern with the use of asparaginase is the development of antibodies to the enzyme that can result in hypersensitivity reactions which would necessitate a switch to an alternative asparaginase formulation. The SmPC for Oncaspar® states that hypersensitivity reactions of Grade 2 or higher are seen in ≥20% of patients treated with pegaspargase. This rate appears high but should be interpreted in the context that SmPC data was based on patients treated with the recommended dose of 2,000 to 2,500 IU/m^2 and includes some patients treated with 2nd line pegaspargase following hypersensitivity to native E. coli enzyme, a scenario known to increase the risk of hypersensitivity to pegaspargase (53-55).

In contrast, and of more relevance to UK clinical practice, when used in >3,200 patients in UKALL 2003 at the reduced dose of 1,000 IU/m^2 hypersensitivity reactions were experienced by only 2% of patients across the entire study treated with between 4 and 12 doses of pegaspargase (n=54/3,126).

Vora et al, in their publication of the UKALL 2003 protocol suggest that hypersensitivity rates of 20-40% are to be expected for native E. coli-derived asparaginase (2). Rates of hypersensitivity reported across studies identified by systematic review are variable and range from 0–13% for native E. coli asparaginase (see Table 29 and Appendix 4), compared with 0–8% for pegaspargase (Table 29), and in some cases no difference between the two preparations (CCG-1962 (11) and DFCI-91-01 (59)). However, these rates reflect only hypersensitivity of Grade 3 or higher, and when milder allergic reactions are also considered, significantly higher rates are observed with the native E. coli enzyme (p=0.02; DFCI-91-01 (59)). In additional studies of native E. coli enzyme Bowman et al report 13% Grade 3 or higher hypersensitivity, but 25% incidence of any grade hypersensitivity (COG P9906 (52)), while Wacker et al report 8% Grade 4 hypersensitivity, but 76% incidence of hypersensitivity leading to a switch in asparaginase formulation (POG 8602 (25)). Vrooman et al (DFCI 00-01 (86)) report 20% of patients developing hypersensitivity that required a switch to Erwinia-derived asparaginase.

Limited data was identified in the systematic review for Erwinia-derived asparaginase as a 1st line asparaginase and none comparing with pegaspargase; Moghrabi et al report that when used 1st line, 6% of Erwinia-treated patients develop hypersensitivity resulting in a treatment switch to native asparaginase (9). Note that a lower dose of Erwinase than is used effectively in clinical practice today was administered in the Moghrabi study, but the reported hypersensitivity rates were broadly consistent with the SmPC for Erwinia that reports hypersensitivity in the 1–10% range (9, 10).

4.14.2 *Strengths and limitations of the clinical evidence base for the technology*

Relevance of the evidence base to UK clinical practice

Evidence supporting the use of pegaspargase has been accrued over a number of years, driven by academic and international collaborations. The clinical community recognise the need for and place great value on pegaspargase in the treatment of ALL as evidenced by its inclusion, as a 1st line asparaginase, in a large number of completed and ongoing UK-based and international study protocols. Since 2003 in the UK, trial protocols and guidelines have mandated that pegaspargase be given as 1st line asparaginase for ALL, and NHS England included pegaspargase in baseline commissioning in 2013.

Since 2003, the vast majority of patients with ALL in the UK and Ireland have been treated within the UKALL studies, UKALL 2003 (2, 4), UKALL 2011 (3), and UKALL14 (12), in which pegaspargase is mandated as 1st line asparaginase treatment; UKALL 2003 enrolled 97% of eligible paediatric and young adult patients (3), while UKALL14 currently accounts for approximately 85% of adult patients (Expert opinion). Patients who haven't taken part in the trials have either been referred to one of the trial centres or been treated as per the trial protocol. As such these trials have not only provided or will provide a large amount of data directly relevant to UK clinical practice but also demonstrate that clinicians are familiar with and recognise the value of using pegaspargase for the 1st line treatment of ALL in children, adolescents and adults.

Dosing

In CCG-1962 and many of the supporting studies presented, the dose of pegaspargase was in line with the SmPC recommended dose: 2,500 IU/m^2 for children/adolescents, and 2,000 IU/m^2 for adults.

However, in all three UKALL trial protocols pegaspargase has been dosed at 1,000 IU/m^2, regardless of age. This is the dose that UK clinicians, independent of any influence from the manufacturer, recognise as providing the appropriate risk-benefit profile for these patients, and continue to use in clinical practice. When comparing the long term outcomes of EFS and OS from >3,000 paediatric and young adult patients in UKALL 2003 with those from CCG-1962 and the pooled estimates generated from the wider evidence base, the UKALL regimens provide numerically superior outcomes to any other study, even at this reduced dose. The use of this reduced dose is therefore supported by a robust and substantial evidence base, and has provided the clinical community with confidence in its continued use in two further UKALL protocols in both

paediatric and young adult, and adult patients, respectively (UKALL 2011, and UKALL14).

Comparative data

ALL treatment regimens are complex, with potential for multiple treatment phases and chemotherapeutic agents, and variations in the length of treatment periods, dosing, and dosing frequency. Across the studies identified for use in this submission the use of asparaginase specifically differed by timing (i.e. introduced at induction or post-induction), type used at each phase (some studies switched from one formulation to another) and the phase of treatment at which randomisation to asparaginase formulations occurred. Very few studies were identified that provided a direct head-to-head comparison of pegaspargase with E. coli asparaginase with all other treatment variables being equal. The pivotal study CCG-1962 was the only study identified that compared native and pegaspargase on a randomised, head-to-head basis where patients were randomised to different asparaginase formulations from induction.

Other limitations

Other limitations of the evidence base including the relative lack of adult data compared with that available in children and adolescents and lack of any comparative data versus Erwinia-derived asparaginase have been described previously in Section 4.14.1.

4.15 *Ongoing studies*

Between 2003 and 2011, 97% of eligible children and young adults (up to the age of 25) with ALL in the UK and Ireland were treated in the UKALL 2003 protocol, as described previously (see Section 3.6 and 4.3).

UKALL 2011 and UKALL14 are ongoing protocols assessing children and young adults, and adults, respectively.

The protocols for all three studies mandate that pegaspargase is given as 1st line asparaginase treatment from induction as part of multi-agent chemotherapy, and will see the majority of eligible patients in the UK treated.

Protocol details have been described previously in Section 3.6.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

A comprehensive search of the peer-reviewed literature was conducted to identify and select relevant cost-effectiveness studies.

5.1.1.1 Objectives

Gather general published data relevant to decision-making in England on clinical efficacy, safety and toxicity of pegaspargase in all age groups of patients newly diagnosed with acute lymphoblastic leukaemia (ALL).

Provide evidence for the cost-effectiveness of pegaspargase as part of a chemotherapeutic protocol compared with native E. Coli-derived asparaginase and Erwinia-derived asparaginase (crisantaspase, Erwinase®) in patients newly diagnosed with ALL.

5.1.1.2 Search strategy

Databases

The following sources were used for search:

- Medline (via the Pubmed – NLM platform), all records from treatment inception to December 31, 2015
- Embase (via the OVID platform), all records from treatment inception to December 31, 2015
- Cochrane Database of Systematic Reviews 2005 to December 31, 2015
- EBM Reviews - Cochrane Central Register of Controlled Trials December 2015
- EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012
- EBM Reviews - ACP Journal Club 1991 to December 2015
- EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2015
- EBM Reviews - Health Technology Assessment 4th Quarter 2015
- NHS Economic Evaluation Database 4th Quarter 2015

Full details of the search strategy are provided in Appendix 6.

Study Population

Acute lymphoblastic leukaemia was searched for explicitly (via controlled syntax (line 1 and 2 of the Medline strategy) and free-text (line 3 to 6 of the Medline strategy)), as well as more broadly, using free text for the broader population groups: lymphocytic leukaemia or lymphoblastic leukaemia. This was to ensure any unlikely deficiencies in indexing or referencing to the acute stage of the broader lymphoblastic leukaemia population. Accordingly, any rogue references which are implicitly acute stage but are not explicitly defined as such, can be picked up in the literature via screening.

Intervention and clinical comparators

Patients newly diagnosed with ALL who have received any type of the following asparaginase as part of a chemotherapeutic protocol:

- Main intervention: Pegaspargase (Oncaspar®) derived from E.coli
- Clinical comparator: 'Native' (non-pegylated) asparaginase derived from E. coli
- Clinical comparator: Crisantaspase (Erwinase®) derived from Erwinia chrysanthemi

Search terms for interventions were incorporated using both their formal and informal naming. In Medline, in addition to free text, the MeSH term "asparaginase" was incorporated. In Embase, in addition to free text, the relevant controlled syntax using the Embase Thesaurus for the drugs was also incorporated.

Economic parameters

To ensure broad inclusion of studies reporting and examining specific costs related to the treatment of newly diagnosed ALL patients eligible for treatment with asparaginase as part of a chemotherapeutic protocol, the search was run without recourse to any intervention filters (asparaginase). This opens a broader field of results for this review. A number of cost-effectiveness related terms were included in the search but limited to the abstract or title. The same process was used for Embase by using the Embase Thesaurus.

5.1.1.3 Study Selection

Limits

Limits were applied (where the databases allowed) to exclude studies carried out on animals as well as to limit returns to English Language studies and to studies for which an abstract was available.

Inclusion and exclusion criteria

Inclusion criteria:

- Studies focused on the treatment of newly diagnosed ALL patients reporting and/or evaluating economic parameters of treating ALL patients with a chemotherapeutic protocol that includes at least one asparaginase as 1st line or 2nd line agent (2nd line being defined here as post-hypersensitivity event).

Exclusion criteria:

- Studies not directly evaluating the cost effectiveness of at least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patient
- Studies in refractory/relapsed ALL patients defined here as at a minimum the second course of chemotherapy following a relapse or for refractory ALL patients
- Non-English language studies
- Studies that includes other malignancies besides ALL

- Comments, editorials, systematic reviews, reviews

5.1.2 *Description of identified studies*

Among the cost-effectiveness studies published, none of them were deemed relevant to decision-making in England.

5.1.3 *Quality assessment of identified studies*

Not applicable.

5.2 *De novo analysis*

5.2.1 *Patient population*

Pegaspargase has been used for treating patients with ALL in the UK for over a decade; since 2003 it has been the standard of care asparaginase for paediatric, adolescents and young adult (AYA) patients.

Positive results from the initial paediatric protocol, UKALL 2003, led to its incorporation into the current protocol UKALL11 and also into the current adult protocol, UKALL 14. Pegaspargase is thus administered as the 1st line asparaginase (as a part of multi agent chemotherapy) in the UK as part of the UKALL protocols which are seen as standard of care. For example, more than 97% of eligible newly diagnosed paediatric patients were treated using the UKALL 2003 protocol over the 7 years it was in place (3).

Recognising the value of pegaspargase and to overcome the inequity of "postcode prescribing", the clinical community sought to have pegaspargase included in NHS England baseline commissioning, which was effective from April 2013 (13).

Asparaginase is routinely used in the NHS for the treatment of newly-diagnosed ALL patients. Relapsed and older patients do not routinely receive pegaspargase and were therefore not considered as part of this submission. UK treatment protocols also use different dosing regimens than other countries, and versus that recommended in the SmPC (i.e. 1,000 IU/m², rather than 2,500 IU/m²).

This submission only considers pegasargase in newly-diagnosed ALL patients. Current use of asparaginase in the NHS is in the newly-diagnosed setting for patients <65 years (UKALL 2011 & UKALL14). Relapsed and older patients do not routinely receive pegaspargase and were therefore not considered a part of this submission, as they would not be relevant for the NHS decision-maker.

This submission, therefore, reflects the patient population in the UK in which asparaginase is routinely used and at the appropriate doses used in UK practice

In order to make the model relevant to the UK protocols, and thus the NHS, the economic evaluation therefore considers these two separate patient groups, newly diagnosed with ALL in England:

1. Paediatric patients (i.e., children, adolescents and young adults (AYAs)) – aged ≤25 years. The model used published data involving a large cohort of >3,200 patients for whom data is available, treated with the UKALL 2003 protocol. Within

this group, a further split is made between high-risk (HR), intermediate-risk (IR) and standard-risk (SR) patients as per the UKALL 2003 protocol (2, 4).

2. Adults – aged from 26 to 65 years. These patients are treated according to the ongoing UKALL14 protocol. Within this group, a further split is made between those aged ≤40 years and those aged ≥41 years and those eligible or not for transplant as per the UKALL14 protocol (12).

The two patient groups are distinct in terms of age-range, each having bespoke treatment regimens (described in Table 43). These two populations are modelled separately for Paediatric and Adults with ALL, as each have different treatment pathways, different outcomes and often utilise different settings of NHS resources and care.

The split between Paediatric and Adult patients in the model is derived from Cancer Research UK 2011-2013 data (1). Of 644 new ALL cases diagnosed per year in those aged 0–65, 74.4% would be aged less than 25 years and 25.6% would be aged between 26 and 65 years, respectively.

- For those aged <25 years, the average age from the CRUK data is 7.3 years (1). However, the model uses the median age of 5 years reported in the Vora et al. 2013 study in the reference case as this is more representative of the treated ALL population in the UK (2, 4).
- For those aged 26–40 years, the extrapolated average age from the CRUK data is 31.2 (≈31) years.
- For those aged 41–65, the extrapolated average age from the CRUK data is 52.6 (≈53) years.

5.2.2 *Model structure*

Newly diagnosed ALL patients usually receive treatment according to the current UKALL treatment protocols over a defined period of time, and the exact treatment used will be determined by factors including age and risk group. Asparaginase forms the backbone of these regimens, but is associated with hypersensitivity to the enzyme. Pegaspargase has a lower rate of hypersensitivity (See Section 5.3.1.4). In addition previous preparations of asparaginse required multiple administrations by IM injection and pegaspargase provides a more favourable administration profile, requiring less frequent injections.

All outcomes of interest are observed and reported in trials from treatment commencement up to 5 years in terms of OS, EFS, and hypersensitivity. A decision tree (DT) was therefore the most appropriate model structure to use to model the differences in hypersensitivity and costs associated with the use of the products modelled.

Patients enter the model at treatment initiation for newly diagnosed ALL. Respective of their age, patients follow treatment phases and receive asparaginase dosing as per the UKALL2003 (≤25 years) and UKALL14 (26-65 years) protocols.

As patients experience outcomes in terms of OS & EFS during the treatment phase, a Markov model was also incorporated to allow extrapolation over the patient's lifetime.

The final model therefore combines a decision tree and a health state transition Markov model.

Decision tree: The DT has a 5-year time horizon from treatment initiation (Figure 19 and Figure 20). The DT covers the treatment duration and depicts the patient flow according to the dosing, frequency and potential hypersensitivity to asparaginase. It accounts for the potential switch from one form of asparaginase to another – E.coli (native or pegylated) or Erwinia-derived – as hypersensitivity to a specific form of asparaginase occurs as defined in UKALL 2003 (94) and UKALL14 protocols (12).

Markov model: The Markov model also begins from ALL treatment initiation.

In paediatric patients, the Markov model has 3 health states (Figure 21):

1. Event-free survival (EFS);
2. Survival with relapse/secondary tumour (R/ST);
3. Death (Overall survival, OS).

The Markov model is used to account for potential R/ST and death during treatment from treatment initiation to 5-year post-treatment.

In Adults, the Markov model has 2 health states (Figure 22):

1. Alive
2. Death (OS).

Expert opinion stated that for adult patients, it is assumed that EFS and OS are equivalent, and the Markov model is therefore used to account for deaths occurring during the treatment phases.

Thus, for both Paediatric and Adult patients the DT and the Markov model are run in parallel to ensure that only patients in the EFS state continue to receive asparaginase treatment per the protocols, and any events are accounted for. Beyond 5 years post-treatment initiation, the Markov model is also used to extrapolate over the patient's remaining lifetime time horizon.

To accurately reflect the treatment algorithms used during the treatment period, the Markov model uses cycles that correspond to the different treatment phases of the UKALL 2003 and UKALL14 protocols, expressed in weeks.

- Paediatric population: seven cycles (induction, consolidation, interim maintenance 1, delayed intensification 1, interim maintenance 2, delayed intensification 2 and continuation)
- Adults: five cycles (induction, intensification, consolidation 1, consolidation 3 and maintenance)

Model cycle lengths correspond to the treatment phase lengths.

The main advantage of pegaspargase is the reduced number of administrations required due to the preferential half-life (six doses of either native asparaginase or Erwinase for

every one dose of pegaspargase), which means that in practice, hypersensitivity occurs in a later treatment phase than the other two products (i.e. induction for native asparaginase and Erwinase, but intensification for pegaspargase). Hypersensitivity usually occurs after 2 doses of asaparaginase which is the reason for this difference.

In order to account for this, a cycle correction was applied for the dosing of native E.coli asparaginase and Erwinase in case of hypersensitivity, dividing the number of native E.coli asparaginase and Erwinase injections by 3 or 6 depending on the initial dosing schedule of 6 or 12 injections, respectively. Most patients experience hypersensitivity at the 2nd dose given and so were thus assumed to discontinue treatment with native E.coli asparaginase and Erwinase after the 2nd injection).

Beyond the end of the treatment phase, patients no longer receive asparaginase therapy and the Markov model has a yearly cycle. Half-cycle correction is no longer applied as this is no longer clinically relevant.

An assumption is that pegaspargase, native asparaginase and Erwinase are equivalent in terms of OS and EFS, and because all the outcomes of interest are experienced during the treatment phase, a cost minimisation analysis (CMA) is an alternative modelling methodology that can be used to represent the decision problem. The decision tree and Markov model are also used in the CMA. This is presented in Section 5.8.3, as this demonstrates the actual impact on the NHS.

Figure 19 and Figure 20 show the corresponding DT in paediatric and adults patients, respectively. The figures only show the branch where 1st line asparaginase is pegaspargase (treatment sequence 1, Section 5.2.3). Treatment sequences in which native E.coli asparaginase or Erwinase are used as 1st line asparaginase are not shown, but are presented in the model.

Figure 19: Treatment flow in Paediatric patients (UKALL2003 (2, 4))

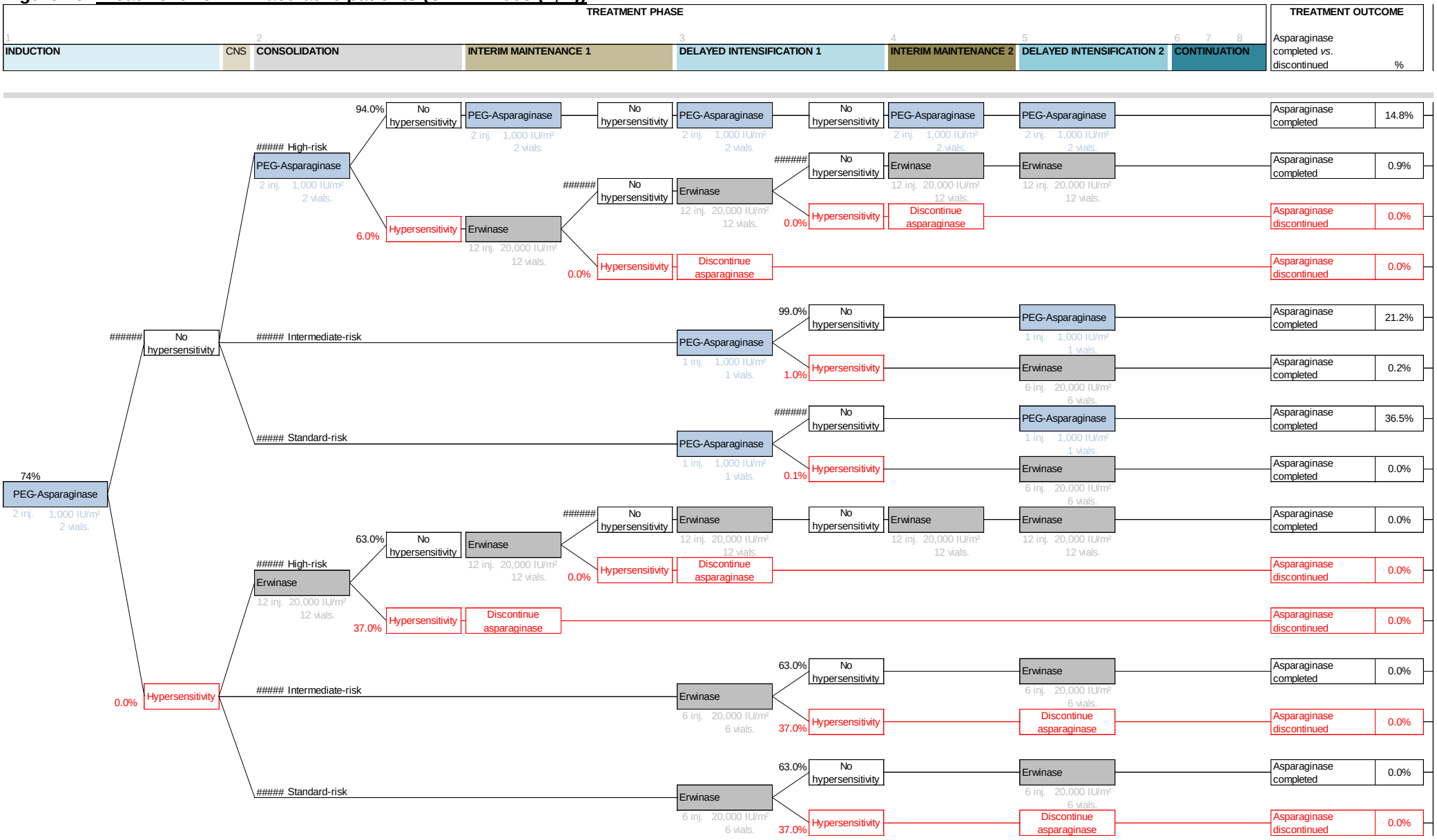


Figure 20: Treatment flow in Adults (UKALL14 (12))

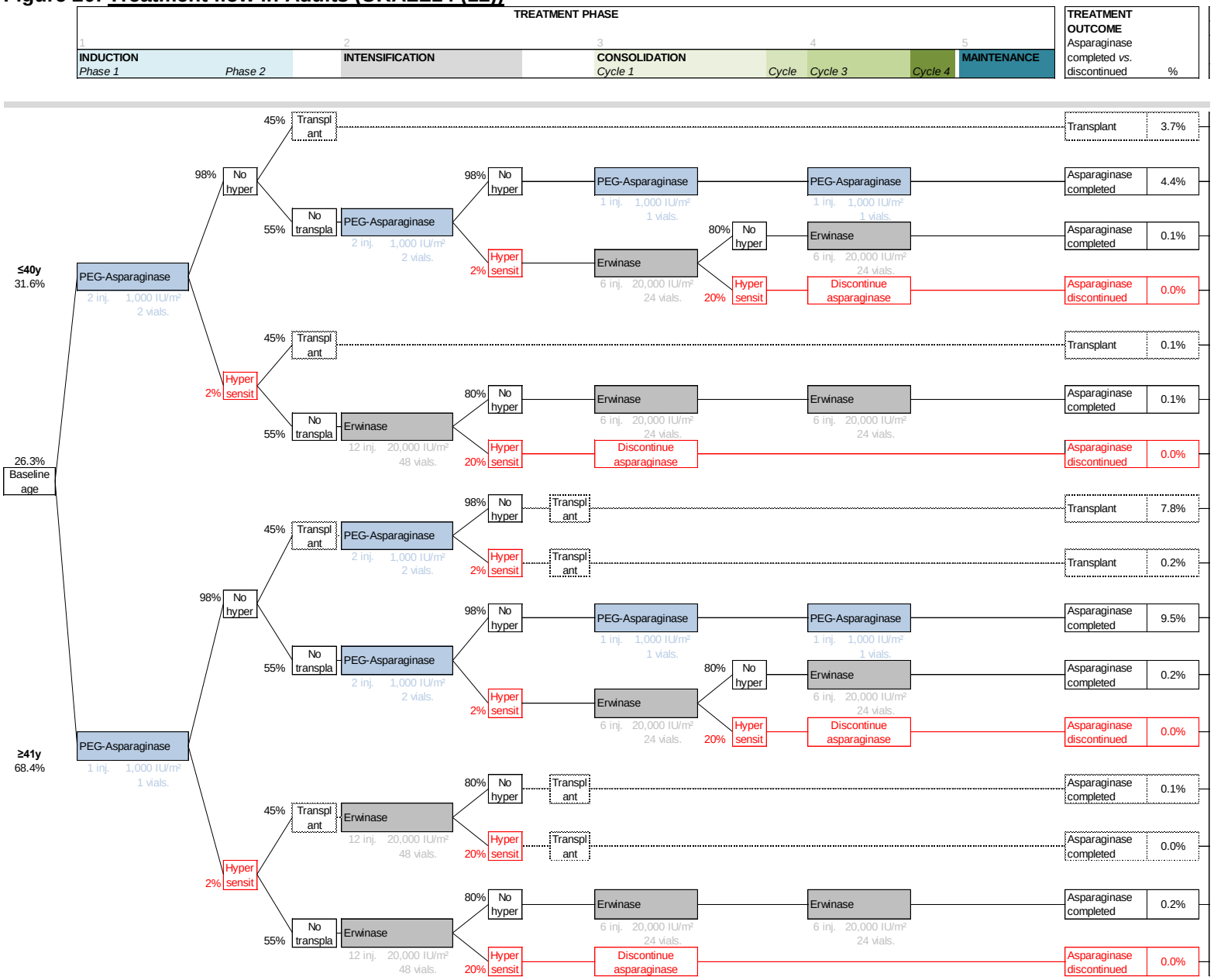
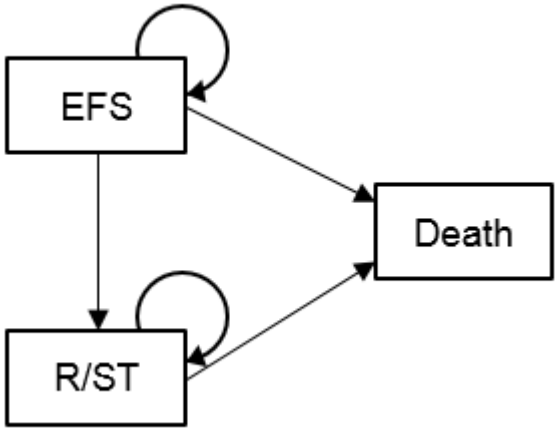
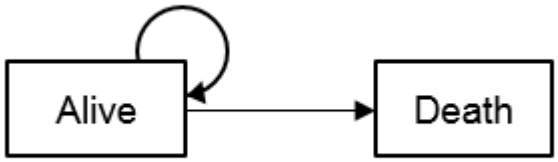


Figure 21: Markov model schematic (paediatric patients)



Abbreviations: EFS, event-free survival; R/ST, relapse/secondary tumour.

Figure 22: Markov model schematic (adults)



Transplant:

In adult patients, allogeneic transplant is currently the treatment of choice for eligible adults in first complete remission. At present, a group of adults with ALL in whom the risk of relapse is less than the risk of sibling allogeneic SCT, cannot be defined. Accordingly, the UKALL14 adult protocol continues to propose sibling allogeneic SCT for every eligible patient where a sibling donor is available (12). Based on data from a previous UKALL protocol (UKALLXII, that utilised native asparaginase) 47% of patients had a sibling donor transplant (95), and this value was used in the base case analysis to define the proportion of adult patients who receive a transplant. However, patients may also be transplanted via an unrelated donor, such that the total proportion of patients receiving a transplant may be higher in practice. This scenario was considered in sensitivity analysis in which a range of transplant rates were used.

Patients who receive a transplant cease to receive asparaginase (12). As asparaginase treatment is ceased once patients have a transplant, a simplification was made in the model to simply distinguish between patients who are eligible or not eligible for transplantation (assuming the 47%:53% in the base case (95)).

It was assumed that all patients eligible for transplantation undergo transplantation post-induction, at which point they asparaginase treatment is ceased. As the treatment

regimen and associated patient outcome will then depend on the success or failure of the transplant, and asparaginase will no longer be used, specific transplant costs and outcomes of transplantation were not accounted for in the analysis. Transplanted patients were assumed to accrue the same utilities as non-transplanted patients. There is a lack of data available as the UKALL14 trial is still ongoing, so previous trial data (95), as suggested by the clinical expert, was used to calculate the proportion of patients eligible for a transplant. This was tested in sensitivity analysis.

EFS & OS:

If asparaginase treatment was completed as per the UKALL 2003 and UKALL14 protocols, which represent current UK clinical practice, then EFS and OS would be assumed to be the same irrespective of the four asparaginase treatment sequences employed (See Section 5.2.3).

This assumption was based on clinical data demonstrating that pegylated and native E.coli asparaginase have equivalent efficacy in terms of EFS and OS, when used as 1st line asparaginase treatment (Section 4.14). In studies comparing native E. coli asparaginase and Erwinia-derived asparaginase, long term outcomes are significantly worse for the Erwinia enzyme, although at doses that are lower than are now used in practice (See Appendix 4: Duval 2002 (24), Moghrabi 2007/Silverman 2010 (9, 20); 10,000 IU/m^2 twice weekly or 25,000 IU/m^2 weekly vs 60,000 IU/m^2 weekly in UKALL protocols (3)). Experts validated the assumption that, given the limitations of the evidence, pegaspargase, E. coli asparaginase and Erwinia-derived asparaginase could be assumed to be equivalent for OS and EFS.

Asparaginase discontinuation:

Patients who have experienced hypersensitivity to both their 1st and 2nd line asparaginase and have had to discontinue this treatment were assumed to have a lower EFS and OS (a relative risk of 0.95 was assumed in the base case based on expert opinion).

Trial data was used to populate the model and this was validated by expert opinion. We sought the advice of clinical experts to assess the applicability of the clinical parameters and to approximate some of the clinical parameters where relevant UK data was lacking.

5.2.2.1 Key features of the de novo analysis

Table 37: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	5-year post treatment initiation	Consistent with the 5-year EFS and OS estimates usually reported in the literature and clinical protocols
	Lifetime	NICE recommendation (96)
Were health effects measured in QALYs; if not, what was used?	Health effects are measure in QALYs	NICE recommendation (96)
Discount of 3.5% for utilities and costs	Paediatric: 3.5% QALYs and 3.5% Cost Adults: 3.5% QALYs and 3.5% Cost	NICE recommendation (96)
Perspective (NHS/PSS)	NHS/PSS	NICE recommendation (96)

Abbreviations: EFS, event-free survival; NHS, National Health Service; OS, overall survival; PSS, Personal Social Services; QALYs, quality-adjusted life years.

5.2.3 *Intervention technology and comparators*

The following asparaginase sequences were considered in the analysis (Figure 23):

1. Pegaspargase 1st line >> switch to Erwinase 2nd line in case of hypersensitivity to pegaspargase;
2. Native E.coli asparaginase 1st line >> switch to Erwinase 2nd line in case of hypersensitivity to native E.coli asparaginase;
3. Erwinase 1st line >> switch to pegaspargase 2nd line in case of hypersensitivity to Erwinase;
4. Erwinase 1st line >> switch to native E.coli asparaginase 2nd line in case of hypersensitivity to Erwinase.

In the protocols of both UKALL 2003 & UKALL14, Erwinase is stated to be used only when a hypersensitivity to an E.coli-derived asparaginase product occurs (thus not 1st line use). The dose is stated to be six doses of Erwinase for every dose of pegaspargase replaced (12, 94). This was also confirmed by the experts consulted.

In case of hypersensitivity to both asparaginase formulations used in 1st and 2nd lines, asparaginase treatment was discontinued.

In UK practice both the UKALL2003 and UKALL14 protocols include Erwinase only as a 2nd line asparaginase treatment after hypersensitivity has occurred to 1st line asparaginase. This was confirmed by the clinical experts interviewed.

However, Erwinase was listed as a comparator in the NICE scope and, as it's UK indication does not limit its use to a specific line of asparaginase treatment, it was

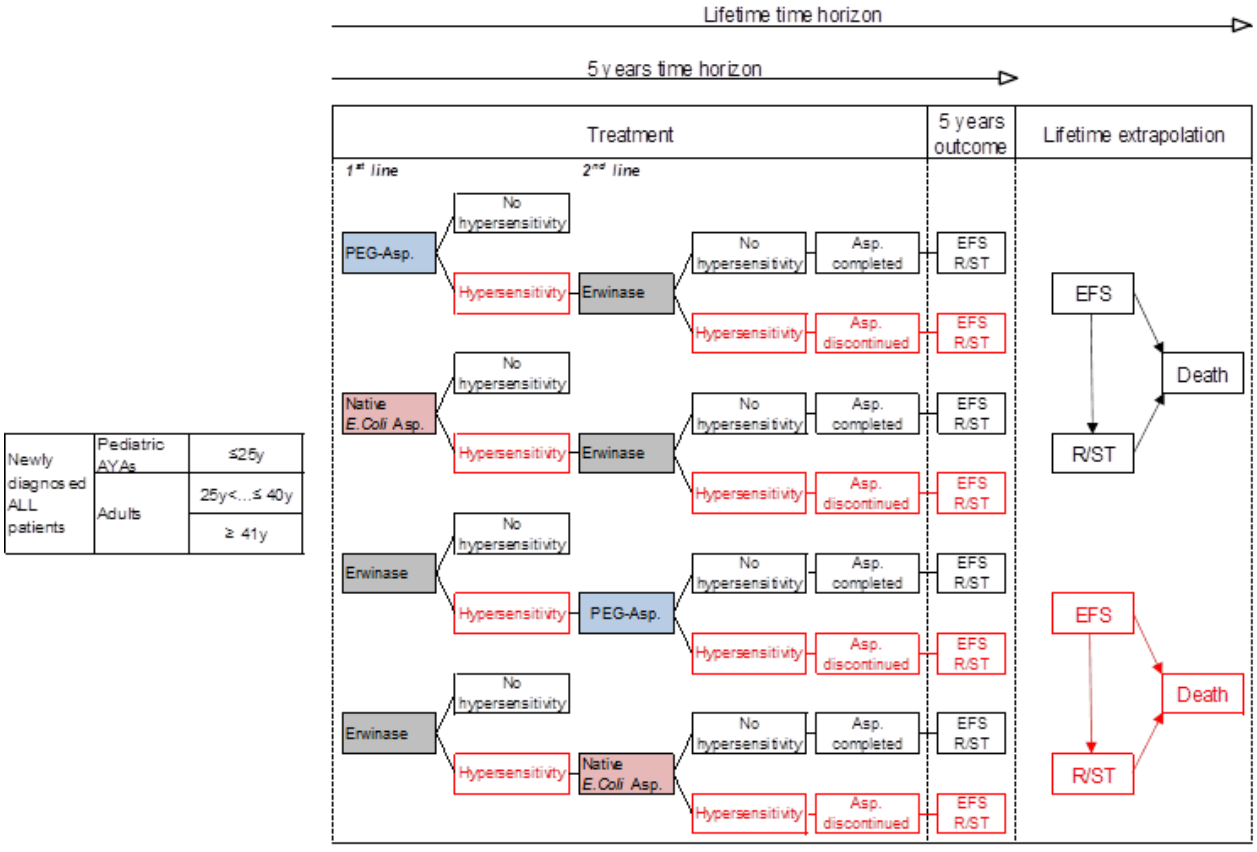
included in the analysis as 1st line comparator to pegaspargase and native E.coli asparaginase 1st line.

Although historically pegaspargase was given to patients following hypersensitivity to native *E.coli* enzyme, with the availability of Erwinase, patients experiencing hypersensitivity to pegylated or native E.coli enzyme would in practice no longer be switched to the other *E.coli* enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinase following hypersensitivity to E.coli-derived asparaginase products (3, 12).

As such the following two scenarios have not been modelled

1. Pegaspargase 1st line with a switch to native E.coli asparaginase 2nd line in case of hypersensitivity to pegaspargase;
2. Native E.coli asparaginase 1st line with a switch to pegaspargase 2nd line in case of hypersensitivity to native E.coli asparaginase

Figure 23: Overview of intervention and comparators in the model



Abbreviations: ALL, acute lymphoblastic leukaemia; AYAs, adolescents and young adults; E.coli Asp, Escherichia coli asparaginase; EFS, event-free survival; R/ST, relapse/secondary tumour; PEG-Asp, pegaspargase.
The R/ST health state is not considered in Adults where EFS and OS are assumed to be the same.

5.3 *Clinical parameters and variables*

5.3.1 *How are clinical data incorporated into the model?*

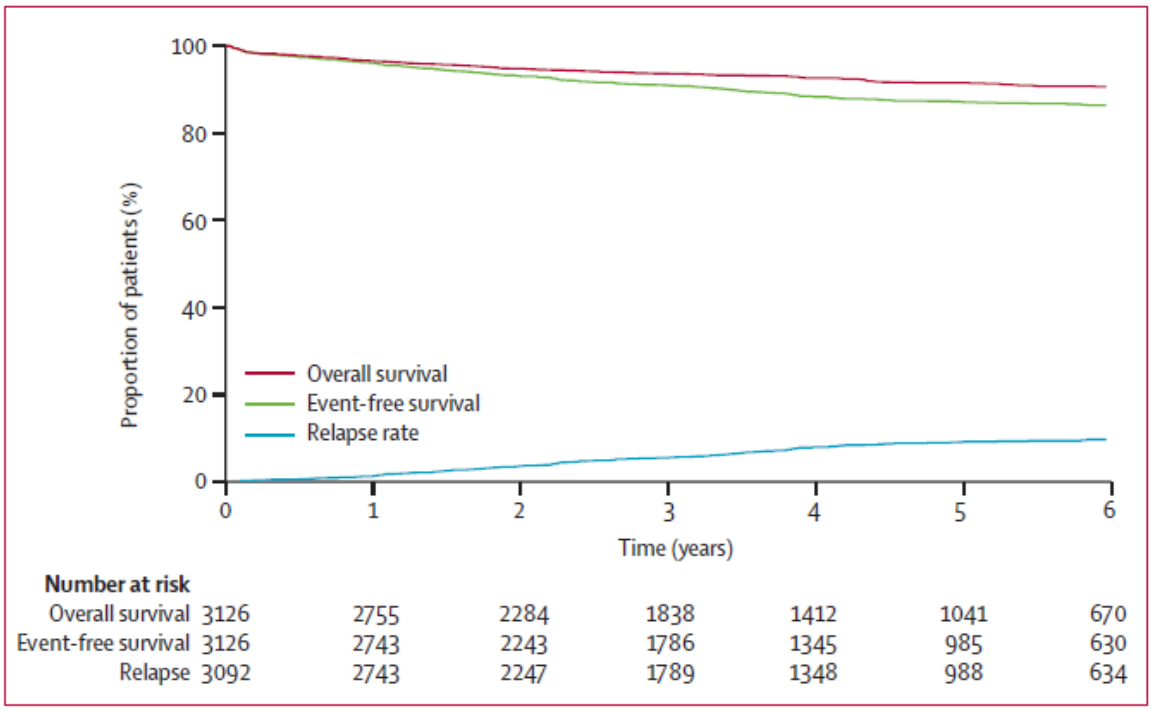
5.3.1.1 EFS and OS in Paediatric Patients

Paediatric OS rates have improved vastly over the past few decades. The 5-year EFS and OS estimates for those who completed asparaginase treatment were derived from the UKALL2003 trials results (2, 4). In the base case:

- 5-year OS: 95%, 90% and 80% for SR, IR and HR groups, respectively.
- 5-year EFS: 90%, 85% and 75% for the SR, IR and HR groups, respectively.

Visual examination of the overall survival curve presented in the UKALL 2003 study (2, 4) suggested a near linear pattern over time until 5 years (Figure 24).

Figure 24: Overall EFS and OS in the UKALL2003 study (2, 4)



Therefore, a fixed instantaneous rate of event (death and R/TS) over time was assumed. This instantaneous event rate was computed as follows:

$$\text{Rate} = -[\ln(1-x)]/5$$

with x being the 5-year probability of the event (for example 10% for a 5-year EFS of 90%)

For the relatively small number of patients who have had to discontinue asparaginase because of hypersensitivity to both 1st and 2nd line asparaginase, a reduction of 5% was assumed for EFS and OS (i.e. EFS when asparaginase discontinued = 0.95 x EFS when asparaginase completed) based on expert opinion).

When extrapolating to a lifetime time horizon, beyond the 5 years modelled in the DT, EFS patients were considered as cured (expert opinion) and were subject to general

mortality risk taken from the Office of National Statistics life table for England weighted by the male/female proportion reported in the UKALL 2003 study, i.e. 57% male and 43% female (2, 4, 97). No further transition to R/ST was allowed for these patients in the model. R/ST patients still alive at 5 years were also subject to the general mortality risk but increased by 90% (i.e. x1.9 general mortality; expert opinion). These patients could no longer transition to the EFS health state.

5.3.1.2 EFS and OS in Adults

Adult patients have a lower EFS and OS than paediatric patients. Results of recent trials suggest that up to 90% of children may be cured of their disease. Adult patients with ALL now have a 90% chance of entering first complete remission (CR) with modern chemotherapy. However, most patients still relapse, and leukaemia-free survival with three to seven years of follow-up is only 30-40% (12).

In Adults, it was assumed that EFS = OS according to expert opinion. Due to the successful EFS & OS results seen over several years in UKALL 2003 in paediatric and AYA patients, the adult UKALL14 protocol which is currently recruiting patients between 25 and 65 years old, now includes pegaspargase. This is the first time pegaspargase has been administered to adults as part of a UK treatment protocol and the protocol currently includes the paediatric established dose of 1,000 IU/m^2. As this protocol is still enrolling patients, data are not available for the UK adult population for pegaspargase when dosed at 1,000 IU/m^2. Therefore expert opinion was sought to support the inputs into the model.

The UKALL14 trial is further stratified between patients ≤40 years and ≥41 years, and because age is a key determinant of OS & EFS, it was assumed that the stated lower limit of 30% was applied to the patients ≥41 years, whilst the upper limit of 40% was applied to the patients <40 years.

Visual inspection of the OS curves published by Fielding et al 2008 (5) from multiple UKALL adult trials conducted in the UK suggested a non-linear pattern of survival over time.

Figure 25: Overall OS in UKALL trials in adults over 35 years (5)

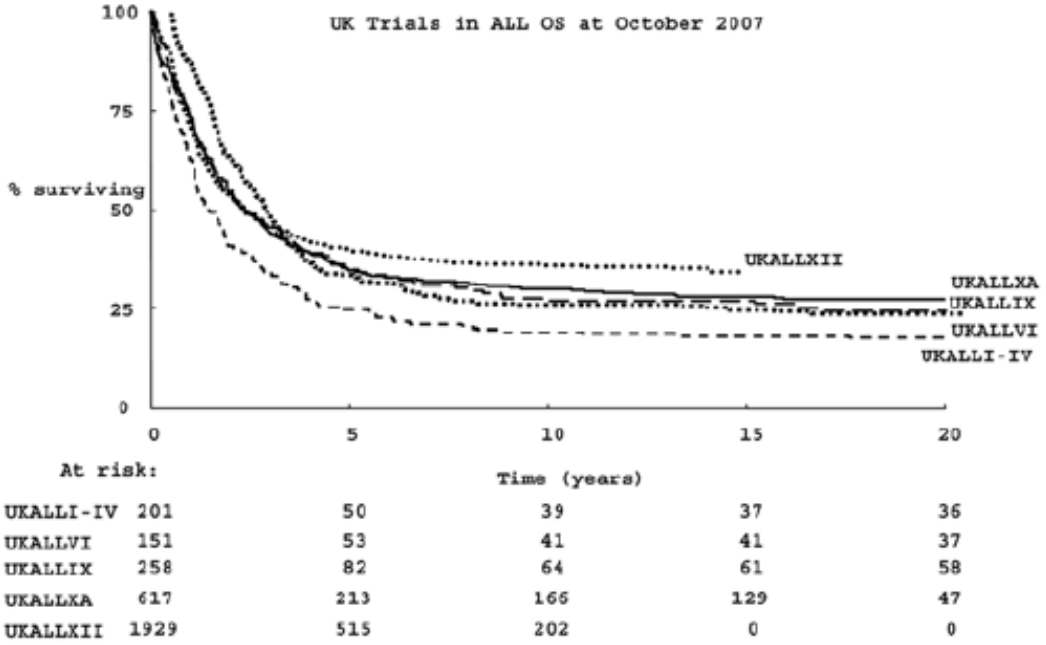


Figure 1. Successive UK trials in adult acute lymphoblastic leukemia (ALL) in the past 35 years: overall survival.

Therefore, a Weibull curve $S(t) = e^{-\alpha t^{\beta}}$ was fitted on 2 points: the 5-year OS reported in the UKALL14 protocol (assuming 40% for patients ≤40 years and 30% for patients ≥41 years) and the 40-year OS set at 0% (i.e. all patients would have died 40-year after ALL diagnosis and treatment initiation).

As for the paediatric patients, adults who have had to discontinue asparaginase because of recurrent hypersensitivities were applied an OS reduction of 5% (i.e. OS when asparaginase discontinued = 0.95 x OS when asparaginase completed).

In the absence of data, no distinction was made between male and female OS in adults.

5.3.1.3 Dose of pegaspargase

In the UKALL2003 and UKALL14 trial protocols pegaspargase has been dosed at 1,000 IU/m^2, regardless of age. This is the dose that UK clinicians, independent of any influence from the manufacturer, recognise as providing the appropriate risk-benefit profile for these patients, and continue to use in clinical practice. When comparing the long term outcomes of EFS and OS from >3,200 paediatric and young adult patients in UKALL 2003 with those from CCG-1962 (2,500 IU/m^2) and the pooled estimates generated from the wider evidence base, the UKALL regimens provide numerically superior outcomes to any other study, even at this reduced dose. The use of this reduced dose is therefore supported by a robust and substantial evidence base, in teerms of patients numbers treated, and has provided the clinical community with confidence in its continued use in two further UKALL protocols in both paediatric and young adult patients, and adult patients, respectively (UKALL 2011, and UKALL14).

5.3.1.4 Risk of hypersensitivity

A key concern with the use of asparaginase is the development of antibodies to the enzyme that can result in hypersensitivity reactions which would necessitate a switch to an alternative asparaginase formulation. The SmPC for Oncaspar states that hypersensitivity reactions of Grade 2 or higher are seen in ≥20% of patients treated with pegaspargase. This rate appears high but should be interpreted in the context that SmPC data was based on patients treated with the recommended dose of 2,000 to 2,500 IU/m^2 and includes some patients treated with 2nd line pegaspargase following hypersensitivity to native E. coli enzyme, a scenario known to increase the risk of hypersensitivity to pegaspargase (53-55).

In contrast, and of more relevance to UK clinical practice, when used in >3,000 patients in UKALL 2003 at the reduced dose of 1,000 IU/m^2 hypersensitivity reactions were experienced by only 2% of patients across the entire study treated with between 4 and 12 doses of pegaspargase (n=54/3,126), with a range of <1% seen in clinical SR patients and 6% in clinical HR patients.

Vora et al, in their publication of the UKALL 2003 protocol suggest that hypersensitivity rates of 20-40% are to be expected for native E. coli-derived asparaginase (2). Rates of hypersensitivity reported across studies identified by systematic review are variable and range from 0–13% for native E. coli asparaginase (see Table 29 and Appendix 4), compared with 0–8% for pegaspargase (Table 29), and in some cases no difference between the two preparations (CCG-1962 (11) and DFCI-91-01 (59)). However, these rates reflect only hypersensitivity of Grade 3 or higher, and when milder allergic reactions are also considered, significantly higher rates are observed with the native E. coli enzyme (p=0.02; DFCI-91-01 (59)). In additional studies of native E. coli enzyme Bowman et al report 13% Grade 3 or higher hypersensitivity, but 25% incidence of any grade hypersensitivity (COG P9906 (52)), while Wacker et al report 8% Grade 4 hypersensitivity, but 76% incidence of hypersensitivity leading to a switch in asparaginase formulation (POG 8602 (25)). Vrooman et al (DFCI 00-01 (86)) report 20% of patients developing hypersensitivity that required a switch to Erwinia-derived asparaginase.

Limited data was identified in the systematic review for Erwinia-derived asparaginase as a 1st line asparaginase and none comparing with pegaspargase; Moghrabi et al report that when used 1st line, 6% of Erwinia-treated patients develop hypersensitivity resulting in a treatment switch to native asparaginase (9). Note that a lower dose of Erwinase than is used effectively in clinical practice today was administered in the Moghrabi study, but the reported hypersensitivity rates were broadly consistent with the SmPC for Erwinia that reports hypersensitivity in the 1–10% range (9, 10).

Risk of hypersensitivity with each of the asparaginase formulations were taken from the literature as described above, and confirmed by expert opinions.

- For pegaspargase, risk of hypersensitivity leading to treatment switch was assumed to be 2% for both 1st and 2nd line asparaginase therapy, based on 1st line hypersensitivity observed in UKALL 2003 (2, 4). In the absence of data, 2nd line hypersensitivity data was assumed to be equivalent that seen in 1st line. As described previously, UKALL 2003 was considered the most appropriate study

given that it accounts for the vast majority of ALL treatment in the UK at a dose of 1,000 IU/m^2. The rates were also validated by the experts.

- For native E. coli asparaginase, risk of hypersensitivity was assumed to be 20% for both 1st (86) and 2nd line (assumed to be the same as for the 1st line).
- For Erwinase, risk of hypersensitivity was assumed to be 6% for 1st line (9) and 37% for 2nd line (98). For hypersensitivity at 1st line, a lower dose of Erwinase than is used effectively in clinical practice today was administered in the Moghrabi study, but the reported hypersensitivity rate (6%) is broadly consistent with the SmPC for Erwinia that reports hypersensitivity in the 1–10% range (9, 10).

A discussion on published hypersensitivity rates for all three asparaginase formulations is provided in Section 4.14.

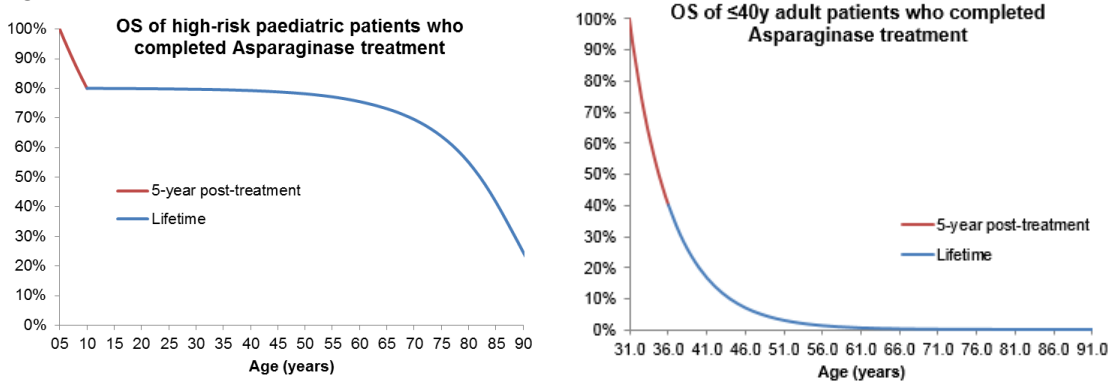
Risks of hypersensitivity were assumed to be the same for both paediatric and adult patients, as validated by expert opinion.

5.3.2 *Transition probabilities (99)*

The Markov model does not use transition probabilities per se but uses the survival curves to model the patient population evolution through the OS, EFS and the R/ST (Paediatric) health states. Similarly, the survival curve is used to model patient population evolution from live to death in Adults (EFS=OS assumption).

Illustrations of survivorship functions are provided in Figure 26 for the OS of high-risk paediatric patients (baseline age of 5 years) and ≤40 years adult patients (baseline age of 31 years) who completed asparaginase treatment.

Figure 26: Illustrations of survival curves



5.3.3 *Clinical expert assessment of applicability of clinical parameters*

Baxalta sought the advice of clinical experts to assess the applicability of the clinical parameters and to approximate some of the clinical parameters where relevant UK data was lacking.

Four clinical experts were approached, with one paediatric and one adult specialist agreeing to participate in this activity.

When selecting the clinicians to approach, Baxalta considered the following:

- Clinician experience of all three asparaginase products under consideration (Pegaspargase, native asparaginase and Erwinase).
- Clinicians actively involved in the current adult and paediatric trials, who had a knowledge of the current and historic protocols.
- Clinicians who are actively involved in ALL treatment.

This was to ensure the difference between the products under consideration could be assessed, in light of the paucity of head-to-head data, especially considering that the native asparaginase product has not been routinely used in the NHS in paediatric patients since before the UKALL 2003 trial and prior to the UKALL14 adult trial and as Erwinase is usually reserved for 2nd line use.

Baxalta shared the relevant model schematic and a list of questions with each clinical expert prior to interview, to give them time to consider their responses. This was specific to the patient population (paediatric or adult) they had particular expertise in. This was followed up by a direct interview with each clinician.

Paediatric expert feedback

As pegaspargase has formed part of routine clinical practice as 1st line asparaginase therapy since 2003, there is extensive experience in the use of the product in this setting. Conversely, as the native asparaginase product had not been used in clinical practice for a number of years, the expert commented that junior doctors are no longer used to dealing with hypersensitivity reactions as they occur so infrequently with pegaspargase.

The paediatric expert also validated the model structure as an accurate representation of the UKALL 2003 protocol and endorsed the rates of hypersensitivity used for the three products in the model.

The expert also stated that, in the UKALL 2011 study, there are blocks of steroids given in induction so if native E.coli asparaginase or Erwinase are used instead of pegaspargase there would “likely be increased hypersensitivity rates” when injected during the days where no steroids are given. In contrast, pegaspargase will be given during steroid dosing, meaning that any hypersensitivity with pegaspargase, although rare, will mostly occur in the consolidation stage. According to basic principles of immunology, hypersensitivity predominantly occurs on the 2nd asparaginase dose meaning a switch to another asparaginase for the 3rd dose. This supports the rationale for our model applying hypersensitivity incidence at induction for the native asparaginase and Erwinase products, as the 3rd dose of these asparaginases would be given during this phase of treatment.

The expert stated that a benefit of using pegaspargase was its sustained half-life, meaning fewer injections are required. For every six injections of either native asparaginase or Erwinase, only one of pegaspargase is required, and this will have a substantial impact on both the patient and their carer (in terms of pain, hypersensitivity risk, events like bruising, etc) and the NHS (in terms of increased administrations and observation time). After induction, most paediatric patients are treated as day cases, such that using pegaspargase may result in a reduction in hospital visits (depending on the other treatments required).

Overall survival for standard risk patients has increased by 10% from the ALL97-99 trial to UKALL 2003 and the substitution of native E.coli asparaginase with pegaspargase was suggested to play an important part to this improvement.

Adult expert feedback

Due to the success of using pegaspargase in the paediatric population, a UK-specific protocol was recently commenced (UKALL14), which covers around 85% of the adult patients in UK. In addition, adults not actively participating in the trial receive the protocol regimen of pegaspargase. The protocol formed the basis for our economic model as it reflects the current way that pegaspargase is used in the UK for Philadelphia negative patients. Unfortunately, no outcome data is yet available for this patient population from UKALL14.

Due to the lack of published adult data representative of the way in which patients are treated in the UK (according to the current UKALL 14 protocol), the adult clinician stated that the paediatric data relating to hypersensitivity could be used as a proxy for the adult population.

When questioned on the time it takes for a hypersensitivity reaction to occur, the expert commented that this is likely to happen early in the treatment phase, typically at the 2nd or 3rd administration of either of the three products. As for the paediatric population, this is our rationale for enabling the model's functionality to account for hypersensitivity during the induction phase for the native E.coli asparaginase and Erwinase products. As there is a maximum number of two infusions of pegaspargase given during induction for adult patients, these patients would likely only have a hypersensitivity reaction to pegaspargase post-induction, consistent with the approach taken for paediatric patients.

The expert advised using equivalent 5-year OS and EFS rate as a conservative estimate for adults. This is a key parameter evaluated by the current UKALL14 trial.

The expert stated that we can reasonably assume OS and EFS equivalence between pegaspargase, native E.coli-derived asparaginase and Erwinase.

When asked on the dosing equivalence of native asparaginase or Erwinase, the expert advised that every intravenous infusion of pegaspargase is replaced by six IM injections of either native E.coli enzyme or Erwinase. They stated that the adult population was prone to thrombocytopoenia, and thus commonly experience pain and bruising when having an injection

The expert stated that equivalence in AE rates could be assumed between the different types of asparaginase, especially as the side effects (e.g. abnormal liver function tests) are likely to be attributable to the asparaginase itself, rather than the specific formulation.

Quality of life/ Patient experience

- IM injections are very painful and a lot of patients develop bruising due to thrombocytopenia
- When patients experience hypersensitivity, this is usually an anaphylactic episode, which can be very frightening for the patient, especially as it can be life-threatening. Patients also have a delay in their treatment whilst this is resolved,

during which time, they feel as if “nothing is being done” for what is a very serious condition.

The above factors are likely to cause anxiety, pain, decreased mobility/activities of daily living and have a detrimental effect on QoL.

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

There was no health-related quality of life data available from clinical trials.

5.4.2 *Mapping*

There was no mapping carried out for health-related QoL data. QoL data used in the model were derived from the literature (43, 100).

In addition, patient level data was unavailable to undertake any mapping activity.

5.4.3 *Health-related quality-of-life studies*

A comprehensive search of the peer-reviewed literature was conducted to identify and select relevant health related quality of life studies. Overall objectives of the search have been described previously in Section 5.1.1.1

5.4.3.1 Search strategy

Databases

The following sources were used for search:

- Medline (via the Pubmed – NLM platform), all records from treatment inception to December 31, 2015
- Embase (via the OVID platform), all records from treatment inception to December 31, 2015
- Cochrane Database of Systematic Reviews 2005 to December 31, 2015
- EBM Reviews - Cochrane Central Register of Controlled Trials December 2015
- EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012
- EBM Reviews - ACP Journal Club 1991 to December 2015
- EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2015
- EBM Reviews - Health Technology Assessment 4th Quarter 2015
- NHS Economic Evaluation Database 4th Quarter 2015

Study population, and intervention and clinical comparators have been described previously in Section 5.1.1.2. Full details of the search strategy are provided in Appendix 8.

Measurement of health effects

To ensure broad inclusion of studies reporting specific health-related QoL data of newly-diagnosed ALL patients eligible for treatment with asparaginase as part of a chemotherapeutic protocol, the search was run without recourse to any intervention

filters (asparaginase). This opens a broader field of results for this review. A number of health-related quality of life terms were included in the search but limited to the abstract or title. The same process was used for Embase by using the Embase Thesaurus.

5.4.3.2 Study Selection

Limits

Limits were applied (where the databases allowed) to exclude studies carried out on animals as well as to limit returns to English Language studies and to studies for which an abstract was available.

Inclusion and exclusion criteria

- Inclusion criteria: Studies focused on the treatment of newly-diagnosed ALL patients reporting patient related outcomes of treating ALL patients with a chemotherapeutic protocol that includes at least one asparaginase as 1st line or 2nd line agent (second line being defined here as post-hypersensitivity event during the first course of a chemotherapeutic treatment of ALL).
- Studies that provided data for measuring or evaluating health effects of the main intervention used in a clinical setting (can include clinical studies comparing the main intervention to relevant clinical comparators)

Exclusion criteria:

- Studies not directly evaluating or measuring the health effect of at least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patient.
- Studies in refractory/relapsed ALL patients defined as at a minimum the second course of chemotherapy following a relapse or for refractory ALL patients
- Non-English language studies
- Studies that includes other malignancies besides ALL
- Comments, editorials, systematic reviews, reviews

Table 38: Included HRQL studies

Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes
DFCI-95-01	Furlong 2012 (43)	USA/ Canada	Comparative, asparaginase preparations (native vs. Erwinase) vs. controls	Child (n=749)	HRQL scores to calculate QALYs measured using HEALTH UTILITIES INDEX® (HUI®) Mark 2 (HUI2) and Mark 3 (HUI3)	Treatment phases - Induction - Consolidation / Intensification - Maintenance	Standard and high risk patients were treated with one of two types of asparaginase, native or Erwinia asparaginase, beginning in the induction phase	Reduction of 0.172 QALYs or 63 QALDs with native vs. controls. The difference (native minus Erwinase) in mean HRQL scores for HUI2 was -0.05 (0.88 – 0.93, p=0.005) and for HUI3 was -0.07 (0.85 – 0.92, p=0.007) in favour of Erwinase.
DFCI 05-001	Place 2015 (30)	USA Canada 2005-2010	Comparative efficacy of PEG vs native in treating young patients with newly diagnosed ALL	Patients with newly diagnosed ALL aged 1-18 years who achieved complete remission	Toxicity of PEG vs Native Secondary Endpoint: Efficacy, Ab formation, ASPase activity, QoL, MRD,	- Induction - Consolidation - Reinduction - Maintenance	Randomization at consolidation PEG 2500 IU/m^2 i.v.: Induction: 1 dose Consolidation: 15 doses (every 2 weeks) All phases 1st line Native: 25000 IU/m^2 i.m.: Consolidation: 30 doses (weekly) No Induction 2nd Line	In both the parent-proxy report and the patient report, significantly more treatment and procedural anxiety was reported in the Native group than in the PEG group at both T1 & T2 (T1 - Before the first post-induction dose of asparaginase T2 - During asparaginase treatment between weeks 10 and 15 of consolidation phase 2)
BFM Protocols AIEOP 2000 / A5971 / 99–04 / 99–05 / AALL0331 / AALL0232 / AEIOP 91-01 / AEIOP 91-	Rae 2014 (101)	USA Canada Italy 1996-2010	Two-arm uncontrolled comparison of health effects and monetary costs of hospital treatments for BFM and DFCI consortia's treatment	Child 0-18 On-therapy or Off-therapy patients treated according to a BFM-based or DFCI protocol	QALYs per patient Mean monetary costs to hospitals	BFM vs. DFCI	Lower doses of asparaginase with BFM than with DFCI protocol	No significant difference between treatment intensity groups Mean HRQL was lowest during the first treatment phase and highest during the off-therapy phase HRQL score from phase 1 (induction) to 5 (off-therapy) BFM => 0.72 - 0.92

Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes
03 / AEIOP 95-01 / AEIOP 95-02 DFCI Protocols 95-01 / 2000-01			strategies					DFCI => 0.66 - 0.90 QALYs - 5-yr period (0 - 3 - 5% discount) BFM => 4.40 - 4.14 - 3.99 DFCI => 4.37 - 4.12 - 3.96
DCOG ALL-10 vs. DCOG ALL-9	Van Litsenburg 2010 (102)	Dutch	Single-centre comparison of QoL and costs associated with DCOG ALL-10 (incl PEG) vs. DCOG ALL-9 (incl native)	Child (n=33)	QoL, direct costs of care, and costs per QALY for the two most recent Dutch ALL protocols; DCOG ALL-10 (incl PEG) vs. DCOG ALL-9 (incl native)		ALL-10 (incl PEG) vs. ALL-9 (incl native)	Clinically important difference in overall QoL in favour of PEG protocol (scores 0.80 vs. 0.85). Mean direct medical costs were between €85,821–127,255, depending on risk group. In-hospital days and daycare accounted for 50%; 33% was spent during the induction phase. Costs per QALY were €3,871–8,708. Costs per QALY gained for treatment according to PEG protocol were €19,730
DFCI-ALL protocol intensification therapy	Vrooman 2014 (103)	USA	Comparison of HRQL in a randomised clinical trial in children/ adolescents with ALL receiving either IV PEG or IM native	Child (n=202)	HRQL	Treatment phases - Consolidation / Intensification	IM native weekly or IV PEG every-other-week over 30 weeks	Significant difference in Treatment Anxiety (p=0.024), and in Procedural Anxiety, with greater anxiety reported with the IM native arm

Abbreviations: ALL, acute lymphoblastic leukaemia; HRQL, health-related quality of life; IM, intramuscular; IV, intravenous; native, native E.coli-derived asparaginase; PEG, pegaspargase; QALD, quality adjusted life day; QALY, quality adjusted life year.

5.4.4 *Key differences*

Not applicable. QoL data was not available from clinical trials or from mapping exercises.

5.4.5 *Adverse reactions*

The differentiating factor between the different types of asparaginase products modelled is the rate of hypersensitivity, which was endorsed by the clinical experts, and literature (See Section 5.3.1.3).

Expert clinicians reported that IM injections are very painful and a lot of patients develop bruising due to thrombocytopenia, especially adult patients, who receive native E.coli asparaginase and Erwinase via IM injections. As pegaspargase has fewer IM injections in paediatric patients and is administered intravenously in adults, this effect is not as profound. No data was available to allow a utility decrement for IM versus IV administration to be estimated. As such the model conservatively does not account for this difference.

The clinical expert stated that when adult patients experience hypersensitivity, this is usually an anaphylactic episode, which can be very frightening for the patient, especially as it can be life-threatening. Patients will also have a delay in their treatment whilst this is resolved, during which time, they feel as if “nothing is being done” for what is a very serious condition.

These factors are likely to cause anxiety, pain, decreased mobility/ activities of daily living, which are domains in the EQ-5D, but this data is not currently available.

In order to model the detrimental effect of a hypersensitivity reaction, in the absence of trial data, a utility decrement from a NICE clinical guideline for anaphylaxis of 0.014 was applied to reflect the impact of hypersensitivity on patient health-related quality of life (NICE CG 134, table 12 (104)). This value was derived assuming 5 days QoL lost per recurrence of anaphylaxis equating to a utility decrement of 5/365.25 or 0.014). This was assumed to be the most relevant estimate for the UK population.

5.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

In the absence of UK-specific health-related quality of life data for ALL, the relative differences between population norms and the ALL treatment phases reported by Furlong et al. 2012 (43) using the HUI2 and HUI3 (Table 38) were applied to published UK EQ-5D population norms (105), adjusting for baseline patient age. We could not map the HUI data to obtain EQ5D values as the patient level data was unavailable.

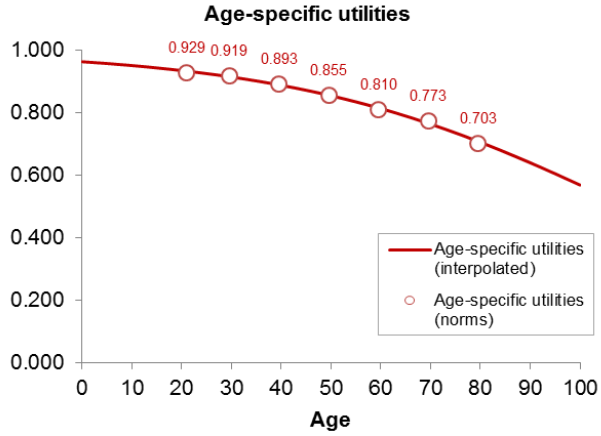
The published UK EQ-5D population norms values were interpolated with a logistic regression (105), EQ-5D index population norms UK England-specific TTO value sets Table 3.6, p. 30), shown in Figure 27. Utilities as reported by Furlong et al and calculated utility decrement from UK norms are shown in Figure 28 and Table 39.

Table 40 shows how the calculated utility decrements were applied in each treatment phase for both paediatric and adult patients.

In addition, a 20% utility decrement from age-adjusted population norms for paediatric patients in the R/ST health state was assumed.

At the end of treatment, patients were assumed to return to population norms again.

Figure 27: Interpolated age-specific utilities (EQ-5D population norms)



Interpolated age-specific EQ-5D population norms, $U(age) = \frac{1}{1+e^{(0.030.age+3.259)}}$, with R^2=0.995.

Figure 28: Utility decrement during treatment phases as reported by Furlong et al. 2012 with the HUI2 and HUI3 (43)

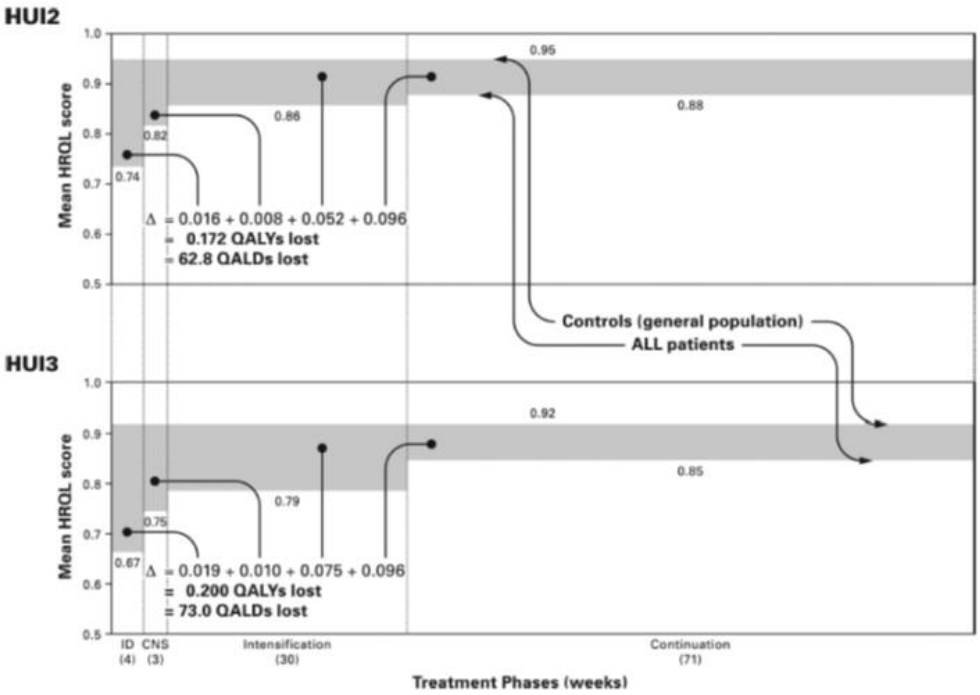


Fig. 1.
Quality-adjusted life years (QALYs) and days (QALDs) lost by ALL patients during active treatment phases according to HUI2 and HUI3 systems. During induction, CNS and intensification treatment phases there were no differences in mean HRQL scores between E. coli and Erwinia asparaginase treatment groups so the results for these 3 phases are based on pooled data from both groups. During continuation there were significant differences in mean HRQL between the asparaginase groups so the results for this phase are based on data from only the E.coli group.

Table 39: Relative utility decrements calculated from Furlong et al. 2012 (43)

Population norms				
HUI2	0.95	0.95	0.95	0.95
HUI3	0.92	0.92	0.92	0.92
ALL treatment phase	**Ind.**	**CNS**	**Int.**	**Cont.**
HUI2	0.74	0.82	0.86	0.88
HUI3	0.67	0.75	0.79	0.85
Relative utility decrement				
HUI2	22%	14%	9%	7%
HUI3	27%	18%	14%	8%
Average	**25%**	**16%**	**12%**	**7%**

Abbreviations: Ind., induction; CNS: central nervous system; Int., intensification; Cont., continuation.

Table 40: Utility decrements applied in the model

Paediatric	Ind.	Cons.	IM 1	DI 1	IM 2	DI 2	Cont.	End week
	25%	16%	12%	12%	12%	12%	7%	0%
Adults	Ind.	Int.	Cons. 1	Cons. 3	Maint.	End week		
	25%	25%	12%	12%	7%	0%		

Abbreviations: Ind., induction; Int., intensification; Cons.,consolidation; Cont., continuation; Maint., maintenance; IM, interim maintenance; DI, delayed intensification.

5.4.6.1 Clinical expert assessment of applicability of health state utility values

In the absence of formal health-related quality of life data in ALL, the experts consulted could not comment on the health state utility values and assumptions. Nevertheless, they stressed the fact that anaphylaxis was a frightening experience for patients. They also stated that an increased number of injections, when switched from pegaspargase to native asparaginase or Erwinase, impacted negatively on the patient experience.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 *Resource identification, measurement and valuation studies*

Studies reporting resource use, as identified in the systematic review described in Section 5.1, are summarised in Table 41.

Table 41: Studies reporting resource data

ASP/ Phase	Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes	Applicability to clinical practice in England
Native vs PEG	Cost-minimisation analysis of native vs. PEG	Peters 1995 (106) *Hoelzer* *Linker* *Goettlieb*	USA	Cost-minimisation analysis of native vs. PEG	Adults	Costs per treatment phase, chemotherapeutic protocol, and patient stay	Treatment phases - Induction - Consolidation / Intensification - Maintenance	*Hoelzer Paper* Native at 5,000 U/m /day (IV) on days 1 to 14. PEG at 2,000 IU/m (IV) on day 1 only. *Linker Paper* Native at 6,000 IU/m (IM) on days 17 to 28 (12 days) for induction, 12,000 IU/m (IM) on days 2, 4, 7, 9, 11, and 14 (6 days) for consolidation. PEG at 2,500 IU/m (IM) on day 1 only for induction, dose on day 1 only for consolidation *Gottlieb Paper* Native at 500 IU/kg on days 22 to 31 (10 days) for induction therapy. PEG at 2,500 IU/m (IV) on day 1 only	*Hoelzer Paper* PEG cheaper regardless of dose, patient weight/ body surface area, or inpatient or outpatient administration Savings were $3,790.70 or $4,770.70, depending on the size of the patient. In the outpatient setting, PEG savings of $475.70 to $1,455.70. *Linker Paper* Induction, PEG saves $3,554.50 to $3,905.94 per patient. Outpatient save of $749.50 to $1,100.94 Consolidation therapy, PEG savings dependent on patient size. Combined total charges, save for PEG of $434.72 to $5,531.88, depending on patient size. *Gottlieb Paper* Induction, PEG savings of $3,632.58 per patient. Total outpatient charges showed savings of $1,337.58 per patient for PEG.	Not Applicable, Different protocol and treatment Scheme
Native	To determine the overall costs of ALL	Rahiala 2000 (107)	Nordic	To determine the overall costs of ALL	Child (n=11)	Direct and patient-specific costs for overall ALL treatment	Treatment phases - Induction - Consolidation / Intensification	Induction schedule consisted of Pred (60 mg/m^2 for 6 wk), weekly Vcr and Doxo, four doses of intrathecal Mtx and a 10-day course of native. Delayed intensification for IR and HR patients included Dexa (10 mg/m^2 for 4 wk), 6-thioguanine (60 mg/m^2 for 2 wk), four	Total direct costs per patient with ALL were, on average, $103,250 ($74,342, $91,207 and $136,973 for children with SR, IR and HR ALL). Induction therapy accounted for $36,254 per patient. The price of intensification was $5,705/m^2 according to SR protocols, $11,171/m^2 according to IR protocols,	Not Applicable, Different protocol and treatment Scheme

ASP/ Phase	Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes	Applicability to clinical practice in England
								doses of Vcr, Dauno and native, one dose of Cyclo (1 g/m^2) and Ara-C in repeated pulses	and \$2,453/m^2 according to HR protocols. \$48,276 (47%) could be assessed as patient-specific costs. Therapy accounted for \$30,201 (\$12,553–58,027) per patient, of which induction therapy accounted for 40%. Whole treatment of ALL required 150 hospital days, and the total costs were about \$100,000 per patient. The treatment costs varied markedly among risk groups. Although induction accounted for 35% of all costs, cytostatic drugs accounted for only 13%. Thus, anticancer chemotherapy was only a minor expense in cancer treatment.	
Native vs PEG	CCG 1962	Kurre 2002 (108)	USA	Comparison of native and PEG	Child (n=118)	Average wholesale price less 15% for native is \$48.28 for the 10,000- unit vial and PEG is \$1,182.53 for the 3,750- unit vial. These vial costs range from \$40 to \$183 native and \$1,113 to \$1,477 for PEG. Inpatient costs were derived by multiplying the average length of stay by the median cost provided by the participating	Treatment phases - Induction - Delayed Intensification 1 & 2	PEG received one dose, 2,500 units/m^2, in each of three phases: induction, DI1, and DI2. Patients assigned to receive native received nine doses at 6,000 units/m^2 during induction and 6 doses in each delayed intensification phase, administered 3 times a week	Overall therapy costs were similar. Patients treated with PEG incurred total medical and nonmedical cost of \$13,261 during induction, compared with \$14,989 for native. Taking all 3 phases into account, the payer cost for PEG therapy was \$667 (2%) higher than native therapy. Societal costs were similar in both arms, with only a \$12 (<1%) difference favouring the native arm	Not Applicable, Different protocol and treatment Scheme

ASP/ Phase	Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes	Applicability to clinical practice in England
						institutions. The median daily inpatient cost was $1,296 (range, $940 to $2,211).				
Native vs PEG	DCOG ALL-10 vs. DCOG ALL-9	Van Litsenburg 2010 (102)	Dutch	Single-centre comparison of QoL and costs associated with DCOG ALL-10 (incl PEG) vs. DCOG ALL-9 (incl native)	Child (n=33)	QoL, direct costs of care, and costs per QALY for the two most recent Dutch ALL protocols; DCOG ALL-10 (incl PEG) vs. DCOG ALL-9 (incl native)		ALL-10 (incl PEG) vs. ALL-9 (incl native)	Clinically important difference in overall QoL in favour of PEG protocol (scores 0.80 vs. 0.85). Mean direct medical costs were between €85,821–127,255, depending on risk group. In-hospital days and daycare accounted for 50%; 33% was spent during the induction phase. Costs per QALY were €3,871–8,708. Costs per QALY gained for treatment according to PEG protocol were €19,730	Not Applicable, Different protocol and treatment Scheme
Native vs PEG	DCOG ALL-10 vs. DCOG ALL-9	Van Litsenburg 2011 (109)	Dutch	Retrospective cost-effectiveness analysis of treatment with DCOG ALL-10 (incl PEG) vs. DCOG ALL-9 (incl native) chemotherapy	Child (n=50)	Costs per LYS were calculated. The cost-effectiveness ratio determined. LYS calculated based on national 5-year event-free survival	Treatment phases - Induction - Consolidation / Intensification - Maintenance	ALL-10 (incl PEG) vs. ALL-9 (incl native)	Mean total costs were $115,858 (ALL-9) and $163,350 (ALL-10) per patient. Hospital admissions (57%) and medication (11–17%) were important drivers. Costs per LYS were $1,962 (ALL-9) and $2,655 (ALL-10) and the cost-effectiveness ratio was $8,215 ALL-10 was cost-effective even with a relatively short life expectancy of 42.5 years	
Native vs PEG	Cost-minimisation analysis of	Bauters 2013 (110)	Belgium	Cost-minimisation analysis of PEG vs.	Child (n=37)	Direct drug cost (per vial) plus hospital cost per day-clinic visit or daily hospital cost	Treatment phases - Induction	Treatment according to EORTC 58081 protocol	If a patient was treated exclusively with one product, the cost per patient per treatment was €4,487	Not Applicable, Different protocol and

ASP/ Phase	Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes	Applicability to clinical practice in England
	PEG vs. native over 1 year			native over 1 year		Other costs and indirect costs were not included			(native), €50,326 (Erwinase) and €4,717 (PEG). Total cost for the Belgian population is estimated at €738,269 for patients started on first-line native and €434,801 for PEG. Mean cost per patient was €10,547 for first-line native and €6,211 for PEG, indicating a cost reduction of 40%	treatment Scheme
Native vs PEG	DCOG ALL-10	Tong 2013 (56)	Dutch	Cost-analysis of native vs. PEG vs. Erwinase	Child (n=84)	Treatment costs were calculated based on patient level data, and related to the occurrence of allergy to PEG	Treatment phases - Consolidation / Intensification	Hypothetically: native (5,000 IU/m2, twice weekly) for a duration of 30 weeks. Peg IV 2,500 IU/m2 every 2 weeks. Erwinase 20,000 IU/m2 3x wk	Overall costs of treatment with native, followed by a switch to PEG, and then to Erwinase (in case of allergy) were $70,402. This was equivalent to PEG as first- line (followed by Erwinase in case of allergy), which had overall costs of $71,810. The costs were highest when using native in the first-line followed by Erwinase second line ($103,474)	Not Applicable, Different protocol and treatment Scheme
Native	<u>BFM Protocols</u> AIEOP 2000 / A5971 / 99–04 / 99–05 / AALL0331 / AALL0232 / AEIOP 91-01 / AEIOP	Rae 2014 (101)	USA Canada Italy 1996-2010	Two-arm uncontrolled comparison of health effects and monetary costs of hospital treatments for BFM and DFCI consortia's treatment	Child 0-18 On-therapy or Off-therapy patients treated according to a BFM-based or DFCI protocol	QALYs per patient Mean monetary costs to hospitals	BFM vs. DFCI	Lower doses of asparaginase with BFM than with DFCI protocol	No significant difference in mean total treatment cost between treatment intensity groups <u>Treatment costs per patient (0 - 3 - 5% discount)</u> BFM => $96,898- $88,704 - $88,480 [33,354] DFCI => $94,233 - $93,494 - $93,026 [48,284]	Not Applicable, Different protocol and treatment Scheme

ASP/ Phase	Study	Author year	Country(ies)	Aim of the study	Population	Primary Outcome Measures	Treatment phases	ASP exposure & Drug Dose	Outcomes	Applicability to clinical practice in England
	91-03 / AEIOP 95-01 / AEIOP 95-02 DFCI Protocols 95-01 / 2000-01			strategies						

Abbreviations: ALL, acute lymphoblastic leukaemia; IM, intramuscular; IV, intravenous; native, native E.coli-derived asparaginase; PEG, pegaspargase.

5.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

Asparaginase forms the backbone of chemotherapeutic regimens used in current clinical practice. As three different types of asparaginase are being compared in the model (native E.coli asparaginase, pegaspargase and Erwinase), with the remainder of the chemotherapeutic regimen unaltered, only costs associated with the three asparaginase products were modelled, some of which were derived from NHS reference costs or PbR tariffs.

The main difference between the products is their associated risk of a hypersensitivity reaction. The reference cost for "Allergy or Adverse Allergic Reaction", HRG WH05Z, was used (2014/15 £470) (111). This was used for each hypersensitivity reaction, and is potentially an underestimate, especially for patients requiring an ITU stay due to a life-threatening reaction. For comparison purposes the elective unit cost for HRG WH05Z is substantially higher (£1,840) (111) than the average used in the model .

Costs used for administration time required for each injection or infusion were considered to be equivalent, with each assumed to take half an hour. Due to the risk of hypersensitivity of all asparaginase products, patients should be monitored for an hour post injection or infusion, as per pegaspargase SmPC. This is especially important should a patient develop an anaphylactic reaction, where prompt intervention can be life-saving. As all forms of asparaginase carry a risk of hypersensitivity, this was assumed to also be clinically relevant for native E.coli-derived asparaginase and Erwinase.

Due to the nature of the intervention, a minimum of a band 6 nurse would be required to treat the patient. Relevant costs are listed below, as derived from PSSRU (112):

- **Administration cost**: half hour, band 6, patient contact = £54.50
- **Monitoring cost**: 1 hour per SmPC, band 6, patient contact = £109
- **Total cost per injection/ infusion** = £163.50

The adult clinical expert stated that most adult patients are ill enough to require all phases of their treatment in hospital, whereas the paediatric expert stated that, although the induction treatment phase for paediatric patients occurs in a hospital (in-patient) setting, subsequent treatment phases usually occur in a day-case setting.

As the clinical experts advised that for every 1 dose of pegaspargase, six doses of either native E.coli asparaginase or Erwinase would be required, there could be up to five extra day-case visits attributable to the comparators, the tariff costs for which are listed in Table 42. As such, native E.coli enzyme and Erwinase could both be associated with an additional cost of £1,630 for every set of six doses compared with pegaspargase (five extra administrations for eligible patients). However, we have not accounted for this in the model meaning that the analysis is extremely conservative, and we have just applied a standard cost of administration and monitoring as listed above.

Table 42: Day-case related HRG codes for chemotherapy

Description	Unit Cost	Reference
Chemotherapy delivery – first attendance	£389	NHS Ref Costs 2014/15* - HRG code SB14Z (111)

Description	Unit Cost	Reference
Chemotherapy – subsequent attendance	£326	NHS Ref Costs 2014/15* - HRG code SB15Z (111)

5.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

The experts consulted couldn't comment on the cost values and assumptions.

5.5.2 *Intervention and comparators' costs and resource use*

Table 43 summarises the frequency and dosing of the different asparaginase formulations by treatment phase. Pegaspargase dosing was taken from the paediatric UKALL2003 protocol and the adult UKALL14 protocol.

According to experts, six native E.coli asparaginase and Erwinase dosing would correspond to one pegaspargase dose. This is supported by the UKALL 2011 protocol, appendix 19, which states that (in case of hypersensitivity) each dose of pegaspargase should be replaced with 6 doses of Erwinase (3).

Table 43: Asparaginase dosing and frequency

Paediatric/AYAs UKALL2003	**Ind.**	**Cons.**	**IM 1**	**DI 1**	**IM 2**	**DI 2**	**Cont.**
High-risk							
Week	*1 w*	*5 w*	*14 w*	*22 w*	*30 w*	*38 w*	*46 w*
PEG-Asp.	2 × 1,000 IU/m²	2 × 1,000 IU/m²	2 × 1,000 IU/m²	2 × 1,000 IU/m²	2 × 1,000 IU/m²	2 × 1,000 IU/m²	
Native E.Coli Asp.	12 × 10,000 IU/m²	12 × 10,000 IU/m²	12 × 10,000 IU/m²	12 × 10,000 IU/m²	12 × 10,000 IU/m²	12 × 10,000 IU/m²	
Erwinase	12 × 20,000 IU/m²	12 × 20,000 IU/m²	12 × 20,000 IU/m²	12 × 20,000 IU/m²	12 × 20,000 IU/m²	12 × 20,000 IU/m²	
Intermediate risk							
Week	*1 w*	*5 w*	*10 w*	*18 w*	*25 w*	*33 w*	*40 w*
PEG-Asp.	2 × 1,000 IU/m²			1 × 1,000 IU/m²		1 × 1,000 IU/m²	
Native E.Coli Asp.	12 × 10,000 IU/m²			6 × 10,000 IU/m²		6 × 10,000 IU/m²	
Erwinase	12 × 20,000 IU/m²			6 × 20,000 IU/m²		6 × 20,000 IU/m²	
Standard-risk							
Week	*1 w*	*5 w*	*10 w*	*17 w*	*24 w*	*32 w*	*39 w*
PEG-Asp.	2 × 1,000 IU/m²			1 × 1,000 IU/m²		1 × 1,000 IU/m²	
Native E.Coli Asp.	12 × 10,000 IU/m²			6 × 10,000 IU/m²		6 × 10,000 IU/m²	
Erwinase	12 × 20,000 IU/m²			6 × 20,000 IU/m²		6 × 20,000 IU/m²	

Adults UKALL14	**Ind.**	**Int.**	**Cons.** *(for those ineligle for transplant)*			**Maint.**
			Cycle 1	*Cycle 2*	*Cycle 3*	
≤40y						
Week	*1 w*	*9 w*	*13 w*		*17 w*	*25 w*
PEG-Asp.	2 × 1,000 IU/m²	2 × 1,000 IU/m²	1 × 1,000 IU/m²		1 × 1,000 IU/m²	
Native E.Coli Asp.	12 × 10,000 IU/m²	12 × 10,000 IU/m²	6 × 10,000 IU/m²		6 × 10,000 IU/m²	
Erwinase	12 × 20,000 IU/m²	12 × 20,000 IU/m²	6 × 20,000 IU/m²		6 × 20,000 IU/m²	
≥41y						
Week	*1 w*	*9 w*	*13 w*		*17 w*	*25 w*
PEG-Asp.	1 × 1,000 IU/m²	2 × 1,000 IU/m²	1 × 1,000 IU/m²		1 × 1,000 IU/m²	
Native E.Coli Asp.	6 × 10,000 IU/m²	12 × 10,000 IU/m²	6 × 10,000 IU/m²		6 × 10,000 IU/m²	
Erwinase	6 × 20,000 IU/m²	12 × 20,000 IU/m²	6 × 20,000 IU/m²		6 × 20,000 IU/m²	

Abbreviations: ALL, acute lymphoblastic leukaemia; AYAs, adolescents and young adults; Cons., consolidation; DI, delayed intensification; HRQL, health-related quality of life; IM, interim maintenance; Ind., induction; Int., intensification; IU, international unit; IV, intravenous; Maint., maintenance; native E.coli Asp, native E.coli-derived asparaginase; PEG-Asp, pegaspargase; w, weeks.

Table 44: Unit costs associated with the technology in the economic model

Items	PEG-asparaginase	Native E.coli asparaginase	Erwinase	Reference to section in submission
Technology cost	£1296.19 per vial			Commercial in confidence
		£70.87 per vial		Historic price paid by NHS as product unlicensed
			£613 per vial	BNF
Administration cost	£163.50	£163.50	£163.50	PSSRU (112)

Abbreviations: PEG, pegylated
PEG-asparaginase 3,750 IU vial; native E.coli asparaginase 10,000 IU vial; Erwinase 10,000 IU vial.

Asparaginase treatment costs depend on the patient body surface area (expressed in m^2). To compute the age-adjusted body surface area of paediatric patients in England, the median weight and height were retrieved from the Royal College of Paediatrics and Child Health growth charts for boys and girls from 0 to 18 years (113). Both Du Bois and Mosteller formulas were computed and averaged. The body surface area used in the model is the age-specific weighted average between males (57%) and females (43%) as reported in the UKALL2003 study (2).

Above the age of 18 years, the average body surface area was taken from a UK study of adult cancer patients and was assumed to be 1.79m^2 (114).

For asparaginase administration cost, it was assumed that every patient had 30 minutes of contact (band 6 nurse) at £54.50 for the administration and 1 hour (as per pegaspargase SmPC) of contact (band 6 nurse) at £109 for post administration monitoring (112). Administration cost was assumed to be the same for all three asparaginases, as described in Section 5.5.1.1.

5.5.3 *Health-state costs and resource use*

No health state costs and resource use were considered.

5.5.4 *Adverse reaction unit costs and resource use*

The cost of managing hypersensitivity was assumed to be £470 per occurrence, as described in Section 5.5.1.1.

Table 45: List of adverse reactions and summary of costs included in the economic model

Adverse events	Items	Value	Reference to section in submission
Hypersensitivity to asparaginase		£470	HRG WH05Z (111)

5.5.5 *Miscellaneous unit costs and resource use*

No other costs and resource use were considered.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

A list of all variables used in the economic analysis is provided in Table 46.

Table 46: Summary of variables applied in the economic model

Variable	Paediatric				Reference	Adults			Reference
Age group (%)		74.4%			Cancer Research UK		25.6%		Cancer Research UK
Grouping		HR	IR	SR			≤40y	≥41y	
(%)		21.4%	29.1%	49.5%	Vora et al. 2013		32.1%	67.9%	Cancer Research UK
Age (years)		5	5	5	Vora et al 2013		31	53	Cancer Research UK
Body surface (m²)		0.75	0.75	0.75	RCPCH		1.79	1.79	Sacco et al. 2010
Eligible for transplant		–	–	–			47%	47%	Goldstone et al. 2008
Health utilities decre	Ind.	25%	25%	25%		Ind.	25%	25%	
	Cons.	16%	16%	16%		Int.	25%	25%	
	IM 1	12%	12%	12%	Assumption	Cons.1	12%	12%	Assumption (decrement
	DI 1	12%	12%	12%	(decrement from	Cons.3	12%	12%	from Furlong et al. 2012)
	IM 2	12%	12%	12%	Furlong et al. 2012)	Maint.	7%	7%	
	DI 2	12%	12%	12%		–	–	–	
	Cont.	7%	7%	7%		–	–	–	
Hypersensitivity									
Risk of hypersensitivity									
PEG-Asp.									
1st line	Ind.	2%	2%	2%	Vora et al. 2013	Ind./Int.	2%	2%	Assumed to be the
2nd line	DI 1/Cons.	2%	2%	2%	Vora et al. 2013	Int.	2%	2%	same as for paediatric
Native E.Coli Asp.									
1st line	Ind.	20%	20%	20%	Vrooman et al. 2010	Ind.	20%	20%	Assumed to be the
2nd line	DI 1/Cons.	20%	20%	20%	Assumed to be the same as 1st line	Int.	20%	20%	same as for paediatric
Erwinase									
1st line	Ind.	6%	6%	6%	Moghrabi et al. 2007	Ind.	6%	6%	Assumed to be the
2nd line	DI 1/Cons.	37%	37%	37%	Vrooman et al. 2016	Int.	37%	37%	same as for paediatric
Impact									
Utility decrement		0.014	0.014	0.014	NICE CG134		0.014	0.014	NICE CG134
Cost (£)		£470	£470	£470	HRG 2014/15		£470	£470	HRG 2014/15
5-year outcomes									
Asp. completed									
OS (%)		95%	90%	80%	Assumption from Vora		40%	30%	UKALL14
EFS (%)		90%	85%	75%	et al. 2013		–	–	Assumption EFS=OS
Asp. discontinued									
RR for OS		0.95	0.95	0.95	Assumption		0.95	0.95	Assumption
RR for EFS		0.95	0.95	0.95	Assumption		–	–	Assumption EFS=OS
Impact of R/ST[2]									
Utility decrement (%)[1]		20%	20%	20%	Assumption		–	–	
Increased mortality (%)[3]		90%	90%	90%	Assumption		–	–	

[1] Decrement (%) from EQ-5D age-specific UK population norms.
[2] For Paediatric only. In Adults, EFS is assumed to equal OS.
[3] From England life table.
Abbreviations: RCPCH: Royal College of Paediatrics and Child Health
HR: High-risk; IR: Intermediate risk; SR: Standard risk.
Ind.: Induction; Int.: Intensification; Cons.:Consolidation; Cont.: Continuation; Maint.: Maintenance.; IM: Interim maintenance; DI: Delayed intensification
R/ST: Relapse/Secondary Tumour
OS: Overall survival; EFS: Event-free survival.
RR: Relative risk, i.e.EFS(Asp. discontinued) = RRÍEFS(Asp. completed)

5.6.2 *Assumptions*

The assumptions are listed here for ease of reference, but have been explained in the above sections of the document:

- As the decision problem is comparing the different types of asparaginase, the concomitant medications would remain unchanged as such the only difference between pegaspargase, native asparaginase and Erwinase lies in the sequencing, dosing, frequency and cost of the asparaginase formulations used. The administrations of the other chemotherapeutic agents do not differ between the four treatment branches compared and as such have not been included.
- Six native E.coli asparaginase and Erwinase doses correspond to one pegaspargase.
- The model only considers a difference in the occurrence of hypersensitivity between the different asparaginase formulations. The occurrence of other potential side effects of asparaginase such as pancreatitis, thrombosis, hyperglycaemia, liver function abnormalities are assumed to be the same between the different asparaginase formulations and are not accounted for in the model (confirmed by the experts consulted).
- The risks of hypersensitivity per asparaginase formulations are assumed to be the same for both paediatric and adult populations, based on expert opinion.
- A cycle correction is applied for the dosing of native E.coli asparaginase and Erwinase in case of hypersensitivity. Patients with hypersensitivity do not receive full native E.coli asparaginase and Erwinase dosing (hypersensitivity occurring at the 2nd injection) (Expert opinion).
- A utility decrement of 0.014 is applied to reflect the impact of hypersensitivity on patient health-related quality of life (104).
- In paediatric patients, 5-year OS were assumed to be 95%, 90% and 80% for the SR, IR and HR groups, respectively. The 5-year EFS are assumed to be 90%, 85% and 75% for the SR, IR and HR groups, respectively.
- In Adults, EFS and OS are assumed to be the same (no R/ST health state).
- In Adults, 5-year OS is assumed to be 40% in ≤40 year group (upper bound of published range) and 30% in the ≥41 year group (upper bound of published range) (12).
- Transplantation costs and outcomes are not accounted for as these patients no longer receive asparaginase.
- Patients who discontinue asparaginase during the treatment phase have a poorer 5-year outcome (EFS and OS) as compared to those who fulfil asparaginase treatment as per protocol (a decrease of 5%).
- Paediatric patients who are event-free survivors at 5-year are considered to be cured. In the lifetime extrapolation they are given the same utility and the same risk of mortality that the general population.
- Paediatric patients who are in the R/ST state at 5-year cannot transition to the EFS state and are given a decreased utility of 20% and an increased risk of mortality of 90% as compared to the general population.
- No health state costs are assumed for EFS and R/ST states.
- The cost of managing hypersensitivity was assumed to be £470 per occurrence.

- The age-specific patient body surface is derived from a weighted average (57% males and 43% females) of the Du Bois and Mosteller formulas computed from UK growth charts until the age of 18 years. Beyond 18 years of age, a body surface of 1.79m² is assumed.
- Administration cost was assumed to be the same for all asparaginases and set at £163.50.

5.7 *Base case results*

5.7.1 *Base case incremental cost effectiveness analysis results*

Base case results are presented in Table 47.

Pegaspargase 1st line followed by Erwinase 2nd line dominates native E.coli asparaginase 1st line followed by Erwinase 2nd line and Erwinase 1st line followed by native E.coli asparaginase 2nd line (lower cost and higher QALYs gained).

Erwinase 1st line followed by pegaspargase 2nd line provides small QALYs gained as compared to pegaspargase 1st line followed by Erwinase 2nd line. However, the ICER of this strategy is far above the £20,000/QALY threshold (£8,627,243/QALY gained).

Table 47: Base case results

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.>Erwinase	£7,871	17.3431	—	—	—
Native Asp.>Erwinase	£12,612	17.2926	-£4,741	0.0504	-£94,029
Erwinase>Native Asp.	£48,149	17.3396	-£40,277	0.0035	-£11,541,184
Erwinase>PEG-Asp.	£48,234	17.3477	-£40,362	-0.0047	£8,627,243

Abbreviations: ASP, asparaginase; ICER, incremental cost-effectiveness ratio; PEG-Asp, pegaspargase; QALYs, quality-adjusted life years.

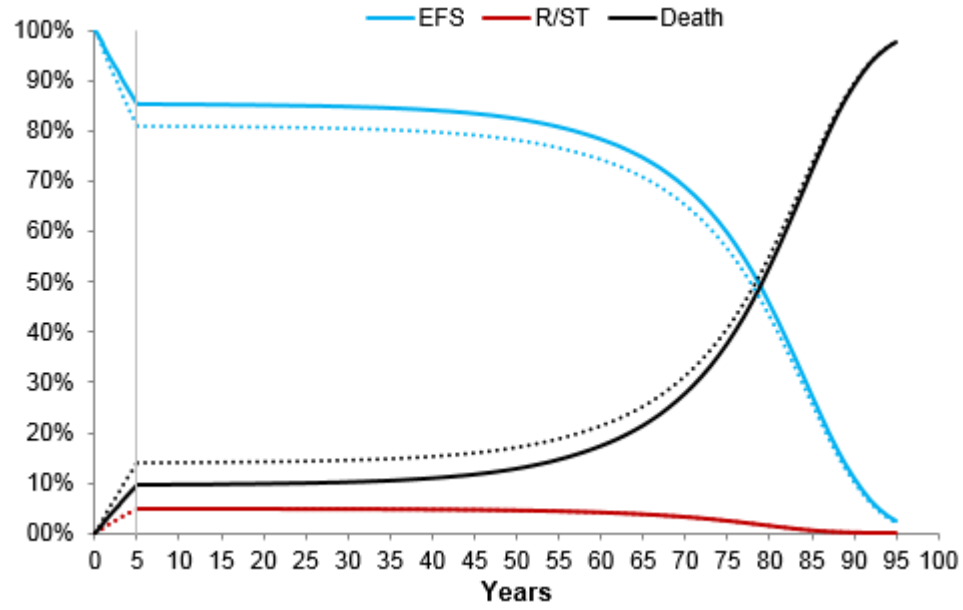
5.7.2 *Clinical outcomes from the model*

The 5-year clinical outcomes of the model perfectly match the clinical assumptions entered (5-year OS and EFS).

Figure 29, Figure 30, and Figure 31 show the Markov traces for paediatric (weighted by risk groups) and adult (≤40 years and ≥41 years) patients, respectively. QALYs accrue by applying the age-adjusted utility values from UK-England population norms (105) to the proportion of patients in each health state over time (Markov traces). Relative utility decrements are applied for the treatment phases from UK-England age-adjusted population norms (43). A relative utility decrement of 20% from age-adjusted population norms is applied for the R/ST health state in the paediatric population (see Section 5.4.6).

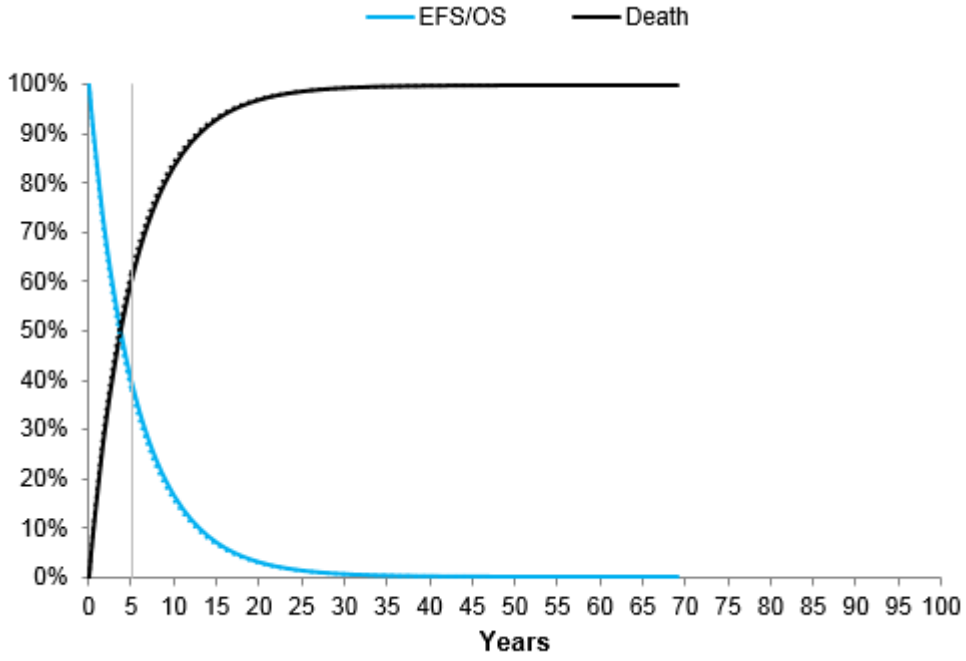
There was no difference between the different formulations of asparaginase, only between patients who completed or discontinued asparaginase treatment.

Figure 29: Paediatric patients



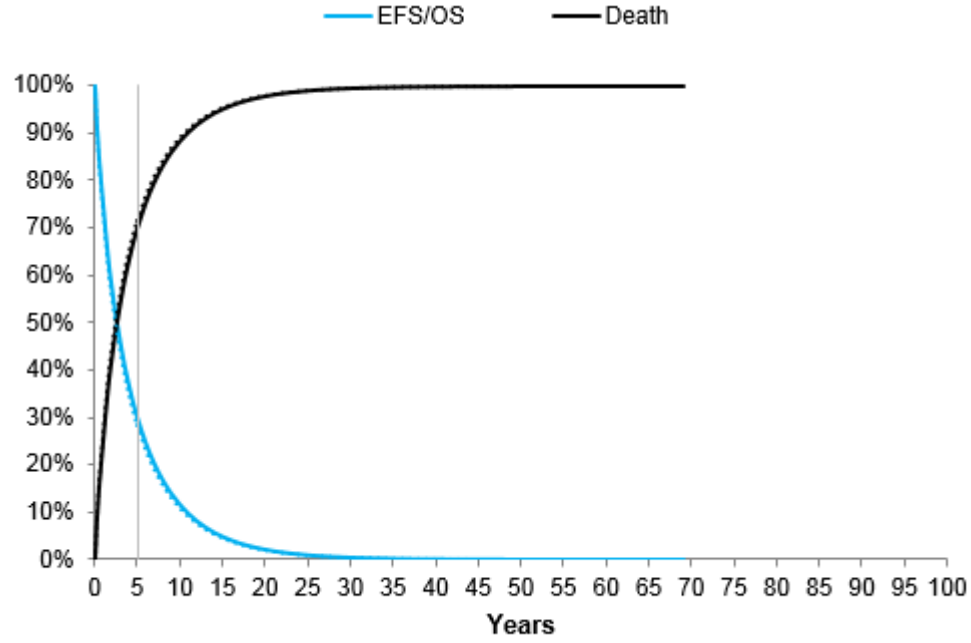
Abbreviations: EFS, event-free survival; R/ST, relapse/secondary tumour.
21.4% HR, 29.1% IR, and 49.5% SR with a base case age of five years (2).

Figure 30: Adult patients (26-40 years)



Abbreviations: EFS, event-free survival; OS, overall survival.
Base case age of 31 years (1)

Figure 31: Adult patients (≥41 years)



Abbreviations: EFS, event-free survival; OS, overall survival.
Base case age of 53 years (1)

5.7.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

The model does not use health state costs, hence a summary of health state costs is not provided.

The favourable hypersensitivity rates and administration profile of pegaspargase (vs native asparaginase and Erwinase) result in cost savings for the NHS (Table 49).

This also impacts on the administration time and potential resource savings, especially for paediatric patients and others eligible for day-case care, where one dose of pegaspargase equates to six doses of either native asparaginase or Erwinase.

In addition, paediatric patients have fewer painful injections whilst adult patients have infusions (instead of injections of native asparaginase or Erwinase) and also fewer administrations. This results in a decreased cost, increased patient and carer quality of life, and a favourable impact on the NHS.

Table 48: Summary of QALY gain by health state

Item	QALY			
	PEG-Asp.—Erwinase	Native Asp.—Erwinase	Erwinase—PEG-Asp.	Erwinase—Native Asp.
EFS	16.6747	16.6265	16.6792	16.6714
R/ST	0.6683	0.6662	0.6685	0.6682
Total	17.3431	17.2927	17.3478	17.3396
Increment (PEG-Asp-Erwinase relative to other treatment sequences)				
EFS	—	0.0482	-0.0045	0.0033
R/ST	—	0.0021	-0.0002	0.0001
Total	—	0.0504	-0.0047	0.0035
% absolute increment				
EFS	—	95.8%	95.8%	95.8%
R/ST	—	4.2%	4.2%	4.2%
Total	—	100.0%	100.0%	100.0%

Abbreviations: Abbreviations: EFS, event-free survival; R/ST, relapse/secondary tumour.

Table 49: Summary of predicted resource use by category of cost

Item	Average treatment cost			
	PEG-Asp.—Erwinase	Native Asp.—Erwinase	Erwinase—PEG-Asp.	Erwinase—Native Asp.
Technology cost	£6,980	£7,716	£43,348	£43,076
PEG-Asp.	£6,650	£0	£399	£0
Native Asp.	£0	£2,144	£0	£127
Erwinase	£330	£5,571	£42,949	£42,949
Administration cost	£878	£4,769	£4,857	£5,039
PEG-Asp.	£839	£0	£50	£0
Native Asp.	£0	£4,145	£0	£233
Erwinase	£40	£625	£4,807	£4,807
Hypersensitivity	£12	£127	£29	£34
Total	£7,871	£12,612	£48,234	£48,149
Absolute increment				
Technology cost	—	£735	£36,368	£36,095
Administration cost	—	£3,891	£3,978	£4,161
Hypersensitivity	—	£115	£16	£21
Total	—	£4,741	£40,362	£40,277

% absolute increment				
Technology cost	—	15.5%	90.1%	89.6%
Administration cost	—	82.1%	9.9%	10.3%
Hypersensitivity	—	2.4%	0.0%	0.1%
Total	—	100.0%	100.0%	100.0%

Abbreviations: ASP, asparaginase; PEG-Asp, pegaspargase.

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

5.8.1.1 Inputs

Table 50 summarises the parameters included in the PSA and the distributions used to determine their values. These parameters were considered for PSA to investigate their collective impact on the ICER based on their known SE, if and whenever available, around the base case estimate. A SE of 5% of the mean was assumed for the purpose of PSA where the SE is unknown. Discount rates for costs and QALYs and the dosing and treatment regimens were excluded from the PSA.

Table 50: Values and distributions used in the probabilistic sensitivity analysis

Variable	Base value	SE	Distribution
Paediatric population			
% paediatric	74.4%	0.11	Beta
High-risk	21.4%	0.03	Dirichlet
Intermediate-risk	29.1%		
Standard-risk	49.5%		
Average age (paediatrics)	5.0	5.61	Normal
Health utility decrements during treatment (paediatrics)			
Ind.	25.0%	0.04	Beta
Cons.	16.0%	0.02	Beta
IM 1	12.0%	0.02	Beta
DI 1	12.0%	0.02	Beta
IM 2	12.0%	0.02	Beta
DI 2	12.0%	0.02	Beta

Variable	Base value	SE	Distribution
Cont.	7.0%	0.01	Beta
Risk of hypersensitivity (paediatrics) - Native E. Coli Asparaginase			
1st line – Ind.	20.0%	0.10	Beta
2nd line – High-risk Cons.	20.0%	0.10	Beta
2nd line – Intermediate-risk DI 1	20.0%	0.10	Beta
2nd line – Standard-risk DI 1	20.0%	0.10	Beta
Risk of hypersensitivity (paediatrics) – Pegaspargase			
1st line – Ind.	2.0%	0.02	Beta
2nd line – High-risk Cons.	2.0%	0.02	Beta
2nd line – Intermediate-risk DI 1	2.0%	0.02	Beta
2nd line – Standard-risk DI 1	2.0%	0.02	Beta
Risk of hypersensitivity (paediatrics) – Erwinase			
1st line – Ind.	6.0%	0.01	Beta
2nd line – High-risk Cons.	37.0%	0.06	Beta
2nd line – Intermediate-risk DI 1	37.0%	0.06	Beta
2nd line – Standard-risk DI 1	37.0%	0.06	Beta
Impact of hypersensitivity (paediatrics)			
Disutility	0.014	0.002	Beta
Cost	£470.32	£137.48	Gamma
5y outcomes – Asparignase completed (paediatrics)			
High-risk – OS	80%	0.11	Beta
High-risk – EFS	75%	0.11	Beta
Intermediate-risk – OS	90%	0.09	Beta
Intermediate-risk – EFS	85%	0.10	Beta
Standard-risk – OS	95%	0.09	Beta

Variable	Base value	SE	Distribution
Standard-risk – EFS	90%	0.09	Beta
5y outcomes – Asparignase discontinued (paediatrics)			
High-risk – RR on OS	0.95	0.09	Beta
High-risk – RR on EFS	0.95	0.09	Beta
Intermediate-risk – RR on OS	0.95	0.09	Beta
Intermediate-risk – RR on EFS	0.95	0.09	Beta
Standard-risk – RR on OS	0.95	0.09	Beta
Standard-risk – RR on EFS	0.95	0.09	Beta
Impact of R/ST (paediatrics)			
Utility decrement	20%	0.03	Beta
Increased mortality	90%	0.09	Beta
Adult population			
% adults ≤ 40y	32.1%	0.05	Beta
Average age ≤40y	31.0	4.74	Normal
Average age ≥41y	53.0	8.11	Normal
Body surface area	1.79	0.27	Normal
% receiving transplant ≤40y	47.0%	0.05	Beta
% receiving transplant ≥41y	47.0%	0.05	Beta
Health utility decrements during treatment (adults)			
Ind.	25.0%	0.04	Beta
Int.	25.0%	0.04	Beta
Cons. 1	12.0%	0.02	Beta
Cons. 3	12.0%	0.02	Beta
Maint.	7.0%	0.01	Beta

Variable	Base value	SE	Distribution
Risk of hypersensitivity (adults) - Native E.Coli Asparaginase			
1st line ≤40y Ind.	20.0%	0.10	Beta
1st line ≥41y Ind.	20.0%	0.10	Beta
2nd line ≤40y Int.	20.0%	0.10	Beta
2nd line ≥41y Int.	20.0%	0.10	Beta
Risk of hypersensitivity (adults) – Pegaspargase			
1st line ≤40y Ind.	2.0%	0.02	Beta
1st line ≥41y Ind.	0.0%	0.02	Beta
1st line ≥41y Int.	2.0%	0.02	Beta
2nd line ≤40y Int.	2.0%	0.02	Beta
2nd line ≥41y Int.	2.0%	0.02	Beta
Risk of hypersensitivity (paediatrics) – Erwinase			
1st line ≤40y Ind.	6.0%	0.01	Beta
1st line ≥41y Ind.	6.0%	0.01	Beta
2nd line ≤40y Int.	37.0%	0.06	Beta
2nd line ≥41y Int./Cons. 1	37.0%	0.06	Beta
Impact of hypersensitivity (adults)			
Disutility	0.014	0.002	Beta
Cost	£470.32	137.48	Gamma
5y outcomes – Asparaginase completed (adults)			
≤40y OS	40.0%	0.08	Beta
≥41y OS	30.0%	0.05	Beta
5y outcomes – Asparaginase discontinued (adults)			
≤40y RR on OS	0.95	0.09	Beta
≥41y RR on OS	0.95	0.09	Beta

Variable	Base value	SE	Distribution
Drug costs			
Native E.Coli Asparaginase	£70.87	10.85	Gamma
Pegaspargase	£1,296.19	198.40	Gamma
Erwinase	£613.00	93.83	Gamma
Administration costs	£163.50	25.03	Gamma

5.8.1.2 Results

The results of 1,000 simulations were plotted on the cost-effectiveness plane (Figure 32), and the cost-effectiveness acceptability curve (CEAC) was calculated (Figure 33). All simulation results lie in the north-east and south-east quadrants of the cost-effectiveness plane, indicating that pegaspargase – Erwinase is always more effective than Native Asparaginase – Erwinase. Furthermore, the majority of the simulations and the probabilistic mean fall in the south-east quadrant, indicating that pegaspargase – Erwinase is a dominant treatment strategy. The CEAC shows that pegaspargase – Erwinase has a 77.9% probability of being below the £20,000 willingness to pay threshold when compared with Native Asparaginase - Erwinase.

Figure 32: Cost-effectiveness plane for Pegaspargase - Erwinase vs. Native Asparaginase - Erwinase

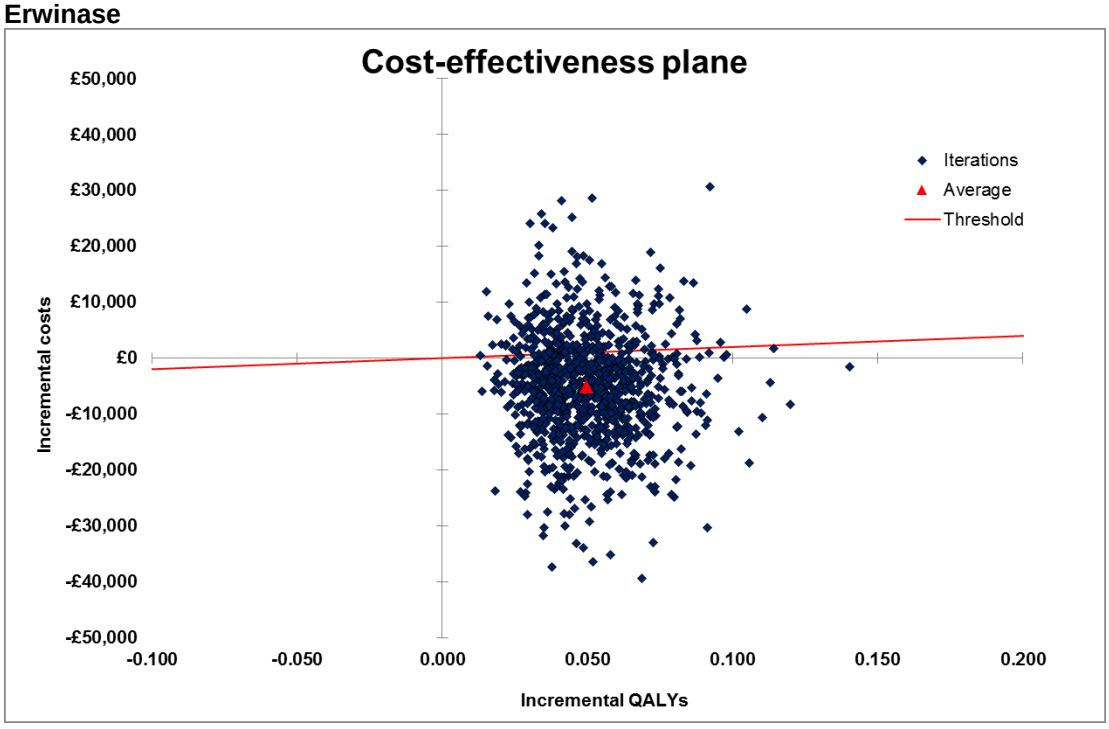


Figure 33: CEAC for Pegaspargase - Erwinase vs. Native Asparaginase - Erwinase

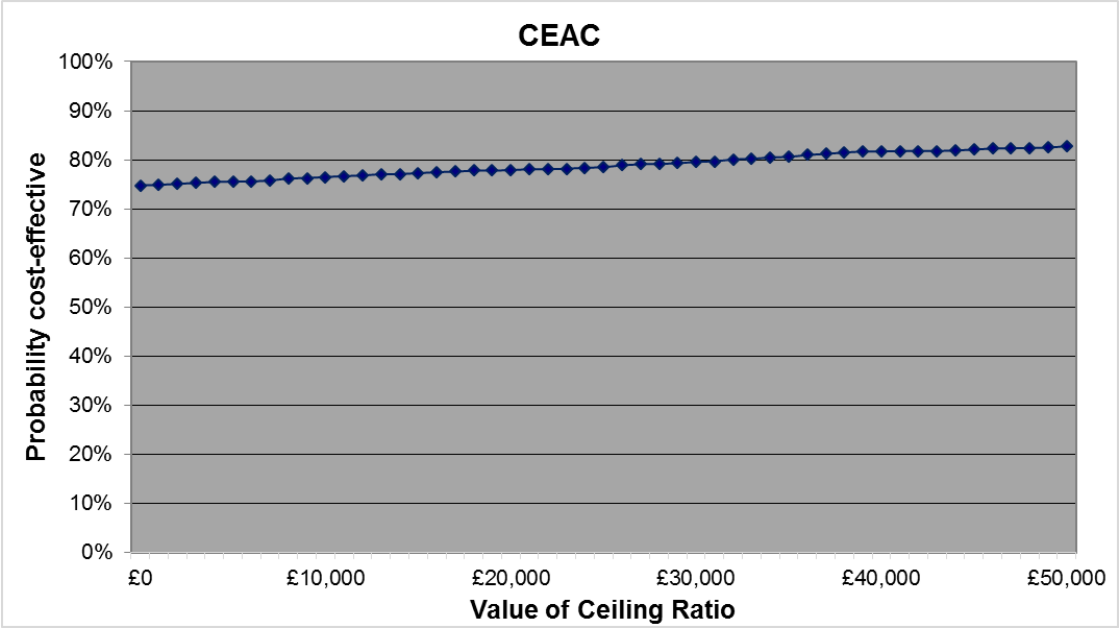
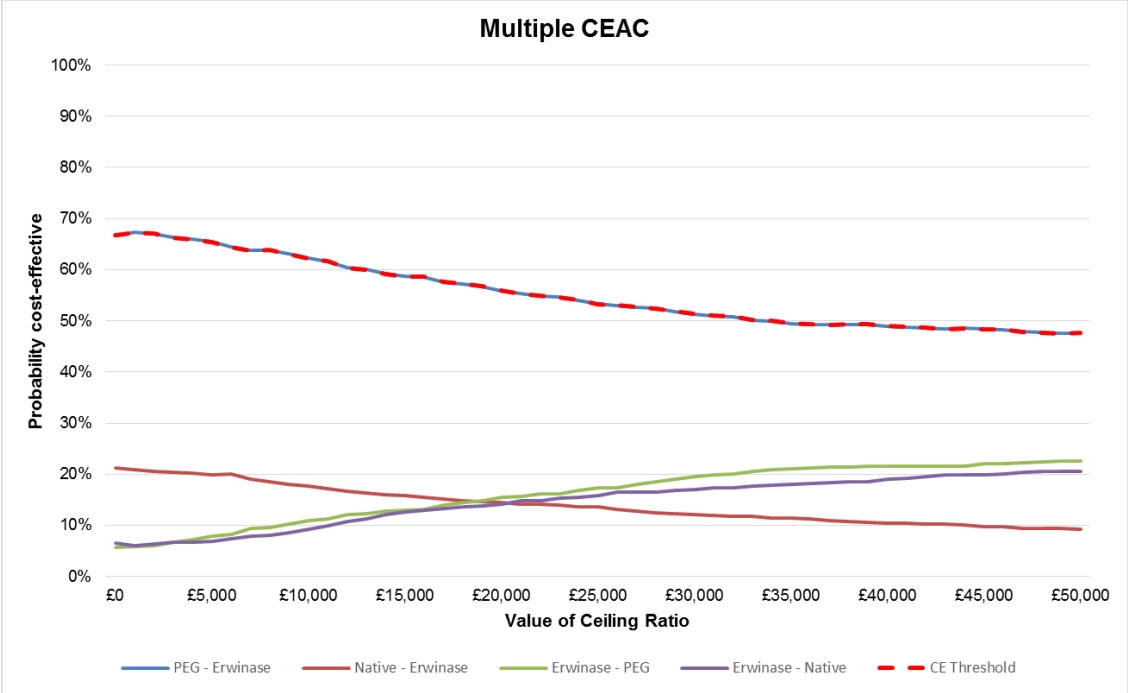


Figure 34: Multiple CEAC for Pegaspargase - Erwinase vs all treatment strategies



A multiple CEAC was also produced to compare pegaspargase - Erwinase to all three treatment strategies. Figure 3 shows that pegaspargase - Erwinase is cost-effective for all values of the ceiling ratio up to £50,000.

5.8.1.3 Discussion of variation between base case and PSA results

The results from the PSA and base case analysis are very similar, the probabilistic mean produced a slightly greater cost-saving with pegaspargase (-£5,095) and a marginally better QALY gain (0.0496), producing an ICER of -£102,805.

5.8.2 *Deterministic sensitivity analysis*

5.8.2.1 Inputs

Deterministic sensitivity analysis (DSA) was performed on all inputs included in the model apart from the dosing and treatment regimens, and a tornado diagram was produced. Table 51 summarises the variables included in the tornado diagram and the relative variation used for each.

Table 51: Variations used on base case values used in the deterministic sensitivity analysis

Variable		Relative Variation	Rationale
Risk group		±30% of high risk patients	A common variation in parameter inputs was included in the DSA to determine the relative sensitivity of model outcomes to different model inputs. Exploration of uncertainty in parameter inputs was assessed through the PSA and a variety of scenario analyses
% paediatric		±30%	
% adults < 41y		±30%	
Administration costs		±30%	
Average age (paediatrics)		±30%	
Body surface area (paediatrics)		±30%	
Health utility decrements during treatment (paediatrics)		±30%	
Disutility associated with hypersensitivity (paediatrics)		±30%	
5y outcomes - OS/EFS (paediatrics)		±30%	
Impact of R/ST (paediatrics)	Utility decrement	±30%	
	Increased mortality	±30%	
Average age (adults)	≤40y ≥41y	±30%	
Body surface area (adults)		±30%	
% receiving transplant	≤40y ≥41y	±30%	
Health utility decrements during treatment (adults)		±30%	
Disutility associated with hypersensitivity (adults)		±30%	

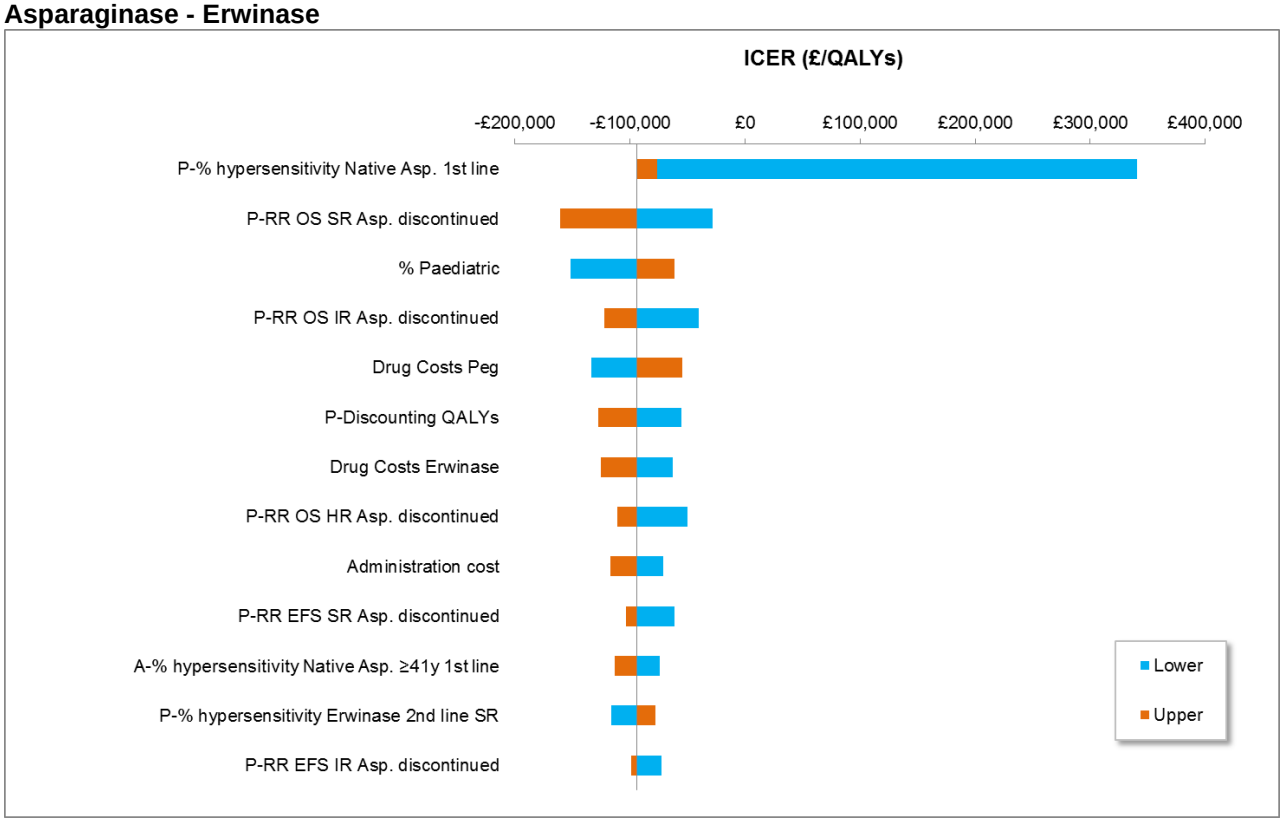
Variable		Relative Variation	Rationale
5y outcomes (adults)	OS/EFS	±30%	
Drug costs	Native	±30%	
	Pegaspargase	±30%	
	Erwinase	±30%	
Risk of hypersensitivity (paediatrics)	Native	0.0 – 40.0%	Avramis grade 3 & 4 = 0% Vora at al. = 40%
	Pegaspargase	0.0 – 6.0%	Vora
	Erwinase	±30%	
Risk of hypersensitivity (adults)	Native	0.0 – 40.0%	Avramis grade 3 & 4 = 0% Vora at al. = 40%
	Pegaspargase	0.0 – 6.0%	Vora
	Erwinase	±30%	
Cost of hypersensitivity (paediatrics)		£72 - £611	Min value: NICE CG134 Anaphylaxis Costing Statement 2011. Cost of emergency hospital treatment in A&E. NHS Reference Costs 2014-15. HRG code: VB11Z.
Cost of hypersensitivity (adults)		£72 - £611	
Discounting (paediatrics)	QALYs Costs	1.5% - 5.0%	A common variation in parameter inputs was included.
Discounting (adults)	QALYs Costs	1.5% - 5.0%	A common variation in parameter inputs was included

5.8.2.2 Results

Figure 35 shows the results of the DSA conducted on the ICER for pegaspargase – Erwinase vs Native Asparaginase – Erwinase. Figure 35 shows the thirteen parameters to which the ICER is most sensitive. The diagram shows that the ICER is stable for the variation of most of the parameters, however it is unstable when the hypersensitivity rate for 1st line treatment with Native Asparaginase for the paediatric population is varied.

When the hypersensitivity rate is set to 0%, i.e. less than the 2% base rate used for pegaspargase, the ICER reaches £340,630.

Figure 35: Tornado diagram for DSA results (ICER) of Pegaspargase - Erwinase vs Native Asparaginase - Erwinase



5.8.3 *Scenario analysis*

A range of scenarios were run to explore the uncertainty in model parameters. Table 52 presents the ICER for each scenario for pegaspargase – Erwinase vs the other treatment strategies. The results show that pegaspargase remains cost-effective vs all treatment strategies for all of the scenarios run.

When the minimum hypersensitivity rates are used in the model, the incremental QALYs between Pegaspargase – Erwinase vs Native Asparaginase – Erwinase is 0. In this scenario, Pegaspargase – Erwinase was shown to produce a cost-saving of £159.

Table 52: Scenario analysis

Scenario	PEG – Erwinase Vs. Native – Erwinase ICER (quadrant)	PEG – Erwinase Vs. Erwinase – PEG ICER (quadrant)	PEG – Erwinase Vs. Erwinase – Native ICER (quadrant)
Base case	PEG dominant	£8,725,004 (SW)	PEG dominant
100% paediatric population	PEG dominant	£5,917,762 (SW)	PEG dominant
100% adult population	PEG dominant	£123,644,929 (SW)	PEG dominant
Minimum cost of	PEG dominant	£8,722,031 (SW)	PEG dominant

Scenario	PEG – Erwinase Vs. Native – Erwinase ICER (quadrant)	PEG – Erwinase Vs. Erwinase – PEG ICER (quadrant)	PEG – Erwinase Vs. Erwinase – Native ICER (quadrant)
hypersensitivity			
Maximum cost of hypersensitivity	PEG dominant	£8,726,059 (SW)	PEG dominant
Minimum rate of hypersensitivity	-	PEG dominant	PEG dominant
Maximum rate of hypersensitivity	PEG dominant	£2,121,333 (SW)	PEG dominant
1.5% discount rate for paediatric population	PEG dominant	£5,138,376 (SW)	PEG dominant
Oncaspar dose per SpC	PEG dominant	£8,555,431 (SW)	PEG dominant
Minimum cost of native	PEG dominant	£8,725,004 (SW)	PEG dominant
Maximum cost of native	PEG dominant	£8,725,004 (SW)	PEG dominant
Average paediatric age = 1	PEG dominant	£8,558,688 (SW)	PEG dominant
Average paediatric age = 18	PEG dominant	£9,452,180 (SW)	PEG dominant

Table 53: Cost minimisation analysis: PEG - Erwinase vs. Native - Erwinase

PEG - Erwinase vs. Native - Erwinase			
Scenario	**Incremental costs**	**Incremental QALYs**	**ICER**
Cost Minimisation	-£354	0.00	NA

5.8.4 *Summary of sensitivity analyses results*

The model is able to demonstrate that pegaspargase - Erwinase is cost-effective when compared with:

- Native Asparaginase – Erwinase
- Erwinase – Pegaspargase
- Erwinase – Native Asparaginase

The results of the model are robust in the face of uncertainty in both the parameter inputs, as well as the structural assumptions required to construct the model. All

scenarios indicated that Pegaspargase – Erwinase is cost-effective at the £20,000 willingness to pay threshold.

5.9 *Subgroup analysis*

No subgroup analysis was undertaken.

The cost-effectiveness model considered the main age groups of interest in the treatment of newly diagnosed ALL, namely:

- Paediatric/AYAs ≤25 years (UKALL2003 protocol (94))
- Adults (25–65 years) with the distinction between those above and below 40 years and between those eligible or not for transplant as described in the UKALL14 protocol (12).

Patients >65 years were not considered as the current UKALL trial evaluating patients in this age group (UKALL60+ (14))predominantly uses drugs other than asparaginase, and the decision problem would thus not apply in most cases.

5.10 *Validation*

5.10.1 *Validation of de novo cost-effectiveness analysis*

As there is no consistent standard of care for the way that ALL is treated, UK-specific protocols were used to define the model structure as this is relevant for UK decision-makers. Although there is published data pertaining to the paediatric population, there is a paucity of data for the adult population.

In order to validate the assumptions used in the model, experts familiar with current and historic protocols were approached (as detailed in Section 5.3.3) to validate inputs and provide expert opinion for inputs that lacked data. The experts consulted agreed with the DT model structure used as well as inputs, as described. As the experts consulted have extensive experience in treating patients with this disease, they were best-placed to provide insight, which is why this method was undertaken, especially considering the difference in dosing regimens used in the UK relative to other countries (1,000 IU/m^2) and the resultant favourable OS, EFS, hypersensitivity rate results.

5.11 *Interpretation and conclusions of economic evidence*

The main strength of the evaluation is that it is relevant to UK decision-makers as the model reflects the current standard of care for UK patients in both the paediatric and adult population, and also uses associated UK-specific data, where available.

The main limitations are in the lack of head-to-head data, especially in the adult population. Key inputs were also validated by experts in the different specialties to ensure the values used were reflective of UK experience, especially as the regimens differ from other countries, so the data transferability could be questioned.

Some values are also very variable in the data reported, and we have been conservative in our use of the data e.g. the rate of hypersensitivity for the native product has an upper reported limit of hypersensitivity of 76% (25), but we used a UK-referenced upper bound of 40% in our model, and the lower reference case amount of 20%. These figures were validated by both adult and paediatric experts.

The base case demonstrated that pegaspargase used 1st line dominated or was more cost effective than all the other interventions modelled. In order to evaluate the uncertainty, we also undertook extensive sensitivity analyses, per Section 5.8 above. This showed stability in all of the ICERs and results obtained, except when the native asparaginase hypersensitivity rate was modelled to be lower than the hypersensitivity rate for pegaspargase reported. Extensive trials undertaken in various countries, over a long period of time has shown that pegaspargase has a lower rate of hypersenstivitity than native asparaginase, so this is clinicially highly implausible.

This should be considered alongside the benefits to patients in terms of the reduced rate of hypersensitive reactions and reduced number of administrations to a predominantly paediatric population, who experience anxiety and pain. In addition, when asked on the dosing equivalence of native asparaginase or Erwinase, the expert advised that every intravenous infusion of pegaspargase is replaced by six IM injections of either native E.coli enzyme or Erwinase. They stated that the adult population was prone to thrombocytopoenia, and thus commonly experience pain and bruising when having an injection.

An assumption is that pegaspargase, native asparaginase and Erwinase are equivalent in terms of OS and EFS, and because all the outcomes of interest are experienced during the treatment phase, a cost minimisation analysis (CMA) is an alternative modelling methodology that can be used to represent the decision problem, as this demonstrates the actual impact on the NHS. The decision tree and Markov model are also used in the CMA. This resulted in a cost saving of £354 per patient, and further demonstrates the cost benefits of continued use of pegaspargase 1st line in the NHS, as well as the continued use in ongoing trials in both patient populations (UKALL11 & UKALL14), which will lead to further data in the disease area.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

ALL is an acute, rapidly progressing, and life-threatening form of cancer involving lymphocyte-producing cells called lymphoblasts. ALL is rare, with an average of 744 new cases of ALL diagnosed in the UK between 2011 and 2013 (644 in patients aged <65 years), accounting for 0.2% of all new cancer diagnoses, and 9% of all new leukaemia diagnoses (1). Incidence is strongly related to age with 54% of ALL cases in the UK being diagnosed in children aged 0–14 years (2011–2013 data) (1).

Positive results from the initial paediatric protocol, UKALL 2003, led to its incorporation into the current protocol UKALL 2011 and also into the current adult protocol, UKALL14.

Pegaspargase is thus administered as the 1st line asparaginase (as a part of multi-agent chemotherapy) in the UK as part of the UKALL protocols which are seen as standard of care. For example, circa 97% of eligible newly diagnosed paediatric patients were treated using the UKALL 2003 protocol over the 7 years it was in place (3), with circa 85% of the adult population receiving pegaspargase (expert opinion). These proportions of patients were therefore used in year 1 of the budget impact model.

Recognising the value of pegaspargase, and to overcome the inequity of "postcode prescribing", the clinical community sought to have pegaspargase included in NHS England baseline commissioning, which was effective from April 2013 (13).

Patient population

UKALL 2003 and UKALL14 trial protocols were used in the model, consistent with our submission, as they account for paediatric, adolescent and young adult patients as well as adult patients up to the age of 65 years. Cancer research data was obtained to determine the number of patients per age group, namely <25 years for the UKALL 2003 protocol and between 25 and 65 years for the UKALL14 trial – a total of 644 patients (as per Table 54 below).

Patients >65 years were not considered as the current UKALL trial evaluating patients in this age group predominantly uses drugs other than asparaginase, and the decision problem would thus not apply in most cases.

As most treatment phases are completed in the first year, we have only used incident data to reflect newly-diagnosed patients, hence the number of patients remain constant year on year.

As pegaspargase is the standard of care for the patient population under consideration, it is assumed that there will be no change in the proportion of eligible patients over the next 5 years.

The agreed NHS list price, as used in our economic model, is £1296.19, which has been shown to be cost-effective.

In order to assess the impact on the NHS budget over the next 5 years, the estimated number of patients treated by the NHS is presented in Table 54. As the paediatric and adult population are treated differently, we have presented them separately below.

Table 54: Estimation of patients eligible for treatment

	2016	2017	2018	2019	2020
Incident ALL cases					
Paediatric	479	479	479	479	479
Adults	165	165	165	165	165
Total	644	644	644	644	644

Abbreviations: ALL, acute lymphoblastic leukaemia.
Paediatric patients: 0–25 years, adult patients: 26–65 years.

Costs included

Pegaspargase is currently used as the 1st line treatment option for most patients in the UK due to its use in ongoing UKALL trials (UKALL11 & UKALL14).

6.2 *Resource savings*

Costs associated with treating a hypersensitive reaction

Asparaginase forms the backbone of chemotherapeutic regimens used in current clinical practice. As three different types of asparaginase are being compared in the model (native E.coli asparaginase, pegaspargase and Erwinase), with the remainder of the chemotherapeutic regimen unaltered, only costs associated with the three asparaginase products were modelled, some of which were derived from NHS reference costs or PbR tariffs.

The main difference between the products is their associated risk of a hypersensitivity reaction. The reference cost for “Allergy or Adverse Allergic Reaction”, HRG WH05Z, is (2014/15 £470) (111). This cost is saved for each hypersensitivity reaction avoided, and is potentially an underestimate, especially for patients requiring an ITU stay due to a life-threatening reaction. The elective unit cost for HRG WH05Z is £1,840.

Administration costs

Each administration of pegaspargase would need to be replaced by 6 administrations (ref protocol appendix, as above) of either native asparaginase or erwinase. We have assumed that an injection or infusion would take half an hour of a band 6 nurse’s time, with the patient requiring observation of an hour afterwards to monitor for hypersensitivity, especially as, should the patient have an anaphylactic reaction, immediate intervention would be required.

Due to the nature of the intervention a minimum of a band 6 nurse would be required to treat the patient. Relevant costs are listed below, as derived from PSSRU (112):

- Administration cost: half hour, band 6, patient contact = £54.50
- Monitoring cost: 1 hour per SmPC, band 6, patient contact = £109

- Total cost per injection/ infusion = £163.50

There is therefore a cost saving of £163.50 per administration, equating to £817.50 for the additional five administrations per dose.

Hospital (day case) visits

The adult clinical expert stated that most adult patients are ill enough to require all phases of their treatment in hospital, whereas the paediatric expert stated that, although the induction treatment phase for paediatric patients occurs in a hospital (in-patient) setting, subsequent treatment phases usually occur in a day-case setting.

As the clinical experts advised that each dose of pegaspargase would equate to 6 doses of either native E.coli asparaginase or Erwinase, there could be up to five extra day-case visits attributable to the comparators, the tariff costs for which are listed in Table 42. As such, native E.coli enzyme and Erwinase could both be associated with an additional cost of £1,630 for every set of six doses compared with pegaspargase. (5 extra administrations for the eligible patients). However, we have not accounted for this in the model meaning that the analysis is extremely conservative, and we have just applied a standard cost of administration and monitoring as listed above.

Table 55: Day case-related HRG codes for chemotherapy

Description	Unit Cost	Reference
Chemotherapy delivery – first attendance	£389	NHS Ref Costs 2014/15* - HRG code SB14Z (111)
Chemotherapy – subsequent attendance	£326	NHS Ref Costs 2014/15* - HRG code SB15Z (111)

This would also potentially reduce the capacity burden of the NHS.

6.3 *Budget impact*

Assuming that the current protocols continue to be used in Engalnd, this shows that there is no difference in cost to the NHS over the next 5 years and that the overall treatment regimen (cost/QALY) is cost-effective (Table 56).

Additionally, when all the costs associated with the treatment are considered in a cost minimisation model (presented in sensitivity analysis) - this shows that the total impact on the NHS due to asparaginases, and their associated impact on the number of patients who get a hypersensitive reaction was a saving of £354 per patient (when using pegaspargase 1st line vs. native asparaginase 1st line) (as per Section 5.8).

Table 56: Budget Impact

	2016	2017	2018	2019	2020
% usage pegaspargase					
Paediatric	97%	97%	97%	97%	97%
Adults	85%	85%	85%	85%	85%

	2016	2017	2018	2019	2020
Patients treated					
Paediatric	465	465	465	465	465
Adults	140	140	140	140	140
Total	605	605	605	605	605
Annual cost					
Paediatric	£3,354,137	£3,354,137	£3,354,137	£3,354,137	£3,354,137
Adults	£700,730	£700,730	£700,730	£700,730	£700,730
Total	£4,054,866	£4,054,866	£4,054,866	£4,054,866	£4,054,866
Annual net impact					
Paediatric	£0	£0	£0	£0	£0
Adults	£0	£0	£0	£0	£0
Total	£0	£0	£0	£0	£0
Cumulative net impact					
Paediatric	£0	£0	£0	£0	£0
Adults	£0	£0	£0	£0	£0
Total	£0	£0	£0	£0	£0
% usage pegaspargase					
Paediatric	97%	97%	97%	97%	97%
Adults	85%	85%	85%	85%	85%

Paediatric: 0-25y; Adults: 26-65y

6.4 *Additional factors not included in analysis*

This is an unusual situation, as the product under consideration is the current standard of care, and there would be a potential decrease in outcomes, patient experience, etc. if this was no longer available, as per comments in the NICE scoping feedback.

The budget impact model should be considered alongside the cost minimisation model, as this reflects the holistic impact of altering the products considered, and the associated increase in overall costs to the NHS due to additional drug administrations and also the management of additional hypersensitivities should one of the comparators be used instead of pegasparage.

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8 Appendices

Appendix 1: SmPC and EPAR

Appendix 2: Search strategy for relevant studies

Appendix 3: Additional trial information (CCG-1962 and UKALL 2003)

Appendix 4: Outcomes evidence from non-pegylated asparaginase studies

Appendix 5: Feasibility assessment for NMA

Appendix 6: Search strategy for cost-effectiveness studies

Appendix 7: Quality assessment of cost-effectiveness studies

Appendix 8: Search strategy for measurement and valuation of health effects

Appendix 9: Checklist of confidential information

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Single technology appraisal

Pegaspargase for treating acute lymphoblastic leukaemia [ID863]

Dear Bronwyn,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd, and the technical team at NICE have looked at the submission received on 3 March 2016 from Baxalta. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Thursday 14 March 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Tucker, Technical Lead (helen.tucker@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Please clarify why section 1.2 (page 16) of the company submission states that "Pegaspargase received marketing authorisation from the EMA on 14th January 2016 for the treatment of people with newly diagnosed ALL". The marketing authorisation from the European Medicines Agency states that "Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients" and therefore does not appear to restrict the use of pegaspargase to people with newly diagnosed ALL.

A2. Please provide the 2 tables from reference 50 (Silverman 2013, Blood) and confirm that the abstract is the full publication.

A3. Page 12 of the company submission states that "The UKALL protocols have seen clinicians adopt pegaspargase at a dose of 1,000 IU/m^2, lower than the SmPC recommended dose of 2,000–2,500 IU/m^2. UKALL 2003 provides favourable long term outcomes and safety evidence at this reduced dose for more than 3,200 children and young adult ALL patients treated between 2003 and 2011, accounting for more than 97% of the eligible ALL population over that time. This data has provided the clinical community with confidence to continue to use 1,000 IU/m^2 pegaspargase as the standard of care in the ongoing UKALL 2011 paediatric protocol and adopt it in the adult UKALL14 protocol."

Please clarify whether there are any head to head clinical studies (RCT or non-RCT) comparing 1,000 IU/m^2 with 2,500 IU/m^2 pegaspargase. If such studies exist, please provide the full references and PDFs of the studies. If such studies do not exist, please provide the justification as to why the results from studies with a 2,500 IU/m^2 dosing can be extrapolated to the 1,000 IU/m^2 pegaspargase treatment group used in the health economic model.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The absence of a significant difference in costs, overall survival (OS) or event-free survival (EFS) does not mean that these input parameters can be

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assumed to be equal for all treatment strategies in the cost-effectiveness analysis. The submitted economic model does not allow for a difference in OS and EFS between treatments. Please provide a modified version of the model which allows for differing curves between treatments, so that numerical differences can be assessed for their impact on the incremental cost effectiveness ratio (ICER) and so that in the probabilistic survival analysis (PSA) the curves can fluctuate independently. In addition, please modify the model, if necessary, to allow for differences in incidence of serious adverse events and different health-related quality-of-life decrements.

B2. Section 5.3.3 (pages 157-159) of the company submission states that 4 clinicians were invited for expert advice and 2 agreed to participate. It further states that these clinicians received a list of questions in advance to consider their responses, followed by an interview. Since many important input parameters of the cost-effectiveness model are based on expert opinion, please provide the following:

a. Justification as to why only 4 clinicians were approached,

b. The list of questions that have been asked to the clinicians and the minutes of the interviews.

B3. **Priority question:** Hypersensitivity is the only toxicity that has been included in the economic model. However several other serious adverse events were also reported in section 4.13 (Table 32-36) of the company submission. Despite the absence of significant differences in the incidence of serious adverse events, it is relevant to provide a complete assessment of the costs and quality of life impact of different asparaginase treatment including all relevant serious adverse events. Please provide a modified version of the economic model which includes the costs and quality of life impact of the recorded serious adverse events.

B4. Most evidence about EFS and incidence of hypersensitivity is based on other administrations of asparaginase (including differences in dose and number of injections), raising the question of the generalisability of the results from these studies to clinical practice in England. In order to address this question, please provide scenario analyses in which PEG-asparaginase (PEG) has both a better OS and EFS (e.g. based on CCG-1961) and a worse OS and EFS (e.g. based on DFCI-91-01).

B5. On page 130 and Table 34 (page 131) of the company submission it is reported that the incidence of hypersensitivity is higher in the high-risk group, since these patients receive higher cumulative dose of PEG. However, in the cost-effectiveness model, the incidence of hypersensitivity is similar for all 3 risk groups and only occurs after 2 injections. Consequently, the higher incidence of hypersensitivity in the high risk group is not incorporated in the economic model. Please provide a modified version

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of the economic model in which the higher incidence of hypersensitivity in the high risk group is incorporated into the model in accordance with the findings in Table 34.

B6. Please provide the justification for the assumption that the rate of hypersensitivity is similar in adult patients compared with children.

B7. Page 133 of the company submission states that PEG as 2nd line asparaginase followed after native E.coli increases the risk of hypersensitivity to PEG. Please clarify whether this would also apply to PEG followed after Erwinase.

B8. Page 39 of the company submission states that hypersensitivity may cause a delay in treatment and thereby impact on the health-related quality-of-life. Please clarify whether the occurrence of hypersensitivity would also impact on the administration of the other treatments for ALL. If so, please comment on what the subsequent consequences on health care costs, survival and health-related quality-of-life would be.

B9. **Priority question:** Please explain how the incidence of hypersensitivity after E.coli was estimated. It does not appear that the estimate of 20-40% is supported by the evidence in Table 8, paragraph 4.6 of the Appendix and Table 32 of the company submission. In addition, there is a large difference between the rate of hypersensitivity for PEG (2%) and that of native E.Coli asparaginase (20%). Please clarify whether the 2% was based on grade 3/4 allergy whilst the 20% was based on silent inactivation. If that is the case, please provide new estimates of hypersensitivity that are all based on the same definition.

B10. It is noted that the health-related quality-of-life estimates were derived from the study by Furlong et al, in which parents had filled in the health utility index (HUI) as a proxy for their children. Please explain why these estimates are also considered to be valid for adult patients.

B11. Please provide the justification for choosing a reduction of 20% in health-related quality-of-life for patients with relapsed/refractory ALL.

B12. **Priority question:** Please provide estimates for the health care costs for the EFS and relapse/secondary tumour (R/ST) state as the proportion of patients in each health state may differ slightly, given that the EFS and OS is lower in patients experiencing hypersensitivity. In addition, please provide a modified version of the economic model incorporating these costs.

B13. Page 154 of the company submission states that “R/ST patients still alive at 5 years were also subject to the general mortality risk but increased by 90% (i.e. x1.9 general mortality; expert opinion).” Please provide the justification for the increase in mortality of 90% for patients with relapsed/refractory ALL.

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B14. Please provide the justification for the decrease in EFS and OS of 5% in patients who discontinue asparaginase treatment. For example, are there studies available showing differences in EFS or OS between patients continuing and discontinuing asparaginase treatment? In addition, please provide the justification for the assumption that the hazard ratio is similar for all risk and age groups.

B15. The age of the paediatric population in the economic model is based on the median age of the patients as that age was considered to more informative than the average age. However, the age of adults in the economic model is based on the extrapolated mean age of the patients.

a. Please explain why the median age was not considered to be more informative for adults.

b. Please provide the mean age of the paediatric population.

B16. Please explain why the half-cycle correction was considered no longer clinically relevant after the treatment period.

B17. For the modelling of the survival curve over time, the expected distribution was based solely on visual inspection. Please evaluate the fit of different parametric survival functions (Weibull, Exponential, Lognormal, Loglogistic and Gompertz) for OS and EFS in line with the Decision Support Unit (DSU) recommendations (as set out in the technical support document 14) and provide the justification for the distributions chosen.

B18. Please provide the justification for the assumption that EFS=OS for the adult population. Please clarify whether the assumption implies that the time between recurrence and death is very short.

B19. Please provide a scenario analysis that allows vial-sharing for the different asparginase formulations.

B20. In the scenario analyses in which the age of the children were set at 1 and 18 years, the body surface area (BSA) does not appear to have been adjusted. Please correct these scenarios to align the BSA with the age of the patient.

Section C: Literature searching

C1. Please re-run the following searches:

a. Include the term lymphatic leukaemia/leukemia in PubMed and The Cochrane Library. A quick title only search undertaken by the ERG for “lymphatic leukemia” in PubMed retrieved over 1000 results. Therefore it is possible that key papers have been missed with the exclusion of this term.

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b. Include lymphatic leukaemia in the Embase searches as the current searches only include lymphatic leukemia.

C2. Please explain why MeSH terms were limited to Major Topic in PubMed but were exploded in The Cochrane Library. Limiting the terms to Major Topic could mean that relevant articles were missed.

C3. Please provide the rationale for limiting the searches to English only.

C4. Please provide the details and search strategies for all manual searches mentioned in the Appendices 2.2.4, 6.4 and 8.4.

C5. Please explain why the search results were limited to 31 December 2015, yet were conducted on 31 January 2016.

C6. Please clarify how the 'No Animals' limit was implemented in PubMed and Embase searches.

C7. Please clarify whether published/validated study design filters were used to limit to:

a. trials in the clinical effectiveness searches;

b. economic outcomes in the cost-effectiveness searches; and

c. health related quality of life outcomes in the measurement and valuation of health effects searches.

If validated filters were used, please provide details of the source or reference of these filters. If filters were not validated or verified, please provide justification for these facets for each search strategy and database. It is possible that publications have been missed by not using a validated study design filter relevant to the specific database.

C8. Please explain why study design filters were applied in The Cochrane Library as Cochrane resources are considered to be study design specific databases. Please comment on whether possible relevant publications may have been missed because of the application of the study design filters.

C9. Please provide the results for the separate databases in The Cochrane Library searches.

Clinical effectiveness: Systematic review 2

C10. Please re-run all searches in Systematic review 2 to include ASNase which is a valid synonym for asparaginase.

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C11. Please provide the rationale for Systematic review 1. In addition, please confirm that all papers found in Systematic review 1 were also found in Systematic review 2.

C12. Please clarify what the objectives were for Systematic review 2 as these differ between section 4.1.2 of the company submission and Appendix 2. Section 4.1.2 states that Systematic review 2 "was conducted to comprehensively update the first systematic review. The objectives were the same as in the first review." Appendix 2 states that the objectives of Systematic review 2 were "to identify and select relevant clinical and cost-effectiveness studies".

C13. Please amend section 4.1.2.1 of the company submission so that it is clear which databases have been searched, what dates (treatment inception or database inception) and on what platform.

Search strategies for Cost-effectiveness and Health-related quality-of-life

C14. Please provide the flowcharts/schematic diagrams detailing the Cost-effectiveness searches and health-related quality-of-life searches in the company submission.

Pegaspargase for treating acute lymphoblastic leukaemia [ID863]

Baxalta responses to **the ERG's questions**

Section A: Clarification on effectiveness data

A1. Please clarify why section 1.2 (page 16) of the company submission states that "Pegaspargase received marketing authorisation from the EMA on 14th January 2016 for the treatment of people with newly diagnosed ALL". The marketing authorisation from the European Medicines Agency states that "Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients" and therefore does not appear to restrict the use of pegaspargase to people with newly diagnosed ALL.

An error on our part. The words "newly diagnosed" shouldn't have been used at this point when discussing the marketing authorisation and indication.

We explain later in the dossier (Section 1, Table 1; and in Section 3.6) how the MA/indication does indeed encompass all patients with ALL, but how in clinical practice, only newly-diagnosed ALL patients have asparaginase incorporated into their treatment, with our submission positioned accordingly.

To clarify, Section 1.2 (page 16) should just read: "Pegaspargase received marketing authorisation from the EMA on 14th January, 2016."

The marketing authorisation indication is stated elsewhere in section 1.2: "Oncaspar is indicated as a component of antineoplastic combination therapy in ALL in paediatric patients from birth to 18 years, and adult patients."

A2. Please provide the 2 tables from reference 50 (Silverman 2013, Blood) and confirm that the abstract is the full publication.

The abstract is the full publication. The publication is based on an oral presentation. The two tables are provided at the bottom of this document (Appendix 1), or alternatively, can be accessed via the following link: http://www.bloodjournal.org/content/122/21/838?sso-checked=true.

A3. Page 12 of the company submission states that "The UKALL protocols have seen clinicians adopt pegaspargase at a dose of 1,000 IU/m^2, lower than the SmPC recommended dose of 2,000–2,500 IU/m^2. UKALL 2003 provides favourable long term outcomes and safety evidence at this reduced dose for more than 3,200 children and young adult ALL patients treated between 2003 and 2011, accounting for more than 97% of the eligible ALL population over that time. This data has provided the clinical community with confidence to continue to use 1,000 IU/m^2 pegaspargase as the standard of care in the ongoing UKALL 2011 paediatric protocol and adopt it in the adult UKALL14 protocol."

Please clarify whether there are any head to head clinical studies (RCT or non-RCT) comparing 1,000 IU/m2 with 2,500 IU/m2 pegaspargase. If such studies exist, please

provide the full references and PDFs of the studies. If such studies do not exist, please provide the justification as to why the results from studies with a 2,500 IU/m2 dosing can be extrapolated to the 1,000 IU/m2 pegaspargase treatment group used in the health economic model.

There are no studies that provide a head-to-head comparison of pegaspargase used at 1,000 IU/m2 and 2,500 IU/m2 doses.

It is reasonable to assume that the lower 1,000 IU/m2 pegaspargase dose used in UKALL 2003 might have reduced relative efficacy than if a higher dose (2,000–2,500 IU/m2 dose, as recommended in the SmPC, and used in other studies) were used. It would also be reasonable to assume that a lower dose would result in lower toxicities.

Comparison of the outcomes of the pooled analysis with those of UKALL 2003, into which >3,200 patients were enrolled and treated with 1,000 IU/m2 doses of pegaspargase, shows that the efficacy of pegaspargase dosed at 1,000 IU/m2 is at least as good as that of a 2,500 IU/m2 dose. In UKALL 2003:

- Five-year EFS was 87.3%.
- Five-year OS was 91.6%.

On this basis, we feel the results from studies using a 2,500 IU/m2 dose can justifiably be extrapolated to the 1,000 IU/m2 pegaspargase treatment group in our model.

The 1000 IU/m2 dose was also chosen by clinicians, initially in the UKALL 2003 trial, and this has remained the dose for the paediatric population protocols in the subsequent UKALL11 trial, and is also the dose in the adult UKALL14 trial.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The absence of a significant difference in costs, overall survival (OS) or event-free survival (EFS) does not mean that these input parameters can be assumed to be equal for all treatment strategies in the cost-effectiveness analysis. The submitted economic model does not allow for a difference in OS and EFS between treatments. Please provide a modified version of the model which allows for differing curves between treatments, so that numerical differences can be assessed for their impact on the incremental cost effectiveness ratio (ICER) and so that in the probabilistic survival analysis (PSA) the curves can fluctuate independently. In

addition, please modify the model, if necessary, to allow for differences in incidence of serious adverse events and different health-related quality-of-life decrements.

Despite the systematic search of the scientific literature, we haven't found any robust, comparative evidence on potential OS and EFS differences between the different asparaginases and asparaginase sequences. This absence of difference was confirmed by clinical experts' opinion. In addition, asparaginase is used with different dosing/frequency within multi-treatment chemotherapy regimens. It is thus very difficult to isolate the effect of asparaginase alone on OS and EFS. This is further demonstrated by [redacted] The model was thus built assuming that the same OS and EFS will apply to all asparaginases. Allowing for differing survival curves that fluctuate independently and randomly in the PSA could actually lead to inconsistent PSA iterations with unrealistic survival difference between different asparaginases.

The structure of the submitted model for both the adult and paediatric patients represents how patients in the NHS are treated per protocols, and there is insufficient robust, comparative data that utilises similar regimens (e.g in terms of dose, patient stratification, etc.) to enable an accurate comparison in the model.

The UKALL14 protocol introduction also states that EFS and toxicities have been seen to be similar between native and pegaspargase.This was fully endorsed by expert clinicians.

Although we have adapted the model to add the requested functionality, we would be unable to provide robust comparative OS and EFS data to explore within the model. We have addressed the SAE and health-related quality of life query in our response to question B3.

B2. Section 5.3.3 (pages 157-159) of the company submission states that 4 clinicians were invited for expert advice and 2 agreed to participate. It further states that these clinicians received a list of questions in advance to consider their responses, followed by an interview. Since many important input parameters of the cost-effectiveness model are based on expert opinion, please provide the following:

a. Justification as to why only 4 clinicians were approached,

The field of ALL disease is small and the number of true experts reflect this. We concentrated on communicating with those clinicians who could add greatest value to the submission based on experience and expertise

Due to the rare nature of acute lymphoblastic leukaemia, there are a limited number of clinicians who met the criteria stated in section 5.3.3 of our submission;

- Clinician experience of all three asparaginase products under consideration (Pegaspargase, native asparaginase and Erwinase).
- Clinicians actively involved in the current adult and paediatric trials, who had a knowledge of the current and historic protocols.
- Clinicians who are actively involved in ALL treatment.

This was to ensure the difference between the products under consideration could be assessed, in light of the paucity of head-to-head data, especially considering that the native

asparaginase product has not been routinely used in the NHS in paediatric patients since before the UKALL 2003 trial and prior to the UKALL14 adult trial and as Erwinase is usually reserved for 2nd line use.

There was thus a limited number of eligible clinicians – 4 of whom Baxalta approached, with 2 agreeing to participate. One clinician had particular experience in treating adult patients, the other paediatric patients.

b. The list of questions that have been asked to the clinicians and the minutes of the interviews.

The list of questions is enclosed in appendix 2, which included reviewing the model schematics to ensure they reflected clinical practice.

The clinicians approached wished to remain anonymous and as such, we have enclosed a summary of their responses:

- **Risk of hypersensitivity**:
  - **Paediatric Clinician:** agreed with the inputs from the Vora paper (2003), and the differences in risk of hypersensitivity rates between products. Stated this is now hardly ever seen in clinical practice in the paediatric population [since using pegylated asparaginase].
    Adult Clinician: stated that the paediatric data could be used for the adult population in the lack of comparable adult data, as the rates used seemed to be a plausible assumption. This data is currently being collected in the UKALL14 protocol, but is not yet available.
- **Time to hypersensitivity**:
  - **Paediatric & Adult clinicians:** A hypersensitive reaction is likely to happen early in the patient's treatment, e.g. at the 2nd administration of either of the 3 products. This is because it takes a few administrations to build up the antibodies, with the reaction occurring thereafter.
- **5 yr OS & EFS**:
  - **Paediatric & Adult clinicians:** We can reasonably assume OS & EFS equivalence between Pegylated asparaginase, native asparaginase and erwinase.
- **Dosing equivalence**:
  - **Paediatric & Adult clinicians:** Native asparaginase & Erwinase have a similar dosing schedule due to the much shorter half life compared with pegylated asparaginase. Every administration of Pegylated asparaginase is replaced by 6 IM injections of either native asparaginase / Erwinase
- **Extra hospital visits (e.g. outpatient/ daycase):**
  - **Adult Clinician**: As most patients receive all their treatment as inpatients, substituting native / Erwinase would not result in any additional hospital visits (they would otherwise not have had)
  - **Paediatric Clinician**: Most patients receive their induction as inpatients, but subsequent treatments in outpatient/ daycase settings. Substituting native / Erwinase would therefore result in additional hospital visits (they would otherwise not have had).
- **Equivalence in risk of other A/Es:**

    - **Adult & Paediatric Clinicians:** Aside from hypersensitivity, we can assume equivalence in side effect / AE rates between the different types of asparaginase, esp. as the side effects (e.g. abnormal LFTs) are likely to be attributable to the asparaginase itself, rather than the formulation (adult clinician).
- **Quality of Life/ Patient experience**:
    - **Adult Clinician**:
        - IM injections are very painful and a lot of patients develop bruising due to thrombocytopenia
        - When patients get hypersensitivity, this is usually an anaphylactic episode, which is very frightening for the patient, esp. as it is potentially life-threatening.
        - Patients having a hypersensitive reaction also have a delay in their treatment whilst this is resolved, during which time, they feel as if "nothing is being done" for what is a very serious disease.

B3. **Priority question:** Hypersensitivity is the only toxicity that has been included in the economic model. However several other serious adverse events were also reported in section 4.13 (Table 32-36) of the company submission. Despite the absence of significant differences in the incidence of serious adverse events, it is relevant to provide a complete assessment of the costs and quality of life impact of different asparaginase treatment including all relevant serious adverse events. Please provide a modified version of the economic model which includes the costs and quality of life impact of the recorded serious adverse events.

We used a conservative assumption that there was no difference in the rates of adverse events, due to the following factors:

- The submitted model intended to compare multiple asparaginase sequences in line with the appraisal scope. Therefore, a decision tree structure was preferred to model the potential switches only when hypersensitivity occurs and the other toxicities were realistically assumed to have the same incidence regardless the asparaginase sequence considered.

- The studies that do report adverse events, are not granular enough to demonstrate *how the model could be adjusted* to accurately reflect how the events would occur in the model (e.g. at which decision or chance nodes, the risk per arm, cost or QoL decrement, etc.).

- [redacted]There are no comparative studies between the 3 comparators to our knowledge; most studies reported in section 4 are single arm, and differ widely in aspects like dosing regimen, patient stratification, etc. [redacted]as reported in our submission.

- Asparaginase is used with other medicines and it is challenging to attribute the AE differences to asparaginase and not the concomitant medication or indeed the disease itself

- This was a key question we posed to the clinical experts, all of whom stated that, other than hypersensitivity, there was *no discernible difference in adverse reactions between the products and that we should assume equivalence.* This has been highlighted in the UKALL14 protocol as well.

- This was therefore not built into the model, based on clinician opinion and also, a lack of data per "arm" to be able to populate the model, as the risk of each adverse event would also be dependent on other factors, e.g. patient characteristics like age, concomitant diseases, etc.

- There was also a lack of data on the incremental costs and quality of life associated with each potential adverse event in this patient population.

[redacted]

- Adding the other toxicities in the decision tree would have make it even less traceable (i.e. much larger tree). Moreover, finding the appropriate evidence at which treatment phase these other AEs occur is challenging. Therefore, we assumed the same incidence of other toxicities for all model branches (this was confirmed by the experts consulted) and did not take them into account for simplicity reasons as their respective costs and QoL impacts would have cancelled each other out in the ICER ratio.

B4. Most evidence about EFS and incidence of hypersensitivity is based on other administrations of asparaginase (including differences in dose and number of injections), raising the question of the generalisability of the results from these studies to clinical practice in England. In order to address this question, please provide scenario analyses in which PEG-asparaginase (PEG) has both a better OS and EFS (e.g. based on CCG-1961) and a worse OS and EFS (e.g. based on DFCI-91-01).

In an attempt to ensure that inputs relevant to the English clinical setting were used, data relevant to this setting of care, like the dosing regimens and associated data available for this were identified (i.e. Vora, 2013). This is an important consideration as there are large variations in the protocols in different countries, patient risk groups, etc., and the UK uses a lower dose than other countries (1000 units/m² vs 2500 units/m²). The EFS and OS rates for the paediatric population was therefore taken from a trial involving over 3,200 patients, with the adult data being taken from a historic UK trial. All these inputs were validated by clinicians (per question B2).

There is a lack of data per "decision tree arm" to assess differences between the products and SR1, run in August 2015, [redacted] making data inputs challenging and adding to the uncertainty, especially in light of the varying results stated in the question above (i.e. one "better" and one "worse") – both of which use protocols not relevant to UK practice, making the generalisability of these inputs questionable. The studies mentioned are also not all comparative.

The clinicians also stated that equivalence in OS and EFS can be assumed between the different forms of asparaginase. The UKALL14 protocol also states: “lower rate of high titre antibody formation with pegaspargase, but similar rates of adverse events and similar EFS”

In our original submission, we stated that SR1 identified only three studies which allowed to a certain extent direct comparison between pegaspargase and E. coli-ASP (CCG 1962, CCG 1961 and DFCI ALL 91-01). Of these three studies the only one where patients were randomised to either pegaspargase or E. coli-ASP at induction was CCCG 1962. In CCG 1961 patients were randomised at consolidation (CCG 1961) or at intensification (DFCI ALL 91-01). These three studies do not allow to calculate pooled estimates given the marked differences across them:

- Patients not being exposed to any asparaginase at induction in DFCI ALL 91-01, vs being exposed to E. coli-ASP in CCG 1961 and to either pegaspargase or E. coli-ASP at induction in CCG 1962
- Patients being SR and HR in DFCI ALL 91-01, HR in CCG 1961 and SR in CCG 1962.

However, on consideration of the ERG’s request, we have now run the model to adopt the “best” and “worst” case scenarios highlighted by the ERG in this question.

<u>The results</u>:

CCG-1961:

EFS = 81% (native followed by peg - arm) vs 72% (native only – arm)

OS = 89% (native followed by peg - arm) vs 83% (native only - arm)

Note: Not stratified by risk group.

Erwinase the same as in the base case (95/90/80)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,547**	**21.7074**	—	—	—
Native Asp.—Erwinase	£12,273	20.1873	-£3,726	1.5201	-£2,451 (PEG dominant)
Erwinase—PEG-Asp.	£44,900	22.1356	-£36,353	-0.4281	£84,914 (SW quadrant)
Erwinase—Native Asp.	£44,781	22.1248	-£36,234	-0.4174	£86,810 (SW quadrant)

DFCI-91-01:

EFS = 78% (peg) vs 84% (native)

OS = not separately reported between asparaginases randomization = 88% was applied to both native and pegaspargase in the model

Note: Not stratified by risk group.

Erwinase the same as in the base case (95/90/80)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,528**	**21.4008**	—	—	—
Native Asp.—Erwinase	£12,380	21.5903	-£3,852	-0.1895	£20,326 (SW quadrant)
Erwinase—PEG-Asp.	£44,900	22.1356	-£36,372	-0.7348	£49,501 (SW quadrant)
Erwinase—Native Asp.	£44,781	22.1248	-£36,253	-0.7240	£50,070 (SW quadrant)

We acknowledge that in the scenario analysis based on the results of DFCI-91-01 (in which OS and EFS were worse with pegaspargase compared with native asparaginase treatment), performed as requested by the ERG, that the resultant ICER cast uncertainty on the cost-effectiveness of pegaspargase. We wish to highlight, however, several caveats with regard to considering the EFS and OS rates reported in DFCI-91-01:

- Given the scarcity of native and pegaspargase head-to-head data, particularly in the UK, DFCI-91-01 was included in our submission as a supporting study since it included a randomisation to native or pegaspargase treatments. Patients in this study were not, however, exposed to asparaginase at induction, which is certainly not the case in current UK protocols where pegaspargase is administered at induction.

- The purpose of the paper reporting the results of DFCI-91-01 (Silverman 2001) was to compare that protocol with earlier DFCI protocols. Other randomisations, in addition to the type of asparaginase used, were performed, but did not result in statistically significant improvements in EFS. The EFS rates of 84% for native asparaginase and 78% for pegaspargase, used, as requested, in this sensitivity analysis, were not significantly different (p=0.29).

- The relative rates for EFS reported in DFCI-91-01 for native and pegaspargase, are inconsistent with those reported in numerous other studies, discussed in our submission, in which EFS (and OS) rates are consistently higher with pegaspargase versus native asparaginase treatment.

- Patients in the US and Canada were enrolled in the study between 1991 and 1995 when pegaspargase wasn't available, and so are not very applicable to current UK clinical practice.

- Even when taking into consideration the above, and despite the other uncertainties outlined in our submission, the results of the economic evaluation demonstrate a lower total cost of Peg-erwinase than native erwinase, albeit with a slightly lower number of total QALYs. However, this is based on a statistically non-significant difference in EFS. This demonstrates that the worst case scenario, still renders pegaspargase a cost-effective treatment for ALL.

B5. On page 130 and Table 34 (page 131) of the company submission it is reported that the incidence of hypersensitivity is higher in the high-risk group, since these patients receive higher cumulative dose of PEG. However, in the cost-effectiveness model, the incidence of hypersensitivity is similar for all 3 risk groups and only occurs after 2 injections. Consequently, the higher incidence of hypersensitivity in the high risk group is not incorporated in the economic model. Please provide a modified version of the economic model in which the higher incidence of hypersensitivity in the high risk group is incorporated into the model in accordance with the findings in Table 34.

In the paediatric model, the average hypersensitivity rates for each treatment were applied across the model irrespective of patient clinical risk grouping. This was a conservative approach for consistency with the same approach taken in the native asparaginase and erwinase treatments, due to lack of granular data. However, as requested, we applied the different rates of hypersensitivity to pegaspargase, reported in Table 34 of the submission, to the model, the outputs of which are presented in Table 1 below.

In the adult model, patients receive between three and six doses of pegaspargase depending on patient age and transplant eligibility, irrespective of clinical risk classification. Accordingly, in the absence of any UKALL14 adult hypersensitivity data, the 2% average hypersensitivity incidence rate observed in UKALL 2003, which incorporates paediatric patients from clinical standard- intermediate- and high-risk groups (n=3,126) was applied throughout the adult model for the estimated risk of hypersensitivity reaction to pegaspargase from the 2nd dose onward, and validated by clinical expert.

Table 1: Revised paediatric results using the submission model

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	£8,251	22.1364	—	—	—
Native Asp.—Erwinase	£12,352	22.0633	-£4,101	0.0731	-£56,072 (PEG dominant)
Erwinase—PEG-Asp.	£44,901	22.1347	-£36,650	0.0017	-£21,676,868 (PEG dominant)
Erwinase—Native Asp.	£44,781	22.1248	-£36,530	0.0116	-£3,160,100 (PEG dominant)

B6. Please provide the justification for the assumption that the rate of hypersensitivity is similar in adult patients compared with children.

Due to the lack of published adult data representative of the way in which patients are treated in the UK, the adult ALL clinical expert consulted advised that the paediatric data relating to hypersensitivity could be used as a proxy for the adult population.

Please also refer to our response to question B2 of this document.

B7. Page 133 of the company submission states that PEG as 2nd line asparaginase followed after native E.coli increases the risk of hypersensitivity to PEG. Please clarify whether this would also apply to PEG followed after Erwinase.

There is no trial data to show pegaspargase use following Erwinase administration. Indeed, Erwinase is used following pegaspargase in trial protocols; Erwinase is not currently used 1st line in clinical practice as supported by the clinical trial protocol.

An important clarification is that both pegaspargase and Native asparaginase are derived from E-coli, whilst Erwinase is derived from chrysanthemum, so are different formulations of asparaginase. Per the SPC for Erwinase, the products are therefore immunologically distinct: http://www.medicines.org.uk/emc/medicine/31063

4.1 Therapeutic indications

Erwinase is used in combination with other anti-neoplastic agents to treat acute lymphoblastic leukaemia. It may also be used in other neoplastic conditions where depletion of asparagine might be expected to have a useful effect. Patients receiving treatment with L-asparaginase from Escherichia coli, and who develop hypersensitivity to that enzyme may be able to continue treatment with Erwinase as the enzymes are immunologically distinct.

B8. Page 39 of the company submission states that hypersensitivity may cause a delay in treatment and thereby impact on the health-related quality-of-life. Please clarify whether the occurrence of hypersensitivity would also impact on the administration of the other treatments for ALL. If so, please comment on what the subsequent consequences on health care costs, survival and health-related quality-of-life would be.

The above comment was made by clinicians during our discussions on the treatment of patients to reflect their experience of how a patient is impacted should they have a hypersensitivity reaction. There is no known data to quantify what the effect would be of the treatment delay on parameters like health care costs, survival or quality of life and the clinicians were unable to provide any specific data on this. It should be noted that this is also likely to differ based on the type of reaction, patient characteristics, and their response to treatment for the reaction. There is also no granular data to populate this in the model. As there is a demonstrated lower risk of hypersensitivity of pegaspargase vs both native and erwinase, any inputs we modelled would likely favour pegaspargase, so not including this is a conservative approach.

B9. **Priority question:** Please explain how the incidence of hypersensitivity after E.coli was estimated. It does not appear that the estimate of 20-40% is supported by the evidence in Table 8, paragraph 4.6 of the Appendix and Table 32 of the company submission. In addition, there is a large difference between the rate of hypersensitivity for PEG (2%) and that of native E.Coli asparaginase (20%). Please clarify whether the 2% was based on grade 3/4 allergy whilst the 20% was based on silent inactivation. If that is the case, please provide new estimates of hypersensitivity that are all based on the same definition.

The estimate of 20–40% hypersensitivity is merely the hypersensitivity rate suggested by Vora et al in their 2013 publication and not a rate we are trying to justify with the evidence provided in Table 8 and Table 32, nor the basis of our adopting the hypersensitivity rate of 20% for native E.coli-derived asparaginase leading to treatment switch used in our model.

2% is the rate of serious adverse events of asparaginase hypersensitivity as reported in Vora 2013 (Table 5 in their manuscript). No other rates for hypersensitivity of lesser grade/intensity are provided in either of the Vora 2013/2014 publications or supplementary materials. (Note that in UKALL 2003, hypersensitivity rates to pegaspargase ranged from 0.1–6% depending on the clinical risk grouping of patients and these different rates are accounted for in the paediatric model).

The important point is whether or not a hypersensitivity reaction resulted in an asparaginase treatment switch, irrespective of the severity/definition of the hypersensitivity reaction.

Our model accounts for hypersensitivity reactions, of any severity, that lead to an asparaginase treatment switch.

We base our 20% rate of hypersensitivity to native asparaginase not on silent inactivation, but on the Vrooman 2010 publication (DFCI ALL 00-01) in which a rate of 20% of hypersensitivity to native asparaginase, leading to a treatment switch to Erwinase, was observed in paediatric patients newly diagnosed with ALL (n=215).

In Vrooman et al 2010, hypersensitivity reactions were classified as mild (local reaction only at IM injection site, including erythema and/or swelling) or severe (defined as all other allergic reactions, including rash or urticaria beyond the injection site, lip/tongue swelling, respiratory distress, or hypotension). Patients were switched to Erwinase upon the occurrence of either a mild or severe hypersensitivity reaction.

The issue here is not the incidence rate or severity of hypersensitivity reactions to asparaginase in and of themselves, but whether or not the hypersensitivity reactions (of any severity) resulted in an asparaginase treatment switch.

The only rate for hypersensitivity to pegaspargase provided by Vora et al 2013/2014 is 2% - which were exclusively serious adverse events - resulting in a treatment switch to Erwinase.

In DFCI ALL 00-01 (Vrooman 2010), 20% of patients experienced hypersensitivity reactions to native asparaginase – a range of mild to severe grades – all of which, however, irrespective of severity, resulted in a treatment switch to Erwinase.

As discussed in our submission, rates of hypersensitivity to asparaginase are variable. In COG P9906, a rate of 13% Grade 3 or higher hypersensitivity to native asparaginase was reported, increasing to 25% incidence when considering any grade of hypersensitivity reaction. Study POG 8602 reported 8% Grade 4 hypersensitivity, but 76% incidence of hypersensitivity to native asparaginase leading to treatment switch. On this basis, therefore, we consider our 20% incidence rate for hypersensitivity reactions to native asparaginase necessitating a treatment switch, to be both justifiable, and conservative.

Sensitivity analysis on this parameter was undertaken in our submission, which showed no effect on the results.

B10. It is noted that the health-related quality-of-life estimates were derived from the study by Furlong et al, in which parents had filled in the health utility index (HUI) as a proxy for their children. Please explain why these estimates are also considered to be valid for adult patients.

There is currently a lack of quality of life data for the adult population, and this was thus used as an assumption, validated by expert opinion.

B11. Please provide the justification for choosing a reduction of 20% in health-related quality-of-life for patients with relapsed/refractory ALL.

As the NICE methods guide requires extrapolation to a lifetime time horizon, this was built in as a health state to reflect those patients who did not have EFS (especially for paediatric patients, there is a high OS rate).

There is no data available, so an assumption was made. Due to the nature of the disease, it was felt that a 20% decrement in health related quality of life was a conservative estimate.

When varying the decrement using the submission model for the paediatric model, the effect on the ICER was negligible, which was also explored in the submission sensitivity analysis, at a range of 30%, as shown in Table 2, Table 3, and Table 4 below.

Table 2. Original results with 20% decrement for paediatric population

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,545**	**22.1294**	—	—	—
Native Asp.—Erwinase	£12,352	22.0633	-£3,807	0.0662	-£57,547
Erwinase—PEG-Asp.	£44,900	22.1356	-£36,355	-0.0061	£5,917,762
Erwinase—Native Asp.	£44,781	22.1248	-£36,236	0.0046	-£7,917,480

Table 3. Utility decrement of 50% for paediatric population

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,545**	**21.8412**	—	—	—
Native Asp.—Erwinase	£12,352	21.7761	-£3,807	0.0652	-£58,394
Erwinase—PEG-Asp.	£44,900	21.8473	-£36,355	-0.0061	£6,005,144
Erwinase—Native Asp.	£44,781	21.8367	-£36,236	0.0045	-£8,033,903

Table 4. Utility decrement of 5% for paediatric population

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,545**	**22.2735**	—	—	—
Native Asp.—Erwinase	£12,352	22.2069	-£3,807	0.0666	-£57,132
Erwinase—PEG-Asp.	£44,900	22.2797	-£36,355	-0.0062	£5,875,019
Erwinase—Native Asp.	£44,781	22.2689	-£36,236	0.0046	-£7,860,525

B12. **Priority question:** Please provide estimates for the health care costs for the EFS and relapse/secondary tumour (R/ST) state as the proportion of patients in each health state may differ slightly, given that the EFS and OS is lower in patients experiencing hypersensitivity. In addition, please provide a modified version of the economic model incorporating these costs.

The UKALL 2003 study protocol states that it costs on average £50,000 to treat one child with relapse ALL (and more if the patients receives a stem cell transplant). However, when asked about the annual cost of a patient who relapses or develops a secondary tumour, the

paediatric ALL expert advised that the £50,000 cost was a gross underestimate and is more likely to be in the region of £150,000.

In addition to the average annual R/ST cost, the assumption made of EFS being equal across the asparaginases is being seen as a conservative approach, due to lack of comparative clinical data between all three asparaginases.

To our knowledge there are no costing studies or economic analyses for the EFS health state in paediatric and adult patients, nor for the R/ST health state in adult ALL patients. The model was therefore not able to be modified.

B13. Page 154 of the company submission states that "R/ST patients still alive at 5 years were also subject to the general mortality risk but increased by 90% (i.e. x1.9 general mortality; expert opinion)." Please provide the justification for the increase in mortality of 90% for patients with relapsed/refractory ALL.

Most trials report outcomes up to 5 years from treatment commencement, with a lack of long-term follow up data. As the NICE methods guide requires extrapolation to a lifetime time horizon, with most patients being in the event-free survival state, an assumption was made that, if patients relapse, they have a poor response to treatment, so these patients have a high mortality risk relative to the rest of the patient population (EFS patients are effectively cured, and thus follow the normal population event risk), which was based on feedback from clinical experts.

In two observational follow-up studies of relapsed ALL patients, Oriol et al 2010 stated a 5 year OS of 10%, and Fielding, et al 2007 reported an OS rate of 7% at 5 years. These reported OS rates support our mortality risk increase of 90%.

B14. Please provide the justification for the decrease in EFS and OS of 5% in patients who discontinue asparaginase treatment. For example, are there studies available showing differences in EFS or OS between patients continuing and discontinuing asparaginase treatment? In addition, please provide the justification for the assumption that the hazard ratio is similar for all risk and age groups.

We are not aware of any studies that report OS or EFS data for patients who have discontinued asparaginase treatment, and therefore used an estimate of 5%.

This is relevant to a relatively small number of patients, as they would have had to have a hypersensitivity reaction to both e-coli-derived and chrisanthimum–derived products.

Varying the EFS/OS rate to 20% following asparaginase discontinuation still yields a cost-effective ICER for pegaspargase as shown in Table 5.

Table 5. Applying a 20% reduction to EFS/OS following discontinuation of asparaginase treatment – ICER base case results using the submission model.

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£7,871**	**17.3262**	—	—	—
Native Asp.—Erwinase	£12,612	17.1241	-£4,741	0.2021	-£23,454
Erwinase—PEG-Asp.	£48,234	17.3450	-£40,363	-0.0188	£2,146,684
Erwinase—Native Asp.	£48,149	17.3122	-£40,278	0.0140	-£2,883,393

B15. The age of the paediatric population in the economic model is based on the median age of the patients as that age was considered to more informative than the average age. However, the age of adults in the economic model is based on the extrapolated mean age of the patients.

a. Please explain why the median age was not considered to be more informative for adults.

b. Please provide the mean age of the paediatric population.

UKALL14 is ongoing and so no median age for adult patients being treated on this protocol is available yet. Consequently, our model used extrapolated average adult ages based on CRUK data as this was the only data of relevance to the UK adult ALL patient population available to us.

The mean age of the paediatric ALL population according to CRUK is 7.3 years. The mean age of the paediatric population in UKALL 2003 is not provided in the Vora publications. Only the median age (5 years) is provided. This value was used in the model in favour of the mean age provided by CRUK (7.3 years) as it was considered more informative and robust (based on n=3,200), and more relevant (97% of eligible patients were enrolled) to the UK paediatric ALL patient population.

As requested, when using the mean age of 7.3 years for paediatric patients, the ICER is still dominant for pegaspargase (Table 6).

Table 6. ICER for mean age of 7.3 years for children, using the submission model.

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£8,545**	**21.9103**	—	—	—
Native Asp.—Erwinase	£12,352	21.8449	-£3,807	0.0654	-£58,168
Erwinase—PEG-Asp.	£44,900	21.9164	-£36,355	-0.0061	£5,981,814
Erwinase—Native Asp.	£44,781	21.9058	-£36,236	0.0045	-£8,002,820

B16. Please explain why the half-cycle correction was considered no longer clinically relevant after the treatment period.

The half cycle correction was applied to account for the switch to an alternative form of asparaginase following a hypersensitive reaction, especially as this was stated to be earlier in the induction phase for native asparaginase or erwinase than pegaspargase, due to the larger number of administrations (six doses of native asparaginase/ erwinase for every administratin of pegaspargase).

In order to meet NICE's methods guide, lifetime extrapolation was then applied, but as there was no active treatment or switching undertaken in the lifetime extrapolation's heath states, half-cycle correction was not applied due to this not being clinically relevant.

B17. For the modelling of the survival curve over time, the expected distribution was based solely on visual inspection. Please evaluate the fit of different parametric survival functions (Weibull, Exponential, Lognormal, Loglogistic and Gompertz) for OS and EFS in line with the Decision Support Unit (DSU) recommendations (as set out in the technical support document 14) and provide the justification for the distributions chosen.

In Paediatrics, the survival curves reported in the UKALL 2003 (Vora et al. 2013) study clearly suggested a near-linear pattern over time until 5 years. Therefore, a fixed instantaneous rate of event (death/relapse/secondary tumor) over time can be reasonably assumed in lieu of parametric survival functions.

In Adults, and in the absence of data from the ongoing UKALL14 protocol, we used the curves reported by Fielding et al 2008 from multiple UKALL adult trials conducted in the UK. As these multiple curves suggested a non-linear pattern of survival over time, we used a Weibull parametric function that was fitted on 2 points only.

We acknowledged that the graph from Fielding 2008 in Adults could have been digitized in order for us to fit different parametric functions. However, the graph is of poor quality and has multiple curves overlapping. This renders digitization impractical. In addition, the model had to accommodate flexibly the 30% to 40% EFS assumption at three to seven years of follow-up in Adults. The model also needed to accommodate for different assumptions for patients ≤40 years and those ≥41 years of age (and Fielding 2008 did not report curves per

age-group). Finally, the models assumed that survival was the same regardless of the asparaginase used. The fit of different parametric functions was thus not deemed necessary.

B18. Please provide the justification for the assumption that EFS=OS for the adult population. Please clarify whether the assumption implies that the time between recurrence and death is very short.

The assumption that EFS = OS for the adult population was provided by the clinical expert interview, due to the lack of reported data in the UK patient population.

This does imply that the time between recurrence and death is very short, and it is important to note that adult patients are treated with different protocols than younger patients (<25 years), due to the possible differing nature of the disease and additional co-morbidities in adults. The OS and EFS rates are therefore also lower those seen in the paediatric population modelled.

B19. Please provide a scenario analysis that allows vial-sharing for the different asparginase formulations.

The multiagent chemotherapy regimens the patients are on are very complicated, customised to the clinical risk grouping of the patient, and thus likely asynchronous to the regimens of other ALL patients receiving treatment in the same clinic. In addition, opened vials of enzyme would have to be stored, raising shelf-life and sterility issues. On this basis, vial sharing wouldn't be practical in the treatment of patients with ALL.

Due to the relatively rare nature of the disease, it would be challenging to plan and deliver a service where there were enough patients requiring the product during any given setting of care (some patients are treated in hospital, others day case, etc) to be able to realise a vial-sharing scenario.

B20. In the scenario analyses in which the age of the children were set at 1 and 18 years, the body surface area (BSA) does not appear to have been adjusted. Please correct these scenarios to align the BSA with the age of the patient.

This has now been addressed in the revised model, the results for which are presented below (Table 7).

Table 7. Scenario analysis, Paeds age 1 and paeds age 18 with BSA varied accordingly

	PEG - Erwinase vs. Native - Erwinase			PEG - Erwinase vs. Erwinase - PEG			PEG - Erwinase vs. Erwinase - Native		
Scenario	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Paed Age = 1	**-£3,017**	**0.05**	**-£59,209**	**-£40,468**	**-0.0047**	**£8,558,688**	**-£40,384**	**0.0035**	**-£11,450,464**
Paed Age = 18	**-£9,700**	**0.05**	**-£210,157**	**-£40,468**	**-0.0043**	**£9,452,180**	**-£40,384**	**0.0032**	**-£12,638,828**

Section C: Literature searching:

C1. Please re-run the following searches:

a. Include the term lymphatic leukaemia/leukemia in PubMed and The Cochrane Library. A quick title only search undertaken by the ERG for "lymphatic leukemia" in PubMed retrieved over 1000 results. Therefore it is possible that key papers have been missed with the exclusion of this term.

We conducted all searches to include the term lymphatic leukaemia/leukemia in the PubMed and The Cochrane Library searches retrieved in total 24 new studies as described in the table below. Among these 24 studies, no one was deemed of interest for the current submission.

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	Cost-Effectiveness Search	Health-Related Quality of Life Search
C1a	Addition in the Clinical Conditions Search of **lymphatic leukemia[Title/Abstract] OR lymphatic leukaemia[Title/Abstract]**	**Medline (PubMed)**	**8**	**5**	**10**
	Addition in the Clinical Conditions Search of **lymphatic leukemia.ab,ti. or lymphatic leukaemia.ab,ti.**	**The Cochrane Library**	**0**	**0**	**1**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*0*	*0*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*0*	*0*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*0*	*0*	*0*
		Cochrane Central Register of Controlled Trials <December 2015>	*0*	*0*	*1*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*0*	*0*
		Health Technology Assessment <4th Quarter 2015>	*0*	*0*	*0*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*0*	*0*

Please refer to Appendix 3 for detailed list of studies

b. Include lymphatic leukaemia in the Embase searches as the current searches only include lymphatic leukemia.

We conducted all searches to include the term lymphatic leukaemia in the Embase searches and didn't retrieve any additional study described in the table below.

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	Cost-Effectiveness Search	Health-Related Quality of Life Search
C1b	Addition in the Clinical Conditions Search of **lymphatic leukaemia.ab,ti.**	**Embase**	**0**	**0**	**0**

Please refer to Appendix 3 for detailed list of studies

C2. Please explain why MeSH terms were limited to Major Topic in PubMed but were exploded in The Cochrane Library. Limiting the terms to Major Topic could mean that relevant articles were missed.

We agree with the comment that in order to be consistent in the searching methodology through the different databases, MeSH Terms should have been exploded as well in the PubMed / Medline searches.

In order to confirm we didn't miss any relevant study, we have conducted the search by exploding the MeSH Terms in the PubMed search and retrieved additional 93 studies as described below. Among these 93 studies, 3 full text manuscripts were reviewed and no one was eventually deemed of interest for the current submission.

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	Cost-Effectiveness Search	Health-Related Quality of Life Search
C2	Replacement in the Clinical Conditions Search of Precursor Cell Lymphoblastic Leukemia-Lymphoma[MeSH Major Topic]) OR Leukemia, Biphenotypic, Acute[MeSH Major Topic]) by **Precursor Cell Lymphoblastic Leukemia-Lymphoma[MeSH Terms]) OR Leukemia, Biphenotypic, Acute[MeSH Terms])**	**Medline (PubMed)**	**23**	**31**	**39**

Please refer to Appendix 3 for detailed list of studies

C3. Please provide the rationale for limiting the searches to English only.

Due to language proficiencies, only English studies were included

C4. Please provide the details and search strategies for all manual searches mentioned in the Appendices 2.2.4, 6.4 and 8.4.

Manual searches were conducted in January 15, 2016 to identify any new relevant publication and/or studies on top of the ones identified through the systematic literature review in the above mentioned databases.

Specific searches for the condition "Acute lymphoblastic leukemia" (and any other relevant synonyms) and "asparaginase" (and any other relevant synonym) didn't retrieve any additional relevant study.

Specific websites and databases that were used for manual searches are listed below:

ClinicalTrialsGov database (https://clinicaltrials.gov/ct2/search/advanced)

ASH http://www.bloodjournal.org/search?sso-checked=true

ASPHO: http://aspho.org/meetings/annual-meeting/archive

CALGB: https://www.calgb.org/Public/meetings/meeting_presentations.php

Google: www.google.com

In addition to the above mentioned website, Cost-Effectiveness and Health-Related Quality of Life specific manual searches were also conducted within the following website

ISPOR: http://www.ispor.org/

NHS: http://www.nhs.uk/

NICE: https://www.nice.org.uk/

SMC: https://www.scottishmedicines.org.uk/

C5. Please explain why the search results were limited to 31 December 2015, yet were conducted on 31 January 2016.

We are using a pre-defined protocol with a time cut-off for studies included to ensure similar number of studies and results will be retrieved whenever the search will be conducted. The last search was thus conducted on 31 January 2016.

C6. Please clarify how the 'No Animals' limit was implemented in PubMed and Embase searches.

Medline: Exclusion criteria: NOT (animals[MeSH Terms] NOT humans[MeSH Terms])

Embase: Exclusion criteria: [not (nonhuman or animal or animal experiment).sh.]

The Cochrane Library: Exclusion criteria: [not (nonhuman or animal or animal experiment).sh.]

C7. Please clarify whether published/validated study design filters were used to limit to:

a. trials in the clinical effectiveness searches;

Clinical queries search strategies for MedLine were based on NCBI recommendations which were based and updated from the work from Haynes RB et al. 1

Clinical queries search strategies for Embase and The Cochrane Library were based on OVID Search Platform recommendations.

b. economic outcomes in the cost-effectiveness searches; and

Common knowledge and internal expertise were the basis of the searching strategy. No published/validated study design filters were used.

c. health related quality of life outcomes in the measurement and valuation of health effects searches.

Common knowledge and internal expertise were the basis of the searching strategy. No published/validated study design filters were used.

C8. Please explain why study design filters were applied in The Cochrane Library as Cochrane resources are considered to be study design specific databases. Please

[1] (Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ. 2005 May 13; Haynes RB, Wilczynski NL for the Hedges Team. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. BMJ. 2004 May 1;328(7447):1040.)

comment on whether possible relevant publications may have been missed because of the application of the study design filters.

We agree with the comment that additional study design filters might have led to some missing articles or studies.

We conducted the search by removing these study design filters in The Cochrane Library and retrieved additional 10 studies as described in the table below. Among these 10 studies, 5 abstracts or full text manuscripts were reviewed and one was eventually deemed of interest for the current submission.

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	Cost-Effectiveness Search	Health-Related Quality of Life Search
C8	Study design filter removed from The Cochrane Library search: ~~(clinical and trial).ab,ti. or clinical trials.sh. or clinical trial.pt. or random*.ab,ti. or random allocation.sh. or "therapeutic use".sh.~~	**The Cochrane Library**	**10**	**n/a**	**n/a**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*1*	*n/a*	*n/a*
		Cochrane Central Register of Controlled Trials <December 2015>	*9*	*n/a*	*n/a*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*n/a*	*n/a*
		Health Technology Assessment <4th Quarter 2015>	*0*	*n/a*	*n/a*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*n/a*	*n/a*

Please refer to Appendix 3 for detailed list of studies

Summary of the additional study identified and impact on the current submission:

We don't expect any impact of this additional reference on the current submission given that most of the results were already published in previous publications (Seibel 2008; Nachman 2009; Panosyan 2004). Furthermore, this study induced remission using only native and not pegaspargase, and the authors commented that because of the high incidence of allergic reactions to the pegylated enzyme observed following the use of native asparaginase in induction, the protocol for their subsequent high-risk trial dictated that all patients receive pegaspargase in induction and all subsequent phases (Seibel 2008).

							Patient Population				Asparaginase Dose / Phase(s)		Outcome (PEG vs Comparator)		Safety (grade 3 or 4)
Clinical trial	Author	Date	Scope	Country	Trial design	Outcome Measures	Inclusion Criteria	Child (number of patients)	Ages (years)	Risk Level	PEG	Native	EFS / DFS	Anti-ASNase Antibody status	Allergy / Hypersensitivity
CCG-1961 Subgroup analysis (PEGase arm - High Risk Patients)	Ko RH.	2015	1996-2002	USA	To determine whether the prevalence of Ab formation in the HR ALL patients is a predictor of poor treatment outcome	Assessment of the incidence of clinical allergy and end-induction antiasparaginase (anti-ASNase) antibodies in children with high-risk acute lymphoblastic leukemia treated with pegylated (PEG) Escherichia coli ASNase	Newly diagnosed High-Risk Previously untreated	1'155	1-9	HR	Single monthly doses of PEG ASNase (2500 IU/m2 per dose) during postinduction courses	All patients received native ASNase during induction 9 doses / 6'000 IU/m2	5-yr: PEG ASNase-containing regimen 80%: Patients with negative antibody titer 77.7%: Patients with positive antibody titer((p=.68)	Post-Induction: 28.5% patients have apositive antibody titer (>1:1) Those patients were 2.41 times more likely to have an allergic reaction to PEG ASNase postinduction than patients who had a negative antibody titer (OR, 2.41; 95% CI, 1.49-3.89; P<.001)	Con: 35.2% (NAT) - 28.6% (PEG) - 33.3% (ERW) IM1: 27.6% (NAT) - 21.3% (PEG) - 8.1% (ERW) DI1: 3.2% (NAT) - 4.8% (PEG) - 5.4% (ERW) IM2: 0% (NAT) - 10.4% (PEG) - 7.6% (ERW) DI2: 5.9% (NAT) - 1.8% (PEG) - 2.6% (ERW)

C9. Please provide the results for the separate databases in The Cochrane Library searches.

Please find in the Table below, the results for the separate databases in The Cochrane Library Searches.

	DataBases	Clinical Evidence Search	Cost Effectiveness Evidence Search	Health Related Quality of Life Evidence Search
Identified Studies before 1st pass analysis and review	*Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>*	*1*	*0*	*8*
	ACP Journal Club <1991 to Dec 30, 2015>	*0*	*0*	*0*
	Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*0*	*0*	*1*
	Cochrane Central Register of Controlled Trials <December 2015>	*227*	*41*	*222*
	Cochrane Methodology Register <3rd Quarter 2012>	*0*	*0*	*0*
	Health Technology Assessment <4th Quarter 2015>	*0*	*0*	*0*
	NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*0*	*0*

Clinical effectiveness: Systematic review 2

C10. Please re-run all searches in Systematic review 2 to include ASNase which is a valid synonym for asparaginase.

We conducted all searches to include ASNase which is a valid synonym for asparaginase and didn't retrieve any additional that were not identified through the initial search.

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	Cost-Effectiveness Search	Health-Related Quality of Life Search
C10	Addition in the Drug therapies / Intervention Search of **ASNase[All fields]**	**Medline (PubMed)**	**0**	**n/a**	**n/a**
	Addition in the Drug therapies / Intervention Search of **ASNase.af.**	**The Cochrane Library**	**0**	**n/a**	**n/a**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*0*	*n/a*	*n/a*
		Cochrane Central Register of Controlled Trials <December 2015>	*0*	*n/a*	*n/a*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*n/a*	*n/a*
		Health Technology Assessment <4th Quarter 2015>	*0*	*n/a*	*n/a*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*n/a*	*n/a*
		Embase	**0**	**n/a**	**n/a**

C11. Please provide the rationale for Systematic review 1. In addition, please confirm that all papers found in Systematic review 1 were also found in Systematic review 2.

Systematic review 1 was designed to specifically identify evidence to allow a comparison of pegaspargase and native E.coli-derived asparaginase for the 1st line treatment of ALL in newly diagnosed children and adolescents, for regulatory purposes. This search was conducted in August 2015. The objectives of systematic review 1 were to:

- To evaluate the efficacy and safety of pegaspargase when used as the 1st line asparaginase therapy in ALL treatment.
- To assess the efficacy and safety of pegaspargase compared with native asparaginase when used as the 1st line asparaginase therapy in ALL treatment.

Systematic review 2 was conducted to broaden the search of systematic review 1, to identify evidence for pegaspargase, native E.coli-derived asparaginase, and Erwinia-derived asparaginase, irrespective of patient age group and line of treatment. It was also to identify evidence pertaining to cost and quality of life, as systematic review 1 focused on the clinical evidence. This search was conducted in 31st January 2016.

Systematic review 2 found all the papers originally found by systematic review 1. Systematic review 2 also identified a further five publications providing pegaspargase data and four additional studies providing data on Erwinia-derived asparaginase.

C12. Please clarify what the objectives were for Systematic review 2 as these differ between section 4.1.2 of the company submission and Appendix 2. Section 4.1.2 states that Systematic review 2 "was conducted to comprehensively update the first systematic review. The objectives were the same as in the first review." Appendix 2 states that the objectives of Systematic review 2 were "to identify and select relevant clinical and cost-effectiveness studies".

Systematic review 1 was designed to specifically identify evidence to allow a comparison of pegaspargase and native E.coli-derived asparaginase for the 1st line treatment of ALL in newly diagnosed children and adolescents, for regulatory purposes. This search was conducted in August 2015. The objectives of systematic review 1 were to:

- To evaluate the efficacy and safety of pegaspargase when used as the 1st line asparaginase therapy in ALL treatment.
- To assess the efficacy and safety of pegaspargase compared with native asparaginase when used as the 1st line asparaginase therapy in ALL treatment.

Systematic review 2 was conducted to broaden the search of systematic review 1, to identify evidence for pegaspargase, native E.coli-derived asparaginase, and Erwinia-derived asparaginase, irrespective of patient age group and line of treatment. It was also to identify evidence pertaining to cost and quality of life, as systematic review 1 focused on the clinical evidence. This search was conducted in 31st January 2016.

C13. Please amend section 4.1.2.1 of the company submission so that it is clear which databases have been searched, what dates (treatment inception or database inception) and on what platform.

This information provided in Appendix 2 (Section 2.2.1) of the submission, should read as follows:

2.2.1 Databases searched and service provider

A comprehensive search of the peer-reviewed literature was conducted to identify and select relevant clinical and cost-effectiveness studies. The following sources were used for search:

· Medline (via the Pubmed – NLM platform), all records from database inception to December 31, 2015

· Embase (via the OVID platform), all records from database inception to December 31, 2015

· Cochrane Database of Systematic Reviews (via the OVID platform) 2005 to February 12, 2016

  · EBM Reviews - Cochrane Central Register of Controlled Trials December 2015

  · EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012

  · EBM Reviews - ACP Journal Club 1991 to December 2015

  · EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2015

  · EBM Reviews - Health Technology Assessment 4th Quarter 2015

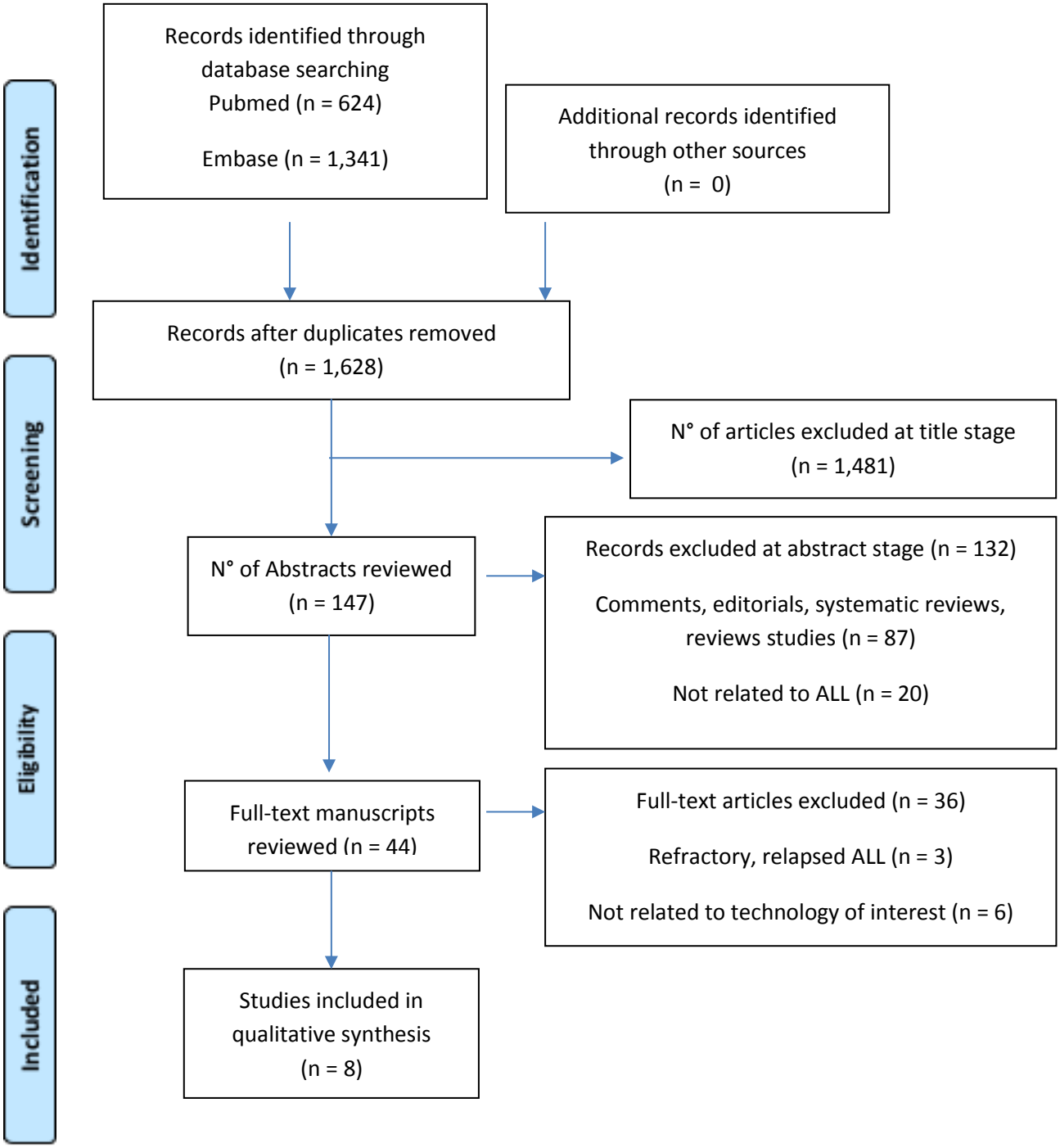
  · NHS Economic Evaluation Database 4th Quarter 2015

2.2.2 Date of search

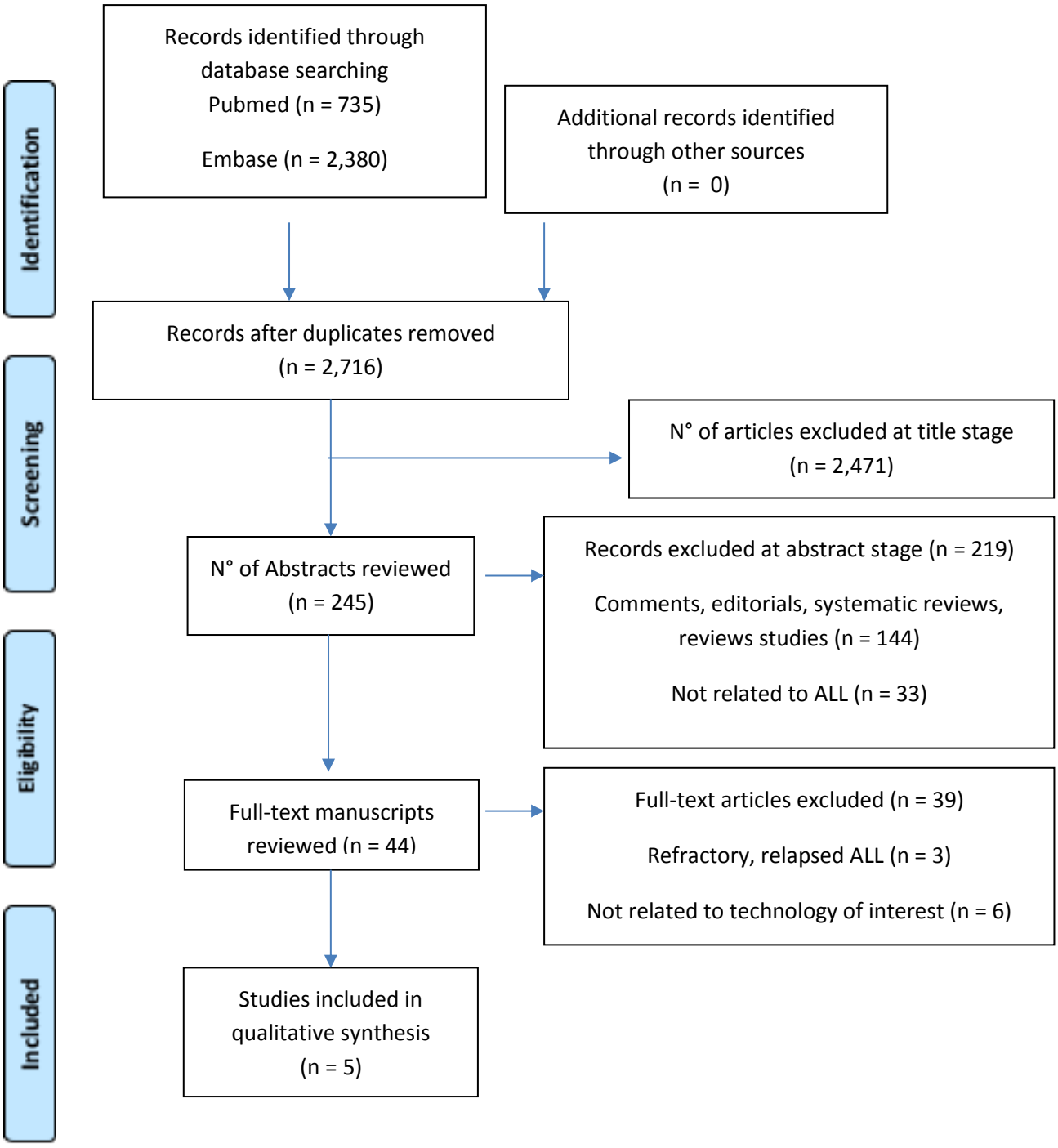
Searches in all databases were conducted on January 31, 2016.

C14. Please provide the flowcharts/ schematic diagrams detailing the Cost-effectiveness searches and health-related quality-of-life searches in the company submission.

Cost-effectiveness evidence search study flow diagram:



Health-related quality of life evidence search study flow diagram:



Appendix 1: Tables from Silverman 2013 publication (Reference 50 in submission)

Table 1

ASP-related Toxicity and Nadir Serum ASP activity (NSAA) during Consolidation

	IM E.coli (N=231)	IV PEG (N=232)	p-value
Allergy	9%	12%	0.36
Pancreatitis	9%	11%	0.54
Thrombosis	11%	6%	0.07
Median NSAA (wk 11 of Consolidation)	0.096 IU/mL	0.758 IU/mL	<0.01
% pts with NSAA ≥ 0.1 IU/mL (wk 11 of Consolidation)	46%	99%	<0.01

Table 2

Outcome by Patient Characteristics

	N	4-yr EFS	p-value
All eligible pts	551	86%	
Risk Group			
SR	268	94%	<0.01
HR	190	87%	
VHR	52	79%	
Age			
1-10 yrs	398	88%	0.06
≥10 yrs	153	80%	
Phenotype			
B-precursor	482	85%	0.58
T-ALL	69	88%	
End-Induction MRD (B-ALL only)			
Low (<0.001)	338	91%	0.03

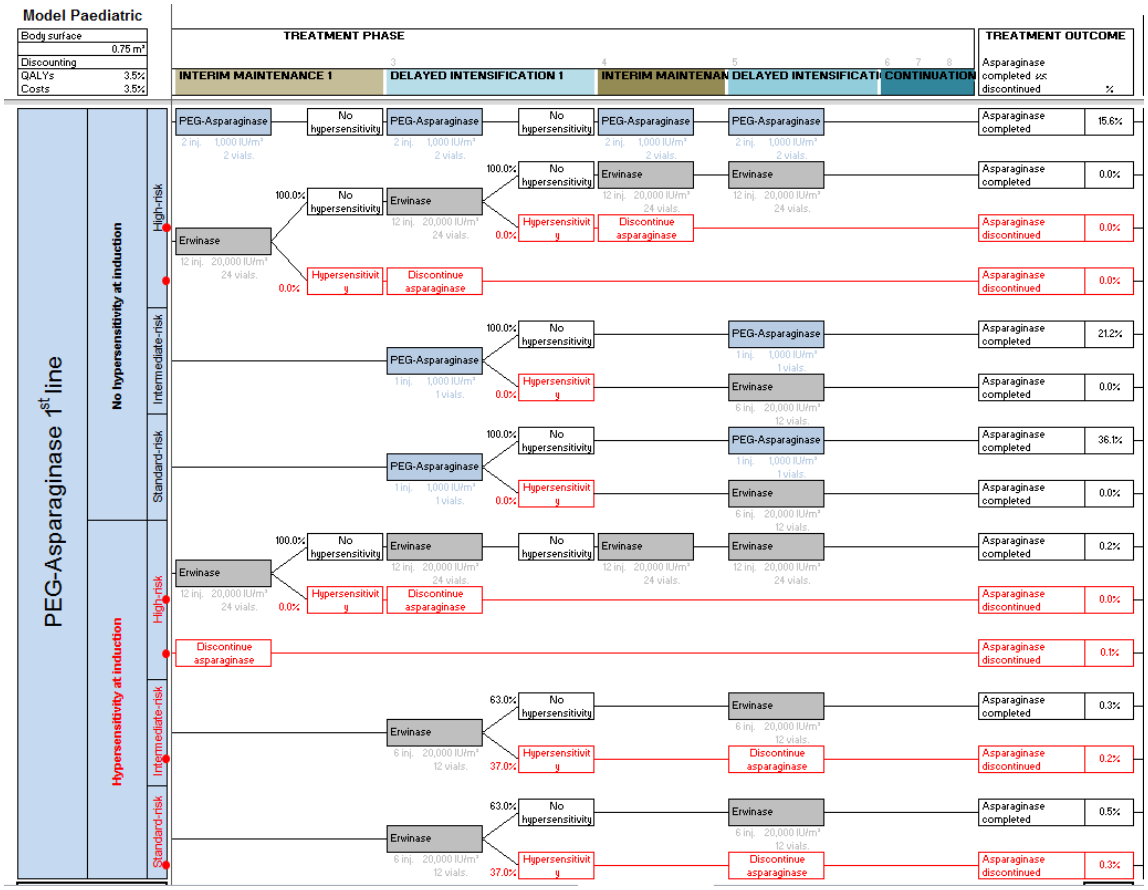
	N	4-yr EFS	p-value
High (≥0.001)	40	77%	
Cytogenetics			
Normal	131	87%	0.92
High Hyperdiploid (HeH)	145	89%	0.14
HeH with trisomies 4 + 10	88	95%	0.07
TEL/AML1	97	98%	<0.01
Hypodiploid (<45)	8	88%	0.91
MLL-R	10	60%	<0.01
BCR-ABL	16	69%	0.01
ASP Randomization			
E.coli ASP	231	90%	0.31
PEG	232	92%	

Appendix 2: Questions posed to clinical experts

Paediatric Patients:

Please comment on whether the model structure is an accurate representation of the UKALL 2003 protocol

Paediatric Schematic (based on UKALL2003)



Paediatric Population Questions:

Clinical Practice:

- What proportion of patients are treated per UKALL2011 protocol? How are patients outside of the trial treated?
- What is the treatment pathway for patients receiving asparaginase (e.g. setting of care, etc)
- Does this differ due to which form of asparaginase is administered administered?
- Is Erwinase ever used 1st line in UK clinical practice?

Structure and data input validation

- We have assumed that dosing equivalence for Native = Peg dose x 6, based on the UKALL protocol – Is this reasonable/would you use an alternative number?
- For the simplified model, the paediatric population is considered as 0-25yrs (as AYA patients are treated the same as the paediatric population).
  - Do you agree?
  - If not, how should this population be considered?
- We have applied a proportional spilt of patient numbers by Risk group according to the Vora et al. UKALL2003 study:
  - 49% standard-risk, 29% intermediate-risk and 21% high-risk
    - Do you agree? If not, what proportions should be applied?

Hypersensitivity:

- What are the most common adverse events associated with hypersensitivity in these patients?
- Would all hypersensitivities trigger a switch to Erwinase?
  - If not, what proportion of patients would remain on Pegaspargase or native Asparaginase?
- How are each of these hypersensitivities usually treated?
- *Time to Hypersensitivity:* When are the hypersensitivities most likely to occur?
  - In which treatment phase do hypersensitivities usually occur?
  - Does this delay treatment and affect outcome?
- *Rate of Hypersensitivity*: How frequently do each of these Hypersensitivities occur in usual practice?
  - The Vora paper states 2% ave for Peg, 30% ave for native.
    - Do you agree ?
    - If not, what values would you assign?

Check assumptions:

- Other than hypersensitivity, are all other side effects/ AEs (e.g. Pancreatitis, Liver toxicity, etc) are assumed to be equivalent (Peg vs native vs Erwinase), or, if not, what are the associated risk proportions?
- Per the trial protocols, the model assumes patients who develop a hypersensitivity to e-coli-derived product will switch directly to Erwinase (i.e. will not be given another e-coli derived product 2nd line).
  - Is this reflective of clinical practice? If not, how would this differ?

5 year outcomes

- Do patients who have had to discontinue asparaginase because of hypersensitivity have a poorer 5y outcome (EFS/OS) as compared to those who completed asparaginase?
  - If so, what would the reduction in 5y EFS/OS be for those who discontinued vs. those who completed asparaginase treatment?

Lifetime extrapolation

- 5-year survival rates have been extrapolated for the lifetime time horizon using the assumption that patients who are event-free after 5 years are cured. Is this a valid assumption?
- Relapse/Secondary Tumour:
  - Is an annual cost to the NHS of £50,000 on average a reasonable assumption?
  - What is the proportional increase in risk of death for this patient population?
- What proportion of these patients achieve EFS and after how long?

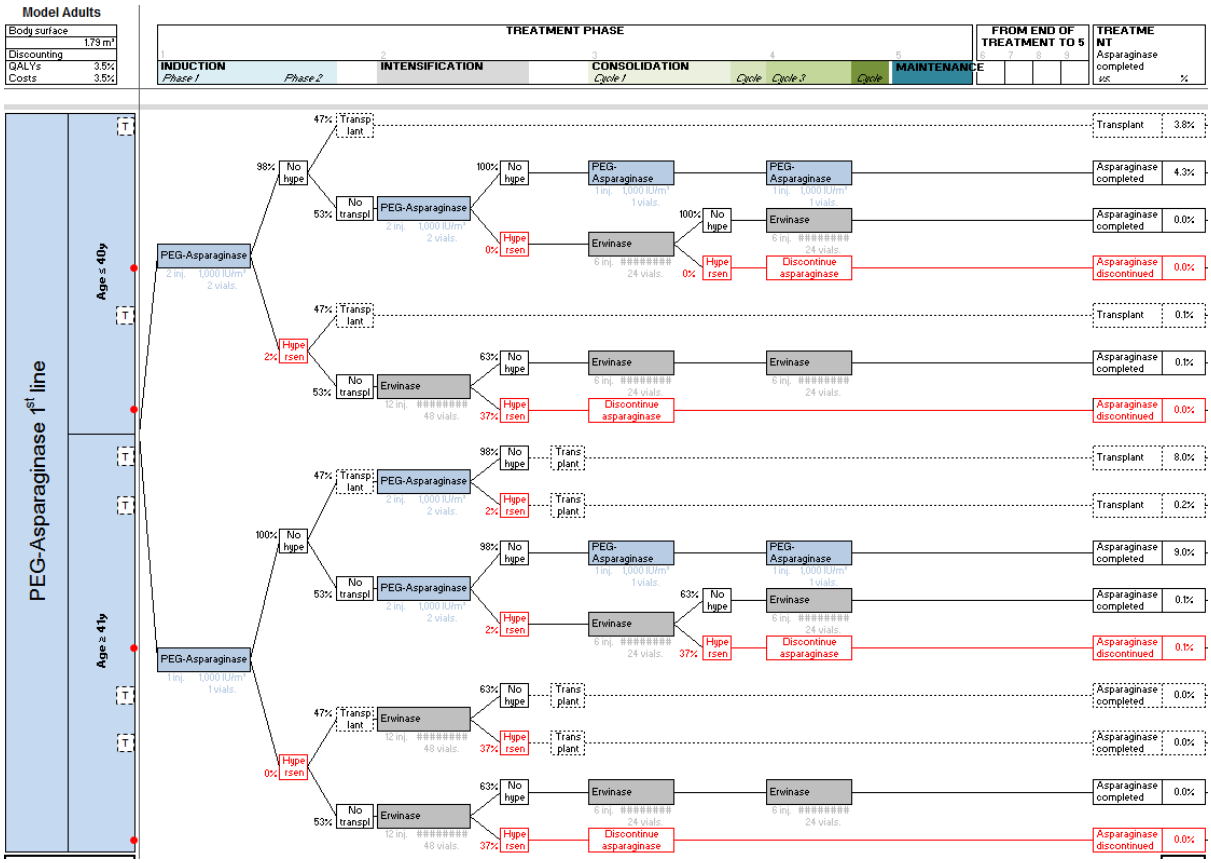
Quality of life (QoL)

- What is the impact on QoL of a hypersensitivity?

Adult Population Questions:

Please comment on whether the model structure is an accurate simplified representation of the UKALL 14 protocol

Adult Schematic (Based on UKALL14)



Adult Population Questions:

Question
Clinical Practice: - What proportion of patients are treated per UKALL14 protocol? How are patients outside of the trial treated? - What is the treatment pathway for patients receiving asparaginase (e.g. setting of care,etc) - Does this differ due to which form of asparaginase is administered administered? - Is Erwinase ever used 1st line in UK clinical practice?
Structure and data input validation - We have assumed that dosing equivalence for Native = Peg dose x 6, based on the UKALL protocol – Is this reasonable/would you use an alternative number?
Data sources for model, incl, - Based on your experience, please provide clinically plausible values for the following outcomes, per comparator. o OS o EFS - Are you aware of any data to support the efficacy? o If not what are your estimates of efficacy? - Do patients who have had to discontinue asparaginase because of hypersensitivity have a poorer 5y outcome (EFS/OS) as compared to those who completed asparaginase? o If yes, what would be the reduction in 5y EFS/OS for those who discontinued vs. those who completed?
Adverse Events: - Is there a difference in AE rates (e.g. Pancreatitis, Liver toxicity, hypoglycaemia, etc) across all formulations of asparaginase? ▪ Please provide clinically plausible values for these for use in the model (based on your anecdotal experience)
Hypersensitivity: - What are the most common adverse events associated with hypersensitivity in these patients? - Would all hypersensitivities trigger a switch to Erwinase (per protocol)? o If not, what proportion of patients would remain on Pegaspargase or native Asparaginase? - How are each of these hypersensitivities usually treated? - *Time to Hypersensitivity:* When are the hypersensitivities most likely to occur? o In which treatment phase do hypersensitivities typically occur? o Does this delay treatment and affect outcome? - *Rate of Hypersensitivity*: How frequently do each of these Hypersensitivities occur in usual practice? (peg vs native vs Erwinase) o The Vora paper states 2% ave for Peg, 30% ave for native asparaginase, for paediatric patients - Does this differ by Age, co-morbidity, or any other factors?
Quality of life - What is the impact on QoL of a hypersensitivity? - What else could impact the patient's QoL?

Appendix 3. Additional systematic review questions (C1–C14)

ERG Section C Questions	Modification	Databases	Number of new articles found *(duplicates from other databases searches removed)*		
			Clinical Effectiveness Search	**Cost-Effectiveness Search**	**Health-Related Quality of Life Search**
C1a	Addition in the Clinical Conditions Search of **lymphatic leukemia[Title/Abstract] OR lymphatic leukaemia[Title/Abstract]**	**Medline (PubMed)**	**8**	**5**	**10**
	Addition in the Clinical Conditions Search of **lymphatic leukemia.ab,ti. or lymphatic leukaemia.ab,ti.**	**The Cochrane Library**	**0**	**0**	**1**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*0*	*0*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*0*	*0*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*0*	*0*	*0*
		Cochrane Central Register of Controlled Trials <December 2015>	*0*	*0*	*1*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*0*	*0*
		Health Technology Assessment <4th Quarter 2015>	*0*	*0*	*0*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*0*	*0*
C1b	Addition in the Clinical Conditions Search of **lymphatic leukaemia.ab,ti.**	**Embase**	**0**	**0**	**0**
C2	Replacement in the Clinical Conditions Search of Precursor Cell Lymphoblastic Leukemia-Lymphoma[MeSH Major Topic]) OR Leukemia, Biphenotypic, Acute[MeSH Major Topic]) by **Precursor Cell Lymphoblastic Leukemia-Lymphoma[MeSH Terms]) OR Leukemia, Biphenotypic, Acute[MeSH Terms])**	**Medline (PubMed)**	**23**	**31**	**39**
C8	Study design filter removed from The Cochrane Library search: ~~**(clinical and trial).ab,ti. or clinical trials.sh. clinical trial.pt. or random*.ab,ti. or random allocation.sh. or "therapeutic use".sh.**~~	**The Cochrane Library**	**10**	**n/a**	**n/a**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*1*	*n/a*	*n/a*
		Cochrane Central Register of Controlled Trials <December 2015>	*9*	*n/a*	*n/a*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*n/a*	*n/a*
		Health Technology Assessment <4th Quarter 2015>	*0*	*n/a*	*n/a*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*n/a*	*n/a*
C10	Addition in the Drug therapies / Intervention Search of **ASNase[All fields]**	**Medline (PubMed)**	**0**	**n/a**	**n/a**
	Addition in the Drug therapies / Intervention Search of **ASNase.af.**	**The Cochrane Library**	**0**	**n/a**	**n/a**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*n/a*	*n/a*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*0*	*n/a*	*n/a*
		Cochrane Central Register of Controlled Trials <December 2015>	*0*	*n/a*	*n/a*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*n/a*	*n/a*
		Health Technology Assessment <4th Quarter 2015>	*0*	*n/a*	*n/a*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*n/a*	*n/a*
		Embase	**0**	**n/a**	**n/a**
ALL ERG REQUESTS COMBINED		**Medline (PubMed)**	**31**	**36**	**49**
		The Cochrane Library	**10**	**0**	**1**
		Cochrane Database of Systematic Reviews <2005 to Dec 30, 2015>	*0*	*0*	*0*
		ACP Journal Club <1991 to Dec 30, 2015>	*0*	*0*	*0*
		Database of Abstracts of Reviews of Effects <4th Quarter 2015>	*1*	*0*	*0*
		Cochrane Central Register of Controlled Trials <December 2015>	*9*	*0*	*1*
		Cochrane Methodology Register <3rd Quarter 2012>	*0*	*0*	*0*
		Health Technology Assessment <4th Quarter 2015>	*0*	*0*	*0*
		NHS Economic Evaluation Database <4th Quarter 2015>	*0*	*0*	*0*
		Embase	**0**	**0**	**0**

List of newly identified studies :

Authors	Title	Journal	Year of Publication	Database / Topic	ERG Section C related questions	Comment &/or Reason for Exclusion
Sullivan, M. P.;Chen, T.;Dyment, P. G.;Hvizdala, E.;Steuber, C. P.	Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology group study	Blood	1982	Cochrane EBMR Clinical	ERG Section C1a	Duplicate
Andersen, C. L.;Siersma, V. D.;Hasselbalch, H. C.;Lindegaard, H.;Vestergaard, H.;Felding, P.;de Fine Olivarius, N.;Bjerrum, O. W.	Eosinophilia in routine blood samples and the subsequent risk of hematological malignancies and death	American journal of hematology	2013	Cochrane EBMR HRQoL	ERG Section C1a	Non relevant - Not Eligible
Mabed, M.;Aref, S.;Fouda, M.;El-Sharawy, S.	Chlorambucil plus theophylline vs chlorambucil alone as a front line therapy for B-cell chronic lymphatic leukemia	Leukemia & lymphoma	2004	Cochrane EBMR HRQoL	ERG Section C1a	Duplicate
Maisnar, V.;Chroust, K.	Treatment of associated anemia in different hematological disorders with epoetin alpha	Neoplasma	2004	Cochrane EBMR HRQoL	ERG Section C1a	Duplicate
Sullivan, M. P.;Chen, T.;Dyment, P. G.;Hvizdala, E.;Steuber, C. P.	Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology group study	Blood	1982	Cochrane EBMR HRQoL	ERG Section C1a	Duplicate
Mishra, V.;Vaaler, S.;Brinch, L.	A prospective cost evaluation related to allogeneic haemopoietic stem cell transplantation including pretransplant procedures, transplantation and 1 year follow-up procedures	Bone Marrow Transplant	2001	Medline CE	ERG Section C1a	Duplicate
Pearce, N. E.;Howard, J. K.	Occupation, social class and male cancer mortality in New Zealand, 1974-78	Int J Epidemiol	1986	Medline CE	ERG Section C1a	Non relevant - Not Eligible
van der Byl, G.;Cerica, A.;Sala, M. G.	Retroperitoneal lipomas: A case report	J Ultrasound	2012	Medline CE	ERG Section C1a	Non relevant - Not Eligible
Venuta, F.;Rendina, E. A.;Pescarmona, E. O.;de Giacomo, T.;Flaishman, I.;Guarino, E.;Ricci, C.	Ambulatory mediastinal biopsy for hematologic malignancies	Eur J Cardiothorac Surg	1997	Medline CE	ERG Section C1a	Non relevant - Not Eligible
Weinmann, M.;Becker, G.;Einsele, H.;Bamberg, M.	Clinical indications and biological mechanisms of splenic irradiation in chronic leukaemias and myeloproliferative disorders	Radiother Oncol	2001	Medline CE	ERG Section C1a	Non relevant - Not Eligible
Choudhry, V. P.;Marwaha, R. K.;Goyal, D. P.;Sarya, A. K.	Evaluation of prednisolone and vincristine with and without L-asparaginase in acute lymphatic leukemia	Indian J Pediatr	1983	Medline Clinical	ERG Section C1a	No abstract available / Too old - backbone treatment

	of childhood					
Jenkins, R.;Perlin, E.	Severe hepatotoxicity from Escherichia coli L-asparaginase	J Natl Med Assoc	1987	Medline Clinical	ERG Section C1a	Non relevant - Not Eligible
Leventhal, B. G.;LePourhiet, A.;Halterman, R. H.;Henderson, E. S.;Herberman, R. B.	Immunotherapy in previously treated acute lymphatic leukemia	Natl Cancer Inst Monogr	1973	Medline Clinical	ERG Section C1a	Non relevant - Not Eligible
Leventhal, B. G.;Skeel, R. T.;Yankee, R. A.;Henderson, E. S.	L-asparaginase (NSC-109229) plus azaserine (NSC-742) in acute lymphatic leukemia	Cancer Chemother Rep	1970	Medline Clinical	ERG Section C1a	No abstract available / Too old - backbone treatment
Misset, J. L.;De Vassal, F.;Delgado, M.;Ribaud, P.;Musset, M.;Dorval, T.;Machover, D.;Jasmin, C.;Hayat, M.;Schwarzenberg, L.;Mathe, G.	An intensive care chemo- or chemoimmunotherapy regimen for patients with intermediate and poor-prognosis acute lymphatic leukemia and leukemic lymphoblastic lymphosarcoma: preliminary results with 14-month median follow-up	Recent Results Cancer Res	1982	Medline Clinical	ERG Section C1a	Non relevant - Not Eligible
O'Meara, A.;Daly, M.;Hallinan, F. H.	Increased antithrombin III concentration in children with acute lymphatic leukaemia receiving L-asparaginase therapy	Med Pediatr Oncol	1988	Medline Clinical	ERG Section C1a	Non relevant - Not Eligible
Ollenschlager, G.;Roth, E.;Linkesch, W.;Jansen, S.;Simmel, A.;Modder, B.	Asparaginase-induced derangements of glutamine metabolism: the pathogenetic basis for some drug-related side-effects	Eur J Clin Invest	1988	Medline Clinical	ERG Section C1a	Duplicate
Sullivan, M. P.;Chen, T.;Dyment, P. G.;Hvizdala, E.;Steuber, C. P.	Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology group study	Blood	1982	Medline Clinical	ERG Section C1a	Duplicate
Aaronson, N. K.;Taphoorn, M. J.;Heimans, J. J.;Postma, T. J.;Gundy, C. M.;Beute, G. N.;Slotman, B. J.;Klein, M.	Compromised health-related quality of life in patients with low-grade glioma	J Clin Oncol	2011	Medline HRQoL	ERG Section C1a	Non relevant - Not Eligible
Fogazzi, G. B.;Garigali, G.	The clinical art and science of urine microscopy	Curr Opin Nephrol Hypertens	2003	Medline HRQoL	ERG Section C1a	Non relevant - Not Eligible
Fossen, A.;Abrahamsen, T. G.;Storm-Mathisen, I.	Psychological outcome in children treated for brain tumor	Pediatr Hematol Oncol	1998	Medline HRQoL	ERG Section C1a	Non relevant - Not Eligible
Herbst, C.;Monsef, I.;Skotz, N.;Engert, A.	Eighth biannual report of the Cochrane Haematological Malignancies Group--focus on chronic lymphatic leukemia	J Natl Cancer Inst	2008	Medline HRQoL	ERG Section C1a	Non relevant - Not Eligible
Holzner, B.;Kemmler, G.;Sperner-Unterweger, B.;Kopp, M.;Dunser, M.;Margreiter,	Quality of life measurement in oncology--a matter of the assessment instrument?	Eur J Cancer	2001	Medline HRQoL	ERG Section C1a	Identified initially in SR2 in other database

R.;Marschitz, I.;Nachbaur, D.;Fleischhacker, W. W.;Greil, R.						
Janse, A. J.;Sinnema, G.;Uiterwaal, C. S.;Kimpen, J. L.;Gemke, R. J.	Quality of life in chronic illness: perceptions of parents and paediatricians	Arch Dis Child	2005	Medline HRQoL	ERG Section C1a	Duplicate
Mabed, M.;Aref, S.;Fouda, M.;El-Sharawy, S.	Chlorambucil plus theophylline vs chlorambucil alone as a front line therapy for B-cell chronic lymphatic leukemia	Leuk Lymphoma	2004	Medline HRQoL	ERG Section C1a	Duplicate
Maisnar, V.;Chroust, K.	Treatment of associated anemia in different hematological disorders with epoetin alpha	Neoplasma	2004	Medline HRQoL	ERG Section C1a	Duplicate
Panigrahi, I.;Naithani, R.	Imatinib mesylate: A designer drug	J Assoc Physicians India	2006	Medline HRQoL	ERG Section C1a	Duplicate
Patel, P. S.;Adhvaryu, S. G.;Baxi, B. R.	Tumor markers in leukemia: evaluation of serum levels of different forms of sialic acid, Regan isoenzyme and lactate dehydrogenase	Int J Biol Markers	1991	Medline HRQoL	ERG Section C1a	Duplicate
Wesierska-Gadek, J.;Maurer, M.	Promotion of apoptosis in cancer cells by selective purine-derived pharmacological CDK inhibitors: one outcome, many mechanisms	Curr Pharm Des	2011	Medline HRQoL	ERG Section C1a	Non relevant - Not Eligible
Mishra, V.;Vaaler, S.;Brinch, L.	A prospective cost evaluation related to allogeneic haemopoietic stem cell transplantation including pretransplant procedures, transplantation and 1 year follow-up procedures	Bone Marrow Transplantation	2001	Embase CE	ERG Section C1b	Duplicate
Janse, A. J.;Sinnema, G.;Uiterwaal, C. S. P. M.;Kimpen, J. L. L.;Gemke, K. J. B. J.	Quality of life in chronic illness: Perceptions of parents and paediatricians	Archives of Disease in Childhood	2005	Embase HRQoL	ERG Section C1b	Duplicate
al Rajeh, S.;Kabiraj, M. M.;al Fawaz, I.;Daif, A. K.;al Jarallah, A.	Can cytotoxic drugs cure subacute sclerosing panencephalitis?	Lancet	1995	Medline CE	ERG Section C2	Non relevant - Not Eligible
Al-Nawakil, C.;Willems, L.;Mauprivez, C.;Laffy, B.;Benm'rad, M.;Tamburini, J.;Fontaine, H.;Sogni, P.;Terris, B.;Bouscary, D.;Moachon, L.	Successful treatment of l-asparaginase-induced severe acute hepatotoxicity using mitochondrial cofactors	Leuk Lymphoma	2014	Medline CE	ERG Section C2	Non relevant - Not Eligible
Baskar, G.;Chandhuru, J.;Sheraz Fahad, K.;Praveen, A. S.;Chamundeeswari, M.;Muthukumar, T.	Anticancer activity of fungal L-asparaginase conjugated with zinc oxide nanoparticles	J Mater Sci Mater Med	2015	Medline CE	ERG Section C2	Non relevant - Not Eligible
Benatti, C.;Gnocchi, M.;Travaglino, E.;Invernizzi, R.;Ascari, E.	Chemotherapy-induced leukonychia	Haematologica	2004	Medline CE	ERG Section C2	Non relevant - Not Eligible
Berrueco, R.;Rives, S.;Lopez-Garcia, V. S.;Catala, A.;Toll,	Very high hypertriglyceridemia induced: is	Pediatr Blood Cancer	2011	Medline CE	ERG Section C2	Non relevant - Not Eligible

T.;Estella, J.	plasmapheresis needed?					
Bonney, D.;Razali, H.;Turner, A.;Will, A.	Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin	Br J Haematol	2009	Medline CE	ERG Section C2	Non relevant - Not Eligible
Boos, J.;Nowak-Gottl, U.;Jurgens, H.;Fleischhack, G.;Bode, U.	Loss of activity of Erwinia asparaginase on repeat applications	J Clin Oncol	1995	Medline CE	ERG Section C2	Comment / Editorial
Demlova, R.;Mrkvicova, M.;Sterba, J.;Bernatikova, H.;Stary, J.;Sukova, M.;Mikuskova, A.;Chocholova, A.;Mladosievicova, B.;Soltysova, A.;Behulova, D.;Pilatova, K.;Zdrazilova-Dubska, L.;Valik, D.	Augmenting clinical interpretability of thiopurine methyltransferase laboratory evaluation	Oncology	2014	Medline CE	ERG Section C2	Non relevant - Not Eligible
Dundar, B.;Eren, E.;Oktem, F.;Dundar, N.;Tunc, B.;Canatan, D.	Hyperosmolar non-ketotic syndrome in a child associated with l-asparaginase and prednisolone	Pediatr Int	2007	Medline CE	ERG Section C2	Non relevant - Not Eligible
Foreman, N. K.;Mahmoud, H. H.;Langston, J. W.	99Tcm-HMPAO SPECT and magnetic resonance studies in L-asparaginase induced cerebrovascular accident	Br J Radiol	1992	Medline CE	ERG Section C2	Non relevant - Not Eligible
Hamdan, M. Y.;Frenkel, E. P.;Bick, R.	L-asparaginase-provoked seizures as singular expression of central nervous toxicity	Clin Appl Thromb Hemost	2000	Medline CE	ERG Section C2	Non relevant - Not Eligible
Horowitz, N.;Brenner, B.	Thrombophilia and cancer	Pathophysiol Haemost Thromb	2008	Medline CE	ERG Section C2	Non relevant - Not Eligible
Karabulut, R.;Sonmez, K.;Afsarlar, C.;Turkyilmaz, Z.;Can Basaklar, A.;Kale, N.	Pancreas pseudocyst associated with L-asparaginase treatment: a case report	Acta Chir Belg	2005	Medline CE	ERG Section C2	Non relevant - Not Eligible
Lange, B.	The management of neoplastic disorders of haematopoiesis in children with Down's syndrome	Br J Haematol	2000	Medline CE	ERG Section C2	Non relevant - Not Eligible
Madkaikar, M.;Ghosh, K.;Jijina, F.;Gupta, M.;Rajpurkar, M.;Mohanty, D.	Tuberculosis and immune thrombocytopenia	Haematologica	2002	Medline CE	ERG Section C2	Non relevant - Not Eligible
Ollenschlager, G.;Roth, E.;Linkesch, W.;Jansen, S.;Simmel, A.;Modder, B.	Asparaginase-induced derangements of glutamine metabolism: the pathogenetic basis for some drug-related side-effects	Eur J Clin Invest	1988	Medline CE	ERG Section C2	Duplicate
Omar, K. Z.;Ariffin, H.;Abdullah, W. A.;Chan, L. L.;Lin, H. P.	Streptokinase infusion for asparaginase-induced arterial thrombosis	Med Pediatr Oncol	2000	Medline CE	ERG Section C2	Non relevant - Not Eligible
Piroso, E.;Erslev, A. J.;Caro, J.	Inappropriate increase in erythropoietin titers during chemotherapy	Am J Hematol	1989	Medline CE	ERG Section C2	Non relevant - Not Eligible

Ruble, K.;Lawrence-Kane, P.;Brown, S.	Detection and treatment of central line thrombus: a case study	J Pediatr Oncol Nurs	1994	Medline CE	ERG Section C2	Non relevant - Not Eligible
Saito, T.;Seo, S.;Kanda, Y.;Shoji, N.;Ogasawara, T.;Murakami, J.;Tanosaki, R.;Tobinai, K.;Takaue, Y.;Mineishi, S.	Early onset Pneumocystis carinii pneumonia after allogeneic peripheral blood stem cell transplantation	Am J Hematol	2001	Medline CE	ERG Section C2	Non relevant - Not Eligible
Sandoval, C.;Katz, B.;Stringel, G.;Jayabose, S.;Lebovics, E.	Cholelithiasis and choledocholithiasis after sequential cytarabine and asparaginase	J Pediatr Hematol Oncol	2003	Medline CE	ERG Section C2	Non relevant - Not Eligible
Santos-Garcia, D.;Pardo, J.;Vazquez, F.;Rabunal-Martinez, M. J.;Martin-Vigo, A. I.;de la Fuente-Fernandez, R.	Pure motor lumbosacral radiculopathy after intrathecal chemotherapy	Eur J Neurol	2008	Medline CE	ERG Section C2	Non relevant - Not Eligible
Stams, W. A.;den Boer, M. L.;Beverloo, H. B.;van Wering, E. R.;Pieters, R.	Upregulation of asparagine synthetase and cell cycle arrest in t(12;21)-positive ALL	Leukemia	2005	Medline CE	ERG Section C2	Non relevant - Not Eligible
Tan, M.;Wai, D.;Chng, C. L.;Hwang, W.	Acarbose is an effective treatment for severe hypertriglyceridemia secondary to l-asparaginase and dexamethasone	Leuk Lymphoma	2012	Medline CE	ERG Section C2	Non relevant - Not Eligible
Tang, W.;Ziring, D.;Gershman, G.;French, S.	Role of macrophages and stellate cells in the pathogenesis of veno-occlusive disease: an electron microscopic case study	Exp Mol Pathol	2003	Medline CE	ERG Section C2	Non relevant - Not Eligible
van Galen, K. P.;Zweegman, S.;Ossenkoppele, G. J.	Pancreatic pseudocyst in an adult patient after treatment with pegylated asparaginase	Br J Haematol	2011	Medline CE	ERG Section C2	Non relevant - Not Eligible
Veerman, A. J.;Kaspers, G. J.;Pieters, R.	Cellular drug resistance in childhood leukemia	Ann Hematol	1994	Medline CE	ERG Section C2	Non relevant - Not Eligible
Vetro, C.;Giulietti, G.;Calafiore, V.;Romano, A.;Di Raimondo, F.	A snapshot of asparaginase-induced liver insufficiency	Eur J Haematol	2014	Medline CE	ERG Section C2	Non relevant - Not Eligible
Vigano'D'Angelo, S.;Gugliotta, L.;Mattioli Belmonte, M.;Cascione, M. L.;Pattarini, E.;D'Angelo, A.	L-asparaginase treatment reduces the anticoagulant potential of the protein C system without affecting vitamin K-dependent carboxylation	Thromb Res	1990	Medline CE	ERG Section C2	Non relevant - Not Eligible
Visitsunthorn, N.;Utsawapreechawong, W.;Pacharn, P.;Jirapongsananuruk, O.;Vichyanond, P.	Immediate type hypersensitivity to chemotherapeutic agents in pediatric patients	Asian Pac J Allergy Immunol	2009	Medline CE	ERG Section C2	Non relevant - Not Eligible
Williams, M. S.;Ali, N.;Nonaka, D.;Bloor, A. J.;Somervaille, T. C.	Fatal invasive aspergillosis of the larynx	Eur J Haematol	2013	Medline CE	ERG Section C2	Non relevant - Not Eligible
Zarkowska, T.	BIO 2006 Annual International Convention. The expanding biotech industry of France	IDrugs	2006	Medline CE	ERG Section C2	Duplicate
Zuckerman, E.;Misselevich, I.;Boss, J. H.	Oval cell hyperplasia in asparaginase--induced liver damage	Liver	2002	Medline CE	ERG Section C2	Non relevant - Not Eligible

Artacho-Reinoso, M. J.;Olbrich, P.;Solano-Paez, P.;Ybot-Gonzalez, P.;Lepe, J. A.;Neth, O.;Aznar, J.	Catheter-related Mycobacterium fortuitum bloodstream infection: rapid identification using MALDI-TOF mass spectrometry	Klin Padiatr	2014	Medline Clinical	ERG Section C2	Identified initially in SR2 in other database
Banks, R. S.;Thomas, W.;Mandel, J. S.;Kaune, W. T.;Wacholder, S.;Tarone, R. E.;Linet, M. S.	Temporal trends and misclassification in residential 60 Hz magnetic field measurements	Bioelectro magnetics	2002	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Berglund, E. C.;Lindqvist, C. M.;Hayat, S.;Overnas, E.;Henriksson, N.;Nordlund, J.;Wahlberg, P.;Forestier, E.;Lonnerholm, G.;Syvanen, A. C.	Accurate detection of subclonal single nucleotide variants in whole genome amplified and pooled cancer samples using HaloPlex target enrichment	BMC Genomics	2013	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Berrar, D. P.;Downes, C. S.;Dubitzky, W.	Multiclass cancer classification using gene expression profiling and probabilistic neural networks	Pac Symp Biocomput	2003	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Blaise, D.;Kuentz, M.;Fortanier, C.;Bourhis, J. H.;Milpied, N.;Sutton, L.;Jouet, J. P.;Attal, M.;Bordigoni, P.;Cahn, J. Y.;Boiron, J. M.;Schuller, M. P.;Moatti, J. P.;Michallet, M.	Randomized trial of bone marrow versus lenograstim-primed blood cell allogeneic transplantation in patients with early-stage leukemia: a report from the Societe Francaise de Greffe de Moelle	J Clin Oncol	2000	Medline Clinical	ERG Section C2	Identified initially in SR2 in other database
Bonneterre, J. M.	Long-term efficacy and toxicity of the FEC100 regimen	Oncology (Williston Park)	2004	Medline Clinical	ERG Section C2	Identified initially in SR2 in other database
Civin, C. I.	Reducing the cost of the cure in childhood leukemia	N Engl J Med	1989	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Close, P.;Burkey, E.;Kazak, A.;Danz, P.;Lange, B.	A prospective, controlled evaluation of home chemotherapy for children with cancer	Pediatrics	1995	Medline Clinical	ERG Section C2	Identified initially in SR2 in other database
Craft, A. W.	Childhood cancer--mainly curable so where next?	Acta Paediatr	2000	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Kawano, Y.;Takaue, Y.;Law, P.;Watanabe, T.;Abe, T.;Okamoto, Y.;Makimoto, A.;Sato, J.;Nakagawa, R.;Kajiume, T.;Hirao, A.;Watanabe, A.;Kuroda, Y.	Clinically applicable bulk isolation of blood CD34+ cells for autografting in children	Bone Marrow Transplant	1998	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Kim, B. R.;Choi, J. L.;Kim, J. E.;Woo, K. S.;Kim, K. H.;Kim, J. M.;Kim, S. H.;Han, J. Y.	Diagnostic utility of multiprobe fluorescence in situ hybridization assay for detecting cytogenetic aberrations in acute leukemia	Ann Lab Med	2014	Medline Clinical	ERG Section C2	Duplicate
Kumar, S.;Masood, N.;Adil, S. N.	Old disease, new targets. Part-II, haematological malignancies	J Pak Med Assoc	2009	Medline Clinical	ERG Section C2	Non relevant - Not Eligible

Lee, J.;Tashjian, D. B.;Moriarty, K. P.	Missed opportunities in the treatment of pediatric appendicitis	Pediatr Surg Int	2012	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Levenga, T. H.;Timmer-Bonte, J. N.	Review of the value of colony stimulating factors for prophylaxis of febrile neutropenic episodes in adult patients treated for haematological malignancies	Br J Haematol	2007	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Link, M. P.	Collaborating to conquer cancer: lessons from our children	J Clin Oncol	2013	Medline Clinical	ERG Section C2	Duplicate
Maguire, A.;Welbury, R. R.	Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development	Dent Update	1996	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Nan, X.;Fu, G.;Zhao, Z.;Liu, S.;Patel, R. Y.;Liu, H.;Daga, P. R.;Doerksen, R. J.;Dang, X.;Chen, Y.;Wilkins, D.	Leveraging domain information to restructure biological prediction	BMC Bioinformatics	2011	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Nivison-Smith, I.;Bradstock, K. F.;Dodds, A. J.;Hawkins, P. A.;Szer, J.	Haemopoietic stem cell transplantation in Australia and New Zealand, 1992-2001: progress report from the Australasian Bone Marrow Transplant Recipient Registry	Intern Med J	2005	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Pasut, B.	Home administration of medications in pediatric oncology patients: use of the Travenol infusor	J Pediatr Oncol Nurs	1989	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Poteat, H. T.;Sklar, J.	A simplified polymerase chain reaction assay for detection of chromosomal translocations in hematologic malignancies	Diagn Mol Pathol	1997	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Richardson, R.;Waddington, C.	Allocating resources: community involvement is not easy	Int J Health Plann Manage	1996	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Ruiz-Delgado, G. J.;Gutierrez-Riveroll, K. I.;Gutierrez-Aguirre, C. H.;Gomez-Almaguer, D.;Eyzaguirre-Zapata, R.;Priesca-Marin, M.;Gonzalez-Carrillo, M. L.;Ruiz-Arguelles, G. J.	A single apheresis procedure in the donor may be enough to complete an allograft using the "Mexican method" of non-ablative allografting	Blood Transfus	2009	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Smyth, E. T.;Barr, J. G.;Bamford, K. B.	Surveillance and management of infection in a haematology unit: use of an in-house clinical database	J Hosp Infect	1993	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Tomelleri, C.;Dalla Pellegrina, C.;Chignola, R.	Microplate spectrophotometry for high-throughput screening of cytotoxic molecules	Cell Prolif	2010	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Veenstra, D. L.;Higashi, M. K.;Phillips, K. A.	Assessing the cost-effectiveness of pharmacogenomics	AAPS PharmSci	2000	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Zarkowska, T.	BIO 2006 Annual International Convention. The expanding biotech industry of France	IDrugs	2006	Medline Clinical	ERG Section C2	Duplicate

Zhang, Q.;Cao, Y.;Li, Y.;Zhu, Y.;Sun, S. S.;Guo, D.	A sub-space greedy search method for efficient Bayesian Network inference	Comput Biol Med	2011	Medline Clinical	ERG Section C2	Non relevant - Not Eligible
Albano, E. A.;Odom, L. F.	Supportive care in pediatric oncology	Curr Opin Pediatr	1993	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Beulertz, J.;Bloch, W.;Prokop, A.;Baumann, F. T.	Specific deficit analyses in motor performance and quality of life of pediatric cancer patients--a cross-sectional pilot study	Pediatr Hematol Oncol	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Broers, S.;Kaptein, A. A.;Le Cessie, S.;Fibbe, W.;Hengeveld, M. W.	Psychological functioning and quality of life following bone marrow transplantation: a 3-year follow-up study	J Psychosom Res	2000	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Close, P.;Burkey, E.;Kazak, A.;Danz, P.;Lange, B.	A prospective, controlled evaluation of home chemotherapy for children with cancer	Pediatrics	1995	Medline HRQoL	ERG Section C2	Identified initially in SR2 in other database
Davis, J. L.;Matsumura, L.;Weeks, D. A.;Troxell, M. L.	PAX2 expression in Wilms tumors and other childhood neoplasms	Am J Surg Pathol	2011	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Di Gallo, A.;Felder-Puig, R.;Topf, R. J.	Quality of life from research and clinical perspectives: an example from paediatric psycho-oncology	Clin Child Psychol Psychiatry	2007	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Eiser, C.;Jenney, M. E.	Measuring symptomatic benefit and quality of life in paediatric oncology	Br J Cancer	1996	Medline HRQoL	ERG Section C2	Identified initially in SR2 in other database
Fotiadou, M.;Barlow, J. H.;Powell, L. A.;Langton, H.	Optimism and psychological well-being among parents of children with cancer: an exploratory study	Psychoon cology	2008	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Fukushima, A.	DiffCorr: an R package to analyze and visualize differential correlations in biological networks	Gene	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Hanzelmann, S.;Castelo, R.;Guinney, J.	GSVA: gene set variation analysis for microarray and RNA-seq data	BMC Bioinformatics	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Hinds, P. S.;Oakes, L. L.;Hicks, J.;Anghelescu, D. L.	End-of-life care for children and adolescents	Semin Oncol Nurs	2005	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Hinds, P. S.;Yang, J.;Gattuso, J. S.;Hockenberry, M.;Jones, H.;Zupanec, S.;Li, C.;Crabtree, V. M.;Mandrell, B. N.;Schoumacher, R. A.;Vallance, K.;Sanford, S.;Srivastava, D. K.	Psychometric and clinical assessment of the 10-item reduced version of the Fatigue Scale-Child instrument	J Pain Symptom Manage	2010	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Hino, M.;Shimojo, N.;Ochiai, H.;Inoue, Y.;Ando, K.;Chikaraishi, K.;Ota, S.;Okimoto, Y.;Sunami, S.;Nakamura, R.;Teshima, R.;Sato, Y.;Kohno, Y.	Expression of CD203c on basophils as a marker of immunoglobulin E-mediated (L)-asparaginase allergy	Leuk Lymphoma	2014	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Hooke, M. C.;Garwick, A. W.;Neglia, J. P.	Assessment of physical performance using the 6-minute walk test in	Cancer Nurs	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible

	children receiving treatment for cancer					
Innocenti, F.;Cox, N. J.;Dolan, M. E.	The use of genomic information to optimize cancer chemotherapy	Semin Oncol	2011	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Janse, A. J.;Sinnema, G.;Uiterwaal, C. S.;Kimpen, J. L.;Gemke, R. J.	Quality of life in chronic illness: perceptions of parents and paediatricians	Arch Dis Child	2005	Medline HRQoL	ERG Section C2	Duplicate
Khoshniat, M.;Ghavamzadeh, A.;Larijani, B.;Bahar, B.;Tabatabaei, O.	Effect on growth parameters of bone marrow transplantation with a chemotherapy-only conditioning regimen	Transplant Proc	2003	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Kim, B. R.;Choi, J. L.;Kim, J. E.;Woo, K. S.;Kim, K. H.;Kim, J. M.;Kim, S. H.;Han, J. Y.	Diagnostic utility of multiprobe fluorescence in situ hybridization assay for detecting cytogenetic aberrations in acute leukemia	Ann Lab Med	2014	Medline HRQoL	ERG Section C2	Duplicate
Kim, M. J.;Cho, S. Y.;Lee, W. I.;Park, T. S.;Lee, H. J.	The utility of the multiplex reverse transcriptase-polymerase chain reaction assay in the detection of hematologic malignancies	Ann Lab Med	2013	Medline HRQoL	ERG Section C2	Identified initially in SR2 in other database
Knight, S.;Collins, M.;Takeuchi, Y.	Insertional mutagenesis by retroviral vectors: current concepts and methods of analysis	Curr Gene Ther	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Konig, R.;Ashwell, G.;Hanover, J. A.	Overexpression and biosynthesis of CD4 in Chinese hamster ovary cells: coamplification using the multiple drug resistance gene	Proc Natl Acad Sci U S A	1989	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Kubic, V. L.;Brunning, R. D.	Immunohistochemical evaluation of neoplasms in bone marrow biopsies using monoclonal antibodies reactive in paraffin-embedded tissue	Mod Pathol	1989	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Lehman, T. J.	Current concepts in immunosuppressive drug therapy of systemic lupus erythematosus	J Rheumatol Suppl	1992	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Link, M. P.	Collaborating to conquer cancer: lessons from our children	J Clin Oncol	2013	Medline HRQoL	ERG Section C2	Duplicate
Lof, C. M.;Forinder, U.;Winiarski, J.	Risk factors for lower health-related QoL after allogeneic stem cell transplantation in children	Pediatr Transplant	2007	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Manji, A.;Tomlinson, D.;Ethier, M. C.;Gassas, A.;Maloney, A. M.;Sung, L.	Psychometric properties of the Oral Mucositis Daily Questionnaire for child self-report and importance of mucositis in children treated with chemotherapy	Support Care Cancer	2012	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Mark, H. F.;Przygoda, J. J.;Sikov, W.	Fluorescent in situ hybridization for identifying cytogenetic abnormalities in inadequate and suboptimal specimens	Pathobiology	1998	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Micallef, I. N.;Rohatiner, A. Z.;Carter, M.;Boyle, M.;Slater, S.;Amess, J. A.;Lister, T. A.	Long-term outcome of patients surviving for more than ten years following treatment for acute leukaemia	Br J Haematol	2001	Medline HRQoL	ERG Section C2	Non-relevant endpoints

Muro, M.;Moya-Quiles, M. R.;Marin, L.;Torio, A.;Vallejo, C.;Moraleda, J. M.;Alvarez-Lopez, M. R.	Report of recombinations between HLA loci within two families: utility of high resolution typing	Clin Transplant	2002	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Neville, K. A.;Blaney, S. M.	Leptomeningeal cancer in the pediatric patient	Cancer Treat Res	2005	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Panetta, J. C.;Paugh, S. W.;Evans, W. E.	Mathematical modeling of folate metabolism	Wiley Interdiscip Rev Syst Biol Med	2013	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Panigrahi, I.;Naithani, R.	Imatinib mesylate: A designer drug	J Assoc Physicians India	2006	Medline HRQoL	ERG Section C2	Duplicate
Patel, P. S.;Adhvaryu, S. G.;Baxi, B. R.	Tumor markers in leukemia: evaluation of serum levels of different forms of sialic acid, Regan isoenzyme and lactate dehydrogenase	Int J Biol Markers	1991	Medline HRQoL	ERG Section C2	Duplicate
Ramsey, S.;Schickedanz, A.	How should we define value in cancer care?	Oncologist	2010	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Rose, C.;Rockwell, P.;Yang, J. Q.;Pytowski, B.;Goldstein, N. I.	Isolation and characterization of a monoclonal antibody binding to the extracellular domain of the flk-2 tyrosine kinase receptor	Hybridoma	1995	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Schmidt, E.;Thoennissen, N. H.;Rudat, A.;Bieker, R.;Schliemann, C.;Mesters, R. M.;Zuhlsdorf, M.;Muller-Tidow, C.;Berdel, W. E.	Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis	Ann Oncol	2008	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Szabo, A.;Boucher, K.;Carroll, W. L.;Klebanov, L. B.;Tsodikov, A. D.;Yakovlev, A. Y.	Variable selection and pattern recognition with gene expression data generated by the microarray technology	Math Biosci	2002	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
van Santen, H. M.;Thonissen, N. M.;de Kraker, J.;Vulsma, T.	Changes in thyroid hormone state in children receiving chemotherapy	Clin Endocrinol (Oxf)	2005	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Vonderheid, E. C.;Diamond, L. W.;van Vloten, W. A.;Scheffer, E.;Meijer, C. J.;Cashell, A. W.;Hardman, J. M.;Lai, S. M.;Hermans, J.;Matthews, M. J.	Lymph node classification systems in cutaneous T-cell lymphoma. Evidence for the utility of the Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage	Cancer	1994	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Watson, M.	CoXpress: differential co-expression in gene expression data	BMC Bioinformatics	2006	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Wayne, A. S.;Reaman, G. H.;Helman, L. J.	Progress in the curative treatment of childhood hematologic malignancies	J Natl Cancer Inst	2008	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Wehrli, B. M.;Huang, W.;De Crombrugghe, B.;Ayala, A. G.;Czerniak, B.	Sox9, a master regulator of chondrogenesis, distinguishes mesenchymal chondrosarcoma from other small blue round cell tumors	Hum Pathol	2003	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible

Weinberg, J. L.;Rosenbach, M.;Kim, E. J.;Kovarik, C. L.	Lichen sclerosus et atrophicus-like graft-versus-host disease post stem cell transplant	Dermatol Online J	2009	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Williams, M. E.;Frierson, H. F., Jr.;Tabbarah, S.;Ennis, P. S.	Fine-needle aspiration of non-Hodgkin's lymphoma. Southern blot analysis for antigen receptor, bcl-2, and c-myc gene rearrangements	Am J Clin Pathol	1990	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Zelig, U.;Mordechai, S.;Shubinsky, G.;Sahu, R. K.;Huleihel, M.;Leibovitz, E.;Nathan, I.;Kapelushnik, J.	Pre-screening and follow-up of childhood acute leukemia using biochemical infrared analysis of peripheral blood mononuclear cells	Biochim Biophys Acta	2011	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Zhao, Y.;Pan, W.	Modified nonparametric approaches to detecting differentially expressed genes in replicated microarray experiments	Bioinformatics	2003	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Ziemer, M.;Thiele, J. J.;Gruhn, B.;Elsner, P.	Chronic cutaneous graft-versus-host disease in two children responds to UVA1 therapy: improvement of skin lesions, joint mobility, and quality of life	J Am Acad Dermatol	2004	Medline HRQoL	ERG Section C2	Non relevant - Not Eligible
Abdelali, R. B.;Asnafi, V.;Leguay, T.;Boissel, N.;Buzyn, A.;Chevallier, P.;Thomas, X.;Lepretre, S.;Huguet, F.;Vey, N.;Escoffre-Barbe, M.;Tavernier, E.;Reman, O.;Fegueux, N.;Turlure, P.;Rousselot, P.;Cahn, J. Y.;Lheritier, V.;Chalandon, Y.;Bene, M. C.;Macintyre, E.;Dombret, H.;Ifrah, N.	Pediatric-inspired intensified therapy of adult T-ALL reveals the favorable outcome of NOTCH1/FBXW7 mutations, but not of low ERG/BAALC expression: A GRAALL study	Blood	2011	Cochrane CCTR	ERG Section C8	Non-relevant endpoints
Bertrand, Y.;Thomas, X.;Godfrin, Y.	L-Asparaginase loaded into erythrocytes (GRASPA): Principle and interests in acute lymphoblastic leukemia	Annals of Hematology	2008	Cochrane CCTR	ERG Section C8	Not technology of interest
Bhojwani, D.;Darbandi, R.;Pei, D.;Ramsey, L. B.;Chemaitilly, W.;Sandlund, J. T.;Cheng, C.;Pui, C. H.;Relling, M. V.;Jeha, S.;Metzger, M. L.	Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia	European journal of cancer (Oxford, England :	2014	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Borghorst, S.;Pieters, R.;Kuehnel, H. J.;Boos, J.;Hempel, G.	Population pharmacokinetics of native Escherichia coli asparaginase	Pediatric hematology and oncology	2012	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database

Burkhardt, B.;Woessmann, W.;Zimmermann, M.;Kontny, U.;Vormoor, J.;Doerffel, W.;Mann, G.;Henze, G.;Niggli, F.;Ludwig, W. D.;Janssen, D.;Riehm, H.;Schrappe, M.;Reiter, A.	Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2006	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Chessells, J. M.;Harrison, G.;Lilleyman, J. S.;Bailey, C. C.;Richards, S. M.	Continuing (maintenance) therapy in lymphoblastic leukaemia: Lessons from MRC UKALL X	British journal of haematology	1997	Cochrane CCTR	ERG Section C8	Non-relevant endpoints
Couturier, M. A.;Huguet, F.;Chevallier, P.;Suarez, F.;Thomas, X.;Escoffre-Barbe, M.;Cacheux, V.;Pignon, J. M.;Bonmati, C.;Sanhes, L.;Bories, P.;Daguindau, E.;Dorvaux, V.;Reman, O.;Frayfer, J.;Orvain, C.;Lheritier, V.;Ifrah, N.;Dombret, H.;Hunault-Berger, M.;Tanguy-Schmidt, A.	Cerebral venous thrombosis in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma during induction chemotherapy with l-asparaginase: The GRAALL experience	American journal of hematology	2015	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Faderl, S.;Thomas, D. A.;O'Brien, S.;Ravandi, F.;Garcia-Manero, G.;Borthakur, G.;Ferrajoli, A.;Verstovsek, S.;Ayoubi, M.;Rytting, M.;Feliu, J.;Kantarjian, H. M.	Augmented hyper-CVAD based on dose-intensified vincristine, dexamethasone, and asparaginase in adult acute lymphoblastic leukemia salvage therapy	Clinical lymphoma, myeloma & leukemia	2011	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Gross, S.;Siegel, S.;Coccia, P.	A toxicity study of cyclophosphamide in combination induction therapy in childhood acute lymphocytic leukemia. A report for childrens cancer study group	American journal of pediatric hematology/oncology	1980	Cochrane CCTR	ERG Section C8	Non relevant - Not Eligible
Jenkinson, S.;Koo, K.;Mansour, M. R.;Goulden, N.;Vora, A.;Mitchell, C.;Wade, R.;Richards, S.;Hancock, J.;Moorman, A. V.;Linch, D. C.;Gale, R. E.	Impact of NOTCH1/FBXW7 mutations on outcome in pediatric T-cell acute lymphoblastic leukemia patients treated on the MRC UKALL 2003 trial	Leukemia	2013	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Ko, R. H.;Jones, T. L.;Radvinsky, D.;Robison, N.;Gaynon, P. S.;Panosyan, E. H.;Avramis, I. A.;Avramis, V. I.;Rubin, J.;Ettinger, L. J.;Seibel, N. L.;Dhall, G.	**Allergic reactions and antiasparaginase antibodies in children with high-risk acute lymphoblastic leukemia: A children's oncology group report**	**Cancer**	**2015**	**Cochrane CCTR**	**ERG Section C8**	**Subgroup analysis CCG-1961**

Kwok, C. S.;Quah, T. C.;Ariffin, H.;Tay, S. K.;Yeoh, A. E.	Mitochondrial D-loop polymorphisms and mitochondrial DNA content in childhood acute lymphoblastic leukemia	Journal of pediatric hematology/oncology	2011	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Lauw, Mandy N.;Hubers, Lowiek M.;van Ommen, Cornelia H.;Hutten, Barbara A.;Biemond, Bart J.;Middeldorp, Saskia	Prophylaxis for venous thromboembolism during asparaginase therapy in patients treated for acute lymphoblastic leukemia	Cochrane Database of Systematic Reviews	2012	Cochrane CCTR	ERG Section C8	Non relevant - Not Eligible
Liens, D.;Godfrin, Y.	Red blood cells (RBC) encapsulating L-asparaginase in acute lymphoblastic leukaemia (ALL): current data and clinical development	Annals of Hematology	2011	Cochrane CCTR	ERG Section C8	Not technology of interest
Male, C.;Chait, P.;Ginsberg, J. S.;Hanna, K.;Andrew, M.;Halton, J.;Anderson, R.;McCusker, P.;Wu, J.;Abshire, T.;Cherrick, I.;Mahoney, D.;Mitchell, L.	Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children: Results of the PARKAA Study	Thrombosis and haemostasis	2002	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Moricke, A.;Lauten, M.;Beier, R.;Odenwald, E.;Stanulla, M.;Zimmermann, M.;Attarbaschi, A.;Niggli, F.;Schrappe, M.	Prediction of outcome by early response in childhood acute lymphoblastic leukemia	Klinische Pädiatrie	2013	Cochrane CCTR	ERG Section C8	Non-relevant endpoints
Myers, R. M.;Balsamo, L.;Lu, X.;Devidas, M.;Hunger, S. P.;Carroll, W. L.;Winick, N. J.;Maloney, K. W.;Kadan-Lottick, N. S.	A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group	Cancer	2014	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Qureshi, A.;Mitchell, C.;Richards, S.;Vora, A.;Goulden, N.	Asparaginase-related venous thrombosis in UKALL 2003- re-exposure to asparaginase is feasible and safe	British journal of haematology	2010	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Ranta, S.;Heyman, M. M.;Jahnukainen, K.;Taskinen, M.;Saarinen-Pihkala, U. M.;Frisk, T.;Soderhall, S.;Petrini, P.;Makipernaa, A. M.	Antithrombin deficiency after prolonged asparaginase treatment in children with acute lymphoblastic leukemia	Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis	2013	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Ratei, R.;Schabath, R.;Karawajew, L.;Zimmermann, M.;Moricke, A.;Schrappe, M.;Ludwig, W. D.	Lineage classification of childhood acute lymphoblastic leukemia according to the EGIL recommendations: results of the ALL-BFM 2000 trial	Klinische Pädiatrie	2013	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Ravandi, F.;Faderl, S.;Kebriaei, P.;Kantarjian, H.	Modern treatment programs for adults with acute lymphoblastic leukemia	Current hematologic malignancy reports	2007	Cochrane CCTR	ERG Section C8	Non relevant - Not Eligible

Sirvent, N.;Suciu, S.;Rialland, X.;Millot, F.;Benoit, Y.;Plantaz, D.;Ferster, A.;Robert, A.;Lutz, P.;Nelken, B.;Plouvier, E.;Norton, L.;Bertrand, Y.;Otten, J.	Prognostic significance of the initial cerebro-spinal fluid (CSF) involvement of children with acute lymphoblastic leukaemia (ALL) treated without cranial irradiation: results of European Organization for Research and Treatment of Cancer (EORTC) Children Leukemia Group study 58881	European journal of cancer (Oxford, England :	2011	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Sullivan, E. M.;Jeha, S.;Kang, G.;Cheng, C.;Rooney, B.;Holladay, M.;Bari, R.;Schell, S.;Tuggle, M.;Pui, C. H.;Leung, W.	NK cell genotype and phenotype at diagnosis of acute lymphoblastic leukemia correlate with postinduction residual disease	Clinical cancer research	2014	Cochrane CCTR	ERG Section C8	Non relevant - Not Eligible
Yang, L.;Panetta, J. C.;Cai, X.;Yang, W.;Pei, D.;Cheng, C.;Kornegay, N.;Pui, C. H.;Relling, M. V.	Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	2008	Cochrane CCTR	ERG Section C8	Identified initially in SR2 in other database
Dissemination, Centre for Reviews and	Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis (Structured abstract)	Database of Abstracts of Reviews of Effects	2015	Cochrane DARE	ERG Section C8	Systematic review and meta-analysis / Non-relevant endpoints

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Pegaspargase for treating acute lymphoblastic leukaemia

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name:

[redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation: Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. We support people affected by leukaemia, lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative disorders and aplastic anaemia.

Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey,

running from diagnosis to what happens when treatment stops and includes emotional effects of a blood cancer and help for those caring for a patient. Our focus is purely on information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/resources/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. Like most blood cancers ALL is strongly correlated to age, although unusually the peak incidence is in children (rather than those over 65). Five year survival outcomes vary greatly by age from over 90% in the under 14s, to 66% in those aged 15-24, less than 40% in those aged 25-64 and less than 15% in those aged 64 or older. As such, the prognosis for adult patients is extremely poor.

The most common signs and symptoms are caused by the bone marrow being unable to produce enough normal blood cells. These include anaemia (due to lack of red blood cells), weakness, tiredness, shortness of breath, light-headedness, palpitations, frequent and persistent infections (due to lack of normal white blood cells), purpura (small bruises in skin), nosebleeds, bleeding gums, bleeding and bruising (due to lack of platelets), fever and sweating. Some patients may also have an enlarged liver, spleen or enlarged lymph nodes.

Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Many of these feelings can have a profound impact on both their physical and psychological wellbeing.

ALL does not affect a patient in isolation but instead creates a “ripple effect”. This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis. As such, access to effective treatment and improvements in a patient's quality of life will also have a wider impact on the lives of their family and friends.

Due to its relative rarity and non-specific symptoms, patients are usually diagnosed with ALL following the onset of symptoms, when it has often progressed significantly. NCIN conducted a report of patients ‘Routes to Diagnosis’ which showed that 64% of ALL patients are diagnosed following an

emergency presentation (emergency GP referral or A&E). This figure was the highest of any cancer type in the report.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Whilst survival is a key treatment outcome for patients, improved quality of life is also highly important. Any treatment that offers reduced side effects or positively impacts on patient experience, thus improving patients' quality of life, would be strongly welcomed.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Patients with ALL would often either be treated with multi-agent chemotherapy or stem cell transplantation. A form of asparaginase (of which there are multiple versions available - including pegaspargase) would be part of the multi-agent chemotherapy regimens. There are three different forms of asparaginase used in clinical practice in the UK; Erwinia derived L-asaparaginase (Erwinase®), 'native' Esherichia coli asaparaginase and the pegylated version of the 'native' form (pegaspargase - Oncaspar®).

As was made clear by the clinical experts in the scoping workshop, the vast majority of patients in UK clinical practice would receive pegaspargase as part of their treatment regimen (alongside standard chemotherapy). Very few patients would receive either the 'native' E-coli asparaginase or Erwinia derived L-asaparaginase (Erwinase®) upfront. This is because pegaspargase is a modified (pegylated) version of the 'native' E-coli asparaginase, with reduced hypersensitivity and demonstrates an extended duration of activity. As such, pegaspargase is currently considered to be the standard of care for these patients.

For the small minority who don't tolerate pegaspargase, they would then usually receive Erwinia derived L-asaparaginase (Erwinase®) instead. This is because it is derived from a different enzyme from the other forms, so

produces hyper-sensitivity reactions in different patients (and decreased plasma activity).

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The key benefits of pegaspargase, due to the pegylation, is the reduced potential for hypersensitivity (allergic or anaphylatic) reactions and the increased duration of its activity. Because of this, patients will receive fewer injections, improving the patient experience. Pegaspargase therefore potentially improves the safety of the administration of asparaginase.

This is an extremely unusual appraisal in that this treatment is already widely used in clinical practice. The fact that clinical experts throughout the UK consider this to be the standard of care speaks volumes of the benefits it offers.

Additionally, we would seek further information from NICE regarding how the appraisal is comparing pegaspargase against the standard of care in UK clinical practice (i.e. against itself?).

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Please see previous response.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

A key concern regarding existing NHS treatments for ALL is that pegaspargase is generally accepted to be the current standard of care (in combination with standard chemotherapy). In the absence of pegaspargase, options available to patients would be Erwinia derived L-asaparaginase (Erwinase®) and 'native' E-coli derived asapraginase. When treated with the native form, a proportion of patients demonstrate an increase in hypersensitivity reactions and therefore have fewer treatment options - further minimised if pegaspargase did not receive a postitive recommendation.

We would like to highlight our concern that if NICE does not recommend the use of pegaspargase, access for patients would become limited. Existing options, as stated above, are currently very infrequently used by clinicians in UK clinical practice (due to the availability of pegaspargase). As such, we would consider negative recommendation of and limited access to pegaspargase to be a step backwards in UK clinical practice.

There is also an issue of so called 'silent inactivation' in which there is an immune reaction which inactivates the drug but produces no symptoms in the patient. However, this only occurs in a small minority of patients.

Please list any concerns patients or carers have about the treatment being appraised.

Please see previous response.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

N/A

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

N/A

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Age is a characteristic protected by the equality legislation. ALL is unusual in that the peak incidence is in children (aged under 14). As such, any decision not to recommend pegaspargase would have a disproportionate impact on children compared to the wider population.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Acute lymphoblastic leukaemia (ALL) is a rare, rapidly progressing form of leukaemia.
- ALL has a large symptom burden. Common symptoms include anaemia (due to lack of red blood cells), weakness, tiredness, shortness of breath, light-headedness, palpitations, frequent and persistent infections (due to lack of normal white blood cells), purpura (small bruises in skin), nosebleeds, bleeding gums, bleeding and bruising (due to lack of platelets), fever and sweating.
- There are three different versions of asaparaginase - these are are Erwinia L-asparaginase (Erwinase®), native E-coli and pegaspargase (pegylated

asaparaginase) - these are used in combination with standard chemotherapy.

- Pegaspargase is an effective treatment option for ALL patients. Its key benefits include improved tolerability (fewer allergic and anaphylactic reactions), reduced toxicity and extended duration of activity (the drug stays in the body longer which means that the patient requires fewer injections).
- When considering the fact that pegaspargase (in combination with standard chemotherapy) is considered the standard of care in the treatment of ALL, this appraisal is really about ensuring continued access to existing treatment options rather than expanding the available treatment options.As such, we would consider a non recommendation by NICE (and consequent lack of access to pegaspargase) to be a step backwards in UK clinical practice.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pegaspargase for treating acute lymphoblastic leukaemia

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: The Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

What is the expected place of the technology in current practice?

Pegasparagase use is embedded as standard of care within current childhood acute lymphoblastic leukaemia trials to which > 90% of UK newly diagnosed and relapse patients are recruited. Those treated outside the trial receive treatment according to the standard arms of the trial protocol, which include Pegasparagase.
Pegasparagase was first introduced as standard of care of childhood ALL in the UK as part of a previous trial, UKALL 2003 (October 2003 – June 2009).

The advantages and disadvantages of the technology

Although no randomised trial has shown that Pegasapragase reduces relapse risk compared with the native formulation of E.Coli asparaginase, there are several

advantages to its use including fewer needle sticks (hence better QOL[1]), improved pharmacokinetic and pharmacodynamic[2] and reduced risk of allergic reactions. Also, compared with the previous trial, ALL97/99, the only change in backbone therapy in UKALL 2003 was the use of Pegasparagase instead of E.Coli asparaginase with an associated near halving of relapse risk in UKALL 2003[3].

A**ny additional sources of evidence**

1) Place AE, Stevenson KE, Vrooman LM, Harris MH, Hunt SK, O'Brien JE, Supko JG, Asselin BL, Athale UH, Clavell LA, Cole PD, Kelly KM, Laverdiere C, Leclerc JM, Michon B, Schorin MA, Welch JJ, Lipshultz SE, Kutok JL, Blonquist TM, Neuberg DS, Sallan SE, **Silverman** LB. Lancet Oncol. 2015 Dec;16(16):1677-90

2) Avramis VI, Sencer S, Periclou AP, Sather H, Bostrom BC, Cohen LJ et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood. 2002;99(6):1986-94.

3) Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013 March;14(3):199-209.

Implementation issues

Pegasparagase has been standard of care for treatment of childhood ALL in the UK for over 12 years and its acquisition and delivery cost is already within the NHS budget. NICE approval will have no additional funding implications for the NHS. It's withdrawal, however, will have a major impact on patient care as E.Coli asparaginase requires more frequent painful IM injections (6 replacing one of Pegasparagase), a higher risk (4 -5 fold) of allergic reactions and resultant loss of efficacy, requiring a switch to the much more expensive Erwinase formulation, and an increased incidence of relapse requiring re-induction therapy including a bone marrow transplant at around £150K/relapse.

Equality

If NICE does not approve its use, UK children with ALL will be the only among developed countries to not have access to pegasparagase.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pegaspargase for treating acute lymphoblastic leukaemia

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] , [redacted] submitting on behalf of:

Name of your organisation: NCRI-RCP-ACP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pegaspargase for treating acute lymphoblastic leukaemia

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Depletion of extracellular asparagine by parenteral administration of the enzyme L-asparaginase is a key component of current therapeutic strategies in acute lymphoblastic leukaemia (ALL). De novo ALL in the UK is commonly treated within clinical trials at all ages. We have UKALL2011 (1-24 years), UKALL14 (24-65 years) and UKALL60+ (60 years and over) which cover all age groups as current national trials. These trials are all academic trials and part of the NCRI portfolio. In the younger age groups (less than 65 years old) approximately 80-90% of the incident population are enrolled into these trials
Pegaspargase is regarded as the standard of care for the younger age groups and forms part of the standard chemotherapy agent for paediatric and adolescent patients. There is international consensus about this. Asparaginase is a key drug in treating younger patients with ALL and the pegylated version is hugely advantageous in relation to fewer allergic events or silent inactivations. The duration of action is longer making the depletion of asparagine more effective than multiple doses of shorter acting agent.

Pegylated asparaginase has a longer half-life than the non pegylated forms of the enzyme. It can therefore be given less frequently to patients. This is important as asparaginase is only available in an injectable form. Asparaginase is given intramuscularly (IM) in most contexts (pegylated asparaginase is given intravenously in UKALL 14). The IM injections are painful so the less frequent injections are preferable for patients.

One of the main problems with asparaginase therapy is that patients often develop silent antibodies to the enzyme, decreasing the effectiveness of therapy and their chance of long term cure. The formation of antibodies is less common with the pegylated asparagianse as the drug is less immunogenic compared to other forms of asparagniase.

Very rarely patients will have serious life threatening allergic reactions to pegylated asparaginase. These reactions are less common with pegylated asparaginase than they are with native E.Coli asparaginase, In this situation patients should be given Erwina asparaginase as an alternative.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

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Older patients are more likely to suffer adverse effect of asparaginase but this is any formulation of the drug – it is not limited to the pegylated version. In children, intensive L-asparaginase treatment, typically delivered by pegylated Escherichia coli -derived (PEG-ASP) results in effective asparagines depletion and improves clinical outcomes[1,2,3,4,5,6]. There are pharmacological data with pegylated asparaginase in adults again showing excellent asparagines depletion although the survival data current trials is awaited[7,8]. Currently paediatric and adult patients with a new diagnosis of ALL in the UK are primarily treated within the context of a phase III clinical trial - UKALL 2011 for children and young adults up to the age of 25 years or UKALL 14 for adults aged 25 – 65 years. Both of these trials include the use of pegylated asparaginase within the context of a multi agent chemotherapy protocol as standard therapy. The pegylated asparaginase is funded by the NHS within the context of both clinical trials.
one group of patients who may not require asparaginase therapy are those with Philadelphia positive disease ie those patients where their leukaemia cells have a translocation between chromosome 9 and 22 (the Philadelphia chromosome). There is good evidence that these patients can achieve 100% remission rates with tyrosine kinase inhibitor based induction therapies. As ultimately adult patients with Ph+ ALL are high risk for relapse, those that are eligible will have any remission consolidated with an allogeneic transplant. Current evidence would suggest that this can be achieved without the added risks of asparaginase therapy. Patients with Ph+ ALL do not get asparaginase within the context of UKALL 14.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Children and young adults up to the age of 18 years with ALL should be treated within a principle treatment centre as per NICE guidance (Improving outcomes guidance for children and young people with cancer). Adult units treating acute lymphoblastic leukaemia - British Committee on Standards in Haematology (BCSH) level 4 (highest level) units. The newly updated NICE Improving Outcomes Guidance for Haematological Cancers will clarify place of care for patients with ALL later in 2016.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There are currently no national clinical guidelines for the treatment of patients with ALL in the UK. Although there is no license in the UK it is licensed elsewhere in Europe.This technology is already available and is being used in a standardised way across the NHS in line with current clinical trial protocols. There would be no requirement for additional professional input if the NICE were to approve this technology.

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Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are local and regional network guidelines but no national guidelines. Mostly enrolling patients into national clinical trials is recommended

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Paediatric haematologists have been using PEG asparaginase as standard of care (both within clinical trials and as good clinical practice outside of trials) in the UK since 2003 when the national UKALL 2003 trial opened. In 2006 / 2007 young adult up to the age of 25 years were allowed entry into UKALL 2003. As a consequence they received pegylated asparaginase within that study. The results from UKALL 2003 showed significantly improved outcomes for young adults (aged 16-25 years) treated on this paediatric regimen compared to historical data from the previous adult trial, UKALL XII (5 year event free survival 76% compared to 63%). One of the main reasons for the marked improvements in outcomes for these young adults was thought to be the intensified chemotherapy they received with increased asparagine depletion due to the use of pegylated asparaginase within the trial[9]. That study reported very low rates of allergic reactions to asparaginase within their patient cohort.

The current UK adult ALL trial (UKALL 14) also uses pegylated asparaginase as standard of care. This is the first time that adult patients have been given this drug within the UK. The trial is asking specific questions about toxicity in relation to pegylated asparaginase as well as some scientific questions about asparagine depletion and anti-asparaginase antibody formation.
The design of the trial now reflects standard practice within the UK for patients with ALL.

Thus drug is already in widespread use in the UK and is given to the majority of children adolescents and adults with ALL below the age of 65

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If patients experience anaphylactic reaction or pancreatitis, the drug must be stopped.

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There are clearly defined dose numbers for pegylated asparaginase within each ALL treatment protocol within the UK trials depending on the patient's risk group. For example, children with good risk disease receive fewer doses than children and young adults with high risk disease. If a patient requires an allogeneic transplant (dictated by high risk features such as adverse cytogenetics, age, slow clearance of residual disease etc) then they may only receive a total of 2 doses of pegylated asparaginase as part of their induction therapy.
There are no plans to change these dosing schedules in light of any NICE appraisal process currently. However, other countries are using dose dense pegylated asparaginase regimens in children in order to attempt a reduction in other chemotherapy agents such as anthracyclines. Clinical trials reflecting this practice are likely to be proposed in the UK for children and young people in the future.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The results have been extrapolated to a UK setting and the drug is broadly used

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

This drug is always used in combination

It is not possible to assess this drug's contribution to outcome as a single agent as it is never used as such so the key outcome measures for its success are as assessed as part of overall therapeutic regimen.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Asparaginase is not free from side effects and these can be life-threatening in some circumstances. This is not necessarily due to the pegylated version per se but the fact that the pegylation allows persistence to result in a high degree of asparagine depletion. The risk of complications does not appear to be increased with the use of pegylated asparaginase in children although there is evidence of increasing toxicity with increasing age[9].
Although leukaemia cells are particularly sensitive to asparagine depletion, normal tissues are also sensitive so there are a variety of well documented adverse events. Theses events occur relatively unpredictably. In adults our goal in our current UKALL14 trial is to identify toxicity and try to prevent it. When the trial is complete it may be possible to identify individuals who will have an adverse risk: benefit ratio and stop using this agent. The trial has already identified that it should not be given to patient with Philadelphia chromosome positive ALL. (Manuscript in preparation)

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The manuscript mentioned above relating to the UKALL14 trial deals with toxicities encountered during initial patient cohort in the trial but does not present data on overall outcomes as they are not yet known

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The vast majority of patients (both paediatric and adult) within the UK that are diagnosed with ALL are already receiving Pegylated asparaginase. As a consequence there will be no need for extra education, staff training, extra facilities etc if NICE were to approve this technology.
If NICE were to reject this technology then there would be implications for these patients. Although we used to give other forms of asparaginase in the past, the expertise in these products has now been lost. Patients are more likely to develop hypersensitivity reactions to native asparaginase. Staff would need training in the administration of these older agents. They would also need training in how to monitor and care for patients.
There have been times in recent years when there have not been any available stocks of native asparaginase. It is unacceptable to imagine a situation where PEG

Asparaginase is not recommended by NICE and where no other form of the enzyme is available for a patient.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Not aware

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Pegaspargase for acute lymphoblastic leukaemia

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Annemieke van Dongen-Leunis Marianne Luyendijk, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Ching-Yun Wei acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse Events
ALL	Acute lymphoblastic leukaemia
AYA	Adults and young adults
bd/b.i.d	Twice Daily
BI	Budget impact
BIC	Bayesian information criterion
BM	Bone marrow
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CCG	Children's Cancer Group
CDF	Cancer Drugs Fund
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Cost minimisation analysis
CNS	Central nervous system
CR	Complete response/remission
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company Submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
DI	Delayed intensification
DI no. 1	Delayed intensification cycle number 1
DI no. 2	Delayed intensification cycle number 2
DT	Decision tree
EFS	Event-free survival
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
HPLC	High-performance liquid chromatography
HR	Hazard ratio
HR	High-risk
HRQL	Health-related Quality of Life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IR	Intermediate-risk

IU	International unit
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LYS	Life Year Saved
MA	Marketing authorisation
MeSH	Medical Subject Headings
MRD	Minimal residual disease
M1	Bone marrow status <5% lymphoblasts
M2	Bone marrow status 5–25% lymphoblasts
M3	Bone marrow status >25% lymphoblasts
MTC	Mixed Treatment Comparison
NA	Not applicable
NCI	National Cancer Institute
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not Reported
NS	Not significant
od	Once Daily
OS	Overall survival
PCR	Polymerase chain reaction
PEG-ASP	Pegaspargase
Ph+/–	Philadelphia chromosome positive/negative
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted Life Year(s)
QoL	Quality of life
R/ST	Relapse/secondary tumour
RCT	Randomised Controlled Trial
SAE	Serious Adverse Events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SCT	Stem cell transplant
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SmPC	Summary of product characteristics
SR	Standard-risk
STA	Single Technology Appraisal
UK	United Kingdom
UMC	University Medical Centre
WBC	White blood cell

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The company restricts the submission to "newly diagnosed people with ALL", arguing that "as the use of asparaginase in the UK is driven by the UKALL protocols, the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort". This is not in line with the NICE scope, which specifies the population as "people with ALL".

According to the company, UKALL protocols form the basis of current clinical practice in the UK, with pegaspargase being administered at a dose of 1,000 IU/m^2, lower than that recommended by the SmPC (2,500 IU/m^2). Therefore, the economic model in the CS is based on the lower dose of 1,000 IU/m^2. This is despite the fact that all comparative evidence available for pegaspargase is based on the higher dose of 2,500 IU/m^2.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence presented in the company submission (CS) focuses on two studies:

- CCG-1962, the only randomised head-to-head comparison of pegylated versus native *E. coli*-derived asparaginase given from induction, and
- UKALL 2003, providing evidence for the use of pegaspargase at a dose of 1,000 IU/m^2 in >3,200 children, adolescents and young adults in the UK and Ireland.

In study CCG-1962 a total of 118 children (aged 1–9 years) newly-diagnosed with ALL were randomised to receive either pegaspargase (2,500 IU/m^2 IM on day three of induction and each DI phase) or native asparaginase (6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase). EFS rates at three, five, and seven years, respectively, were similar for those treated with pegaspargase (83%, 78%, and 75%) versus those treated with native asparaginase (79%, 73%, and 66%).

UKALL 2003 enrolled a total of 3,207 children and young adult patients aged 1–24 years, representing 97% of the eligible ALL patient population aged 1–24 years in the UK and Ireland. All patients received treatment with pegaspargase (1,000 IU/m^2 per dose, 4–12 doses) as part of one of three escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. Among all patients enrolled in UKALL 2003: five-year EFS was 87.3%, and five-year OS was 91.6%.

There was no evidence for the comparative effectiveness of pegaspargase with other types of asparaginase in adults.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG disagrees with the company that the two trials in the CS are the most important studies for this assessment. CCG-196 compares pegaspargase with native E-coli asparaginase in children aged 1 to 9 years (N=59 in both groups). Therefore, it is a small study in very young children, covering only a small group of the total population of interest for this

appraisal: people with ALL. UKALL 2003 does not include a relevant comparator and is therefore less relevant for this appraisal.

In Chapter 4.5 of this report we present an overview of all comparative studies relevant for this appraisal. Based on this evidence, the ERG agrees with the company that there is no evidence to suggest that there is a difference in effectiveness or toxicity between pegaspargase and the main comparator: native E-coli-derived asparaginase. However, it is unclear whether this is because of lack of evidence or lack of a difference in effect.

Four studies provided survival data for the comparison of PEG-asparaginase versus native *E. coli* asparaginase. Two studies showed results in favour of PEG-asparaginase (5-y EFS: 81.2% for pegaspargase vs. 71.7% for *E. coli*, Relative Hazard Rate (RHR) for event=1.61, p<0.001 in CCG-1961; and 7-y EFS: 75% for pegaspargase vs. 66% for *E. coli*, p=NS in CCG-1962), one study showed non-significant results in favour of *E. coli* asparaginase (5-y EFS: 78% for pegaspargase vs. 84% for *E. coli*, p=0.29 in DFCI ALL 91-01), and one study showed hardly any differences in OS and EFS between the two interventions (5-y EFS: 90% for pegaspargase vs. 89% for *E. coli*, p=NS in DFCI ALL 05-001). Because a favourable result for *E. coli* asparaginase in terms of OS and EFS cannot be ruled out we have included such a scenario in the economic model.

Two studies provided survival data for the comparison of native *E. coli* asparaginase versus Erwinia asparaginase. Both studies showed significant results favouring *E. coli* asparaginase.

The five studies comparing PEG-asparaginase with native *E. coli* asparaginase showed no significant differences in adverse events profiles between treatments. The two studies comparing native *E. coli* asparaginase with Erwinia asparaginase showed that Erwinia asparaginase was associated with a lower incidence of toxicity.

There is no evidence for the relative effectiveness of pegaspargase versus other asparaginases in adults.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a de novo cost effectiveness model to assess the cost effectiveness of pegaspargase as first line treatment followed by Erwinia-derived asparaginase for the treatment of patients (0-65 years) with newly diagnosed ALL. Native *E. coli* followed by Erwinase and Erwinase followed by either pegaspargase or native *E. coli* were chosen as the most relevant comparators. It is important to note that pegaspargase has been the first line treatment of choice in UK clinical practice since 2003. There is currently no clinical scenario in the UK in which patients would receive native *E. coli* or Erwinase as a first line treatment for ALL. Still, these treatments were chosen as comparators because historically native *E. coli* was used as the first line asparaginase. In addition, Erwinase is licensed in the UK and its indication is not limited to a specific line of therapy.

The model was a combination of a decision tree and a health state transition Markov model. The decision tree started at treatment initiation of newly diagnosed ALL patients. Patients

start with one of the three asparaginase agents and either continue this treatment to the end of the protocol or switch to a different asparaginase treatment. This switch occurs when patients experience hypersensitivity which was assumed to only occur after two administrations of asparaginase. When hypersensitivity arises during second line treatment, asparaginase is discontinued. The decision tree follows the treatment protocol. Since the treatment protocol differs between subgroups, separate decision trees were modelled for the following subgroups: paediatric high risk, paediatric intermediate risk, paediatric standard risk, older adults (41-65 years) and younger adults (26-41 years). The Markov model was different for adults and children. In paediatric patients, the model included three different health states: 'event-free survival (EFS)', 'potential relapse/secondary tumour (R/ST)' and 'death'. In the adult patients it is assumed that EFS and OS are equivalent. Therefore, the Markov model included only two health states: 'alive' and 'death (OS)'. A variable cycle length was used during the treatment period because the different treatment phases all had a unique duration. Once the treatment was completed, the Markov model consisted of yearly cycles. A lifetime horizon was applied.

The model used survival curves to model the patient population evolution through the different health states. Data for OS and EFS of the paediatric patient population were derived from the UKALL 2003 trial. For adults, a range of OS rates were found in different studies. The lower limit of this range (i.e. 30%) was used in the decision model as the five years OS for the older patients aged ≥41 years whereas the upper limit of 40% was used for the younger patients aged ≤40 years.

Utility data were indirectly obtained from the study of Furlong et al. This study did not report quality of life utilities based on the EQ5D, rather it reported responses of parents on the Health Utilities Index (HUI). Utilities were estimated by comparing the reported quality of life for the different treatment phases (remission induction, CNS therapy, intensification, continuation, and initial two year post-treatment) to a control group from the general population. A utility decrement for hypersensitivity was obtained from a NICE clinical guideline for anaphylaxis since no data from the EQ-5D was available.

Cost categories included in the model were: drug acquisition and administration costs and costs of hypersensitivity. Asparaginase treatment was given according to the UKALL 2003 trial protocol for paediatric patients and the UKALL14 protocol for adult patients. It was assumed that six doses of native *E. coli* and Erwinase correspond with one dose of pegaspargase. The total number of vials/units required per administration and cost per administration for separate drugs were calculated based on an average body surface area of patients. For paediatric patients the median height and weight were retrieved from the Royal College of Paediatrics and Child Health (RCPCH) growth charts. For adults the BSA was obtained from a UK study of adult cancer patients (Sacco et al.). Costs of hypersensitivity was based on the reference cost for "Allergy or Adverse Allergic Reaction". All costs were adjusted for the proportion of patients being alive at the start of each new treatment phase.

For the complete patient population, pegaspargase followed by Erwinase is less expensive and yields more QALYs than native *E. coli* asparaginase followed by Erwinase and Erwinase

followed by native *E. coli* asparaginase. Erwinase followed by pegaspargase provides slightly more QALYs (0.0047) than pegaspargase followed by Erwinase, but at higher costs (£40,362), resulting in an ICER of £8,627,243. Similar conclusions can be drawn for the paediatric and adult population separately. One-way deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analyses were conducted. The latter included a cost-minimisation analysis in which identical OS, EFS and hypersensitivity rates for the different treatments were assumed.

The deterministic sensitivity analysis showed that the ICER is most sensitive to the rate of hypersensitivity for first line treatment with native *E. coli* asparaginase for the paediatric population. In all scenarios pegaspargase followed by Erwinase remained dominant over native *E. coli* asparaginase followed by Erwinase and Erwinase followed by native *E. coli* asparaginase. Pegaspargase followed by Erwinase was nearly always cheaper and less effective than Erwinase followed by pegaspargase. The ICER of pegaspargase followed by Erwinase versus Erwinase followed by pegaspargase either increased or decreased but remained very high ranging from £2,121,333 up to £123,644,929. Only when a minimum rate of hypersensitivity was assumed, pegaspargase (first line) became dominant over Erwinase followed by pegaspargase.

The cost-minimisation analysis showed that pegaspargase followed by Erwinase is less expensive than native *E. coli* followed by Erwinase. In addition, the probabilistic sensitivity analysis showed that pegaspargase followed by Erwinase is a dominant treatment strategy (i.e. the majority of the simulations fall in the south-east quadrant). Pegaspargase followed by Erwinase has a 77.9% probability of being below the £20,000 threshold when compared with native asparaginase followed by Erwinase.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a fair extent, and the impact of deviations was found to be small. The ERG confirmed that there was no existing cost effectiveness model for pegaspargase for the current indication.

One point of concern was found by the ERG with respect to how well the treatment implementation in the model reflects clinical practice, as in the most recent treatment protocol for children, only one interim maintenance and delayed intensification course will be administered to the patients. The ERG base case incorporated this change in clinical practice in the UK.

The ERG assessment indicated that the model was presented and reported somewhat imprecise at times, e.g. some discrepancies between the CS and the electronic model were found. Also, a few issues regarding the electronic model were identified that altered the cost effectiveness results.

The inputs for the model were derived from sources that included observational data, an RCT and literature. For many input values clinical expert opinion was used. However, the ERG is

concerned about the approach of the company to seek expert opinion as only two experts were able to give their expert opinion, of the total of four who were approached. From the response to the clarification letter it is clear that more than four clinicians were deemed eligible, but the exact number was not stated. Given the strong reliance of the model on expert opinion, the ERG would have expected that a greater effort would have been made to consult with experts from the UK.

Additionally, the ERG was concerned about the great reliance of the model on single arm studies and observational data, rather than comparative studies. It is likely that values for EFS, OS and hypersensitivity for each of the three formulations in the model come from different settings, with different patient populations and different treatment regimens for ALL. Thus, all reported outcomes should be interpreted with care.

Regarding the many clinical parameters in the model, the ERG questioned the source for many of those, most importantly the rate of hypersensitivity for the three formulations of asparaginase.

It was unclear to the ERG whether all hypersensitivity rates reflect the proportion of patients who require a treatment switch due to hypersensitivity. With respect to the hypersensitivity to native *E. coli*, the ERG agrees that 20% can be considered as a reliable and conservative estimate. However, there is no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinase also reflect the proportion of patients who require a treatment switch. Based on alternative data sources which explicitly report the rate of treatment switching, the ERG used 13.2% and 9% for pegaspargase and Erwinase, respectively, in the ERG base case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4. The CS and response to the clarification letter provided sufficient details for the ERG to appraise the searches. Search strategies were well-translated amongst different resources; and population and intervention/comparator facets were clearly structured.

The evidence submitted includes several RCTs in different populations comparing pegaspargase with *E. coli* asparaginase.

The approach to modelling the treatment pathway for ALL was well thought out, especially modelling each phase in the treatment separately, this allows for a great level of detail in making sure that the pathway represents current treatment practice in the UK.

1.6.2 Weaknesses and areas of uncertainty

Search strategies were limited to English language due to “language proficiencies”. The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice. Searches for adverse events and non-

randomised and non-controlled studies were based on the clinical effectiveness search strategies which included study design filters. It is possible that relevant evidence may have been missed as a consequence of this.

The main weakness in this appraisal is the lack of comparative evidence. There is no evidence for the relative effectiveness of pegaspargase versus other asparaginases in adults; and there is insufficient evidence in children. In addition, there is no comparative evidence for pegaspargase at a dose of 1,000 IU/m^2; which is, according to the company, the basis of current clinical practice in the UK.

Similarly, no comparative data is available regarding the hypersensitivity rates, which greatly influences the reliability of the health economic evaluation. In addition, the reliance on clinical experts for many important assumptions and input values impact the credibility of the model outcomes, especially given that only two experts gave their input.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG defined a new base case analysis. This new ERG base case included the following adjustments:

- Correction of errors in the model
- Use of the mean age instead of the median age in the paediatric patient population
- No second interim maintenance and delayed intensification course.
- Risk of hypersensitivity to pegaspargase based on percentage of patients switching asparaginase treatment.
- Risk of hypersensitivity to Erwinase similar for first and second line treatment and based on percentage of patients switching asparaginase treatment.
- Alternative OS and EFS estimates for the three paediatric risk groups.
- Allow the OS and EFS of the different formulation to vary independently in the probabilistic sensitivity analysis.
- Change the relative reduction in mortality for patients who discontinue asparaginase treatment due to hypersensitivity to two different formulations
- Change the mortality risk for patients in the R/ST state
- Estimating the EFS in the PSA dependent on OS
- Change the timing of the different treatment phases
- Change the standard errors used in the PSA

According to the ERG base-case, pegaspargase-Erwinase is dominant over all three comparators with slightly better quality of life and fewer costs.

Comparing pegaspargase vs native *E. coli* asparaginase (both followed by Erwinase if hypersensitive) showed a cost-saving of £3,754 and a gain in QALYs of 0.0179. For the comparison of pegaspargase (Erwinase) versus Erwinase (native *E. coli*) cost savings of £28,118 were found whilst gaining 0.0179 QALYs. The sequence comparison of pegaspargase (Erwinase) versus Erwinase (pegaspargase) showed cost saving of £28,184 and no difference in QALYs.

Of all the adjustments made, the changes in the hypersensitivity rate for pegaspargase and Erwinia and a larger reduction in OS and EFS in case of discontinuation of asparaginase treatment had the largest impact on the outcomes.

A number of scenarios were explored to study how various assumptions about input values impact the outcomes. These revealed that the outcomes are sensitive to changes in the assumption of equal OS and equal EFS across the three formulations. However, the scenarios explored represented a best case and worst case scenario so these may be unlikely to represent reality in the UK.

Another scenario with noticeable impact on the outcome concerns the number of dosages of native *E. coli* and Erwinase for each dosage of pegaspargase. In the model this was assumed to be 6:1, based on expert opinion. However, other ratios also occur in practice so a 4:1 ratio was applied in a scenario.

2. BACKGROUND

2.1 Critique of company's description of underlying health problem.

This chapter provides a review of the evidence submitted by Baxalta in support of pegaspargase (trade name Oncaspar®) for the treatment of acute lymphoblastic leukaemia (ALL) in newly diagnosed people with ALL. The content is based on information presented in Section 3 of the company's submission (CS): "Health condition and position of the technology in the treatment pathway".

ERG comment: The company restricts the submission to "newly diagnosed people with ALL", Arguing that "as the use of asparaginase in the UK is driven by the UKALL protocols, the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort". "Patients who experience a relapse or are older than 65 would have regimens that do not include pegaspargase.[1]" This is not in line with the NICE scope, which specifies the population as "people with ALL".

Acute lymphoblastic leukaemia (ALL)

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the number of red cells, white cells and platelets in the blood.[2]

ALL is predominantly a disease of childhood, but it affects adults as well. According to the company's submission (CS, page 30): "*Between 2011 and 2013, an average of 744 new cases of ALL were diagnosed in the UK (crude incidence rate 1 per 100,000 males and 1 per 100,000 females), accounting for 0.2% of all new cancer diagnoses in the UK, and 9% of all new leukaemia diagnoses. The incidence of ALL is strongly correlated with age; in the UK between 2011 and 2013 an average of 54% of ALL cases were diagnosed in children aged 0–14 years. Age-specific incidence rates are highest in infants aged 0–4 years and drop sharply through childhood, adolescence, and young adulthood, reaching their lowest point at age 30–34 in males and 35–39 in females. A total of 644 new cases of ALL were diagnosed in patients aged 65 years or younger.*"[3]

Presenting signs and symptoms of ALL are fairly non-specific and include fever, anaemia, petechiae, and bone and joint pain. Staging of the disease and patient risk profile are routinely performed to define ALL subtypes and guide management.[4] A wide range of factors influence prognosis in ALL including patient characteristics, leukaemic cell characteristics and response to initial therapy. Minimal residual disease (MRD) assessments provide a sensitive measure of early treatment response and are frequently used to determine whether patients require further induction therapy.[5]

ERG comment: Overall, the company submission presents an accurate description of the disease. Updated information from Cancer Research UK shows that 818 new cases of ALL in

the UK are expected in 2013: 437 (53%) in males and 381 (47%) in females, giving a male: female ratio of around 11:10.[6]

Burden to patients, carers and society

The psychological burden of the disease is substantial; in an evaluation of the parental-reported emotional and behavioural functioning of children newly diagnosed with ALL, between 21% and 29% of children with ALL were found to be in the at-risk/clinical range for depression and anxiety at 1, 6 and 12 months after diagnosis, compared with a healthy population (15%, $p<0.05$ for both comparisons).[7]

While ALL affects a relatively small proportion of the population, the costs associated with its management are substantial. In England in 2014, there were 26,438 admissions for ALL, resulting in 41,046 bed days (ICD code C91.0).[8] The associated cost-burden relating to ALL admission is estimated to be in excess of £23.6 million (HRG codes PM40 and SA24).[9]

ERG comment: The ERG agrees with this description of the burden to patients, carers and society.

2.2 Critique of company's overview of current service provision

Clinical pathway of care

ALL is not a uniform disease but consists of subgroups with significant differences in terms of clinical presentation, biologic features, course of disease and prognosis.[10] Therefore, the treatment varies depending on patient age and among different subtypes of ALL, but the basic principles are similar. Treatment of ALL consists of four general components: induction, intensification, maintenance, and early CNS prophylaxis. Stem cell or bone marrow transplantation should only be used for selected high-risk patients.[4, 11]

Drugs used during induction typically include vincristine, corticosteroid (e.g. prednisone), cyclophosphamide, anthracyclines (e.g. doxorubicin), and asparaginase.[12] During the consolidation or intensification phase, cytarabine, methotrexate and 6-mercaptopurine are often added with the aim of eradicating residual disease.[12] Maintenance therapy aims to prevent disease relapse and generally includes 6-mercaptopurine, methotrexate, corticosteroids, and vincristine.[12]

Asparaginase therapy

Asparaginase is a core component of ALL regimens, most often given during induction and consolidation for Ph-negative disease.[12] Three formulations of asparaginase are currently available: Escherichia coli-derived (*E. coli*), Erwinia caratovora-derived (Erwinia), and a polyethylene glycol conjugate of *E. coli* L-asparaginase (PEG-asparaginase). These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.[12] Historically, *E. coli*-derived asparaginase was used as the first line therapy; however, a high anti-asparaginase antibody production in 45-75% of patients limits its treatment effectiveness.[13, 14] PEG-asparaginase has a longer half-life which indicates less frequent dosing. Erwinia-derived asparaginase is used when there is clear hypersensitivity reaction to the other formulations.

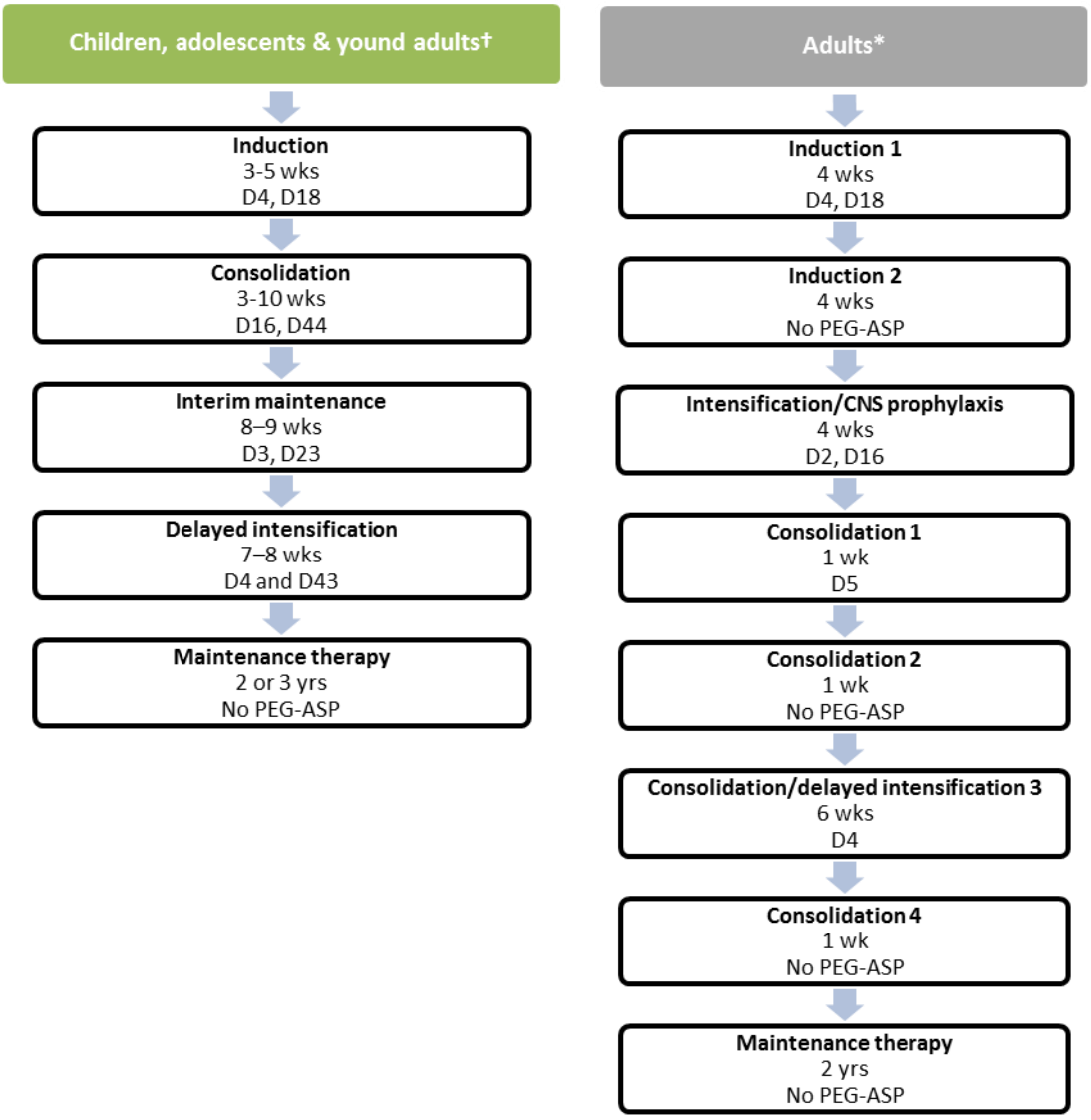
PEG-asparaginase gained marketing authorisation for first line asparaginase use in the United States in 2006 and the European Union licence was approved in January 2016. According to the company, pegaspargase is now the standard of care first line asparaginase therapy, with the majority of ALL patients in the UK receiving this treatment as part of the UKALL protocols or, if not enrolled, receiving treatment based on the protocol, with treatment reimbursed by baseline commissioning (CS, page 32). As such although the licence for pegaspargase does not preclude its use as a second line asparaginase therapy there is not currently a clinical scenario in which pegaspargase would be used as a second line asparaginase therapy, since patients would not receive native *E. coli*- or Erwinia-derived asparaginase as a first line asparaginase (CS, page 32).

With the availability of Erwinia-derived asparaginase, patients experiencing hypersensitivity to pegylated or native *E. coli* enzyme would in practice no longer be switched to the other *E. coli* enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinia-derived enzyme following hypersensitivity to pegaspargase.[15, 16]

A further complication in this field is that native *E. coli*-derived asparaginase is not licensed for use in the UK and is not listed in the BNF. Similarly, unavailability in the United States has seen it removed from United States treatment guidelines.[12],,

An overview of the treatment algorithms for pegaspargase use in clinical practice as detailed in the UKALL protocols is provided in Figure 2.1. These algorithms demonstrate how pegaspargase is used in a number of different phases of treatment and how this differs between paediatric/young adult and adult patients.

Figure 2.1: Algorithms for pegaspargase use in clinical practice



Abbreviations: D, days; PEG-ASP, pegaspargase; wks, weeks
Source: CS, page 34; derived from UKALL 2011 and UKALL 14 protocols.[15, 16]
Wks represent overall length of treatment phase. D represents day of phase on which pegaspargase is administered. Pegaspargase is not administered in some treatment phases as denoted by "No PEG-ASP". Pegaspargase dose 1,000 IU/m^2 throughout.
†In UKALL 2011 duration of treatment phases and total number of pegaspargase doses in each phase vary depending on which of three regimens that patients are assigned to, based on MRD risk. The total number of pegaspargase doses varies between three and seven between regimens.
*In UKALL 14, patients receive between three and six pegaspargase doses depending on their age and whether or not they have had a transplant.

ERG comment: The European Medicines Agency (EMA) has approved pegaspargase (Oncaspar®) for the treatment of patients with ALL on 14 January 2016 for the treatment of ALL. As stated by the company pegaspargase has been included in NHS England baseline commissioning since April 2013, and there is currently no published NICE guidance on the treatment of ALL. In addition, pegaspargase has been the first line asparaginase in UK practice mandated since 2003, being adopted in UKALL protocols for children, adolescents

and young adults (UKALL 2003, which completed enrolment in 2010; UKALL 2011) and for adults (UKALL14).[3]

It is important to note that the UKALL protocols use a dose of 1,000 IU/m^2 for pegaspargase. However, the SmPC recommended dose is higher (2,000-2,500 IU/m^2). Moreover, there is no comparative evidence for this lower dose of pegaspargase versus other types of asparaginase. All trials comparing pegaspargase with *E. coli* asparaginase compared 2,500 IU/m^2 pegaspargase with 6,000 IU/m^2 *E. coli* asparaginase.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the manufacturer)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with ALL	Newly diagnosed people with ALL	As the use of asparaginase in the UK is driven by the UKALL protocols, the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort, as per the protocols described in Section **Error! Reference source not found.**. Patients who experience a relapse or are older than 65 would have regimens that do not include pegaspargase.[1] Our submission therefore meets the scope in that it considers patients of relevance to decision-makers in the NHS.
Intervention	Pegaspargase plus standard chemotherapy	As per scope	NA
Comparator(s)	Non-pegylated forms of: • Escherichia coli-derived L-asparaginase plus standard chemotherapy • Erwinia chrysanthemi-derived L-asparaginase (crisantaspase) plus standard chemotherapy	As per scope Treatment sequences modelled: 1. Pegaspargase >> Erwinia-derived asparaginase 2. Native *E. coli* -derived asparaginase >> Erwinia-derived asparaginase 3. Erwinia-derived asparaginase >> Pegaspargase 4. Erwinia-derived asparaginase >> Native *E. coli* -derived asparaginase	Asparaginase treatment will be given as part of 1st line ALL treatment, and in cases of hypersensitivity reactions, a switch to an alternative (2nd line) asparaginase will be necessary. Although the licence for pegaspargase does not preclude its use as a 2nd line asparaginase therapy there is not currently a clinical scenario in the UK in which pegaspargase would be used in this setting, since patients would not receive native *E. coli*- or Erwinia-derived asparaginase as a 1st line asparaginase. In addition, with the availability of Erwinia-derived asparaginase, patients experiencing hypersensitivity to pegylated or native *E. coli* enzyme would in practice no longer be switched to the other *E. coli* enzyme because of the risk of cross reactivity, and subsequent hypersensitivity. In UK clinical practice, UKALL protocols mandate a switch to Erwinia-derived enzyme following hypersensitivity to pegaspargase.[15, 16] A further complication in this field is that native *E. coli*-derived asparaginase is not licensed for use in the UK. Unavailability in the United States has seen it removed from United States treatment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			guidelines (NCCN 2015).[12] Erwinia derived asparaginase is licensed in the UK and, although the wording of its indication does not limit its use to a specific line of asparaginase therapy,[14] the product is only positioned in treatment protocols as a 2nd line asparaginase.[15-18] Hence, with this context in mind, the current standard of care treatment pathway in the UK is pegaspargase 1st line followed by Erwinia-derived enzyme in cases of hypersensitivity, and this treatment sequence has been modelled. Although not currently part of UK clinical practice and unrealistic given the current unavailability of native *E. coli* enzyme and the 2nd line positioning of Erwinia, alternative switching scenarios of native to Erwinia, Erwinia to pegylated, and Erwinia to native could be clinically possible, and are also modelled.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Treatment response rates • Event-free survival • Asparaginase activity • Adverse effects of treatment • Health-related quality of life	As per scope except for progression-free survival which wasn't included	Event free survival was used in many studies and this outcome will incorporate progression free survival. In addition, there are a large amount of patients, especially paediatric patients, who are cured and as such do not progress.[15, 19, 20]
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope In addition, we will present a cost minimisation analysis	Cost minimisation included as we have conservatively assumed equivalence in outcome (OS & EFS) between the asparaginase products, and the entire treatment period lasts around 2-3 years, with all outcomes of interest being observed during this time. A cost minimisation model would, therefore, allow decision-makers to assess the differences over this time

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	NA	NA	NA
Special considerations including issues related to equity or equality	NA	ALL presents primarily in children, adolescents, and young adults, with 74.4% of cases diagnosed in people aged under 25 years.[6] Equity of treatment for children and young people with cancer is a concern, as evident from the NICE Quality Standard 55 "Cancer services for children and young people".[21] ALL is also an orphan disease.[22] The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer.[23] Therefore, continued access, where appropriate, to a treatment such as pegaspargase should help to promote equality for both younger patients and those with rarer forms of cancer, especially as pegaspargase has a decreased number of infusions and hypersensitivity reactions than native *E. coli*-derived or Erwinia-derived asparaginase.[13, 24] This is what prompted the NHS to adopt the product into baseline commissioning in 2013.[25] As highlighted in feedback provided by NCRI/RCP/ACP, and Royal College of Pathologists and BSH during NICE scoping, a negative appraisal would also put at risk the ongoing clinical protocols in the UK, which would be detrimental to patient care.	

3.1 Population

The patient population described in the final scope are: “People with acute lymphoblastic leukaemia”.[2] This is in line with the patient population described in the license indication for pegaspargase: "Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients".[26]

However, in the CS the company has restricted the population to ‘newly diagnosed people with ALL’, arguing that “the use of asparaginase in the UK is driven by the UKALL protocols”, and that “the patient population whose chemotherapeutic regimen is underpinned by asparaginase is the newly-diagnosed cohort”.[3]

3.2 Intervention

The intervention described in the CS matches the intervention described in the final scope: pegaspargase plus standard chemotherapy. However, the dose used in the economic model is not the recommended dose.

Pegaspargase, a polyethylene glycol conjugate of *E. coli*-derived L-asparaginase, is a bacterial enzyme that depletes circulating asparagine, an essential amino acid on which leukaemic cells, incapable of synthesising asparagine, depend, leading to cell death.

According to the Summary of Product Characteristics (SmPC) issued by the European Medicines Agency (EMA),[27] the recommended dose of pegaspargase in patients with a body surface area ≥0.6 m2 and who are ≤21 years of age is 2500 U (equivalent to 3.3 ml pegaspargase)/m² body surface area every 14 days. Children with a body surface area <0.6 m² should receive 82.5 U (equivalent to 0.1 ml Oncaspar)/kg body weight every 14 days. Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2000 U/m2 every 14 days.

However, according to the company, UKALL protocols form the basis of current clinical practice in the UK,[15, 16, 19, 20] with pegaspargase being administered at a dose of 1,000 IU/m^2, lower than that recommended by the SmPC (2,500 IU/m^2). Therefore, the economic model in the CS is based on the lower dose of 1,000 IU/m^2. This is despite the fact that all comparative evidence available for pegaspargase is based on the higher dose of 2,500 IU/m^2.[24, 28-36]

3.3 Comparators

The comparators in the CS are defined as non-pegylated forms of:

- *Escherichia coli* derived L-asparaginase plus standard chemotherapy, and
- *Erwinia chrysanthemi* derived L-asparaginase (crisantaspase) plus standard chemotherapy

This is in line with the final NICE scope.

3.4 Outcomes

In the NICE final scope, outcomes are defined as follows:

- overall survival
- progression-free survival
- response rate
- adverse effects of treatment
- health related quality of life.

As stated in the table above, these outcomes are included in the CS, except for progression-free survival which wasn't reported in any of the included studies. Instead, event free survival was used in many studies and this outcome incorporates progression free survival according to the company.

3.5 Other relevant factors

The CS states that a patient access scheme (PAS) is not being submitted (CS, Section 2.3.1, page 28).

Regarding equity considerations, the company states that pegaspargase has been designated orphan status by the EMA. In addition, the company states that "equity of treatment for children and young people with cancer is a concern, as evident from the NICE Quality Standard 55 *Cancer services for children and young people*.[21]"

According to the company (CS, Section 2.5, page 29), "Pegaspargase has been the first line asparaginase of choice in UK clinical practice since 2003 with the vast majority of ALL patients receiving treatment under the UKALL protocols (UKALL 2003, UKALL 2011, UKALL 14). In addition, in April 2013 pegaspargase was formally included in baseline commissioning by NHS England, meaning that it is routinely funded.[25]"

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS is based on two systematic reviews to inform the clinical evidence base for pegaspargase and relevant comparators.

The first systematic review (SR1) was designed to identify evidence to allow a comparison of pegaspargase and native *E. coli*-derived for first line treatment of ALL in newly diagnosed children and adolescents. The second systematic review (SR2) was conducted to broaden the search to identify evidence for pegaspargase, native *E. coli*-derived asparaginase, and Erwinia-derived asparaginase, irrespective of age group and line of treatment.

ERG comment: The second systematic review addresses the NICE scope for the current appraisal more closely. Therefore, we will focus on the second systematic review.

4.1.1 Searches

Description and critique of the company's search strategies

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[37] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[38] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness

The CS states that two systematic reviews were conducted to inform the clinical evidence base for pegaspargase and relevant comparators. SR 1 specifically identified evidence to allow a comparison of pegaspargase and native *E. coli*-derived asparaginase. This review was limited to a paediatric and adolescent population and was therefore not in line with the decision problem whose population was paediatric, adolescent, young adult and adult patients with ALL. The objectives of SR2 were "to broaden the search of systematic review 1, to identify evidence for pegaspargase, native *E. coli*-derived asparaginase, and Erwinia-derived asparaginase, irrespective of patient age group and line of treatment."[3] The company confirmed that all papers found in SR1 were found in the broader and more comprehensive SR2 as well as a further nine publications providing data on pegaspargase and Erwinia-derived asparaginase.[39]

Searches for SR2 were conducted on 31 January 2016 in MEDLINE, Embase, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Methodology Register, ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and NHS Economic Evaluation Database (NHS EED). The host provider for each database was provided; the date span of the databases searched and the specific date the searches were conducted were also provided. Detailed search strategies for the database searches were reported in Appendix 2.

The company translated the decision problem into effective search strategies and the population and intervention/comparator facets were clearly structured. An appropriate combination of index terms, free text and synonyms for the interventions and comparators was used. A study design limit to identify clinical trials was applied in MEDLINE and Embase. At the request of the ERG, the company reported that study design search filters were based on NCBI recommendations for MEDLINE; and Ovid search platform recommendations for Embase and the Cochrane Library databases.[39] As the Cochrane Library is considered to be study design specific, the company repeated searches for SR2 in the Cochrane Library databases without study design filters. All searches for SR2 were limited to English language which the ERG felt introduced language bias.

Manual searches were conducted in ClinicalTrials.gov and Google. Conference abstracts from the American Society of Hematology (ASH), American Society of Pediatric Hematology/Oncology *(*ASPHO*)*, Cancer and Leukemia Group B (CALGB) were also searched. Web addresses and the date of searching were provided in response to the ERG clarification letter.[39] The ERG considered this list of supplementary resources to be comprehensive and a useful addition to the database searches. However, the company described the search strategy as ""Acute lymphoblastic leukemia" (and any other relevant synonyms) and "asparaginase" (and any other related synonym)".[39] No further details of the synonyms were provided so it was not possible to assess the effectiveness of this strategy.

Indirect and mixed treatment comparisons

[redacted]

Non-randomised and non-controlled evidence

The same search strategies and databases used for the clinical effectiveness literature searches were used to identify non-RCT evidence. In addition to the limitations already identified, the search strategies for SR2 included a study design search filter for randomised/controlled trials which may have been too restrictive to identify all non-randomised and non-controlled evidence. Whilst the search strategy for SR1 was not in line with the decision problem, so may also have missed relevant evidence.

Adverse events

The same search strategies and databases used for the clinical effectiveness literature searches were used to identify adverse events data. CRD guidance[40] recommends that if searches have been limited by a study design search filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. It is possible that some relevant evidence may not have been identified as a consequence of the study design limits.

Cost effectiveness

The CS states that a comprehensive search of the peer-reviewed literature was conducted to identify and select cost effectiveness studies relevant to decision-making in England on clinical efficacy, safety and toxicity of pegaspargase in all age groups of patients with newly diagnosed ALL.[3]

The searches were conducted on 31 January 2016 in the same databases as searched for in the clinical effectiveness searches: MEDLINE, Embase, CDSR, CENTRAL, ACP Journal Club, DARE, HTA and NHS EED. The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were also provided. Detailed search strategies for the database searches were reported in Appendix 6. In addition, the company manually searched ClinicalTrials.gov, ASH, ASPHO, CALGB, Google, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), NHS Choices, National Institute for Health and Clinical Care Excellence (NICE) and Scottish Medicines Consortium (SMC).

The company translated the decision problem into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into clinical condition and economic outcomes. In the MEDLINE search strategy (Appendix 6) the economic outcomes were combined from line 24 to line 27, instead of line 9 to line 32. This is thought to be a reporting error, rather than a consequential error as the search results suggest the latter. The company did not use a validated study design search filter to find cost effectiveness studies and relied on "common knowledge and internal expertise".[39] The ERG felt the use of a validated study design search filter, truncation and proximity operators would have improved the sensitivity of the cost effectiveness facet of this search strategy. However, it is unlikely that relevant evidence was missed as the search terms that were included were sufficient. A language limit for English only was used which the ERG felt introduced language bias.

Web addresses and the date of searching for manual searching was provided, but the details of the search strategy were not sufficient to assess the effectiveness of this strategy.

A search of other economic resources, such as the CEA Registry and ScHARRHUD, for cost-utility analyses might have been a useful addition to the literature searches.

The ERG requested a flowchart/schematic diagram detailing the results of the cost-effectiveness searches. These were provided in the response to the ERG clarification letter but did not include results from the Cochrane Library.[39] This was thought to be a transcription error.

Search strategy for measurement and valuation of health effects

The CS states that a search was conducted to identify and select relevant health related quality of life (HRQoL) studies in line with the objectives of gathering data relevant to decision-making in England on clinical efficacy, safety and toxicity of pegaspargase in all age groups of patients newly diagnosed with ALL.

Searches were conducted on 31 January 2016 in the same databases as were searched for clinical and cost effectiveness studies: MEDLINE, Embase, CDSR, CENTRAL, Cochrane Methodology Register, ACP Journal Club, DARE, HTA and NHS EED. The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were also provided. In addition, the company manually searched ClinicalTrials.gov, ASH, ASPHO, CALGB, Google, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), NHS Choices, National Institute for Health and Clinical Care Excellence (NICE) and Scottish Medicines Consortium (SMC). Detailed search strategies for the database searches were reported in Appendix 8.[3]

The company translated the decision problem into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into clinical condition and HRQoL outcomes and were correctly combined using Boolean operators. The company did not use a validated study design search filter to find HRQoL studies and relied on "common knowledge and internal expertise".[39] Although a validated study design search filter may have been more comprehensive, the ERG was satisfied that no relevant items were missed. An English language limit was used which the ERG felt introduced language bias.

A detailed search strategy for manual searching was not provided so it was not possible to assess the effectiveness of this strategy. Web addresses and the date of manual searching were provided in the response to the ERG clarification letter.[39]

The ERG requested a flowchart/schematic diagram detailing searches for measurement and valuation of health effects. These were provided but did not include results from the Cochrane Library. This was thought to be a transcription error.

Summary of searching

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional supplementary searches of relevant websites and databases were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[41]

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for SR1 and SR2 are shown in Tables 5 and 6 of the CS (CS, pages 42 and 44). These two tables are combined in Table 4.1 below.

Table 4.1: Eligibility criteria used in the search strategy

	Inclusion criteria SR1	Inclusion criteria SR2
Population	Paediatric and/or adolescent patients with ALL	Patients with ALL
Interventions & comparators	1st line treatment for ALL Pegaspargase or native *E. coli*-derived asparaginase	Patients with ALL who have received any type of the following asparaginase as part of a chemotherapeutic protocol: • Main intervention: Pegylated L-asparaginase derived from *Escherichia coli* • Clinical comparator: 'Native' (non-pegylated) L-asparaginase derived from *Escherichia coli* • Clinical comparator: Crisantaspase (Erwinase) derived from *Erwinia chrysanthemi* Studies not directly evaluating the clinical effectiveness or the safety/tolerability profile of at least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patients, were excluded
Outcomes	The search did not initially restrict to any outcome to allow for identification of all possible reported outcomes	The search did not initially restrict to any outcome to allow for identification of all possible reported outcomes
Study design	Case reports & editorials were excluded	Comments, editorials, systematic reviews or reviews were excluded
Language restrictions	Only English, French & German extracted	English language publications only

Abbreviations: ALL, acute lymphoblastic leukaemia; ASP, asparaginase; PEG-ASP, pegaspargase; RCT, randomised controlled trial; SR1, First systematic review; SR2, Second systematic review

ERG comment: The first systematic review is restricted in terms of population (Paediatric and/or adolescent patients with ALL) and interventions (*Erwinia chrysanthemi* derived L-asparaginase is not included). These restrictions are not in line with the scope. Therefore, the first search does not address the decision problem as described in the NICE scope.

The second search includes all patients with ALL, and all relevant interventions are included. Therefore, both searches together should pick-up all relevant studies. The only major limitation is that there is a language restriction: only English language publications are included.

4.1.3 Critique of data extraction

The CS included 40 publications from SR1 and 48 publications from SR2. The 40 publications (39 studies) from SR1 are described in Table 7 of the CS (CS, pages 46-47),[19, 20, 24, 28, 30-35, 42-54] these are studies including a pegaspargase arm; and Table 30 of the CS (CS, pages 109-113),[24, 51, 55-71] these are studies without a pegaspargase arm, but with a native *E. coli*-derived asparaginase arm. SR2 retrieved nine additional publications: five of these included a pegaspargase arm[29, 36, 72-74] and are described in Table 7 of the CS; the other four evaluated Erwinia derived asparaginase[75-78] and are not listed in any table in the CS.

Full details for two studies: CCG-1962[28] and UKALL 2003,[19, 20] are described in Sections 4.3 to 4.7 of the CS (CS, pages 47-73). According to the company, CCG-1962 is the only trial available that provides direct randomised comparative evidence for pegylated versus *E. coli*-derived asparaginase when given during the induction phase of treatment, and treatment continued through subsequent phases with the randomly assigned asparaginase. However, it only includes a small number of children (N=118) aged 1 to 9 years. UKALL 2003, does provide evidence for the use of pegaspargase in UK and Ireland clinical practice. The enrolled population of >3,200 patients represents 97% of the eligible ALL population in the UK and Ireland aged 1-<25 years.[15] However, it does not provide comparative evidence versus other asparaginases.

Details of most of the other included studies are reported in section 4.8 of the CS (CS, Tables 22-29, pages 76-103). However, no details are reported for the four studies evaluating Erwinia derived asparaginase from SR2.

ERG comment: The CS focuses on two studies: CCG-1962[28] and UKALL 2003.[19, 20] CCG-1962 because it is the only trial that provides direct randomised comparative evidence for pegylated versus *E. coli*-derived asparaginase when given during the induction phase of treatment – although the NICE scope is not limited to treatment during the induction phase; and UKALL 2003 because it provides evidence for the use of pegaspargase in UK and Ireland clinical practice – although it does not provide comparative evidence versus other asparaginases.

The ERG does not agree that these are the main trials of interest for the committee. For a comparative analysis of pegaspargase versus other asparaginases, randomised trials of pegaspargase versus the two comparators and of the two comparators compared with each other in the population as described in the NICE scope (people with ALL) would be most relevant. These studies are described in section 4.5 of this ERG report.

4.1.4 Quality assessment

Quality assessment is reported in the CS in section 4.6 (CS, page 61). However, only two studies are described: CCG-1962[28] and UKALL 2003.[19, 20] No quality assessment is reported for any of the other included studies.

ERG comment: Given that the randomisation process and concealment of treatment allocation was marked as unclear for study CCG-1962, together with the fact that CCG-1962 was an open-label study, this study has considerable risk of bias.

4.1.5 Evidence synthesis

An indirect and mixed treatment comparison is reported in Section 4.11 of the CS (page 127); and a meta-analysis is reported in Section 4.10 of the CS (pages 108-126). Both sections are marked entirely Commercial-in-Confidence.

[redacted]

[redacted]

ERG comment: [redacted]

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[redacted]

[redacted]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The evidence presented in the company submission (CS) focuses on two studies:

- CCG-1962, the only randomised head-to-head comparison of pegylated versus native *E. coli*-derived asparaginase given from induction, and
- UKALL 2003, providing evidence for the use of pegaspargase at a dose of 1,000 IU/m^2 in >3,200 children, adolescents and young adults in the UK and Ireland.

In study CCG-1962 a total of 118 children (aged 1–9 years) newly-diagnosed with ALL were randomised to receive either pegaspargase (2,500 IU/m^2 IM on day three of induction and each DI phase) or native asparaginase (6,000 IU/m^2 IM three times per week, for nine doses in induction, and six doses in each DI phase). EFS rates at three, five, and seven years, respectively, were similar for those treated with pegaspargase (83%, 78%, and 75%) versus those treated with native asparaginase (79%, 73%, and 66%).

UKALL 2003 enrolled a total of 3,207 children and young adult patients aged 1–24 years, representing 97% of the eligible ALL patient population aged 1–24 years in the UK and Ireland. All patients received treatment with pegaspargase (1,000 IU/m^2 per dose, 4–12 doses) as part of one of three escalating-intensity regimens to which patients were assigned depending on their clinical risk classification following induction. Among all patients enrolled in UKALL 2003: five-year EFS was 87.3%, and five-year OS was 91.6%.

There was no evidence for the comparative effectiveness of pegaspargase with other types of asparaginase in adults.

ERG comment: The ERG disagrees with the company that the two trials in the CS are the pivotal studies for this assessment. CCG-196 compares pegaspargase with native *E. coli* asparaginase in children aged 1 to 9 years (N=59 in both groups). Therefore, it is a small study in very young children, covering only a small group of the total population of interest for this appraisal: people with ALL. UKALL 2003 does not include a relevant comparator and is therefore less relevant for this appraisal.

Therefore, we present an overview of all comparative studies relevant for this appraisal in Chapter 4.5 of this report.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

See ERG comments above (Section 4.2).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

See ERG comments above (Section 4.1.5).

4.5 Additional work on clinical effectiveness undertaken by the ERG

There were five RCTs identified in the searches comparing pegaspargase with native *E. coli* asparaginase, and two RCTs comparing native *E. coli* asparaginase with Erwinia asparaginase. These studies are summarised in Table 4.2 below. There was one additional RCT (DFCI-87-01[24] comparing pegaspargase with native *E. coli* asparaginase, but in this study treatment groups were randomised on methotrexate (high dose versus low dose), not on asparaginase.

Table 4.2: RCTs with comparisons of pegaspargase, native *E. coli* asparaginase and Erwinia asparaginase

Trial no.	Intervention	Comparator	Population	Primary study ref.
Pegaspargase versus Native *E. coli* asparaginase				
CCG-1961	Pegaspargase 2,500 IU/m^2 im; N=649 (16-21y: 77)	Native *E. coli* asparaginase 6,000 IU/m^2 im; N=650 (16-21y: 88)	1 to 21 years (Panosyan et al, 2004; Seibel et al, 2008) 16 to 21 years (Nachman et al, 2009) Patients with newly diagnosed higher-risk ALL	Panosyan et al, 2004;[33] Seibel et al, 2008;[31] Nachman et al, 2009[32]
CCG-1962	Pegaspargase 2,500 IU/m^2 im; N=59	Native *E. coli* asparaginase 6,000 IU/m^2 im; N=59	1 to 9 years Patients with standard risk ALL From induction	Avramis et al, 2002[28]
DFCI-91-01	Pegaspargase 2,500 IU/m^2 im; N=106	Native *E. coli* asparaginase 25,000 IU/m^2 im; N=92	1 to ≤18 years Patients with newly-diagnosed ALL (excl. mature B-cell ALL) – Risk: SR, HR, & Infant HR	Silverman et al, 2001[34]
DFCI ALL 05-001	Pegaspargase 2,500 IU/m^2 iv; N=232	Native *E. coli* asparaginase 25,000 IU/m^2 im; N=231	1 to 18 years Patients with newly diagnosed ALL who achieved complete remission – Risk: SR, HR, VHR	Place 2015*;[29] Silverman et al, 2013[42]
DFCI ALL 05-01	Pegaspargase 2,500 IU/m^2 iv; N=29	Native *E. coli* asparaginase 25,000 IU/m^2 im; N=27	1 to 18 years Patients with newly diagnosed ALL who achieved complete response during induction – Risk: SR	Merryman et al, 2010;[35] Silverman et al, 2011;[30] Merryman et al, 2012[36]
Native *E. coli* asparaginase versus Erwinia asparaginase				
DFCI-95-01	*E. coli*-ASP 25000 IU/m2/wk im; N=147	Erwinia 25000 IU/m2/wk im for 20 weeks during the Intensification phase (=post-induction consolidation); N=139	0 to 18 years Patients with newly diagnosed ALL (excl. mature B-cell ALL) - SR & HR	Moghrabi 2007;[55] Silverman et al, 2010[24]
EORTC CLG 58881	*E. coli*-ASP 10000 IU/m2/ twice weekly iv; N=354	*Erwinia*-asparaginase 10000 IU/m2/twice weekly iv; N=346	0 to 18 years Patients with ALL – SR, IR & HR	Vilmer 2000[63] Duval 2002[56]

Abbreviations: ALL, acute lymphoblastic leukemia; ASP, asparaginase; HR, high risk; IR, intermediate risk; SR, standard risk; VHR, very high risk

Table 4.3: Study design and patient population

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
Pegaspargase versus Native *E. coli* asparaginase							
CCG-1961	Seibel 2008[31]	US Enrolment: Sept 1996-May 2002	To determine the relative contributions of length and strength to post-induction intensification (PII)	- Interventional - Prospective - Randomised: to *E. coli*-ASP (part of standard therapy) vs PEG-ASP (part of increased intensity therapy) (post induction for rapid early responders). For HR patients: 1) to doxorubicin with or without dexrazoxane; 2) to once-daily vs twice-daily cranial radiation - Treatment was stratified between rapid and slow early responders (RER and SER) based on the day 7 bone marrow status (<25% blasts [RER] or >25% blasts [SER]) - Multicentre	Patients 1 to 21 years old with high risk ALL	HR	EFS OS
	Panosyan 2004[33]		To determine whether the prevalence of Ab formation in the HR ALL patients is a predictor of poor treatment outcome				ASP antibodies ASP activity
	Nachman 2009[32]		To assess the outcome for young adults with ALL enrolled onto the CCG 1961 study between 1996 and 2002		Patients 16 to 21 years old (young adults) with high risk ALL (subgroup)		EFS OS
CCG-1962	Avramis et al, 2002[28]	Not specified Enrolment: May 1997-Nov 1998	To evaluate safety, efficacy, and PK of a single IM dose of PEG-ASP instead of multiple IM doses of native *E. coli*-ASP in each of 3 phases of therapy	- Interventional - Prospective - Randomised at induction - Multicentre - Phase III - Open-label	Children (1-9 years) with standard-risk ALL	SR	Incidence of high-titre ASP antibodies in DI no. 1
DFCI-91-01	Silverman et al, 2001[34]	US, Canada Enrolment: Dec 1991-Dec 1995	To improve outcome while minimising toxicity	- Interventional - Prospective - Randomised: Central randomisation. All patients randomised to: • High-dose IV 6-MP • Standard-dose oral 6-MP during the first year of post-remission therapy Patients underwent 3 additional	Children (aged 0-18 years) with newly diagnosed ALL (excluding mature B-cell ALL)	SR HR Infant-HR	Not mentioned

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
				randomisations: • To native or PEG-ASP • To doxorubicin continuous infusion or to bolus • To once-daily or twice daily cranial radiation • PEG-ASP was not available in Canada: children treated at Canadian institutions (n=127) were directly assigned to receive *E. coli*-ASP - Multicentre			
DFCI ALL 05-001	Silverman et al, 2013[42] Place et al, 2015[29]	US, Canada Enrolment 2005-2010	To compare the relative toxicity and efficacy of IV PEG-ASP and IM *E. coli* ASP	- Interventional - Prospective - Randomised: following complete remission at induction with 1 dose PEG-ASP, patients were randomised at post-induction to *E. coli*-ASP or PEG-ASP - Phase III - Multicentre	Patients with newly diagnosed ALL aged 1-18 years who achieved complete remission following induction	SR HR VHR	Safety
DFCI ALL 05-01	Merryman et al, 2010[35] Merryman 2012[36]	US, Canada Enrolment 2005-2010	To assess toxicity of ASP particularly potential associated myelosuppression in children and adolescents with ALL	- Interventional - Prospective - Randomised: to *E. coli*-ASP or PEG-ASP at consolidation - Not multicentre	Children and adolescents (1-18 yrs) with newly diagnosed ALL who achieved CR during induction	Standard risk	Not specified
	Silverman et al, 2011[30]		To compare 2 week IV PEG-ASP with weekly IM *E. coli*-ASP in terms of toxicity and ASP levels			Not specified	Median NSAA
Native *E. coli* asparaginase versus Erwinia asparaginase							
DFCI ALL 95-01	Moghrabi 2007[55] Silverman	US, Canada Enrolment: Jan 1996-Sept 2000	To reduce therapy-related morbidity without compromising efficacy	- Interventional - Prospective - Randomised: to *E. coli*-ASP or Erwinia at	Children (aged 0-18 years) with newly	SR HR	Not specified

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
	2010[24]			induction - Multicentre	diagnosed ALL (excluding mature B-cell ALL)		
EORTC CLG 58831, 58832, 58881	Vilmer 2000[63]	France, Belgium, Portugal 58831/58832: enrolment 1983-1989	58831 (1983-1989): to assess cyclophosphamide in SR patients 58832 (1989-1998): to assess omission of CNS radiotherapy plus methotrexate IV high dose 58881 (1990-1993): to assess the toxicity and efficacy of *E. coli*-ASP and Erwinia when given at equal dosage & to assess the value of high doses of cytarabine with high doses of methotrexate during the interval therapy, & to assess the advantage of adding Iv 6-mercaptopurin to conventional maintenance therapy	- Interventional: The manuscript reports on 3 randomised trials, but only 58881 trial has ASP results - Prospective - Randomised: Randomisation differed across the 3 studies - Multicentre	Children with ALL under 18 years of age	58831: SR 58832: IR & HR 58881: SR, IR, HR	EFS
EORTC-CLG 58881	Duval 2002[56]	Belgium, France and Portugal Enrolment: Nov 1990-Oct 1993	Compare toxicity and safety of *E. coli*-ASP and Erwinia	- Interventional - Prospective - Randomised: Randomisation was done centrally and stratified according to: centre; disease (leukemia versus lymphoma); risk factor ("smaller than" 0.8, 0.8-1.19, "bigger than or equal to" 1.2), and immunophenotype (B versus T lineage) for leukemia patients; and by Murphy stage (stage I-II versus III-IV) for lymphoma	Children (aged 0-18 years) with acute lymphoblastic leukemia or lymphoblastic lymphoma	SR HR VHR	EFS

Study	Citation	Country(ies) Time period	Aim	Study design	Population	Risk level	Primary endpoint
				patients. Randomisation was not stratified by the presence of t(9;22). Subsequent randomisations were stratified according to treatment arm and initial risk factor or Murphy stage. - Multicentre - Phase III			

Abbreviations: ALL, acute lymphoblastic leukemia; ASP, asparaginase; CR, complete remission; DI, delayed intensification; *E. coli*-ASP, native Escherichia Coli-derived asparaginase; EFS , event-free survival; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; MP, mercaptopurine; NSAA, nadir serum asparaginase activity; OS, overall survival; PEG-ASP, pegaspargase; PK, pharmacokinetics; RER, rapid early responders; SER, slow early responders; SR, standard risk; US, United States; VHR, very high risk.

Table 4.4: Exposure to asparaginase

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
Pegaspargase versus Native *E. coli* asparaginase						
CCG-1961	Nachman 2009[32] Panosyan 2004[33] Seibel 2008[31]	**Standard therapy** - Induction - Consolidation - Interim maintenance - Delayed intensification - Reconsolidation - Maintenance **Increased intensity therapy** - Induction - Consolidation - Interim maintenance - Delayed intensification - Reconsolidation - Interim maintenance 2 - Delayed intensification 2 - Maintenance 2	**Standard therapy** - Induction: *E. coli*-ASP (all) - Consolidation: No ASP - Interim maintenance: No ASP - Delayed intensification: *E. coli*-ASP (all) - Reconsolidation: No ASP - Maintenance: No ASP **Increased intensity therapy** - Induction: *E. coli*-ASP (all) - Consolidation: PEG-ASP (all) - Interim maintenance: PEG-ASP (all) - Delayed intensification: PEG-ASP (all) - Reconsolidation: PEG-ASP (all) - Interim maintenance 2: PEG-ASP (all) - Delayed intensification 2: PEG-ASP (all) - Maintenance 2: PEG-ASP (all)	- *E. coli*-ASP - PEG-ASP	- *E. coli*-ASP: 6,000 IU/m^2 - PEG-ASP: 2,500 IU/m^2 - if allergy: Erwinia: 6,000 IU/m^2	IM
CCG-1962	Avramis et al, 2002[28]	- Induction: 4 weeks - Consolidation: 4 weeks - Interim maintenance: 2 x 8-week phases - DI: 2 x 8-week phases - Maintenance therapy	Randomisation at induction phase - Induction: *E. coli*-ASP vs PEG-ASP (R) - Consolidation: no ASP - Interim maintenance 1 & 2: no ASP - Delayed intensification 1 & 2: *E. coli*-ASP vs PEG-ASP (as in induction) - Maintenance: no ASP	- PEG-ASP - *E. coli*-ASP	- PEG-ASP: 2,500 IU/m^2 - *E. coli*-ASP: 6,000 IU/m^2	IM
DFCI-91-01	Silverman et al, 2001[34]	- Investigational window (3 days) - Induction (4 weeks) - CNS therapy (3 weeks) - Intensification (30 weeks) - Continuation (until 2 years of CCR)	- Investigational window: no ASP - Induction: no ASP (all) - CNS therapy: no ASP (all) - Intensification: PEG-ASP vs *E. coli*-ASP (R) - Continuation: no ASP (all) In addition to ASP randomisation: - CNS therapy randomisation	- PEG-ASP - *E. coli*-ASP	- PEG-ASP: 2,500 IU/m^2 - *E. coli*-ASP: 25,000 IU/m^2	IM

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
			- Intensification with/without doxorubicin for HR			
DFCI ALL 05-001	Silverman et al, 2013[42] Place et al, 2015[29]	- Induction - Consolidation - CNS intensification (Timing of CNS phase dependent on risk stratification) - Continuation	Randomisation at post-induction - Induction: PEG-ASP - CNS intensification (SR/HR) or consolidation (VHR): *E. coli*-ASP vs IV PEG-ASP (R) - Continuation	- PEG-ASP - *E. coli*-ASP	- *E. col* ASP: 25,000 IU/m^2 weekly (30 doses) - PEG-ASP: IV 2,500 IU/m^2 every 2 wks (15 doses)	- IV (PEG-ASP) - IM (*E. coli*-ASP)
DFCI ALL 05-01	Merryman et al, 2010[35] Silverman et al, 2011[30]	- Induction - Consolidation - CNS therapy - Reinduction - Maintenance	Randomisation at consolidation - Induction: PEG-ASP - Consolidation: *E. coli*-ASP vs PEG-ASP (R) - CNS therapy: *E. coli*-ASP vs PEG-ASP - Reinduction: not specified (all) Maintenance: no ASP (all)	- *E. coli*-ASP - PEG-ASP	- *E. coli*-ASP: weekly IM as 25,000 IU/m^2 - PEG-ASP: every 2-wk as 2,500 IU/m^2	- IM (*E. coli*-ASP) - IV (PEG-ASP)
Native *E. coli* asparaginase versus Erwinia asparaginase						
DFCI ALL 95-01	Moghrabi 2007[55] Silverman 2010[24]	- Induction (4 wk) - CNS therapy (3 wk) - Intensification (30 wk) - Continuation (until Month 24)	- Induction: *E. coli*-ASP vs Erwinia (R) - CNS prevention - Intensification: *E. coli*-ASP vs Erwinia - Continuation: no ASP (all) In addition to ASP randomisation: - CNS randomisation - Intensification with/without dexrazoxane for HR	- *E. coli*-ASP - Erwinia	- *E. coli*-ASP & Erwinia: 25,000 IU/m2	IM
EORTC CLG 58831, 58832, 58881	Vilmer 2000[63]	58831/58832/58881 induction consolidation reinduction maintenance	Protocol 58831/58832 - Induction: *E. coli*-ASP (all) - Consolidation: *E. coli*-ASP (all) - Reinduction: *E. coli*-ASP (all) - Maintenance: no ASP (all) Protocol 58881: - As above but *E. coli*-ASP vs Erwinia	- 58831/58832: *E. coli*-ASP - 58881: *E. coli*-ASP vs Erwinia	- 5883/5883: 5,000 IU/m2/d - 58881: 10,000 IU/m2/d	IV
EORTC-CLG 58881	Duval 2002[56]	- Induction (wk 1-5) - Consolidation (wk 5-9) - Reinduction (wk 1-7)	- Induction: *E. coli*-ASP vs. Erwinia (R) - Consolidation: no ASP (all) - Reinduction: *E. coli*-ASP vs. Erwinia	- Erwinia - *E. coli*-ASP	10,000 IU twice weekly	IV

Study	Citation	Treatment phases	ASP exposure	Type of ASP	ASP dose	Route of administration
		- Maintenance (until Month 24)	- Maintenance: not specified			

Abbreviations: ASP, asparaginase; Carba, Calaspargase pegol Escherichia coli asparaginase; DI, delayed intensification; *E. coli*-ASP, native Escherichia Coli-derived asparaginase; HR, high risk; IM, intramuscular; IR, intermediate risk; IV, intravenous; MRD, minimal residual disease; PEG-ASP, pegaspargase; R, randomised; SR, standard risk; SR Av, standard risk average.

STUDY CCG-1961

Table 4.5: Summary of efficacy for trial CCG-1961

Title: Treatment of Patients With Acute Lymphoblastic Leukemia With Unfavourable Features: A Phase III Group-wide Study						
Study identifier	CCG-1961, NCT00002812					
Design	Interventional, open label, multicentric, partially randomized, Phase III clinical trial investigating combination chemotherapy in treating children with ALL with unfavourable features					
Duration of main phase:	2 years for girls, 3 years for boys					
Duration of Run-in phase:	not applicable					
Duration of Extension phase:	at least 5-year follow-up					
Hypothesis	Superiority of Increased (containing Oncaspar) and/or Prolonged Duration Intensification Chemotherapy over Standard Intensification Chemotherapy in Rapid Early Responder (RER) high risk ALL patients Exploratory: to investigate the addition of doxorubicin vs idarubicin and cyclophosphamide to Intensification chemotherapy in Slow Early Responder (SER) patients Exploratory: to assess the impact of day 7 bone marrow status on outcome					
Seibel et. Al (2008)[31]	Survival analysis in rapid early responder (RER) children and adolescents with high risk ALL					
Treatments groups	All RER patients	RER patients treated across all arms				
SPII patients	RER patients treated with standard intensity chemotherapy (no Oncaspar)					
IPII patients	RER patients treated with increased intensity chemotherapy (Oncaspar)					
SDPII patients	RERs patients treated with standard duration chemotherapy (326 treated with Oncaspar)					
IDPII patients	RERs patients treated with increased duration chemotherapy (324 treated with Oncaspar)					
Endpoints and definitions	Primary endpoint	EFS	EFS was calculated from time of randomization. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first			
	Co-Primary endpoint	OS	OS was calculated from time of randomization. Event considered is death for all causes			
Date of Publication	March 01, 2008					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to treat population at the time of submission for publication (February 2007)					
Descriptive statistics and estimate variability	Treatment group	All RERs	SPII	IPII	SDPII	IDPII
	Number of patients	1299	649	650	651	648
	5-yr EFS (%)	75.5%	71.7%	81.2%	76.0%	76.8%
	± SD (%)	1.8%	2.7%	2.4%	2.6%	2.6%
	5-yr OS (%)	84.7%	83.4%	88.7%	na	na
	± SD (%)	1.5%	2.2%	1.9%	na	na
Effect estimate per	Primary endpoint:	Comparison groups			SPII vs IPII	

comparison	5-yr EFS	Relative Hazard Rate (RHR) for event	**1.61**				
		P-value	P<0.001				
		Comparison groups	SDPII vs IDPII				
		Relative Hazard Rate (RHR) for event	1				
		P-value	P<0.94				
	Primary endpoint: 5-yr OS	Comparison groups	SPII vs IPII				
		Relative Hazard Rate (RHR) for event	**1.56**				
		P-value	P<0.005				
Notes	na: not available						
Analysis description	**Analysis in other relevant publications**						
Nachman et al (2009)[32]	Survival analysis in rapid early responder (RER) and slow early responder (SER) young adults (YA: 16 to 21 years) with high risk ALL						
Treatments groups	All YA patients	Young adult patients treated across all arms					
	YA SPII patients	Young adult RER patients treated with standard intensity chemotherapy (no Oncaspar)					
	YA IPII patients	Young adult RER patients treated with increased intensity chemotherapy (Oncaspar)					
	YA SDPII patients	Young adult RERs patients treated with standard duration chemotherapy (including patients treated with Oncaspar)					
	YA IDPII patients	Young adult RERs patients treated with increased duration chemotherapy (including patients treated with Oncaspar)					
	All YA SER patients	All young adult SER patients					
Endpoints and definitions	Primary endpoint	EFS was calculated from time of randomization. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first					
	Primary endpoint	OS was calculated from time of randomization. Event considered is death for all causes					
Date of Publication	November 01, 2009						
Results and Analysis							
Analysis population and time point description	Intent to treat population in the YA subset of patients at the time of data cut-off (May 2006)						
Descriptive statistics and estimate variability	Treatment group	All YA	YA SPII	YA IPII	YA SDPII	YA IDPII	YA SER
	Number of patients	262	77	88	na	na	53
	5-yr EFS (%)	71.5%	66.9%	81.8%	71.7%	77.1%	70.7%
	± SD (%)	3.6%	6.7%	5.4%	na	na	7.3%
	5-yr OS (%)	77.5%	75.6%	83.2%	na	na	na
	± SD (%)	3.3%	7.7%	6.8%	na	na	na
Effect estimate per comparison	Primary endpoint: 5-yr EFS	Comparison groups	YA SPII vs YA IPII				
		P-value	P=0.07				
		Comparison groups	YA SDPII vs YA IDPII				
		P-value	P=0.48				
	Primary endpoint: 5-yr OS	Comparison groups	YA SPII vs YA IPII				
		P-value	P=0.14				

Notes	na: not available					
Panosyan et al (2004)[33]	Anti-asparaginase antibody status and clinical outcome					
Treatments groups	Group A	Patients with no sign of clinical allergies after exposure to native *E. coli* L-Asparaginase and with a persistent antibody-negative status				
	Group B	Patients who developed mild allergy symptoms but were persistently antibody-negative				
	Group C	Patients who developed clinically significant allergic symptoms and were antibody-positive				
	Group D	Patients with no clinical signs of hypersensitivity but with anti-asparaginase antibodies (silent inactivation)				
Endpoints and definitions	Primary endpoint	Events/patients rates during a 30-month follow-up. Considered events were: relapse at any site, death during remission, or a second malignant neoplasm, whichever occurred first				
Date of Publication	April 01, 2004					
Results and Analysis						
Analysis population and time point description	Intent to treat population in the YA subset of patients at the time of data cut-off (May 2006)					
Descriptive statistics and estimate variability	Treatment group	Group A	Group B	Group C	Group D	
	Number of patients (%)	57 (20%)	27 (10%)	115 (41%)	81 (29%)	
	30-month Events/Patients rate	3/57	2/27	3/115	13/81	
Effect estimate per comparison	Primary endpoint: 30-month Events/Patients rate	Comparison groups	Group A vs all Groups			
		Hazard Ratio Observed	1			
		Hazard Ratio Expected	0.66			
		P-value	NS			
		Comparison groups	Group B vs all Groups			
		Hazard Ratio Observed	1.3			
		Hazard Ratio Expected	0.86			
		P-value	NS			
		Comparison groups	Group C vs all Groups			
		Hazard Ratio Observed	0.6			
		Hazard Ratio Expected	0.38			
		P-value	NS			
		Comparison groups	Group D vs all Groups			
		Hazard Ratio Observed	3.2			
		Hazard Ratio Expected	2.11			
		P-value	P=0.01			
Notes	Patients in Group B and C were treated with Erwinia asparaginase after clinical allergy symptoms appeared in order to continue chemotherapy according to the protocol.					

In the CCG-1961 study, a longer versus more intensive post-induction Intensification (PII) was tested, using a 2 x 2 factorial design for children with higher risk ALL and a rapid marrow response to induction therapy. Between November 1996 and May 2002, 2,078 children and adolescents with newly diagnosed ALL (1 to 9 years old with white blood count

50 000/mm3 or more, or 10 years of age or older with any white blood count) were enrolled. After induction, 1,299 patients with marrow blasts less than or equal to 25% on day seven of induction (rapid early responders) were randomised to standard or longer duration (n = 651 + 648) and standard or increased intensity (n = 649 + 650) PII. Stronger intensity PII improved event-free survival (81% vs 72%, $P < 0.001$) and survival (89% vs 83%, $P = 0.003$) at five years. Differences were most apparent after two years from diagnosis. Longer duration PII provided no benefit. Stronger intensity but not prolonged duration PII improved outcome for patients with higher-risk ALL.[31]

Study CCG 1961 included patients with ALL aged between 1 and 21 years of age with initial WBC count ≥ 50,000/μL and/or age ≥ 10 years. Randomly assigned therapies evaluated the impact of post-induction treatment intensification on outcome. In a separate analysis, outcome and prognostic factors for 262 young adults (16 to 21 years of age) with ALL were examined.[32] Five year event-free and overall survival rates for young adult patients are 71.5% (SE, 3.6%) and 77.5% (SE, 3.3%), respectively. Rapid responder patients (< 25% bone marrow blasts on day 7) randomly assigned to augmented therapy had five year event-free survival of 81.8% (SE, 7%), as compared with 66.8% (SE, 6.7%) for patients receiving standard therapy ($P = 0.07$). One versus two interim maintenance and delayed intensification courses had no significant impact on event-free survival. WBC count more than 50,000/μL was an adverse prognostic factor.[32]

Adverse events

Major toxicities observed in RER patients included osteonecrosis (avascular necrosis) and infections. Osteonecrosis developed in 103 RER patients (59 IPII (PEG); 44 SPII (*E. coli*), $P = 0.13$). The prevalence of infections (including bacteraemia resulting from sepsis or central venous catheter infection) was not statistically different between the combined standard versus increased intensity regimens, regardless of phase of therapy.[31]

Some differences were noted in the use of supportive care interventions. During consolidation, antifungal agents were administered to 9.5% of patients on the increased intensity regimens compared with 3.9% of those on the standard regimens ($P = .001$). During the first interim maintenance period (IM 1), a greater percentage of patients on the increased intensity regimens versus the standard regimens received antifungal agents (4.9% versus 0.8%, $P < 0.001$), total parenteral nutrition (7.3% vs 2.1%, $P < 0.001$), antibacterials (28.8% vs 13.4%, $P < 0.001$) and blood products (20.1% vs 10.1%, $P < 0.001$). Number of days hospitalised was not different between increased intensity versus standard regimens except during consolidation (33.2% versus 23.1% for > 8 days, $P = 0.001$) and IM 1 (26.3% vs 11.5% for 1-7 days and 11.4% vs 3.9% for > 8 days, $P < 0.001$ for both). The only difference between IPII and SPII during delayed intensification (DI 1) was in blood product use 65.2% versus 59.2% ($P = 0.03$). Among patients treated on IPII arms, 54% experienced an allergic reaction to PEG-asparaginase.[31]

In the randomised RER patients, there were 24 deaths (12 SPII, 12 IPII) as a first event. A total of 140 deaths occurred after a relapse or other initial EFS event (e.g. second malignant neoplasms). There were four second malignant neoplasms on the SPII (nasopharyngeal

carcinoma, CML, B-cell lymphoma, acute myelogenous leukemia) and two on IPII (B-cell lymphoma, myelodysplastic syndrome).[31]

STUDY CCG-1962

Table 4.6: Summary of efficacy for trial CCG-1962

Title: A Randomized Comparison of PEG-L-Asparaginase and Native E. coli Asparaginase in the Standard Treatment Arm of CCG-1952 for Standard-Risk Acute Lymphoblastic Leukemia, A Phase II Limited Institution Pilot Study			
Study identifier	CCG-1962		
Design	Randomised, open-label, comparative study conducted as a sub-study of theCCG-1952 trial in order to investigate whether PEG-ASNase would induce lower antibody formation than native *E. coli* ASNase in patients naïve to any asparaginase.		
	Duration of main phase, Duration of Run-in phase, Duration of Extension phase:	18 months, not applicable, at least 3-year follow-up	
Hypothesis	the incidence of high-titre anti-asparaginase antibodies in children treated with Oncaspar should be decreased by at least 50% compared with children treated with native *E. coli* L-asparaginase in DI 1the incidence of high-titre anti-asparaginase antibodies in children treated with Oncaspar should be decreased by at least 50% compared with children treated with native *E. coli* L-asparaginase in DI 2 phase the duration that serum asparaginase levels remained > 0.03 IU/mL and serum asparagine concentration remained <1μM in children treated with Oncaspar or native *E. coli* L-asparaginase in Induction and in DI 1 and DI 2 phases.		
Treatments groups	Regimen N1	Patients treated with Oncaspar (2.500 IU/m2IM) on Day 3 of Induction and Day 3 of each DI.	
	Regimen N2	Patients treated with Native *E. coli* asparaginase (6.000 IU/m2 IM) 3 times weekly for 9 doses during Induction and for 6 doses during each DI phase.	
Endpoints and definitions	Primary endpoint	EFS	Events included: induction death, no induction response, relapse at any site, and second malignant neoplasm.
	Co-Primary endpoint	Anti-asparaginase antibody ratio	High-titre antibody was defined as a level of antibody 2.5 times the average control level. The average antibody level for normal patients and for patients before any asparaginase therapy is 2 U/mL, consequently, high-titre antibody was defined as a level of 5 U/mL or greater and was used as the primary outcome index in the trial
Database lock	December 2001		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		

Descriptive statistics, estimate variability and effect estimate per comparison	Treatment group	Regimen N1 (Oncaspar)	Regimen N2 (Native *E. coli* asparaginase)	P-value
	Number of patients	59	59	
	7-yr EFS (%)	75	66	P=NS
	95% CI (%)	63-87	52-80	
	Anti-asparaginase antibody ratio in Induction	1.3	2.3	P=NS
	± SEM	0.2	0.9	
	Anti-asparaginase antibody ratio in DI 1	1.9	3.0	P=0.001
	± SEM	0.8	0.7	
	Anti-asparaginase antibody ratio in DI 2	2.1	2.1	P=NS
	± SEM	0.8	0.6	

For this study, 118 children with standard risk ALL were given randomised assignments to receive native or pegylated Escherichia coli asparaginase as part of induction and two delayed intensification phases. Patients treated with pegaspargase had more rapid clearance of lymphoblasts from day 7 and day 14 bone marrow aspirates and more prolonged asparaginase activity than those treated with native asparaginase.

In the first delayed intensification phase (DI-1), 26% of native asparaginase patients had high-titre antibodies, whereas 2% of pegaspargase patients had those levels. High-titre antibodies were associated with low asparaginase activity in the native arm, but not in the pegaspargase arm. Adverse events, infections, and hospitalization were similar between arms. Event-free survival at three years was 82%. A population pharmaco-dynamic model using the nonlinear mixed effects model (NONMEM) program was developed that closely fit the measured enzyme activity and asparagine concentrations. Half-lives of asparaginase were 5.5 days and 26 hours for pegaspargase and native asparaginase, respectively. There was correlation between asparaginase enzymatic activity and depletion of asparagine or glutamine in serum. In cerebrospinal fluid asparagine, depletion was similar with both enzyme preparations.[28]

Adverse events

Grade 3 and grade 4 toxic events during the asparaginase-containing phases of chemotherapy are summarised in Table 4.7. Two patients in each arm experienced CNS thrombosis. Other CNS complications included seizures (three patients), tremors after cytarabine therapy (one patient), hemiparesis (two patients), mood disorder requiring psychiatric intervention (one patient), motor weakness after intrathecal methotrexate (one patient), and moderate sensory nerve dysfunction (one patient). Pancreatitis occurred in one patient in each treatment arm during induction therapy. Three patients in each arm experienced hyperglycaemia. In the pegaspargase arm, there were two acute allergic reactions to asparaginase during DI-1. One patient had a grade 1 allergic reaction and another grade 3 hives.[3, 28]

Table 4.7: Patients experiencing grade 3/4 toxicity during asparaginase-containing treatment courses in trial DFCI-91-01

Adverse event, number of patients	Pegaspargase			Native *E. coli* asparaginase		
	IND	DI-1	DI-2	IND	DI-1	DI-2
Assessable patients	59	54	48	59	53	53
CNS thrombosis	1	1	-	2	-	-
Other CNS complications†	-	3	3	-	2	2
Life-threatening infections‡	-	1	1	-	-	1
Bacteraemia	1	6	10	6	2	9
Hyperglycaemia	3	-	-	1	1	1
Coagulopathy§	1	-	-	3	-	-
Nausea/vomiting	-	-	-	2	1	-
Abdominal pain	-	-	3	-	-	1
Abnormal LFT¶	-	-	-	-	2	2
Pancreatitis	1	-	2	1	-	-
Mucositis	-	-	1	-	-	-
Gastric ulcer	-	-	1	-	-	-
Haemorrhagic cystitis	-	-	-	-	1	-
Constipation	-	-	1	-	-	-
Diarrhoea	-	-	1	-	-	-
Allergy to asparaginase	-	1	-	-	-	-

Abbreviations: IND, induction; DI, delayed intensification; CNS, central nervous system; LFT, liver function tests.
† Including seizures, tremors, facial palsy, hemiparesis, peripheral neuropathy, and motor weakness.
‡ Septic shock including hypotension and/or requiring intubation.
§ Prolonged partial thromboplastin time or hypofibrinogenemia.
¶ Aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase greater than 1.5 times the normal value, or total bilirubin greater than 1.5 times the normal value.

Infectious events were the most common toxic events (Table 4.8). Bacteraemia was most frequent, with 17 episodes in each arm during induction and the DI courses. Life-threatening infections (defined as septic shock with hypotension or requiring intubation) occurred in two instances in the pegaspargase arm, and one in the native arm. No case of invasive fungal disease was reported.[3, 28]

Table 4.8: Infectious events during all three asparaginase-containing courses in trial DFCI-91-01

Events, number of patients (%)	Pegaspargase N=59	Native *E. coli* asparaginase N=59
Bacteraemia	17 (29)	17 (29)
Life-threatening sepsis	2 (3)	1 (2)
Pneumonia	2 (3)	2 (3)
Varicella zoster virus	5 (8)	1 (2)
Urinary tract infection	0 (0)	3 (5)
Cellulitis/skin infection	2 (3)	1 (2)
Clostridium difficile	3 (5)	2 (3)
Pneumocystis	0 (0)	1 (2)
Fungal stomatitis	0 (0)	1 (2)
Herpes simplex	0 (0)	1 (2)

STUDY DFCI ALL 91-01

Table 4.9: Summary of efficacy for trial DFCI-91-01

Title: multicenter, randomized study with an intensified post-remission therapy substituting dexamethasone for prednisone and prolonging the ASNase intensification from 20 to 30 weeks in newly diagnosed ALL patients				
Study identifier	DFCI-91-01			
Design	Non-proprietary open label, randomized, multicentric, Phase III clinical trial investigating efficacy and safety of multiple variations of combination chemotherapy in treating children with newly diagnosed ALL.			
	Duration of main phase:	until 2 years from achievement of CR		
	Duration of Run-in phase:	not available		
	Duration of Extension phase:	median follow-up 5 years		
Hypothesis	To determine whether Oncaspar was associated with decrease toxicity compared to native *E. coli* L-asparaginase Impact of asparaginase tolerance on long-term outcome			
Treatments groups	native *E. coli* group	Patients receiving 25.000 IU/m^2 native *E. coli* L-asparaginase (30 doses) throughout treatment phases.		
	Oncaspar group	Patients receiving 2.500 IU/m^2 Oncaspar (15 doses) throughout treatment phases.		
	Low asparaginase tolerance	Patients able to receive asparaginases (independently of the specific formulation) for less than 26 weeks		
	Good asparaginase tolerance	Patients able to receive asparaginases (independently of the specific formulation) for at least 26 weeks		
Endpoints and definitions	Primary endpoint: 5-y EFS	EFS was defined as the time from complete remission to the first outcome event; induction failure and induction deaths were considered events at time zero.		
Date of Publication	March, 2001			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population as to December 1995			
Descriptive statistics and estimate per comparison	Treatment group	native *E. coli*	Oncaspar	P-value
	number of patients	92	106	P=0.29
	5-y EFS (%)	84%	78%	
	± SE (%)	4%	4%	
	Treatment group	Low asparaginase tolerance	Good asparaginase tolerance	P-value
	number of	43	309	

	patients			P<0.01
	5-y EFS (%)	73%	90%	
	± SE (%)	7%	2%	

The DFCI ALL 91-01 study was aimed to improve the outcome of children with newly diagnosed ALL while minimising toxicity. Between 1991 and 1995, 377 patients (age 0-18 years) were enrolled; 137 patients were considered standard risk (SR), and 240 patients were high risk (HR). There was no significant difference in five year EFS based upon risk group (87% ± 3% for SR and 81% 6 3% for HR, P = 0.24). Age at diagnosis was a statistically significant prognostic factor (P = 0.03), with inferior outcomes observed in infants and children nine years or older. Patients who tolerated 25 or fewer weeks of asparaginase had a significantly worse outcome than those who received at least 26 weeks of asparaginase (P < .01, both univariate and multivariate). Older children (at least nine years of age) were significantly more likely to have tolerated 25 or fewer weeks of asparaginase (P < .01). Treatment on Protocol 91-01 significantly improved the outcome of children with ALL, perhaps due to the prolonged asparaginase intensification and/or the use of dexamethasone. The inferior outcome of older children may be due, in part, to increased intolerance of intensive therapy.[34]

Adverse events

Of the patients randomised to PEG-asparaginase, 25% experienced a toxic reaction compared with 36% of *E. coli* randomised patients (*P* = 0.09). PEG-asparaginase was associated with a lower incidence of mild allergic reactions (*P* = 0.02). There was no difference between the two preparations in the rates of dose-limiting toxicities such as severe allergic reaction (*P* = 0.22), severe pancreatitis (*P* = 0.78), or CNS thrombosis (*P* = 1.00).[34]

Of the 352 patients, 43 (12%) patients received less than 25 weeks of asparaginase. The remaining 308 (88%) patients received at least 26 weeks of asparaginase. Of the 43 patients who received less than 25 weeks of asparaginase, 37 (86%) patients experienced an asparaginase-related dose-limiting toxicity including pancreatitis (39% of 43 patients), allergy to one or more preparations (19%), CNS thrombosis/hemorrhage (12%), non-CNS deep venous thrombosis (7%), hyperglycemia (5%), hyperlipidemia (2%), and hepatitis (2%). Asparaginase intolerance was associated with older age at diagnosis, but not with initial type of asparaginase (PEG-asparaginase or native *E. coli*).[34]

STUDY DFCI ALL 05-001

Table 4.10: Summary of efficacy for trial DFCI ALL 05-001

Title: prospective**,** multicenter, randomized study in children (1-18 years) with newly diagnosed ALL following complete remission at induction with one dose PEG-asparaginase, randomised at post-induction to PEG-asparaginase and native E coli asparaginase.	
Study identifier	DFCI ALL 05-001; NCT00400946
Design	prospective**,** open label, randomized, multicentric, Phase III clinical trial investigating efficacy and safety of PEG-asparaginase versus native *E. coli*

	asparaginase in children (1-18 years) with newly diagnosed ALL who achieved complete remission following induction with one dose PEG-asparaginase.			
	Duration induction therapy:		32 days	
	Duration:		median follow-up 6 years	
Hypothesis	to compare the relative toxicity and efficacy of intravenous PEG-asparaginase and intramuscular native *E. coli* asparaginase in children with newly diagnosed ALL			
Treatments groups	native *E. coli* group		Patients receiving 25.000 IU/m^2 native *E. coli* L-asparaginase (30 doses) IM, one per week	
	Oncaspar group		Patients receiving 2.500 IU/m^2 Oncaspar (15 doses) IV, one every 2 weeks	
Endpoints and definitions	Primary endpoint	Safety	the overall frequency of asparaginase-related toxicities (defined as allergy, pancreatitis, and thrombotic or bleeding complications).	
Date of Publication	November, 2015			
Results and Analysis				
Analysis population	Intent to treat population			
Descriptive statistics and estimate per comparison	Treatment group		native *E. coli*	Oncaspar
	number of patients		231	232
	5-year EFS (%)		89%	90%
	95% CI (%)		85–93%	86%–94%
	5-year OS (%)		94%	96%
	95% CI (%)		89%–96%	93%–98%

The aim study DFCI 05-001 was to compare the relative toxicity and efficacy of intravenous PEG-asparaginase and intramuscular native *E. coli* l-asparaginase in children with newly diagnosed acute lymphoblastic leukaemia.

Patients aged 1–18 years with newly diagnosed ALL were enrolled from 11 consortium sites in the USA and Canada. Patients were assigned to an initial risk group on the basis of their baseline characteristics and then underwent 32 days of induction therapy. Those who achieved complete remission after induction therapy were assigned to a final risk group and were eligible to participate in a randomised comparison of intravenous PEG-asparaginase (15 doses of 2500 IU/m² every two weeks) or intramuscular native *E. coli* asparaginase (30 doses of 25 000 IU/m² weekly), beginning at week seven after study entry.[29]

Between 2005 and 2010, 551 eligible patients were enrolled. 526 patients achieved complete remission after induction, of whom 463 were randomly assigned to receive intramuscular native *E. coli* asparaginase (n=231) or intravenous PEG-asparaginase (n=232). Median follow-up was 6.0 years (IQR 5.0–7.1). Five year disease-free survival was 90% (95% CI 86–94) for patients assigned to intravenous PEG-asparaginase and 89% (85–93) for those assigned to intramuscular native *E. coli* l-asparaginase (p=0·58). The median nadir serum asparaginase activity was significantly higher in patients who received intravenous PEG-asparaginase than in those who received intramuscular native *E. coli* asparaginase. Significantly more anxiety was reported by both patients and parent-proxy in the

intramuscular native *E. coli* asparaginase group than in the intravenous PEG-asparaginase group. Scores for other domains were similar between the groups.[29]

Adverse events

The two treatment groups did not differ significantly in the overall frequency of asparaginase-related toxicities (65 [28%] of 232 patients in the intravenous PEG-asparaginase group *vs* 59 [26%] of 231 patients in the intramuscular native *E. coli* l-asparaginase group, p=0.60), or in the individual frequency of allergy (p=0.36), pancreatitis (p=0.55), or thrombotic or bleeding complications (p=0.26).

The most common grade 3 or worse adverse events were bacterial or fungal infections (47 [20%] of 232 in the intravenous PEG-asparaginase group *vs* 51 [22%] of 231 patients in the intramuscular *E. coli* asparaginase group) and asparaginase-related allergic reactions (14 [6%] *vs* 6 [3%]).[29]

In conclusion, intravenous PEG-asparaginase was not more toxic than, was similarly efficacious to, and was associated with decreased anxiety compared with intramuscular native *E. coli* asparaginase, in children with newly diagnosed ALL.[29]

STUDY DFCI ALL 05-01

Table 4.11: Summary of efficacy for trial DFCI ALL 05-01

Title: randomized study in children (1-18 years) with newly diagnosed ALL following complete remission at induction with PEG-asparaginase, randomised at post-induction to PEG-asparaginase and native E coli asparaginase.				
Study identifier	DFCI ALL 05-01; NCT00400946			
Design	Open label, randomized, clinical trial investigating efficacy and safety of PEG-asparaginase versus native *E. coli* asparaginase in children (1-18 years) with newly diagnosed ALL who achieved complete remission following induction with PEG-asparaginase.			
	Duration induction therapy:	NR		
	Duration:	median follow-up 2.8 years		
Hypothesis	To compare two-week IV PEG-asparaginase with weekly IM native *E. coli* asparaginase in terms of toxicity and ASP levels			
Treatments groups	native *E. coli* group	Patients receiving 25.000 IU/m^2 native *E. coli* L-asparaginase (30 doses) IM, one per week		
	Oncaspar group	Patients receiving 2.500 IU/m^2 Oncaspar (15 doses) IV, one every 2 weeks		
Endpoints and definitions	Primary endpoint	Median NSAA	Median nadir serum ASP activity (No further details)	
Date of Publication	December, 2011			
Results and Analysis				
Analysis population	NR			
Descriptive statistics and estimate per	Treatment group		native *E. coli*	Oncaspar
	number of patients		231	232

comparison	EFS (%)	NR	NR
	95% CI (%)		
	OS (%)	NR	NR
	95% CI (%)		

In study DFCI ALL 05-01, all patients with newly diagnosed ALL aged 1-18 years who achieved complete remission were eligible to participate in a randomised comparison of intramuscular (IM) *E. coli* asparaginase and intravenous (IV) PEG-asparaginase during the 30-week multi-agent post-induction Consolidation phase. Beginning at week seven of therapy, patients received either IM *E. coli* asparaginase 25000 IU/m2 weekly x 30 wks or IV PEG-asparaginase 2500 IU/m2 every two weeks x 30 weeks. Between 2005 and 2010, 463 patients were enrolled in the randomised comparison. Median age was five years (range 1.2-17.9 years). There was no significant difference in presenting characteristics between the two arms, except that more patients on the *E. coli* asparaginase arm presented with a mediastinal mass (9% vs 3%, p=0.04). Median follow-up was 2.8 years. Median nadir serum asparaginase activity (NSAA) at each assayed time-point during the Consolidation phase was significantly higher with IV PEG-asparaginase than with IM *E. coli* asparaginase.[30] An NSAA of = 0.1 IU/mL was achieved in 95% of IV PEG-asparaginase patients compared with < 50% of IM *E. coli* asparaginase patients (p<0.01 at each time-point). Event-free survival and overall survival were not reported.

Adverse events

There was no significant difference in asparaginase-related toxicities (allergy, pancreatitis, thrombosis) between the two types of asparaginase. Older patients (= 10 yrs old) had a significantly higher overall rate (p<0.01) of pancreatitis (18% vs 7%) and thrombosis (18% vs 4%), but not of allergy (p=0.49) or infection (p=0.21), compared to younger patients. There was no significant difference in the rates of ASP-related toxicities when comparing IM *E. coli* asparaginase vs IV PEG-asparaginase separately within the two age groups (=10 yrs and < 10 yrs).[30]

STUDY DFCI ALL 95-01

Table 4.12: Summary of efficacy for trial DFCI ALL 95-01

Title: prospective, multicentre, randomized study in children (0-18 years) with newly diagnosed ALL randomised to native E coli asparaginase and Erwinia asparaginase.		
Study identifier	DFCI ALL 95-01	
Design	open label, prospective, multicentre, randomized, clinical trial investigating efficacy and safety of native *E. coli* asparaginase versus Erwinia asparaginase in children (0-18 years) with newly diagnosed ALL (excluding mature B-cell ALL).	
	Duration:	median follow-up 8.6 years
Hypothesis	to evaluate whether acute and late toxicities could be reduced by comparing two asparaginase preparations (*Erwinia* and *Escherichia coli* asparaginase) administered during induction and consolidation	
Treatments groups	native *E. coli* group	Patients receiving 25.000 IU/m^2/week native *E. coli*

		asparaginase IM, for 20 weeks during the intensification phase		
	Erwinia group	Patients receiving 25.000 IU/m^2/week Erwinia asparaginase IM, for 20 weeks during the intensification phase		
Endpoints and definitions	Primary endpoint	Not specified		
Date of Publication	February, 2010			
Results and Analysis				
Analysis population	NR			
Descriptive statistics and estimate per comparison	Treatment group	native *E. coli*	Erwinia	P-value
	number of patients (N=286)	147	139	
	5-year EFS (%)	88.1%	78.1%	NR
	± SE (%)	2.7%	3.5%	
	10-year EFS (%)	84.6%	75.2%	P=0.020
	± SE (%)	3.4%	3.8%	
	5-year OS (%)	93.8%	85.3%	NR
	± SE (%)	2.0%	3.1%	
	10-year OS (%)	93.1%	85.3%	P=0.038
	± SE (%)	2.1%	3.1%	

Between 1996 and 2000, 491 children aged 0–18 years with newly diagnosed ALL (excluding mature B-cell ALL) were enrolled in study DFCI ALL 95-01. Patients were enrolled from five DFCI ALL Consortium institutions in the USA, three in Canada and one in Puerto Rico. Attempts to reduce toxicity included: the addition of a cardioprotectant, dexrazoxane in high risk patients to minimise anthracycline-associated cardiotoxicity,[55] testing alternative preparations of asparaginase,[55] and substituting intrathecal chemotherapy for cranial radiation in lower risk patients.[55]

Two hundred and eighty-six patients (SR and HR/VHR) were randomised to receive either *E. coli* or Erwinia asparaginase 25000 IU/m2/week for 20 weeks during the Intensification phase. Patients randomised to receive Erwinia asparaginase had a significantly inferior 10-year EFS (75.2 ± 3.8% versus 84.6 ± 3.4%, p=0.02) and OS (85.3 ± 3.1% versus 93.1 ± 2.1%, p=0.04). More patients randomised to Erwinia experienced a relapse involving the CNS (7% versus 1%, p<0.01).[24]

Adverse events

Compared with *E. coli* asparaginase, Erwinia asparaginase was associated with a lower incidence of toxicity (10% versus 24%) (Table 4.13). Asparaginase-related toxicities were observed in 21% of the 491 patients. The most frequent toxicities included allergic reactions (13%), pancreatitis (5%) and non–CNS-related thromboses (3%). No patient experienced a symptomatic CNS thrombosis or bleed. Patients aged 10 to 18 years were more likely to experience an asparaginase-related toxicity compared with those younger than 10 years (29% versus 19%, *P* = .03), including a higher incidence of pancreatitis (11% versus 4%) and thromboses (11% versus 2%) but not allergic events (8% versus 14%).[55]

Table 4.13: Adverse events in trial DFCI ALL 95-01

	E. coli	Erwinia	P-value
Total n	147	139	
Any toxicity, %	24	10	< 0.01
Allergy, %	14	6	0.03
Pancreatitis, %	6	2	0.14
Thrombosis, %	5	1	0.17

STUDY EORTC-CLG 58881

Table 4.14: Summary of efficacy for trial EORTC CLG 58881

Title: prospective, multicentre, randomized study in children (under 18 years) with ALL randomised to native E coli asparaginase and Erwinia asparaginase.					
Study identifier	EORTC CLG 58881				
Design	Prospective, multicentre, randomised, Phase III clinical trial investigating efficacy and safety of native *E. coli* asparaginase versus Erwinia asparaginase in children (under 18 years) with ALL or lymphoblastic lymphoma.				
	Duration:	median follow-up 6.9 years (range: 4.8 to 9.0 years)			
Hypothesis	To assess the toxicity and efficacy of *E. coli*-ASP and Erwinia when given at equal dosage				
Treatments groups	native *E. coli* group	Patients receiving 10.000 IU/m^2 twice weekly native *E. coli* asparaginase IV (12 doses), during the induction (week 1 to 5) and re-induction (week 1 to 7) phase			
	Erwinia group	Patients receiving 10.000 IU/m^2 twice weekly Erwinia asparaginase IV (12 doses), during the induction (week 1 to 5) and re-induction (week 1 to 7) phase			
Endpoints and definitions	Primary endpoint	EFS	Calculated from the date of Complete Remission (CR) to the date of first relapse or death. For patients who failed to reach CR by the end of protocol I, the failure was considered as an event at time 0.		
Date of Publication	April 2002				
Results and Analysis					
Analysis population	Intent to treat population				
Descriptive statistics and estimate per comparison	Treatment group		native *E. coli*	Erwinia	Hazard Ratio, P-value
	number of patients		354	346	
	6-year EFS (%)		73.4%	59.8%	HR=1.59 (95% CI: 1.23, 2.06), P=0.0004
	± SE (%)		2.4%	2.6%	
	6-year OS (%)		83.9%	75.1%	P=0.002
	± SE (%)		2.0%	2.3%	

The European Organisation for Research and Treatment of Cancer–Children's Leukemia Group (EORTC-CLG) 58881 trial randomised 700 children with acute lymphoblastic leukemia or lymphoblasticlymphoma to either E .coli– or Erwinia-asparaginase at the same dosage of 10 000 IU/m2 twice weekly to compare toxicity and efficacy.

In the Erwinia-asparaginase arm, more patients failed to achieve complete remission (4.9% versus 2.0%; P = 0.038) and the relapse rate was higher, leading to shorter event-free survival (hazard ratio,1.59; 95% CI, 1.23-2.06; P = 0.0004). The estimate of event-free survival rate (SE) at six years was 59.8% (2.6%) versus 73.4% (2.4%). Overall survival rate at six years was also lower in the Erwinia-asparaginase arm at 75.1% (2.3%) versus 83.9% (2.0%), P = 0.002.[56]

Adverse events

Coagulation abnormalities were more frequent in the *E. coli*–asparaginase than in the Erwinia-asparaginase arm of the study (30.2% versus 11.9%, P < 0.0001). The incidence of other toxicity was not significantly different (Table 4.15).

With the dose scheduling used in this protocol, *E. coli*–asparaginase induced more coagulation abnormalities but was superior to Erwinia-asparaginase for the treatment of childhood lymphoid malignancies.[56]

Table 4.15: Summary of adverse events during induction for trial EORTC CLG 58881

	***E. coli*–asparaginase no. (%) of patients; N = 354**	**Erwinia-asparaginase no. (%) of patients; N = 346**
Allergy (WHO 3-4)	9 (2.5)	9 (2.6)
Coagulation abnormalities	107 (30.2)	41 (11.8)
Neurotoxicity (WHO 3-4)	9 (2.5)	5 (1.4)
Convulsions	6 (1.7)	1 (0.3)
Pancreatitis	1 (0.3)	3 (0.9)
Diabetes requiring insulin	5 (1.4)	2 (0.6)
Liver toxicity (WHO 3-4)	16 (4.5)	13 (3.8)
Infection (WHO 3-4)	18 (5.1)	16 (4.6)
Death	1 (0.3)	2 (0.6)

Summary of results from RCTs

Four studies provided survival data for the comparison of PEG-asparaginase versus native *E. coli* asparaginase (see Table 4.16). Two studies showed results in favour of PEG-asparaginase (5-y EFS: 81.2% for pegaspargase vs. 71.7% for *E. coli*, Relative Hazard Rate (RHR) for event=1.61, p<0.001 in CCG-1961; and 7-y EFS: 75% for pegaspargase vs. 66% for *E. coli*, p=NS in CCG-1962),[28, 31-33] one study showed non-significant results in favour of *E. coli* asparaginase (five year EFS: 78% for pegaspargase vs. 84% for *E. coli*, p=0.29 in DFCI ALL 91-01),[34] and one study showed hardly any differences in OS and EFS between the two interventions (five year EFS: 90% for pegaspargase vs. 89% for *E. coli*, p=NS in DFCI ALL 05-001).[29, 42]

Because a favourable result for *E. coli* asparaginase in terms of OS and EFS cannot be ruled out we have included such a scenario in the economic model.

Two studies provided survival data for the comparison of native *E. coli* asparaginase versus Erwinia asparaginase (see Table 4.16).[24, 55, 56, 63] Both studies showed significant results favouring *E. coli* asparaginase.

Table 4.16: Summary of clinical effectiveness results from RCTs

Study	Population	Outcome	PEG	*E. coli*
Pegaspargase versus Native *E. coli* asparaginase				
CCG-1961	Age: 1 to 21 years Age: 16 to 21 years Patients with newly diagnosed higher-risk ALL; Risk: HR; Post-induction intensification phase	5-yr EFS ± SD (%) 5-yr OS ± SD (%) 5-yr EFS ± SD (%) 5-yr OS ± SD (%)	81.2 ± 2.4% 88.7 ± 1.9% 81.8 ± 5.4% 83.2 ± 6.8%	71.7 ± 2.7% 83.4 ± 2.2% 66.9 ± 6.7% 75.6 ± 7.7%
CCG-1962	Age: 1 to 9 years; Patients with standard risk ALL; Risk: SR; From induction	7-yr EFS, 95% CI (%)	75, 63-87%	66, 52-80%
DFCI-91-01	Age: 1 to ≤18 years; Patients with newly-diagnosed ALL (excl. mature B-cell ALL); Risk: SR, HR, & Infant HR; Post-remission therapy	5-y EFS ± SE (%)	78 ± 4%	84 ± 4%
DFCI ALL 05-001	Age: 1 to 18 years; Patients with newly diagnosed ALL who achieved complete remission; Risk: SR, HR, VHR; Post-induction phase	5-yr EFS, 95% CI (%) 5-yr OS, 95% CI (%)	90, 86–94% 96, 93–98%	89, 85–93% 94, 89–96%
DFCI ALL 05-01	Age: 1 to 18 years; Patients with newly diagnosed ALL who achieved complete response during induction; Risk: SR; Consolidation phase	EFS/OS	NR	NR
Study	**Population**	**Outcome**	**Erwinia**	***E. coli***
Native *E. coli* asparaginase versus Erwinia asparaginase				
DFCI-95-01	Age: 0 to 18 years; Patients with newly diagnosed ALL (excl. mature B-cell ALL); Risk: SR & HR; Induction phase	10-year EFS ± SE (%) 10-year OS ± SE (%)	75.2 ± 3.8% 85.3 ± 3.1%	84.6 ± 3.4% 93.1 ± 2.1%
EORTC CLG 58881	Age: 0 to 18 years; Patients with ALL; Risk: SR, IR & HR; Remission-induction phase	6-year EFS ± SE (%) 6-year OS ± SE (%)	59.8 ± 2.6% 75.1 ± 2.3%	73.4 ± 2.4% 83.9 ± 2.0%

Summary of results for adults

The CS presents three studies with older populations with ages ranging from 17 up to 71 years of age.[72-74] None of these studies includes a control group. Therefore these studies provide no evidence for the relative effectiveness of pegaspargase versus other asparaginases.

Summary of adverse events

The five studies comparing PEG-asparaginase with native *E. coli* asparaginase showed no significant differences in adverse events profiles between treatments.

The two studies comparing equal doses of native *E. coli* asparaginase with Erwinia asparaginase showed that Erwinia asparaginase was associated with a lower incidence of toxicity.

4.6 Conclusions of the clinical effectiveness section

Overall, the ERG agrees with the company that there is no evidence to suggest that there is a difference in effectiveness or toxicity between pegaspargase and the main comparator: native *E. coli*-derived asparaginase. However, it is unclear whether this is because of lack of evidence or lack of a difference in effect. None of the included RCTs was powered to assess equivalence and it was not possible to pool results from different studies.

There is no evidence for the relative effectiveness of pegaspargase versus other asparaginases in adult populations.

It is important to note that the UKALL protocols use a dose of 1,000 IU/m^2 for pegaspargase. However, the SmPC recommended dose is higher (2,000-2,500 IU/m^2). Moreover, there is no comparative evidence for this lower dose of pegaspargase versus other types of asparaginase. All trials comparing pegaspargase with *E. coli* asparaginase compared 2,500 IU/m^2 pegaspargase with 6,000 IU/m^2 *E. coli* asparaginase. In addition, there are no studies that provide a head-to-head comparison of pegaspargase used at 1,000 IU/m2 and 2,500 IU/m2 doses.

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

A comprehensive search of the literature was conducted to identify all relevant cost-effectiveness studies. The CS reported searches for Medline, Embase, the Cochrane Database of Systematic Reviews, and NHS Economic Evaluation. All searches were conducted on 31 January 2016. The search was restricted to English language articles and to studies that were performed in humans. In addition, only articles that contained an abstract were selected and several date restrictions were applied i.e. Medline and Embase was searched for the period 1946 (database inception) to 31 December 2015 and the Cochrane Database was searched for the period 2005-2015. The date restriction applied for the Cochrane Database was not further justified.

Measurement and valuation of health effects

A comprehensive search of the literature was conducted to identify and select relevant health related quality of life studies. This search used the same databases and restrictions as the cost effectiveness search. In addition, search terms were well reported and no validated study design filters were applied.

Resource identification, measurement and valuation studies

The search conducted for the cost effectiveness studies was also used to identify studies reporting resource use. This search included search terms related to resource utilisation and costs (e.g. 'resource utilisation', 'resource costs' and 'costs').

ERG comments: The search strategy applied by the company had several limitations. First, a language restriction to English only was used. Second, no validated study design filter for economic outcomes and health related quality of life was applied; instead common knowledge and internal expertise were the basis of the search strategy. Overall, the whole search was reported inaccurately. Typing errors and discrepancies between the company submission and Appendix 6 were found. For a more detailed critique, see Section 4.1.1.

5.1.2 Inclusion/exclusion criteria used in the <u>study selection</u>

The reviews on cost effectiveness, resource use and health outcomes as reported in the company submission started with a screening on title by one single reviewer. The exclusion criteria for this first screening were not clearly specified; only a rather vague description for this phase of screening was given i.e. 'obviously irrelevant studies (such as animal studies, case reports etc.) were excluded'.

The second stage of the cost effectiveness, health effects and resource use reviews consisted of screening based on abstract. This screening was performed by two reviewers. When there was uncertainty about the relevance of an article, it was included for full text reading. Final data extraction was also done by two reviewers. A third reviewer was consulted in case of disagreement. The applied exclusion criteria can be found in Tables 5.1 and 5.2.

Table 5.1: Inclusion/exclusion criteria for cost effectiveness studies
(Table is based on eligibility criteria as reported in CS Appendix 6 par 6.6)

Inclusion criteria	
Types of studies	Studies focused on the treatment of newly diagnosed ALL patients
Types of participants	Newly diagnosed ALL patients
Types of intervention	Chemotherapeutic protocol for the treatment of ALL that includes at least one asparaginase as first or second line agent
Types of outcomes	Economic parameters
Language	English
Exclusion criteria	
Types of studies	Studies not directly evaluating the cost effectiveness of at least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patients. Comments, editorials, systematic reviews, reviews.
Types of participants	Refractory/relapsed ALL patients; patients that are at minimum in the second course of chemotherapy following a relapse or for refractory ALL patients. Studies that include other malignancies besides ALL.
Language	Non-English

Abbreviation: ALL, acute lymphoblastic leukaemia

Table 5.2: In and exclusion criteria for studies related to the measurement and valuation of health effects
(Table is based on eligibility criteria as reported in CS Appendix 8 par 8.6)

Inclusion criteria	
Types of studies	Studies reporting patient related outcomes Studies focused on the treatment of ALL patients reporting patient related outcomes of treating ALL patients with a chemotherapeutic protocol that includes at least one asparaginase as first line or second line agent (second line being defined here as post-hypersensitivity event).
Types of participants	Patients treated for ALL: patients with a chemotherapeutic protocol that includes at least one asparaginase as first line or second line agent (second line being defined here as post-hypersensitivity event).
Types of intervention	Asparaginase
Types of outcomes	Studies that provided data for measuring or evaluating health effects of the main intervention used in a clinical setting (can include clinical studies comparing the main intervention to relevant clinical comparators)
Language	English
Exclusion criteria	
Types of studies	Studies not directly evaluating or measuring the health effect of at

	least one type of asparaginase as part of a chemotherapeutic protocol for the treatment of ALL patient. Comments, editorials, systematic reviews, reviews
Types of participants	Studies that includes other malignancies besides ALL
Language	Non-English

Abbreviation: ALL, acute lymphoblastic leukaemia

ERG comment: Studies identified from the searches were initially screened by one reviewer. This is not a recommended method.[40, 80] Exclusion criteria of screening on title were not clearly specified.

5.1.3 Included/excluded studies in the cost effectiveness review

The number of potentially relevant studies that were identified and screened based on abstract/title and full text was not reported. In response to the clarification letter,[39] the company provided the PRISMA flow diagram for the cost effectiveness and health related quality of life literature reviews (**Error! Reference source not found.**Figure 5.1 and Figure 5.2).

In total 2006 potentially relevant references were identified of which 44 remained after exclusion of duplicities and screening at title and abstract. Of these 44, eight potentially relevant economic analyses were selected based on full text screening. None of the eight selected studies were deemed relevant for decision-making in England because a different protocol and treatment scheme was used (Table 41 of CS).

The health related quality of life review revealed 3,346 potentially relevant articles. Forty-four of these remained after removing duplicates and screening at title and abstract. After full text screening five potentially relevant articles were selected. The included studies were described in Table 38 of the CS.

In Appendices 6.7 and 8.7 of the CS an overview of excluded studies is given. For 33 studies a reason for exclusion is provided while 44 were selected for full text screening.

Figure 5.1: Cost effectiveness evidence search study flow diagram

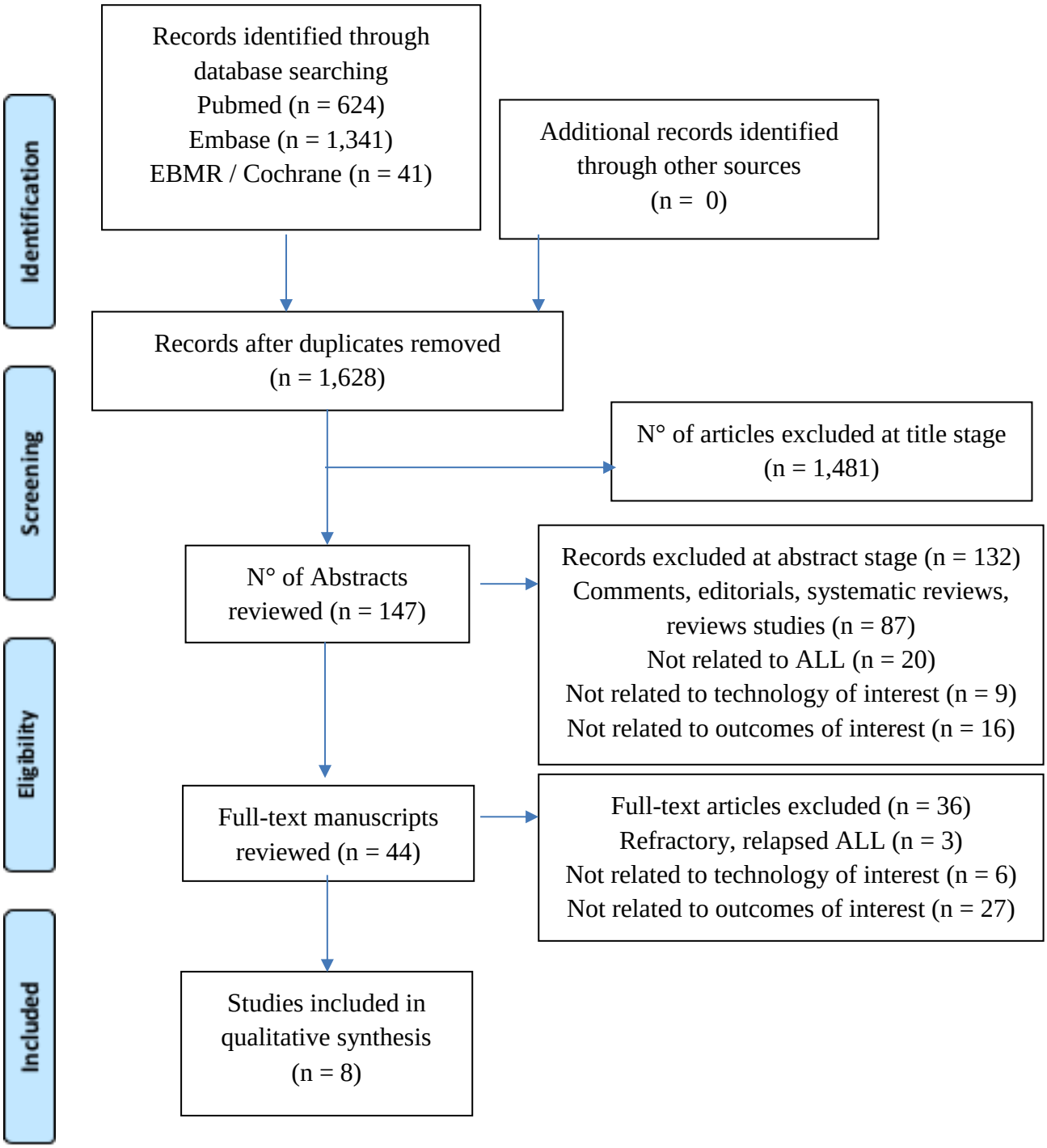
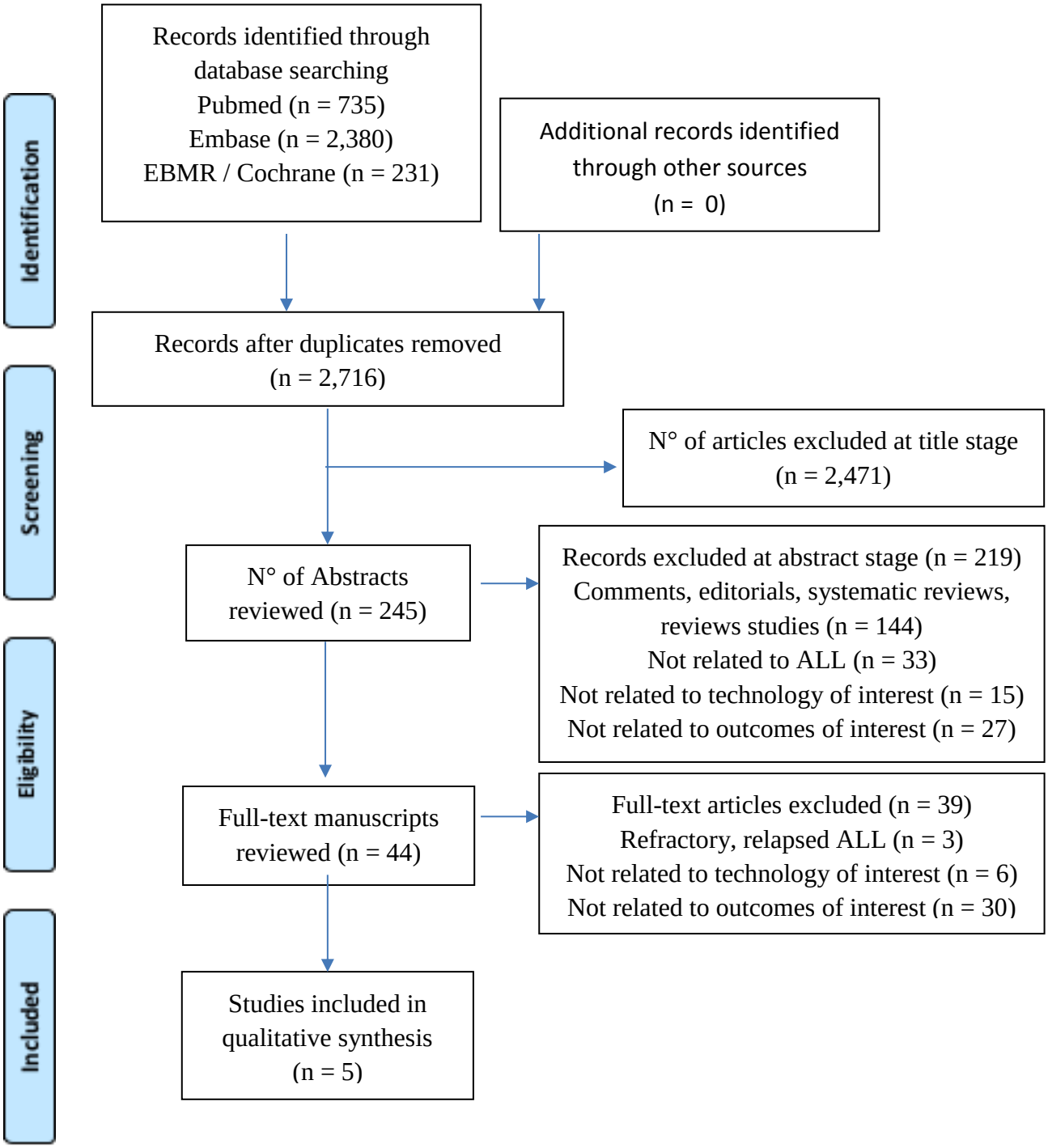


Figure 5.2: Health related quality of life evidence search study flow diagram



5.1.4 Conclusions of the cost effectiveness review

None of the identified cost effectiveness studies were deemed relevant to decision-making in England.

ERG comment: The ERG is concerned about the quality of the cost effectiveness reviews for several reasons. The results of the searches were not clearly reported in the company submission. Discrepancies were observed between the PRISMA results and results reported in the company submission appendices. Typing errors (i.e. the ERG assumes these were typing errors) were observed in the description of the searches (CS Appendices 6 and 8). No validated filters for economic and health related quality of life outcomes were applied. Lastly, the first screening was done by one reviewer only despite the fact that this is clearly not a recommended method. Despite these concerns, the ERG does not expect that the company missed relevant studies. After reading several studies and performing some ad-hoc searches, the ERG did not find any relevant publications that were not identified by the company searches.

Overall, the ERG shares the opinion of the company that the development of a *de novo* model was required.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3 presents a summary of the de novo economic model developed by the manufacturer. The ERG has assessed the company's economic evaluation and their critique is presented in the following sections.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/justification	Signpost (location in CS)
Model	The model was a combination of a decision tree and a health state transition Markov model.	The decision tree follows patients during their treatment pathway for ALL and follow-up for 5 years. Beyond 5 years post-treatment initiation, the Markov model is used to extrapolate over the patient's remaining lifetime time horizon.	Section 5.2. pg 144
States and events	The paths in the decision tree distinguished patients who experienced hypersensitivity and who did not. The Markov model of the paediatric population contained three health states: EFS, R/ST and Death, while only two states were included in the Markov model of adult patients: EFS and Death.	Hypersensitivity is causing a treatment switch to another asparaginase formulation or even, after hypersensitivity to a second formulation, a complete stop of asparaginase treatment.	Section 5.2.2. pg 144
Comparators	Native *E. coli* – Erwinase Erwinase – Pegaspargase Erwinase – Native *E .coli*	These are theoretical possible alternatives for pegaspargase-Erwinase, in current practice though all patients receive pegaspargase in the first line.	Section 5.2.3. pg 151
Natural History	Survival up to 5 years in the paediatric population was based upon EFS and OS. First, OS was estimated and subsequently EFS was subtracted to estimate the proportion of patients in the R/ST state. After 5 years, patients in the EFS were considered to be cured and general background mortality to estimate the probability of death. This general background mortality was increased with 90% for patients in the R/ST state. For adult patients, natural history was estimated from the OS.	Based upon visual inspection, the Company assumed a linear trend for OS and EFS in the paediatric population and a Weibull distribution for OS in the adult population. The 90% increase of mortality in the R/ST state was an assumption based on expert opinion	Section 5.3.1, pg 153
Treatment effectiveness	Similar EFS and OS is assumed between the treatment alternatives. The only difference between the alternatives is the	No statistical differences in OS and EFS were found in studies comparing pegaspargase and native *E. coli*	Section 5.3.1, pg 153

	Approach	Source/justification	Signpost (location in CS)
	hypersensitivity rate		
Adverse event	Only hypersensitivity for asparaginase formulations is taken into account. This hypersensitivity will on average occur after 2 doses. Only hypersensitivity leading to a treatment switch is taken into account.	The assumption that there is no difference in the rates of adverse events is considered conservative by the company. Asparaginase is used with other medicines and it is challenging to attribute the AE differences to asparaginase and not the concomitant medication or indeed the disease itself	Section 5.3.1.4. pg 156 Section 5.4.5, pg 164
Health related quality of life	Different quality of life estimates were used for the different treatment phases and the R/ST health state. No long-term quality of life impact was included for patients in the EFS after 3 years. Quality of life did not differ between alternatives.	Due to absence of UK-specific quality of life data, it was assumed that the reduction in quality of life due to ALL in the US also applied to UK ALL patients. Quality of life utility in the R/ST state was based upon expert opinion.	Section 5.4.6, pg 164
Resource utilisation and costs	Cost categories included in the model were: drug acquisition and administration costs and costs of hypersensitivity. Health state costs for EFS and R/ST were not included.	Based on UK reference costs and expert opinion.	Section 5.5, pg. 166
Discount rates	A 3.5% discount rate was applied for both costs and effects	According to NICE reference case	Section 5.2.2.1, pg. 151
Subgroups	No formal subgroups were considered. However, the model enables the separate calculation of cost-effectiveness for : • Paediatric/AYAs ≤25 years • Adults (25–65 years) with the distinction between those above and below 40 years and between those eligible or not for transplant as	Neither the scope nor the decision problem specified any subgroups.	Section 5.9, pg. 192

	Approach	Source/justification	Signpost (location in CS)
	described in the UKALL 14 protocol.		
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges mainly based on assumptions	Section 5.8, pg. 182

Abbreviations: ALL: Acute lymphoblastic leukaemia, AYA: Adult and Young Adult; EFS, Event-free survival; R/ST, Relapse or secondary tumour, US = United States, UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Population	The NICE scope defined a paediatric and an adult population: newly diagnosed people with ALL aged 0-65 years. Paediatric population: children, adolescents, young adults with ALL aged 0-25 years. Adult population: adults with ALL aged 25-65 years.	Yes	
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	No/Yes	The therapy routinely used and regarded as best practise is the intervention. Patients would not receive *E. coli* or Erwinia as first-line therapy. Patients receiving Erwinia would not switch to *E. coli*. *E. coli* is not licenced for use in the UK and is not listed in the BNF.
Type of economic evaluation	Cost-effectiveness analysis	Yes	Augmented with cost-minimisation analysis
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	No	The model only takes hypersensitivity into account, not other adverse events that may be caused by the treatments
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	5-Years post treatment initiation combined with a lifetime model after the first 5 years.
Synthesis of evidence in outcomes	Systematic review	No	Evidence was used to estimate model parameters on an ad hoc base, without any formal synthesis.
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQOL	Reported directly by patients and/or carers	No	Based on US study using HUI2 and HUI3, filled in by parents for paediatric population. The same values were assumed to be also valid for adults.
Source of preference data for valuation of changes in HRQOL	Sample of public	No, i.e. not the UK public	The utilities were derived from a preference scaling task using a general population sample in Canada
Discount rate	Annual rate of 3.5 on costs and health effects	Yes	

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Equity weighting	No special weighting		
Sensitivity analysis	Probabilistic sensitivity analysis	Partially	Not all potentially relevant parameters were included

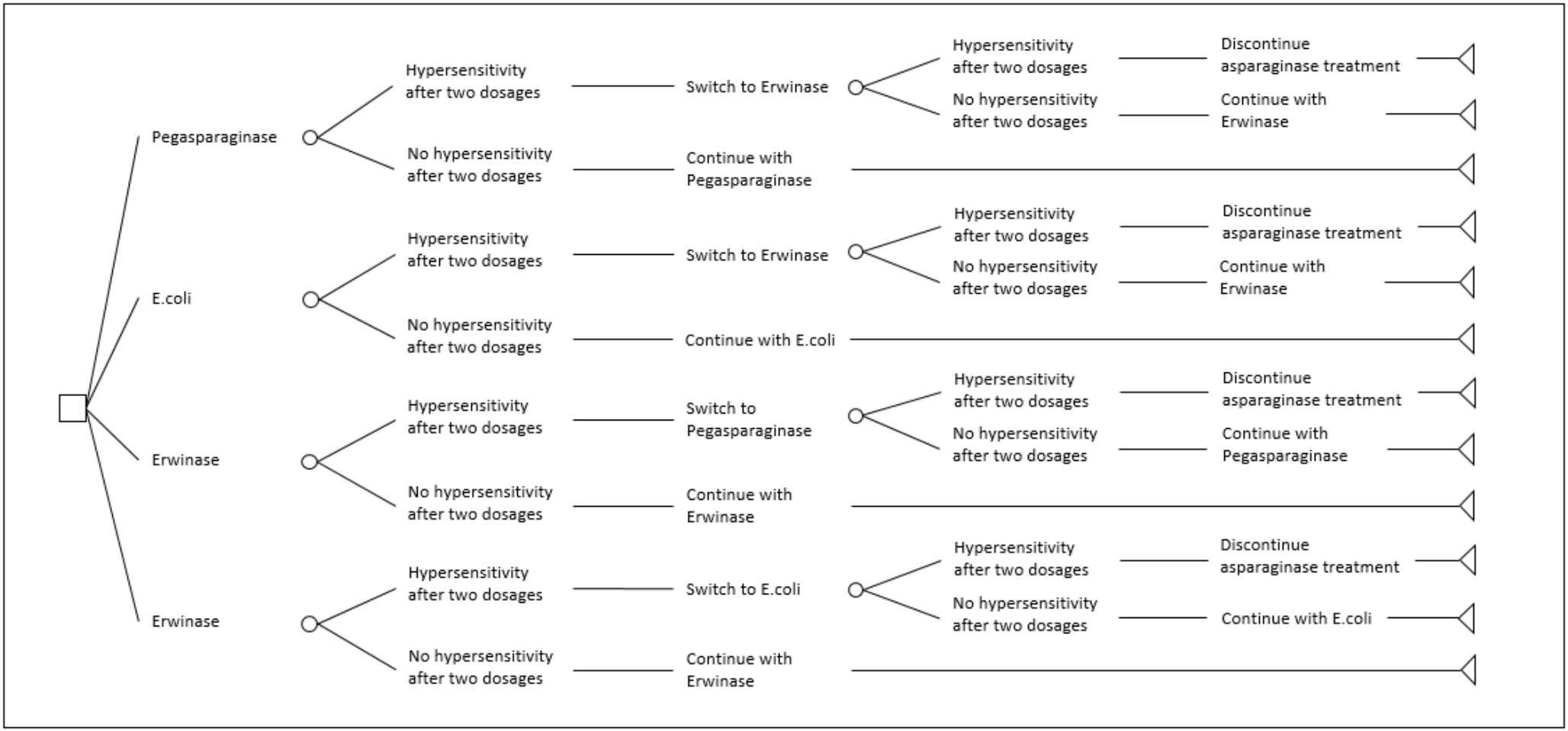
Abbreviations: ALL: Acute lymphoblastic leukaemia; BNF: British National Formulary; HRQOL: Health-related Quality of Life; HUI: Health Utilities Index; NHS: National Health Services; PSS: Personal Social Services; QALYs: Quality-adjusted Life Years; SE: Standard error

5.2.2 Model structure

The final decision model is a combination of a decision tree and a health state transition Markov model. The decision model starts at treatment initiation of newly diagnosed ALL patients. As a first step, a decision tree is used to model the patient flow during treatment administration. It takes into account the dosing, frequency and potential hypersensitivity of asparaginase in different treatment phases. Parallel to the decision tree, a Markov model is used to account for potential relapse/secondary tumour (R/ST) and death. Furthermore, the Markov model is used to extrapolate beyond the time horizon of the clinical trials (five years).

Figure 5.3 shows the general structure of the decision tree. Patient start with one of the three asparaginase agents: pegaspargase, native *E. coli* asparaginase or Erwinase. For all three asparaginase agents, it is assumed that hypersensitivity occurs after two treatment dosages. In case of hypersensitivity, patients switch to a different asparaginase treatment (second line treatment). Otherwise, patients continue the first line treatment for the remaining treatment protocol. During second line treatment, patients may again develop hypersensitivity after two dosages and asparaginase treatment will then be discontinued.

Figure 5.3: General decision tree structure



The timing of the hypersensitivity and the subsequent treatment switch differ between treatment options and age and risk groups. First, fewer administrations are required for pegaspargase compared to native *E. coli* and Erwinase (six dosages of *E. coli* or Erwinase for every dose of pegaspargase) due to a preferential half-life. Consequently, hypersensitivity occurs at a later moment in time (later treatment phase) in patients treated with pegaspargase. Furthermore, the dosing schedule of asparaginase depends upon the age and the risk of the patient (see also Section 5.2.8). This differential dosing schedule also impacts the timing of the hypersensitivity. Older patients and patients classified as high risk develop hypersensitivity earlier in time.

The decision tree for older adults differs slightly from the general model (Figure 5.3) because patients may receive a stem-cell transplantation after the induction treatment phases. For these patients, asparaginase treatment has been ceased.

The structure of the Markov model differs between paediatric and adult patients (Figure 5.4 and Figure 5.5). In paediatric patients, the Markov model has three health states:

1. Event-Free Survival (EFS)
2. Survival with relapse/secondary tumour (R/ST)
3. Death (Overall survival, OS)

In adult patients, the 'alive' health state is not distinguished in EFS and survival with R/ST because it is assumed that EFS and OS are equivalent for adult patients. The CS[3] and the response to the clarification letter[39] state that assumption is based upon expert opinion due to a lack of reported data in the UK patient population. In the response to the clarification letter, it was confirmed that death follows shortly after relapse. Therefore, the Markov model for adult patients has only the following two health states:

1. Alive
2. Death (OS)

During the treatment period, the cycle length of the Markov model was identical to the duration of the different treatment phases. Since every treatment phase has its unique duration, a variable cycle length was used during the treatment period. Once the treatment period was completed, the Markov model consisted of yearly cycles.

Figure 5.4: Markov model (paediatric patients)

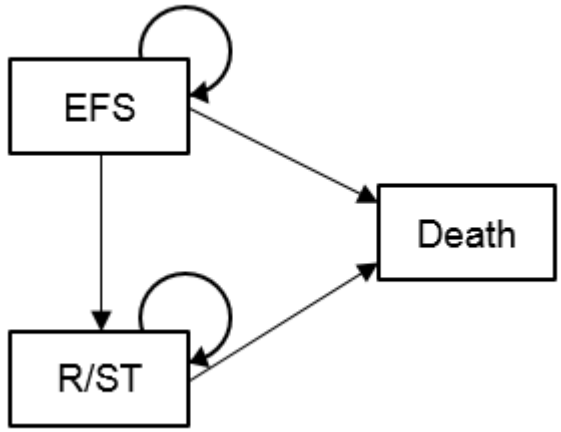
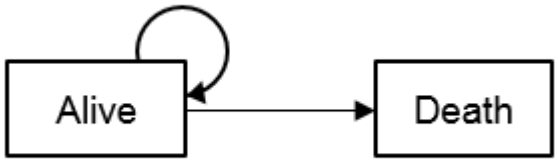


Figure 5.5: Markov model (adult patients)



ERG comment: The combination of a decision tree and Markov model is well suited for the purpose of this evaluation. The decision tree enables the inclusion of a switch in asparaginase treatment in case of hypersensitivity, while the Markov model traces the number of patients alive (without any disease-related event) over time. The model has also been adjusted according to the differences in treatment protocol between risk and age groups.

A point of concern is the assumption that OS is equal to EFS in adult ALL patients. According to the company, this assumption was based upon expert opinion due to a lack of UK evidence. However, one clinical trial showed some differences between five year EFS and OS in adult ALL patients (aged 15-59 years).[81, 82] This study shows a magnitude of a difference that is more or less similar to the difference in EFS and OS in the paediatric population. Thus, only allowing differences between EFS and OS in the paediatric population is inconsistent. However, since the difference between OS and EFS is quite small, the impact on the ICER is expected to be marginal.

A second point of concern is the assumption that hypersensitivity only occurs after two administrations of asparaginase. Several studies in the literature indicate higher rates of hypersensitivity if pegaspargase is administered more frequently.[19, 49, 83] Although it is expected that it would only marginally impact the ICER, it would better reflects clinical

practice to allow the occurrence of hypersensitivity after more than two administrations as well.

Finally, it is questionable whether the yearly cycle length after the end of the full treatment protocol is sufficiently short to capture all relevant events. Considering the fact that the Company did not include any health state costs besides the costs of asparaginase treatment and management of hypersensitivity, it is not expected that a different cycle length would yield different results. Nevertheless, in the case where health state costs are included, the ICER may change slightly.

5.2.3 Population

Two separate groups of newly diagnosed patients with ALL were included in the company submission:

1. Paediatric patients, aged <=25 years. Within this group, a further split is made between high risk (HR), intermediate risk (IR) and standard-risk (SR) patients.
2. Adults, aged 26-65 years. Within this group, a further split is made between those aged <=40 and aged >=41 and those eligible or not for transplant.

According to Cancer Research UK (CRUK) data, of the new ALL cases diagnosed per year in those aged 0–65, 74.4% would be aged less than 25 years and 25.6% would be aged between 26 and 65 years, respectively. The mean age of the paediatric patients within these data is 7.3 and of the adults 31.2 and 52.6 years for the younger (26-40) and older (41-65) age groups, respectively. The median age of paediatric patients as reported by Vora et al. (2013) is five years.

In the health economic model, all inputs were based on the median age for paediatric patients and on the mean age for adult patients. In the clarification letter, the rationale for this discrepancy was asked to the company. The company responded that the age from the UKALL 2003 trial[19, 20] was considered to be more informative and robust (based on n=3,200) and more relevant (97% of eligible patients were enrolled) to the UK paediatric population than the data from CRUK. Since information about the mean age in the UKALL 2003 was missing, it was decided to use the median age for paediatric patients in the health economic model. For adult patients, no other data than the CRUK data is available. Therefore, the CRUK data was considered to be most reliable source for the age of the patients.[39]

Patients that are not included in the submission are older patients (>65 years) and relapsed patients. These patients do not routinely receive pegaspargase and are therefore not considered to be relevant for the NHS-decision maker.

ERG comment: The ERG considers the distinction between paediatric and adult patients in the cost effectiveness analysis to be valuable since both treatment protocol and outcome (EFS and OS) differ substantially between these groups. A further split in risk group and subsequent age groups is also due to differences in treatment and thereby differences in administration of asparaginase. The exclusion of patients older than 65 years and patients

with relapsed/ refractory ALL seems to be reasonable as asparaginase treatment is not part of standard treatment protocol for these patients.

Although the rationale for risk group in the paediatric patient population was clear, it was not apparent from the CS how the three risk groups were defined. It appeared that the risk group classification was taken from the UKALL 2003 trial[19, 20] and was based on three metrics:

1. NCI risk criteria:
    a. NCI standard risk: patients aged < 10 years with a WBC count < 50 x 10^9/L
    b. NCI high risk: patients aged ≥ 10 years or a WBC count ≥50 x 10^9/L
2. Presence of cytogenetic abnormalities (rearrangement of MLL gene, hypodiploidy (<45 chromosomes or intrachromosomal amplification of chromosome 21)
3. Early response to induction therapy assessed by bone marrow morphology on day 8 and 15

However, a slightly different classification is used in the most recent paediatric ALL protocol (UKALL 2011 trial[15]) because minimal residual disease (MRD) at day 29 of induction treatment is also incorporated in the risk group classification. Furthermore, an early response at day 8 or 15 is currently only relevant for patients with no MRD results (due to either inadequate samples or no MRD marker). The distribution of patients according to the newly defined risk group classification is unknown.

Table 5.5 shows the risk group classification for both the UKALL 2003 and UKALL 2011 study.

Table 5.5: Risk group classification in paediatric patients (based upon Vora et al. and UKALL 2011 protocol)

	Standard risk	Intermediate risk	High risk
UKALL 2003	NCI standard risk patients aged <16 yrs. with RER	• Patients aged ≥16 yrs. • NCI high risk patients aged <16 yrs. with RER	• Presence of cytogenetic abnormalities, • >25% of the marrow made of blasts at day 8 for patients with NCI high risk or at day 15 for patients with NCI standard risk.
UKALL 2011	• NCI standard risk and MRD low • NCI standard risk and RER (if MRD not possible)	• NCI high risk or high risk cytogenetics and MRD low • NCI high risk or high risk cytogenetics and RER (if MRD not possible)	• MRD high • SER (if MRD not possible)

RER = rapid early response (<25% blasts at day 8 for patients with NCI high risk and <25% blasts at day 15 for patients with standard risk), SER = slow early response (>25% at day 8 or day 15 for high and standard risk patients, respectively), MRD low = < 0.005% at day 29 inductions

Even in the case that the risk classification from the UKALL 2003[19, 20] is still in use in clinical practice, there is some inconsistency in the distribution of patients over the three risk groups. Figure 2 and Table 5 of Vora et al.[19] report slightly different number of patients in the three risk groups. As a corrected version of Figure 2 has been published on 30 June 2014, it is expected that the numbers in that Figure 2 are correct. Therefore, in the ERG base-case analysis, the distribution of paediatric patients in the three risk groups will be based upon the numbers reported in the corrected Figure 2 instead of Table 5.

The ERG doubts whether the median age of the UKALL 2003 trial[19, 20] is more reliable than data from the CRUK since the inclusion of patients in the UKALL 2003[19, 20] trial has been expanded over time. At the start of the study only patients up to 18 years were eligible, but the upper age limit was increased to 20 years in February 2006 and to 24 years in August 2007. It is therefore possible that the age of the paediatric patients is slightly underestimated since older patients were only eligible in the last five years. Furthermore, health economists aim to use means instead of medians for all estimates used in a model. Therefore, in the ERG base-case analysis, the starting age of paediatric patients is considered to be 7.3 years instead of five years.

5.2.4 Interventions and comparators

The intervention under study is the use of pegaspargase as first line treatment and Erwinase as second line treatment for patients developing hypersensitivity to pegaspargase. This treatment sequence is compared with three alternative treatment sequences (see Table 5.6). Although Erwinase is only used as second line treatment after hypersensitivity to first line asparaginase in current UK practice (UKALL 2003[19, 20] and UKALL 14[16]), its use as first line treatment is considered in two alternatives because Erwinase was listed as a comparator in the NICE scope and its UK indication is not limited to a specific line of asparaginase treatment. Since the administration of *E. coli* after pegaspargase or vice versa is considered unsuitable due to the risk of cross reactivity and subsequent hypersensitivity, these treatment sequence alternatives have not been modelled.

Table 5.6: Treatment alternatives in the cost effectiveness analysis

	1st line Asparaginase	2nd line Asparaginase (in case of hypersensitivity 1st line treatment)
Intervention	Pegaspargase	Erwinase
Comparator 1	*E. coli*	Erwinase
Comparator 2	Erwinase	Pegaspargase
Comparator 3	Erwinase	*E. coli*

Asparaginase (either pegaspargase, *E. coli* or Erwinase) is administered in different phases of ALL treatment. Table 5.7 shows when asparaginase is administered. Note that the weeks represent the timing of the treatment from start of induction treatment (i.e. induction treatment takes five weeks and subsequently, consolidation treatment starts in week six). The total dosage of asparaginase per treatment phase is reported in Section 5.2.8.

Table 5.7: Overview of asparaginase treatment during the complete ALL treatment course (Based on Table 43 in the CS and adjusted according to information in the UKALL 2003 protocol, Vora et al. and UKALL14 protocol)

Paediatric population	**Ind**	**Cons**	**IM 1**	**DI 1**	**IM 2**	**DI 2**	**Cont.**
High risk	1w	6w	15w	23w	31w	39w	47w
Intermediate risk	1w	6w	11w	19w	26w	34w	41w
Standard risk	1w	6w	9w	17w	24w	32w	39w
Adult population	**Ind**	**Int.**	**Cons cycle 1**	**Cons cycle 2**	**Cons cycle 3**	**Maint**	
≤40 years	1w	9w	13w	16w	19w	25w	
≥41 years	1w	9w	13w	16w	19w	25w	

All green marked cells represent treatment phases during which asparaginase is administered.
Abbreviations: Cons = Consolidation, Cont = continuation, DI = delayed intensification, IM = interim maintenance, Ind = Induction, Int = Intensification, Maint = Maintenance

ERG comment: The ERG agrees with the approach of the company to include all possible relevant comparators although these are currently not standard practice in the UK. By including Erwinase as first line treatment in the cost effectiveness analysis, it has been possible to assess the cost effectiveness of pegaspargase fist line-Erwinase second line against all other possible treatment sequences. Since pegaspargase and *E. coli* are immunological similar, it is not realistic that one of these formulations would be administered after hypersensitivity to the other formulations. It is therefore not needed to include that treatment sequence in the evaluation as well.

However, it should be noted that the comparison of pegaspargase followed by Erwinase versus Erwinase followed by pegaspargase does not inform the decision at hand, i.e. should pegaspargase be recommended for routine use within the NHS? This is due to the fact that both the intervention sequence and the comparator sequence contain pegaspargase.

The administration of asparaginase has been based on recent treatment protocols (UKALL 2003 and UKALL14 for paediatric and adult patients, respectively). However, the scheme of the timing of the different treatment phases as reported in the CS[3] did not accurately reflect the timing of the protocols. For paediatric patients, consolidation treatment starts at week 6 instead of week 5 as reported in the CS and the electronic model. Consequently, all subsequent treatment phases start one week later with exception of delayed intensification I and II and interim maintenance II for standard risk patients. For adult patients, the third consolidation cycle starts at week 29 instead of week 25. This has been adjusted in the ERG base-case, and has also been corrected in the time schedule presented in Table 5.7.

Another point of concern with respect to the treatment specification is that in the most recent treatment protocol for children, only one interim maintenance and delayed intensification course will be administered to the patients (UKALL 2011 protocol).[15] This is based on the

findings from the UKALL 2003 study that there is no additional benefit of two interim maintenance and delayed intensification courses compared to one.[19, 20] The ERG base case will therefore incorporate only one delayed intensification course as this best reflects current clinical practice in the UK.

5.2.5 Perspective, time horizon and discounting

A time horizon of five years post treatment initiation and a life time horizon were chosen. The five years post treatment initiation was chosen because five year EFS and OS estimates are usually reported in the literature and clinical protocols. Costs are considered from the NHS and PSS perspective. A discount rate of 3.5% was applied for both the costs and effects.

ERG comment: The ERG concludes that the discount rate and perspective are in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

In the CS, it is assumed that the OS and EFS of the different asparaginase agents are equivalent. This assumption is based upon clinical data demonstrating non-significant differences in OS and PFS between pegylated and native *E. coli* asparaginase as first line treatment (Section 4.14 of the CS). All available studies evaluating long-term outcome of Erwinia-derived asparaginase compared to native *E. coli* asparaginase used lower dosages of Erwinia than common in current clinical practice (10,000 IU/m^2 twice weekly or 25,000 IU/m^2 weekly versus 60,000 IU/m^2 weekly in UKALL protocols). In these studies, long-term outcome was significantly worse for patients treated with Erwinase.[24, 55, 56] However, according to the CS, it is expected by the company that the higher dose of Erwinase is as effective as pegaspargase and *E. coli* asparaginase. This assumption has been confirmed by clinical experts.

Likewise, the comparative clinical evidence regarding pegaspargase used higher dosages than common in current clinical practice in the UK (2,500 IU/m^2 in all comparative studies versus 1,000 IU/m^2 in UK clinical practice). In their response to the clarification letter, the company mentioned that no head-to-head comparisons exist of pegaspargase used at 1,000 IU/m^2 and 2,500 IU/m^2. They argued that it may be reasonable to assume a lower efficacy and fewer side effects at the lower dosage. Since the EFS and OS of the UKALL 2003 (using a dose of 1,000 IU/m^2) were at least as good as that of studies using the 2,500 IU/m^2, the company considered it to be reasonable to use these survival estimates for all formulations.

In the clarification letter, the ERG indicated that the absence of any significant difference in OS and EFS does not mean that these can be assumed to be equal for all treatment strategies. In their response, the Company reported that they did not find any robust comparative evidence on potential OS and EFS differences between the different asparaginase formulations. The absence of any difference was also confirmed by clinical experts. Finally, it was indicated that it is very difficult to isolate the effect of asparaginase on OS and EFS, since asparaginase is used with different dosing/frequency within multi-treatment regimens.

OS and EFS in the paediatric population

The OS and EFS of the paediatric population were derived from the results of the UKALL 2003 trial.[19, 20] The company submission presents the following outcomes for the three risk groups:

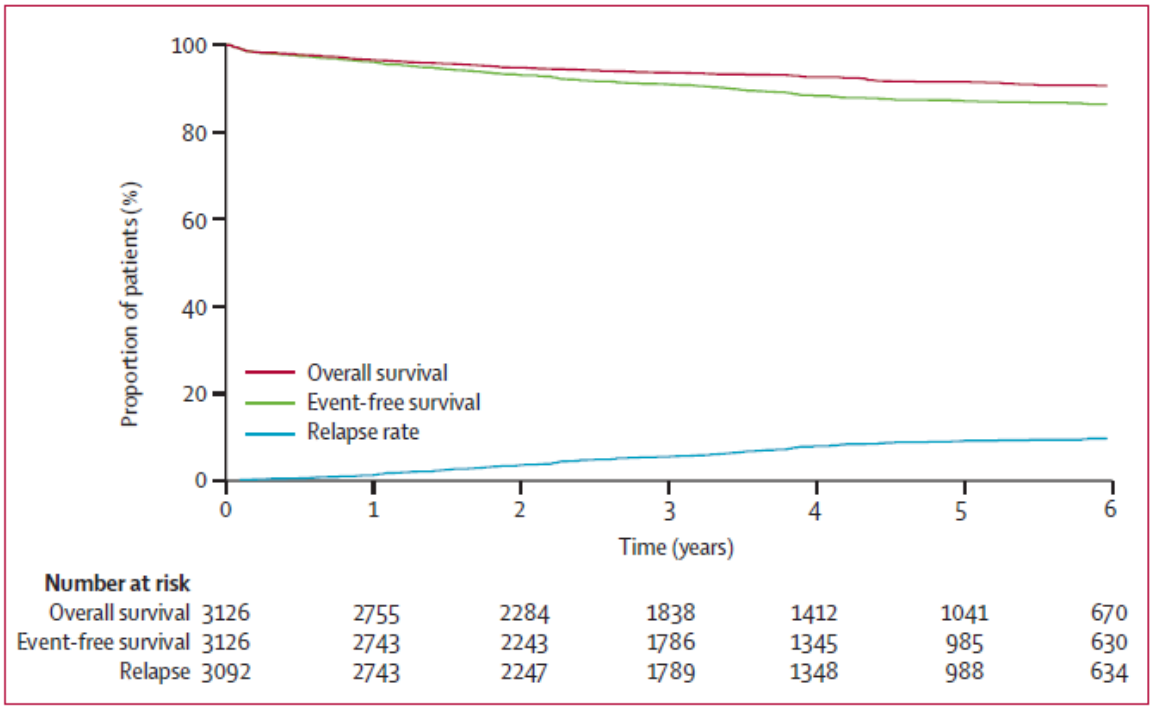
- Five year OS: 95%, 90% and 80% for SR, IR, and HR groups, respectively
- Five year EFS: 90%, 85% and 75% for SR, IR and HR groups, respectively

According to visual examination of the OS and EFS in the total patient group (Figure 5.6), it was suggested that the OS and EFS followed a near linear pattern over time until five years. Therefore a constant instantaneous rate of event (for both R/ST and death) over time was assumed. This instantaneous rate was calculated as follows:

$$Rate = -[\ln(1-x)]/5$$

with x being the 5-year probability of the event

Figure 5.6: OS and EFS in paediatric patients



Abbreviations: OS = Overall survival, EFS = event-free survival

After five years, the patients in the EFS state were considered as cured (based upon expert opinion). A switch from EFS to R/ST was no longer allowed and mortality risk was derived from life tables of the Office of National Statistics. The general mortality risk, weighted by the male/female proportion as observed in the UKALL 2003 study (57% male and 43% female) was applied to patients in the EFS state. For patients in the R/ST state at five years, the general mortality was increased with 90% (multiplied with 1.9) to reflect the larger probability of dying for these patients.

Since the OS and EFS were assumed to be similar for all three asparaginase agents, a switch to another agent did not impact the OS and EFS. However, in case patients also developed hypersensitivity to the second line asparaginase, asparaginase treatment was discontinued. It was assumed (based on expert opinion) that this discontinuation reduced five year EFS and OS both with 5%.

OS and EFS in the adult population

Based on expert opinion, the CS assumes that EFS = OS in adult patients. Therefore, only OS has been included as a relevant outcome for adult patients. The CS states that leukaemia-free survival after three to seven years of follow-up is only 30-40%. In the decision model, the lower limit of 30% is used as the five year OS of patients aged ≥41 years and the upper limit of 40% is applied to the patients aged ≤40 years. The rationale for this division, according to the CS, is that the treatment protocol was already stratified according to this age cut-off and that age is considered a key determinant of OS and EFS.

Based upon visual inspection of survival curves of several UK trials, it was suggested that survival in adults ALL patients had a non-linear pattern. Therefore, a Weibull curve ($S(t) = e^{-\alpha t^{\beta}}$ was fitted on two points: five year OS as reported in the UKALL 14 protocol and the 40-year survival of 0%. Thus, the Weibull model implies the OS of 30 and 40% for patients aged ≥41 years and ≤40 years, respectively. In addition, it incorporates the assumption that all patients must have died after 40 years.

Similar as in the paediatric population, the OS for patients who discontinued both first and second line asparaginase treatment is reduced by 5%.

Hypersensitivity

An important element of the treatment with asparaginase is the rate of hypersensitivity of each of the agents. The comparison of the hypersensitivity rates between studies is complicated due to two reasons: i) use of different dosages of each asparaginase agent, and ii) the inclusion of different severity levels in the definition of hypersensitivity.

The CS explains that the SmPC of Oncaspar states that hypersensitivity reactions of Grade 2 or higher are seen in ≥20% of the patients. However, this rate has been observed in patients treated with dosages of pegaspargase of 2,000 and 2,500 IU/m^2, while a dosage of 1,000 IU/m^2 is used in current UK clinical practice. Furthermore, some of these studies included patients who received pegaspargase as second line asparaginase following hypersensitivity to native *E. coli*. It is known that this sequence increases the risk of hypersensitivity to pegaspargase.

According to the CS, only one study is currently available that reports the hypersensitivity rate of first line pegaspargase at a dosage of 1,000 IU/m^2 .[19] That study showed that overall, 2% of the patients developed hypersensitivity, with a range of <1% in clinical SR patients and 6% in the clinical IR patients. The average rate of 2% is used by the Company as input in the economic model for hypersensitivity both for first and second line pegaspargase treatment. This rate was also validated by clinical experts.

Many different rates of hypersensitivity were reported for native *E. coli* asparaginase. Hypersensitivity rates (grade 3/4) ranged between 0 and 13% in the studies identified by the systematic review of the company (Table 29 of the CS and Appendix 4 of the CS).[3] However, higher rates were observed if milder allergic reactions were included. In one study, the incidence of hypersensitivity leading to a switch in treatment was 76%, while the grade 4 hypersensitivity was only 8%. [57] In the CS it was decided to include a hypersensitivity rate of 20% for native *E. coli* both for first and second line asparaginase. This percentage was based on the percentage reported by Vrooman et al.[75] and indicated the proportion of patients with hypersensitivity leading to a treatment switch.

Limited data was available with respect to the hypersensitivity for Erwinia-derived asparaginase. Only one study reported grade 3/4 hypersensitivity and a few others reported any allergic reaction. In the economic model, a percentage of 6% was used for first line treatment with Erwinase[55] and 37% for second line treatment with Erwinase.[84]

In the clarification letter, the company was asked to reflect on the suitability of the chosen estimates of the hypersensitivity rates since it was found that definition of hypersensitivity may vary between studies. The company indicated that the important point is whether or not a hypersensitivity reaction results in an asparaginase treatment switch, irrespective of the severity/definition of the hypersensitivity reaction (response to clarification letter).[39] In a further clarification of their choices, the company indicated that the hypersensitivity rate for native *E. coli* is considered to be justifiable and conservative given the large range of rates reported in other studies.[34, 57, 58] Furthermore, the company indicated that the 2% hypersensitivity to pegaspargase was the only rate reported by Vora et al. 2013.[19]

ERG comment: As already discussed in the clinical effectiveness section, the ERG agrees with the company that there is no evidence to suggest that there is a difference in effectiveness between pegaspargase, *E. coli* and Erwinase. However, it is unclear whether this is caused by the true absence of differences or a lack of well-powered comparative studies. Since it may be possible that the effectiveness differs between asparaginase formulations, the ERG considers the assumption of equal effectiveness too simplistic. At least, the effectiveness of the different formulations should be varied independently in the probabilistic sensitivity analysis to assess the impact of uncertainty regarding the effectiveness on the ICER. Although the company did not incorporate this uncertainty in a probabilistic sensitivity analysis due to a lack of robust comparative evidence and the risk of unrealistic survival differences, the ERG considers this evaluation necessary to provide valuable insight in the cost effectiveness of pegaspargase. Thus, the ERG requested (and received) in the clarification letter an updated version of the model which includes the functionality required to vary effectiveness independently between treatments. The ERG still incorporated similar effectiveness in the ERG base-case, but independently varied the OS and EFS of the different asparaginase formulations in the PSA.

Survival estimates in paediatric population

The five year OS and EFS reported in the CS for the three risk groups in the paediatric population cannot be reproduced from the reported results of the UKALL 2003 trial.[19, 20]

Both studies did not report the OS and EFS for the three risk groups as defined in Table 5.5. The available evidence that could be reproduced from these studies is shown in Table 5.8. This data was used to inform an ERG-defined base case.

Table 5.8: Reported survival estimates from the UKALL 2003 trial

Patient group	% (95% CI)	Source
5-year overall survival		
Entire population (N=3,126)	91.6 (90.6-92.6)	Vora et al. 2014 – Results section
Low MRD – 1 DI course (N=260)	**97.9 (95.7-100)**	**Vora et al. 2013 – Table 6**
Low MRD – 2 DI courses (N=261)	98.5 (96.9-100)	Vora et al. 2013 – Table 6
Early response – High MRD – standard therapy (N=266)	**88.9 (85.0-92.8)**	**Vora et al. 2014 – Table 2**
Early response – High MRD – Augmented therapy (N=267)	**92.9 (89.8-96.0)**	**Vora et al. 2014 – Table 2**
5-year event free survival		
Entire population (N=3,216)	87.3 (86.1-88.5)	Vora et al. 2014 – Results section
NCI standard risk – MRD high	85.8 (82.1-89.5)	Vora et al. 2013 – Suppl table 2
NCI standard risk – MRD low	94.0 (91.6-96.4)	Vora et al. 2013 – Suppl table 2
NCI high risk – MRD high	72.8 (67.9-77.7)	Vora et al. 2013 – Suppl table 2
NCI high risk – MRD low	94.7 (92.0-97.4)	Vora et al. 2013 – Suppl table 2
Low MRD – 1 DI course (N=260)	94.4 (91.1-97.7)	Vora et al. 2013 – Table 6
Low MRD – 2 DI courses (N=261)	95.5 (92.8-98.2)	Vora et al. 2013 – Table 6
Low MRD (N=1090)	**94**	**Vora et al. 2013 – Suppl. Fig 1c**
High MRD (N=1037)	**79**	**Vora et al. 2013 – Suppl. Fig 1c**
Other (no low or high MRD) (N=999)	86	Vora et al. 2013 – Suppl. Fig 1c
Early response – High MRD – Standard therapy (N=266)	82.8 (78.1-87.5)	Vora et al. 2014 – Table 2
Early response – High MRD – Augmented therapy (N=267)	89.6 (85.9-93.3)	Vora et al. 2014 – Table 2

Bold items were used as for the OS and EFS inputs in the ERG base-case

Abbreviations: NCI: National Cancer Institute; MRD: minimal residual disease; DI: delayed intensification.

Based on this evidence, the ERG decided to use the EFS of the low MRD risk group (94%) for both the SR and IR group, since the EFS did not differ for patients with low MRD in either the NCI high or standard risk group. Evidence regarding the OS is more limited since the OS was not split up by NCI clinical risk and MRD status. Furthermore, five year OS was only reported for the two randomised subgroups (either one or two delayed intensification courses). Since no differences in OS and EFS were found between these two subgroups and patients are currently treated with only one intensification course, the OS for patients with low MRD treated with one DI course (97.9%) was used as the five year OS for patients with SR and IR. It was assumed that the OS in this subgroup was representative for the total

patient population with low MRD and that patients with low MRD had similar OS irrespective of NCI clinical risk group. These assumptions were based on the fact that no differences in EFS were found.

For the HR risk group, five year EFS was available for all HR patients (High MRD, 79%) and for a subset of patients who had been randomised to either standard or augmented therapy. Since patients were only randomised in case of a rapid early response (IR or SR group), this subgroup of patients has a relatively favourable prognosis compared to all patients with high MRD. This has been reflected by the lower five year EFS in all patients with high MRD compared to the EFS in the randomised groups (79%, 82.8 and 89.6% for the complete high MRD group, standard treatment group and augmented therapy group). The ERG considers the EFS in the complete risk group as the most reliable estimate of five year EFS of HR paediatric patients. With respect to five year OS, estimates were only reported for the randomised subgroups with a relatively favourable prognosis. In order to correct for this bias, we assumed that the relative difference between the complete high MRD group and the relatively favourable patient population was similar for the EFS and OS. Consequently, the average five year OS of the two randomised subgroups (90.9%) was reduced with 8.4%[1] to obtain a five year OS for the HR group of 83.3%.

To summarise, the ERG considers the following survival estimates more reliable than those provided by the company and these are therefore included in the ERG base-case analysis:

- Five year OS: 97.9% for the SR and IR group and 83.3% for the HR group
- Five year EFS: 94% for the SR and IR group and 79% for the HR group

Survival estimates in adult population
There is no strong evidence for the five year EFS of 30% for patients aged ≥41 years and 40% for patients aged ≤40 years. However, the ERG did not identify any other more robust estimates and considers the impact of the survival rate on the ICER as minimal given that equal effectiveness is assumed.

Extrapolation of survival
The assumption that paediatric patients are cured if they remain in the EFS until five years is considered to be reliable assumption as only a few events are reported after five years.[85] It is therefore reasonable to use the general mortality risk after five years. The ERG found an error in the model as it used the mortality figures of the female instead of the mortality risk weighted by male/female ratio in the calculations. This error was corrected in the ERG base case (see Section 5.3).

However, the ERG considers a mortality increase of 90% for patients in the R/ST state as far too small. Given that at the age of 10 years the mortality rate in the general population is extremely small, increasing this probability by 90% is a very limited impact on life expectancy. The percentage of R/ST patients still being alive would be 99.78%. The company motivated the 90% reduction in mortality by referring to two studies reporting five year OS

[1] 8.4% = 1 – 79%/((82.8%+89.6%)/2)

of 7-10% in relapsed patients.[86, 87] As the paper by Oriol et al.[86] only pertains to the adult population, the ERG used the Fielding et al study,[87] which reported a 5-year OS of 12% in patients aged below 20 years. In order to arrive at the survival percentage of 12%, it would be necessary to assume a yearly mortality rate of approximately 35%. Thus, we use in our ERG base case an estimate of 35% for the probability of death per year.

Furthermore, there was a small error in the formula to estimate the general mortality risk at each age. The mortality was only based upon females instead of the weighted male/female distribution. This error has been corrected in the ERG base case.

The survival in adult patients is modelled according to a Weibull function and the assumption that all patients have been died after 40 years. Due to a lack of data, the company was unable to explore alternative parametric survival functions. The ERG did not explore other parametric functions, as indeed no data was available for this. We did vary the year that 0% was reached with the survival curve, and those changes had no visible impact on the ICER. The ERG considers it unlikely that alternative survival functions would substantially impact the ICER since equal effectiveness is assumed between the different formulations.

Hypersensitivity rate

The ERG questions whether all hypersensitivity rates used as input for the cost effectiveness analysis reflect the proportion of patients who require a treatment switch due to hypersensitivity to asparaginase. With respect to the hypersensitivity to native *E. coli*, the ERG agrees that 20% can be considered as a reliable and conservative estimate. However, there is no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinase also reflect the proportion of patients who require a treatment switch. The rate of hypersensitivity to pegaspargase is based on the estimate of hypersensitivity in Vora et al. 2013.[19] However, no definition of that rate has been provided and from the reported information it appears most reasonable to assume that the reported percentage reflects the proportion of patients with a grade 3 or 4 adverse event. The ERG found another paper reporting hypersensitivity to pegaspargase given at a dosage of 1,000 IU/m^2.[49] In that paper, the proportion of patients with a treatment switch has explicitly been reported and was 13.2%. The ERG has used this estimate in the ERG base case analysis.

It was also not defined in the original studies[55, 84] that the rates of hypersensitivity to Erwinase reflect the proportion of patients switching treatment. The ERG found an additional study which explicitly stated that 9% discontinued Erwinase due to an allergic reaction.[88] The ERG used this percentage as rate for both first and second line Erwinase. The ERG decided to not distinguish in the hypersensitivity rate between first and second line for Erwinase, because that distinction has not been made for the other two formulations. Furthermore, the evidence for the 37% hypersensitivity to Erwinase after native *E. coli* was based upon intravenous administration, while Erwinase in given IM in the UK. It has been suggested by Vrooman et al.[84] that the relative high rate of hypersensitivity was due to the mode of administrations (IV instead of IM).

Another concern regarding the hypersensitivity rate is that several studies indicated that the hypersensitivity rate increases with more administrations.[19, 49, 83] This has not accurately been reflected in the current decision model as it assumes that the hypersensitivity always occurs after two administrations. However, data was lacking to accurately adjust the model for increasing hypersensitivity rates with more administrations.

Expert opinion
The ERG is concerned about the approach used to find estimates for variables in situations where no data could be found. In those instances, expert opinion was sought by the company. This is not uncommon in company submissions to NICE; however, in this instance only two experts were able to give their expert opinion, of the total of four who were approached.

The ERG requested in the clarification letter a justification why only four experts were approached. In its response, the company indicated that due to the limited number of patients with ALL, and the company's requirement for clinicians to be experienced in all three formulations of asparaginase and actively treating patients, there were only a limited number of eligible clinicians – four of whom the company approached, with two agreeing to participate. One clinician had particular experience in treating adult patients, the other paediatric patients. However, it is not clear to the ERG how large the limited number of eligible clinicians was, from whom the four were selected. Neither was it clear whether it might have been feasible to obtain opinions from more experts. Given the strong reliance of the model on expert opinion, the ERG would have expected that a greater effort would have been made to consult with experts from the UK.

5.2.7 Health related quality of life

Utilities per health state
The literature search regarding quality of life did not identify quality of life utilities for ALL in the UK. Furthermore, none of the identified studies used the EQ-5D to measure quality of life. It was therefore decided to apply the relative difference in quality of life between the general population and the ALL treatment phases as reported by Furlong et al.[89] to published UK EQ-5D population norms.[90] The CS states that this method was chosen because it was not feasible to map the HUI data onto the EQ-5D as patient level data was unavailable.

Furlong et al.[89] report the quality of life in patients aged ≥ 5 years who were treated according to the Dana Farber Cancer Institute (DFCI) Childhood ALL Consortium 95-01 (DFCI 95-01) trial protocol in the United States and Canada. The reported quality of life reflect the responses of parents on the Health Utilities Index (HUI) (both HUI Mark 2 (HUI2) and HUI Mark 3 (HUI3)), because most patients were too young to self-report. HUI assessments were collected for each of the following phases: remission induction (day 23), CNS therapy (second week for those not requiring general anaesthesia or at initiation of the intensification phase), intensification (week three, day 14 of a cycle with asparaginase), continuation (week one, day 0 of a cycle), and initial two year post-treatment (approximately four years after diagnosis). Separate utility values were estimated for HUI2 and HUI3 for each of the treatment phases.

The quality of life of ALL patients was compared with the quality of life in a control group of the general population (Table 5.9). These quality of life utilities in the control group were derived from published summary results of control groups from Canada that matches the patient population with respect to age and gender.[91, 92] The relative difference in quality of life was calculated as follows: $\frac{Utility\ population\ norm - Utility\ ALL\ treatment\ phase}{Utility\ population\ norm}$. In the cost effectiveness analysis, the average relative utility decrement of HUI2 and HUI3 was used. The quality of life post-treatment was not significantly and clinically (≥0.03) different from the control group and therefore assumed to be similar to the norm population.[93]

Although the treatment protocol in the UK is not completely identical to the DFCI protocol, it was assumed that the observed relative utility decrements are applicable to the UK setting (Table 5.10). For paediatric patients, both interim maintenance and delayed intensification phases were considered to be similar to the intensification phase of the DFCI protocol. For adult patients, the consolidation phase was considered to be similar to the intensification phase. Furthermore, a CNS therapy phase was not incorporated in the treatment protocol for adult patients.

Table 5.9: Quality of life utilities and relative utility decrement per treatment phase (Furlong et al.)

Population norms				
HUI2	0.95			
HUI3	0.92			
ALL treatment phase	**Ind.**	**CNS**	**Int.**	**Cont.**
HUI2	0.74	0.82	0.86	0.88
HUI3	0.67	0.75	0.79	0.85
Relative utility decrement				
HUI2	22%	14%	9%	7%
HUI3	27%	18%	14%	8%
Average	**25%**	**16%**	**12%**	**7%**

Abbreviations: Ind., induction; CNS: central nervous system; Int., intensification; Cont., continuation.

Table 5.10: Utility decrements applied in the model

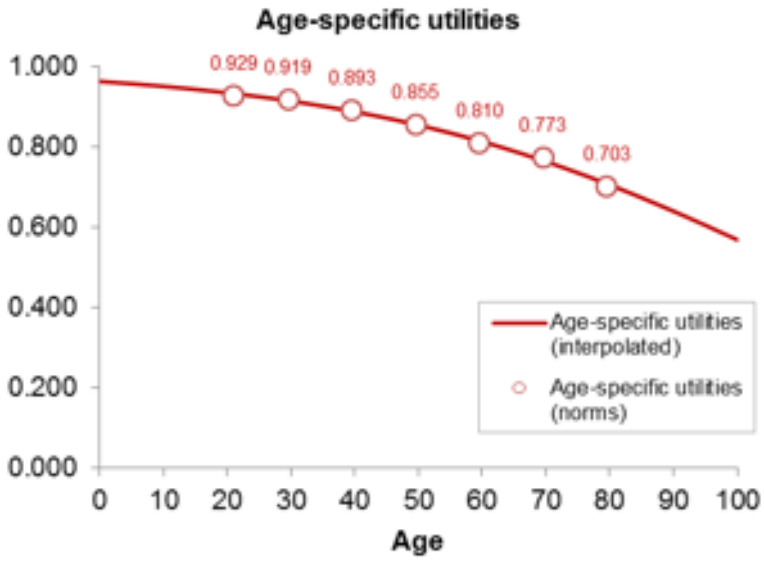
Paediatric	Ind.	Cons.	IM 1	DI 1	IM 2	DI 2	Cont.	End week
	25%	16%	12%	12%	12%	12%	7%	0%
Adults	Ind.	Int.	Cons. 1	Cons. 3	Maint.	End week		
	25%	25%	12%	12%	7%	0%		

Abbreviations: Ind., induction; Int., intensification; IM, interim maintenance;DI, delayed intensification ;Cons.,consolidation; Cont., continuation; Maint, maintenance

In the health economic model, the utility decrements from Table 5.10 were subtracted from age-specific EQ-5D population norms. These population norms were derived from Szende et

al.[90] who reported utilities for different age groups. It was assumed that the reported EQ-5D utility corresponded with the utility at the median age of each age group. For all other ages, a logistic regression was used to interpolate between the observed utility values.

Figure 5.7: Interpolated age-specific utilities (EQ-5D population norms)



Interpolated age-specific EQ-5D population norms, $U(age) = \frac{1}{1+e^{(0.030 age+3.259)}}$, with R^2=0.995.

Besides the utility decrements for the different treatment phases in the EFS health state, a reduction in quality of life of 20% was assumed for paediatric patients in the R/ST state.

Other quality of life considerations

The experience of hypersensitivity can be considered as an anaphylactic episode according to a clinical expert. During this period, patients may be anxious, having pain, decreased mobility and limited in activities of daily living. However, data about the quality of life decrement according to the EQ-5D is not available. Therefore, it is assumed that the utility decrement from a NICE clinical guideline for anaphylaxis of 0.014 also reflect the utility decrement for hypersensitivity.[94] This value was derived assuming five days of full quality of life loss per recurrence of anaphylaxis (5/365 = 0.014).

An important difference between pegaspargase and the two other asparaginase agents is the required number of drug administrations and the type of administration. Six dosages of native *E. coli* or Erwinia are required for each dosage of pegaspargase. Furthermore, in adult patients, pegaspargase is administered by intravenous (IV) instead of intramuscular (IM) injections. These differences may impact the quality of life, because expert clinicians stated that IM injections are very painful and may cause bruising due to thrombocytopenia. However, the economic model conservatively does not account for this difference due to a lack of evidence.

ERG comment: The ERG agrees with the company that there are no UK-specific utilities available for acute lymphoblastic leukaemia. The company has been very transparent regarding the methodology used to derive UK-specific EQ-5D utilities from US/Canadian-specific HUI2 and HUI3 utilities. The ERG considers this approach to be reliable given the fact that any more reliable estimates of UK-specific utilities are missing. However, there are a few points of concerns that need to be addressed.

First, it can be questioned whether the relative difference in utility between patients and the general population are transferable between countries and questionnaires. However, no evidence is available with respect to the validity or invalidity of this approach. In addition, the relative differences were based on the average difference for the HUI2 and HUI3. Usually, the utility values of the HUI2 and HUI3 are separately reported and it is uncommon to use an average utility for these two questionnaires. However, as only the relative reduction is used in the cost effectiveness analysis, the use of the average reduction may be more realistic than using the reduction of one of the two questionnaires.

Another concern reflects the fact the utilities from Furlong et al.[89] were based on parental responses. It has been known that depression, worries and psychological distress from parents is associated with lower perception of the child's quality of life.[95] The quality of life may therefore be underestimated. Furthermore, it is questionable whether these quality of life estimates are also applicable to an adult patient population.

In order to explore the impact of differences in quality of life, the ERG has performed a scenario analysis in which a mapping algorithm is used to estimate EQ-5D utilities from the published HUI3 utilities.[96] However, it should also be noted that the impact of differences in quality of life utilities is marginal as long as similar effectiveness is assumed.

Finally, the assumption of a 20% reduction in quality of life for patients with a relapse is not supported by evidence. Recently, ALL health state descriptions have been valued by the UK general population.[97] One of the valued health states was progressive disease (which may be comparable to being in the R/ST). The estimated utility of that health state was 0.30. The ERG has performed a scenario analysis in which the quality of life was decreased with 68% in order to achieve a utility of 0.30.

5.2.8 Resources and costs

Only costs associated with the three different asparaginase products and monitoring and administration of hypersensitivity were included in the model. The remainder of the chemotherapeutic regimen were considered to be the same.

Drug costs

Drug wastage was accounted for in the calculation of drug acquisition (i.e. in the model patients received only whole vials). In the company submission a table including the costs per vial for the three different asparaginase therapies is presented (see Table 5.11, CS Table 44).

Administration and monitoring costs

Total monitoring and administration costs per injection or infusion were £163.50. This estimate is based on half an hour administration and an hour monitoring of a band 6 nurse (£109 per hour based on PSSRU[98]). Monitoring is necessary due to the risk of hypersensitivity in in all forms of asparaginase.

Asparaginase dosing and regimen

The frequency and dosing of the pegaspargase by treatment phase was obtained from the paediatric UKALL 2003 protocol and the adult UKALL 14 protocol. The treatment of paediatric ALL patients consist of seven treatment phases. According to the UKALL 2003 protocol (Appendix 3 of CS) the paediatric patients at standard risk and intermediate risk receive in total four doses of 1000 U/m2 asparaginase. Two doses are given during induction and the other two during delayed intensification one and two. The paediatric patients at high risk receive in total 12 doses of 1000 U/m2 asparaginase. Two doses each during induction, consolidation, interim maintenance, delayed intensification, interim maintenance 2 and delayed intensification 2.

The treatment of adult ALL patients consist of five treatment phases. According to the UKALL 14 protocol (as described in the company submission p. 36) adult patients between 25 and 40 receive six doses of 1000 U/m2 (two during induction, two during intensification, and one during the two consolidation phases). The adults between 41-65 years receive five doses (one during induction, two during intensification and one during the two consolidation phases).

The frequency of native *E. coli* and Erwinase was assumed to be six times that of pegaspargase. This assumption was based on the opinion of clinical experts. In addition, the UKALL 2011 protocol states that in case of hypersensitivity each dose of pegaspargase should be replaced with six doses of Erwinase. The doses for native *E. coli* and Erwinase are 10,000 IU/m2 and 20,000 IU/m2, respectively. It is not reported where these doses are based on.

Patient weight/BSA

Treatment of ALL patients with asparaginase depends on the body surface area of the patients. To calculate the required drug doses for each treatment regimen, an estimate of body surface area (BSA) was obtained for children and adults separately.

For paediatric patients in England, the median height and weight were retrieved from the Royal College of Paediatrics and Child Health (RCPCH) growth charts for boys and girls from 0-18 years. Based on these data, an age specific weighted average for all age groups was estimated. The median age of children with ALL is five years (based on Vora et al. 2013[19]) and corresponding estimated BSA is 0.75m^2. This value is used in the model.

For adults the average body surface area was obtained from a UK study of adult cancer patients and was assumed to be 1.79m^2.[99]

Table 5.11: Costs per dose

Asparaginase type	Dose	Average BSA	Average dose per patient	Vial size	Vials per dose	Costs per vial	Monitoring costs per dose	Drug costs per dose
Paediatric patients								
PEG	1000 UM/m2	0.75m2	750	3,750	1	1,296.19	163.50	1,296
Native E.	10,000 UM/m2	0.75m2	7,500	10,000	1	70.87	163.50	71
Erwinase	20,000 UM/M2	0.75m2	15,000	10,000	2	613.00	163.50	1,226
Adults								
PEG	1000 UM/m2	1.79m2	1790	3,750	1	1,296.19	163.50	1,296
Native E.	10,000 UM/m2	1.79m2	17900	10,000	2	70.87	163.50	142
Erwinase	20,000 UM/M2	1.79m2	35800	10,000	4	613.00	163.50	2,452

Table 5.12: Costs of treatment phase (based on Tables 43 and 44 CS)

Group	Therapy	Doses 1st-line	Doses 2nd-line	Costs per dose 1st-line (£)	Costs per dose 2nd-line (£)	Monitoring costs per dose - 1st-line (£)	Monitoring costs per dose - second line (£)	Total (£)
Paediatric patients - No hypersensitivity								
High risk	PEG continued	12	Continued	1,296	Continued	164	Continued	17,516
Low/Intermediate	PEG continued	4	Continued	1,296	Continued	164	Continued	5,839
High risk	Native E. continued	72	Continued	71	Continued	164	Continued	16,875
Low/Intermediate	Native E. continued	24	Continued	71	Continued	164	Continued	5,625
High risk	Erwinase continued	72	Continued	1,226	Continued	164	Continued	100,044
Low/Intermediate	Erwinase continued	24	Continued	1,226	Continued	164	Continued	33,348
Adults - No hypersensitivity								
21-40 years	PEG continued	6	Continued	1,296	Continued	164	Continued	8,758
41-65 years	PEG continued	5	Continued	1,296	Continued	164	Continued	7,298
21-40 years	PEG - transplant	2	Transplant	1,296	Transplant	164	Transplant	2,919
41-65 years	PEG - transplant	3	Transplant	1,296	Transplant	164	Transplant	4,379
21-40 years	Native E. continued	36	Continued	142	Continued	164	Continued	10,989
41-65 years	Native E. continued	30	Continued	142	Continued	164	Continued	9,157
21-40 years	Native E. - transplant	12	Transplant	142	Transplant	164	Transplant	3,663
41-65 years	Native E. - transplant	18	Transplant	142	Transplant	164	Transplant	5,494
21-40 years	Erwinase continued	36	Continued	2,452	Continued	164	Continued	94,158
41-65 years	Erwinase continued	30	Continued	2,452	Continued	164	Continued	78,465
21-40 years	Erwinase - transplant	12	Transplant	2,452	Transplant	164	Transplant	31,386
41-65 years	Erwinase - transplant	18	Transplant	2,452	Transplant	164	Transplant	47,079
Paediatric patients - hypersensitivity first line treatment not second line								
High risk	PEG - Erwinase	2	60	1,296	71	164	164	16,982
Low/intermediate	PEG - Erwinase	2	12	1,296	71	164	164	5,732
High risk	Native E. - Erwinase	2	70	71	164	164	164	23,359
Low/intermediate	Native E.- Erwinase	2	22	71	164	164	164	7,663

Group	Therapy	Doses 1st-line	Doses 2nd-line	Costs per dose 1st-line (£)	Costs per dose 2nd-line (£)	Monitoring costs per dose - 1st-line (£)	Monitoring costs per dose - second line (£)	Total (£)
High risk	Erwinase - PEG	2	12	1,226	1,296	164	164	20,295
Low/intermediate	Erwinase - PEG	2	4	1,226	1,296	164	164	8,618
High risk	Erwinase - Native E.	2	70	1,226	71	164	164	19,185
Low/intermediate	Erwinase - Native E.	2	22	1,226	71	164	164	7,935
Adults - hypersensitivity first line treatment (not second line)								
21-40 years	PEG - Erwinase	2	24	1,296	2,452	164	164	65,691
41-65 years	PEG - Erwinase	2*	24	1,296	2,452	164	164	34,305
21-40 years	PEG - transplant	2	Transplant	1,296	Transplant	164	Transplant	2,919
41-65 years	PEG - Erwinase - transplant	2*	12	1,296	2,452	164	164	34,305
21-40 years	Native E. - Erwinase	2	34	71	2,452	164	164	89,396
41-65 years	Native E. - Erwinase	2	28	71	2,452	164	164	73,703
21-40 years	Native E. – Erwinase - transplant	2	7	71	2,452	164	164	22,538
41-65 years	Native E - Erwinase - transplant	2	16	71	2,452	164	164	42,317
21-40 years	Erwinase - PEG	2	6	1,226	1,296	164	164	11,537
41-65 years	Erwinase - PEG	2	5	1,226	1,296	164	164	10,077
21-40 years	Erwinase - PEG - transplant	2	2	1,226	1,296	164	164	5,698
41-65 years	Erwinase - PEG - transplant	2	3	1,226	1,296	164	164	7,158
21-40 years	Erwinase - Native E	2	34	1,226	142	164	164	13,157
41-65 years	Erwinase - Native E	2	28	1,226	142	164	164	11,326
21-40 years	Erwinase - Native E. transplant	2	8	1,226	142	164	164	5,223
41-65 years	Erwinase - Native E. - transplant	2	16	1,226	142	164	164	7,663

Group	Therapy	Doses 1st-line	Doses 2nd-line	Costs per dose 1st-line (£)	Costs per dose 2nd-line (£)	Monitoring costs per dose - 1st-line (£)	Monitoring costs per dose - second line (£)	Total (£)
Paediatric patients - hypersensitivity first line treatment and second line								
All risk groups	PEG - Erwinase disc.	2	2	1,296	1,226	164	164	5,698
All risk groups	Native E. - Erwinase disc.	2	2	71	1,226	164	164	3,248
All risk groups	Erwinase - PEG disc.	2	2	1,226	1,296	164	164	5,698
All risk groups	Erwinase - Native E. disc.	2	2	1,226	71	164	164	3,248
Adults - hypersensitivity first line treatment and second line								
21-40 years	PEG - Erwinase disc.	2	2	1,296	2,452	164	164	8,150
41-65 years	PEG - Erwinase disc.	2*	2	1,296	2,452	164	164	8,150
41-65 years	PEG – PEG transplant	2	1	1,296	1,296	164	164	4379
21-40 years	Native E. - Erwinase disc.	2*	2	142	2,452	164	164	5,814
41-65 years	Native E. - Erwinase disc.	2	2	142	2,452	164	164	5,841
21-40 years	Erwinase - PEG disc.	2	2	2,452	1,296	164	164	8,150
41-65 years	Erwinase - PEG disc.	2	2	2,452	1,296	164	164	8,150
21-40 years	Erwinase - Native E. disc.	2	2	2,452	142	164	164	5,841
41-65 years	Erwinase - Native E. disc.	2	2	2,452	142	164	164	5,841

* These were incorrectly modelled in the electronic model (12 instead of 2)

Costs of hypersensitivity and other adverse events
The main difference between the three treatments is their risk on hypersensitivity reaction. The average costs applied in the model is £470 based on the reference cost for "Allergy or Adverse Allergic Reaction" (HRG WH05Z 2014/15). No other adverse events costs were included in the model.

Hospital costs
Hospital costs of day case visits were mentioned in the company submission however not included in the model. This is considered to be a conservative assumption since six doses of Erwinase and Native E. are required for one dose of PEG which implies higher costs for the comparators.

Health state costs
No health state costs were included in the model. The ERG asked to the company to provide estimates of the health care costs for EFS and R/ST, as the proportion of patients in each health state may differ slightly. However, the company could not provide accurate estimates because no costing studies or economic evaluations were available that incorporate such costs.

ERG comment: The company estimated the BSA for children by using the median age (five years) and the corresponding BSA. The ERG corrected this for the new ERG base-case to mean age.

The ERG was unsure regarding the assumption that the frequency of native *E. coli* and Erwinase is always six times that of pegaspargase. The literature shows that sometimes fewer doses are used.[28] Therefore the ERG explored the effect of varying the doses for native *E. coli* and Erwinase in a scenario analysis. In addition, the doses of native *E. coli* and Erwinase were assumed to be 10,000 IU/m2 and 20,000 IU/m2 in the model, respectively. These doses were not further justified in the CS. However, in the literature different doses were applied (5000 and 6000 IU/m2 for Native E.).[28, 100] Thus, it is unclear to the ERG what dosages would be most realistic in practice.

Another relevant concern regarding the costs of treatment of ALL in children are the drug cost of the second interim maintenance and delayed intensification course. In the most recent protocol, these phases are no longer included in the treatment of children due to a lack of benefit of the second intensification course.[19] Therefore, the ERG base-case only incorporates one interim maintenance and delayed intensification course as this best represents current clinical UK practice.

The ERG agreed with not including hospital costs of day case visits as this is seen as a conservative assumption. Native *E. coli* and Erwinase are expected to have more day case visits because six doses are administered whereas only one dose is administered for PEG. However, no reliable data is available on the setting in which the asparaginase treatment is provided for the various formulations and modes of administration.

The ERG doubted the assumptions that all adverse events other than hypersensitivity were equal for the three treatment groups. Therefore the ERG explored the literature for relevant studies on important adverse events of the treatments (e.g. pancreatitis). However, it appeared that no robust evidence on incidence of adverse events is available in the literature, due to issues regarding dosing and a lack of comparative studies. The impact of adding costs of other adverse events could therefore not be explored.

The ERG agreed with the company that no suitable literature is available to estimate the health state costs. In the UKALL protocol it is stated that a relapse costs on average £50,000 per child. However, it is unclear on what evidence this number is based. The ERG identified two studies that were potentially relevant to estimate EFS health state costs.[101, 102] Both studies provide estimates on hospital costs related to ALL including inpatient costs. However, the estimates of the two studies varied considerably (i.e. from approximately $35,000 (US 1998 dollars) in the study of Kurre et al. 2002[101] up to more than $180,000 (Canadian 2014 dollars) in the study of the Health Quality Ontario and the Toronto Health Economics and Technology Assessment Collaborative).[102] The ERG therefore decided that the evidence was too weak to include a reliable estimate in the model. Nevertheless, not including the health state costs is a limitation of the model.

5.2.9 Cost effectiveness results

The results of the company's base-case are presented in Table 5.13, with all the comparisons against Pegaspargase first line followed by Erwinase second line. This analysis, which combines the paediatric and the adult groups, is shown in Table 5.13. Pegaspargase first line followed by Erwinase second line is less expensive and yields more QALYs than native *E. coli* asparaginase first line followed by Erwinase second line and Erwinase first line followed by native *E. coli* asparaginase second line. Erwinase first line followed by pegaspargase second line provides slightly more QALYs (0.0047), but at higher costs (£40,362), resulting in an ICER of £8,627,243. Similar conclusions can be drawn for the paediatric and adult population separately (Table 5.14 and Table 5.15**Error! Reference source not found.**).

Table 5.13: Base-case cost effectiveness results for the complete patient population

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.>Erwinase	£7,871	17.3431	—	—	—
Native Asp.>Erwinase	£12,612	17.2926	£4,741	-0.0504	Dominated
Erwinase>Native Asp.	£48,149	17.3396	£40,277	-0.0035	Dominated
Erwinase>PEG-Asp.	£48,234	17.3477	£40,362	0.0047	£8,627,243

Table 5.14: Base case cost effectiveness results for paediatric patients

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	£8,545	22.1294	—	—	—
Native Asp.—Erwinase	£12,352	22.0633	£3,807	-0.0662	Dominated
Erwinase—Native Asp.	£44,781	22.1248	£36,236	-0.0046	Dominated
Erwinase—PEG-Asp.	£44,900	22.1356	£36,355	0.0061	£5,917,762

Table 5.15: Base case cost effectiveness results for adult patients

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	£5,913	3.4327	—	—	—
Native Asp.—Erwinase	£13,368	3.4280	£7,455	-0.0047	Dominated
Erwinase—Native Asp.	£57,936	3.4324	£52,023	-0.0003	Dominated
Erwinase—PEG-Asp.	£57,922	3.4332	£52,010	0.0004	£123,446,241

Disaggregated results of the base case incremental cost effectiveness analysis

The CS presented disaggregated results both for costs and for QALYs. A summary of the health state costs was not provided, because the CS only includes costs of asparaginase treatment (including costs of administration and hypersensitivity) for patients in the EFS state. The distribution of the costs over the three cost categories (technology, administration and hypersensitivity) in the four alternatives is shown in Table 5.16. The difference in costs between pegaspargase first line and native *E. coli* asparaginase first line is mainly due to the higher administration costs since native *E. coli* is more frequently administered. The higher costs for the alternatives with Erwinase as first line treatment are mainly caused by the higher technology costs (90% of the total incremental costs). Nevertheless, the administration costs for these two alternatives are more or less similar to the administration costs of native *E. coli* as first line treatment. Table 5.17 presents the breakdown for the QALYs.

Table 5.16: Disaggregated costs per cost category

Item	Average treatment cost			
	PEG-Asp.— Erwinase	**Native Asp.— Erwinase**	**Erwinase— PEG-Asp.**	**Erwinase— Native Asp.**
Technology cost	*£6,980*	*£7,716*	*£43,348*	*£43,076*
PEG-Asp.	£6,650	£0	£399	£0
Native Asp.	£0	£2,144	£0	£127
Erwinase	£330	£5,571	£42,949	£42,949
Administration cost	*£878*	*£4,769*	*£4,857*	*£5,039*
PEG-Asp.	£839	£0	£50	£0
Native Asp.	£0	£4,145	£0	£233
Erwinase	£40	£625	£4,807	£4,807
Hypersensitivity	*£12*	*£128*	*£29*	*£34*
Total	**£7,871**	**£12,612**	**£48,234**	**£48,149**
Absolute increment				
Technology cost	—	£735	£36,368	£36,095
Administration cost	—	£3,891	£3,978	£4,161
Hypersensitivity	—	£115	£16	£21
Total	**—**	**£4,741**	**£40,362**	**£40,277**
% absolute increment				
Technology cost	—	15.5%	90.1%	89.6%
Administration cost	—	82.1%	9.9%	10.3%
Hypersensitivity	—	2.4%	0.0%	0.1%
Total	**—**	**100.0%**	**100.0%**	**100.0%**

Table 5.17: Disaggregated QALYs per health state

Item	QALY			
	PEG-Asp.— Erwinase	**Native Asp.— Erwinase**	**Erwinase— PEG-Asp.**	**Erwinase— Native Asp.**

Item	QALY			
	PEG-Asp.—Erwinase	**Native Asp.—Erwinase**	**Erwinase—PEG-Asp.**	**Erwinase—Native Asp.**
EFS	16.6747	16.6265	16.6792	16.6714
R/ST	0.6683	0.6662	0.6685	0.6682
Total	**17.3431**	**17.2927**	**17.3478**	**17.3396**
Increment (PEG-Asp-Erwinase relative to other treatment sequences)				
EFS	—	-0.0482	0.0045	-0.0033
R/ST	—	-0.0021	0.0002	-0.0001
Total	**—**	**-0.0504**	**0.0047**	**-0.0035**
% absolute increment				
EFS	—	95.8%	95.8%	95.8%
R/ST	—	4.2%	4.2%	4.2%
Total	**—**	**100.0%**	**100.0%**	**100.0%**

ERG comment: The base-case analysis of the manufacturer included some smaller programming errors, thus the outcomes, including the ICER presented here, are incorrect. These errors were corrected by the ERG and the results of this ERG analysis are shown in Section 5.3

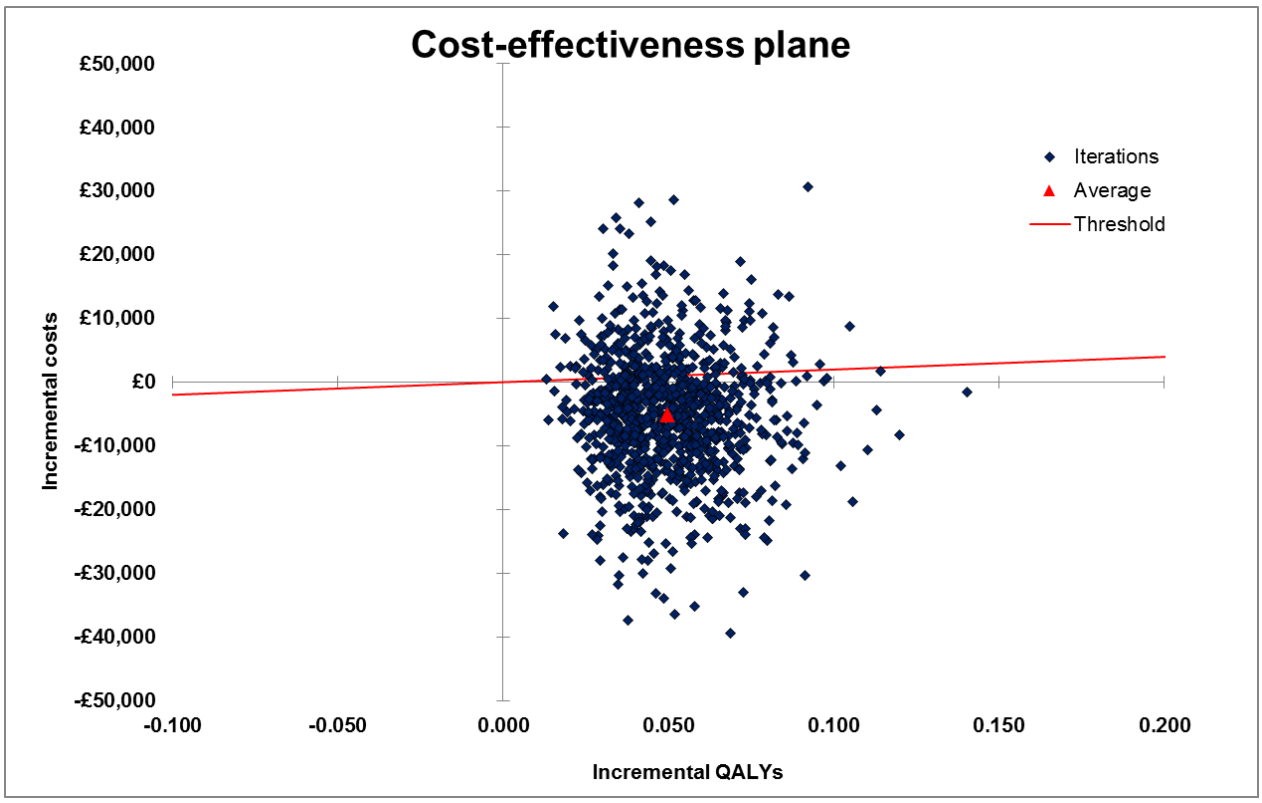
5.2.10 Sensitivity analyses

Probabilistic sensitivity analysis

Table 50 of the CS provides a detailed overview of the values and distributions used in the probabilistic sensitivity analysis. Where possible the known standard errors (SE) were used to define parameter values for the distributions. A SE of 5% of the mean was assumed where the SE is unknown. Discount rates for costs and QALYs and the dosing and treatment regimens were excluded from the PSA.

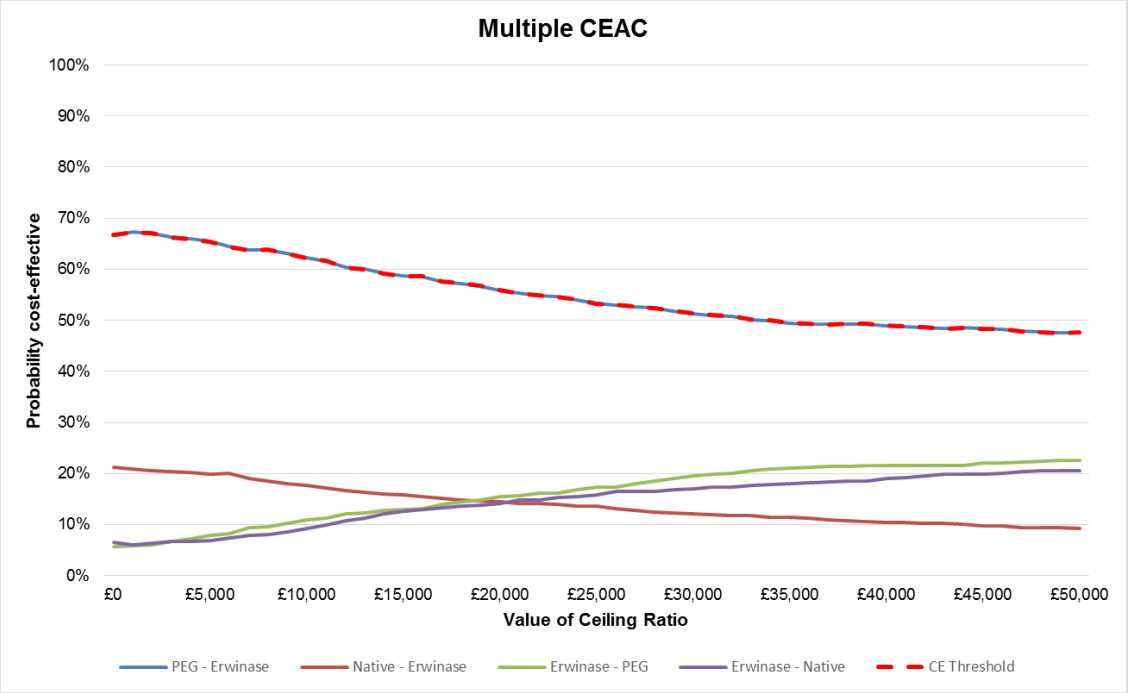
For the comparison of pegaspargase-Erwinase vs. native asparaginase-Erwinase the results of 1,000 simulations were plotted on the cost effectiveness plane (Figure 5.8), and the cost effectiveness acceptability curve (CEAC) was calculated (Figure 34 in the CS). The majority of the simulations fall in the south-east quadrant, indicating that pegaspargase-Erwinase is a dominant treatment strategy. Pegaspargase-Erwinase has a 77.9% probability of being below the £20,000 willingness to pay threshold when compared with native asparaginase-Erwinase.

Figure 5.8: Cost effectiveness plane for pegaspargase-Erwinase vs. native *E. coli* asparaginase-Erwinase (Figure 33 in CS)



A multiple CEAC was also produced to compare pegaspargase-Erwinase to all three treatment strategies. Figure 5.9 shows that pegaspargase-Erwinase is cost effective for all threshold values up to £50,000.

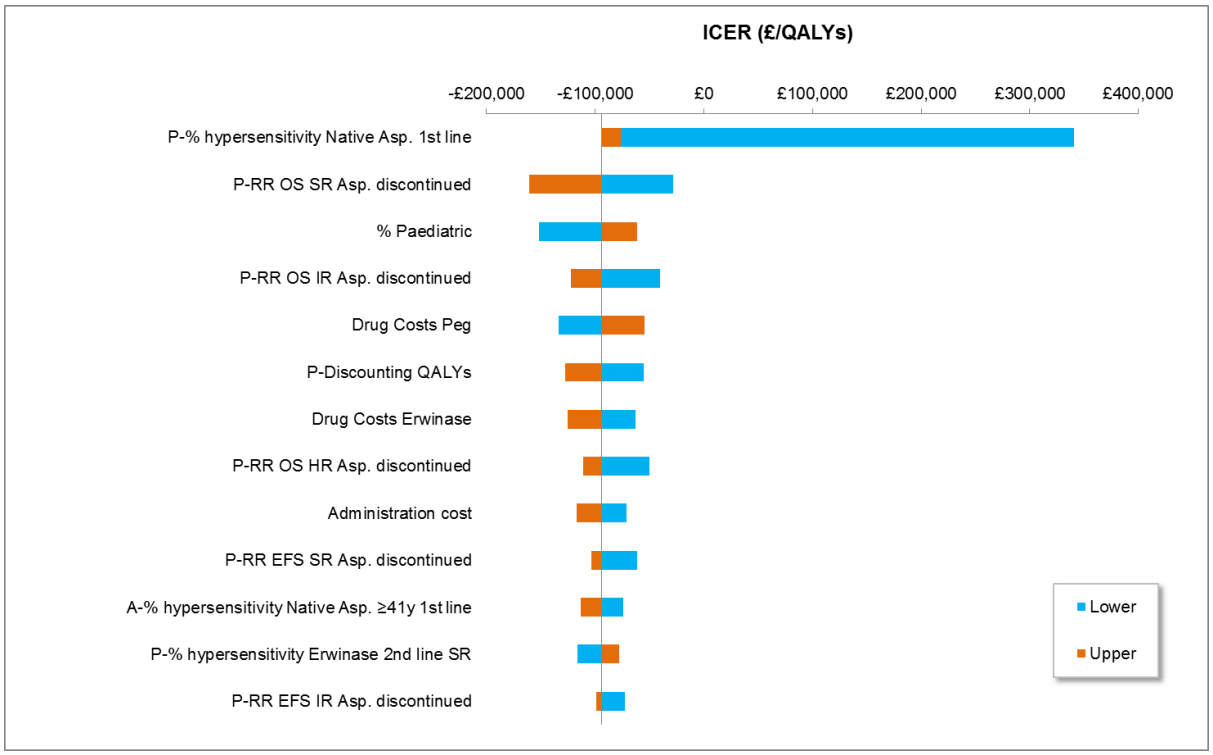
Figure 5.9: Multiple CEAC for pegaspargase-Erwinase vs all treatment strategies



Deterministic univariate sensitivity analysis

A deterministic sensitivity analysis (DSA) was performed on all inputs included in the model apart from the dosing and treatment regimens, and a tornado diagram was produced. Table 51 of the CS summarises the variables included in the tornado diagram and the relative variation used for each. For most variables, a lower and upper limit was defined at ±30% of the mean. This was done to clarify the relative importance of each input variable. Figure 5.10 presents the results for the 13 parameters to which the ICER is most sensitive. It shows that the ICER is stable for variation in most of the parameters; however it is unstable when the hypersensitivity rate for first line treatment with native *E. coli* asparaginase is varied. When the hypersensitivity rate is set to 0%, i.e. less than the 2% base rate used for pegaspargase, pegaspargase no longer leads to an increase but rather a decrease of QALYs.

Figure 5.10: Tornado diagram for DSA results (ICER) of pegaspargase-Erwinase vs native asparaginase-Erwinase



Scenario analysis

The company performed the following scenario analyses:

1. Only the paediatric population
2. Only the adult population
3. Minimum cost of hypersensitivity
4. Maximum cost of hypersensitivity
5. Minimum rate of hypersensitivity
6. Maximum rate of hypersensitivity
7. 1.5% discount rate for both QALYs and costs in the paediatric population
8. Oncaspar dose per SmPC (2500 IU)
9. Minimum cost of native *E. coli*
10. Maximum cost of native *E. coli*
11. Mean paediatric age = 1
12. Mean paediatric age = 18

None of these scenario resulted in a different conclusion regarding the cost effectiveness of pegaspargase-Erwinase in comparison with any other alternative (Table 5.18).

Furthermore, a cost minimisation analysis has been performed assuming completely identical OS, EFS and hypersensitivity rates for either pegaspargase or *E. coli* as first line treatment. As a rationale for this analysis, the CS states that all outcomes of interest are experienced during the treatment phase and therefore a cost-minimisation analysis demonstrates the actual

impact on the NHS. In case similar effectiveness and toxicity is assumed, £354 can be saved by using pegaspargase instead of native *E. coli*.

Additionally, in response to questions in the clarification letter, the company also provided a worst and best case scenario based on a potential difference in EFS and OS between pegaspargase and native *E. coli*. These scenarios were based on evidence from two published trials in the paediatric population. Therefore, differences in EFS and OS were only applied in the paediatric population. The best case scenario used evidence from the CCG-1961 study [31] which shows better EFS and OS for pegaspargase (five year EFS: 81% vs 72%, 5-year OS: 89% vs 83%). The worst case scenario used evidence from the DFCI-91-01 study[34] which shows worse EFS for pegaspargase (five year EFS:78% vs 84%). Since no comparative evidence was available for Erwinase, the EFS and OS for Erwinase remained the same as in the company's base-case. In the worst case scenario, the pegaspargase formulation is at the borderline of being cost effective given the current threshold of £20,000. However, the company indicated that these results should be interpreted with caution, because it is unknown whether the results of the DFCI-91-01 study[34] are applicable to current UK clinical practice. Patients were enrolled between 1991 and 1995 in the US and Canada and did not receive any asparaginase treatment during induction treatment.

Table 5.18: Results scenario analysis

Scenario	PEG – Erwinase Vs. Native – Erwinase ICER (quadrant)	PEG – Erwinase Vs. Erwinase – PEG ICER (quadrant)	PEG – Erwinase Vs. Erwinase – Native ICER (quadrant)
Base case	PEG dominant	£8,725,004 (SW)	PEG dominant
100% paediatric population	PEG dominant	£5,917,762 (SW)	PEG dominant
100% adult population	PEG dominant	£123,644,929 (SW)	PEG dominant
Minimum cost of hypersensitivity	PEG dominant	£8,722,031 (SW)	PEG dominant
Maximum cost of hypersensitivity	PEG dominant	£8,726,059 (SW)	PEG dominant
Minimum rate of hypersensitivity	PEG dominant*	PEG dominant*	PEG dominant
Maximum rate of hypersensitivity	PEG dominant	£2,121,333 (SW)	PEG dominant
1.5% discount rate for paediatric population	PEG dominant	£5,138,376 (SW)	PEG dominant
Oncaspar dose per SmPC	PEG dominant	£8,555,431 (SW)	PEG dominant
Minimum cost of native	PEG dominant	£8,725,004 (SW)	PEG dominant
Maximum cost of native	PEG dominant	£8,725,004 (SW)	PEG dominant
Mean paediatric age = 1	PEG dominant	£8,558,688 (SW)	PEG dominant
Mean paediatric age = 18	PEG dominant	£9,452,180 (SW)	PEG dominant

Scenario	PEG – Erwinase Vs. Native – Erwinase ICER (quadrant)	PEG – Erwinase Vs. Erwinase – PEG ICER (quadrant)	PEG – Erwinase Vs. Erwinase – Native ICER (quadrant)
Best case scenario EFS/OS	PEG dominant	£84,914 (SW)	£86,810 (SW)
Worst case scenario EFS/OS	£20,326 (SW)	£49,501 (SW)	£50,070 (SW)

* The incremental QALYs are 0, and PEG is cost-saving.
Abbreviations: SW: South-West quadrant of CE-plane

ERG comment:

Probabilistic sensitivity analysis
In the CS, it is explained that where possible the known standard error (SE) were used to define parameter values for the distributions, and that a SE of 5% of the mean was assumed where the SE is unknown. However, nowhere in the CS and model are there variables, the SE of which was obtained from literature. In the electronic model, all beta distributions were defined such that they represented the uncertainty had the sample size been 100, regardless of the source of the estimate. As a result, for some input variables the implied SE is 70% of the mean, whereas for others only 2%. For the Gamma distributions, a SE of 100% of the mean was used, where a more realistic assumption would have been e.g. 20% or 30%.

Thus, in the ERG base case we have redefined all the distributions used in the PSA, in order to obtain a more realistic representation of the impact of parameter uncertainty on the outcome. (see Section 5.3)

Deterministic sensitivity analysis
For the deterministic analysis, in general a range from mean +/- 30% of the mean was used. While such blanket width of the interval does give an indication for which parameter the model outcomes are most sensitive, it does not provide any insight in the plausible range of outcomes given the realistic amount of variation to be expected for an input variable. Thus, it would have been preferable to use the 95% confidence intervals based on the PSA distributions for these ranges instead.

In the current analysis we see a large range of ICERs when the percentage of patients with hypersensitivity is varied for native *E. coli*. The range for that percentage is defined as 0% to 40%, which is a very large range, especially when compared to the range for pegaspargase from 0% to 6%. The ERG questions how realistic this difference in width of the ranges is.

Scenario analysis
The ERG regrets that the company chose to vary all hypersensitivity rates at the same time to the lowest or highest value, it would have been more informative to define a worst and best case scenario similar to that done for the EFS and OS.

The fact that changing the dosage of pegaspargase to that based on the SmPC has little impact on the outcomes is not surprising, given that even at the higher dose per m^2 most patients still only require one vial of pegaspargase.

5.2.11 Model validation and face validity check

In the company submission it is described that the assumptions in the model were validated through experts familiar with current and historic protocols (as detailed in Section **Error! Reference source not found.** of the CS). They were asked to validate inputs and provide expert opinion for inputs that lacked data. The experts consulted agreed with the DT model structure used as well as inputs. The company considered that their extensive experience in treating patients with this disease in the UK provided them with the best insight, especially considering the difference in dosing regimens used in the UK relative to other countries (1,000 IU/m^2) and the resultant favourable OS, EFS and hypersensitivity rate results.

ERG comment: As earlier mentioned (ERG comments Section 5.2.6), the ERG considers the reliance on only two experts for feedback on model structure and estimation of input parameters not justified. Given the strong dependence of the model on expert opinion, the ERG would have expected that a greater effort would have been made to consult with experts from the UK.

The ERG undertook a systematic approach of testing to assess the technical validity of the model. Various smaller errors were encountered, but no larger errors were found.

The results of the model appear plausible, given the underlying assumptions of the model. Assuming that EFS and OS are the same for all formulations, and that only the hypersensitivity differs per treatment, the result that pegaspargase followed by Erwinase is slightly more effective than other treatments is credible. The incremental costs of pegaspargase followed by Erwinase compared to the other treatments are also according to expectations.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on several remarks in Section 5.2 of this report the ERG defined a new base-case analysis. This new ERG base case included the following corrections and adjustments:

Correction of errors in the model

- Correction of the risk distribution in paediatric patients.
  The new risk group distribution is based upon Figure 2 instead of Table 5 of Vora et al. 2013, since Figure 2 is identical to Figure 2 of Vora et al. 2014 and therefore considered to be the correct distribution.
- Correction of the background mortality
  The company referred to the mortality of female patients instead of the weighted background mortality according to the male/female ratio. In the ERG base-case, it is now correctly referred to the weighted background mortality
- Correction of some number of administrations in case of hypersensitivity
  In some branches of the health economic model, the number of asparaginase

administrations were not corrected to the assumption that hypersensitivity occurs after two administrations. In the ERG base-case analysis, the maximum number of administrations was always set to two in the case that patients experienced hypersensitivity. Subsequently, the number of administrations for second line asparaginase treatment was adjusted as well.

- Correction of utility after stopping treatment
  The disutility of 20% of patients in the R/ST health state was mistakenly added to the utility of patients in the EFS state, resulting in a utility above one. This has been corrected for in the ERG base-case by subtracting this reduction from the utility in the EFS state.

Adjustments to the model

- Use of the mean age instead of the median age in the paediatric patient population
  In health economics, all analyses should be based on means instead of medians, in order to allow the estimation of the macro costs as the multiplication of the number of eligible patients times the per patient costs. Therefore, the mean age of 7.3 years was used as starting age for the paediatric patient population in the ERG base case.
- No second interim maintenance and delayed intensification course.
  Due to a lack of benefit of a second delayed intensification course, the current treatment protocol for paediatric patients only include one interim maintenance and delayed intensification course. As the most recent protocol best reflects current clinical practice, only one interim maintenance and delayed intensification course has been modelled in the ERG base-case analysis.
- Risk of hypersensitivity to pegaspargase based on percentage of patients switching asparaginase treatment.
  In the Company's base case, the hypersensitivity rate to pegaspargase was based on the reported hypersensitivity rate in the UKALL 2003 trial. However, it was not specified how this rate was defined. Therefore, the ERG could not conclude that this rate reflect the proportion of patients switching asparaginase treatment. The ERG found another study that used pegaspargase at a dosage of 1,000 IU/m^2. In that study, the proportion of patients switching treatment was explicitly specified and was 13.2% (12.3%, 11.6% and 20% for SR, IR and HR, respectively). The risk group specific rates were used in the ERG base case analysis.
- Risk of hypersensitivity to Erwinase similar for first and second line treatment and based on percentage of patients switching asparaginase treatment.
  Erwinase was the only formulations for which hypersensitivity rate differed between first and second line administrations. This was based upon specific evidence of hypersensitivity to Erwinase as second line treatment after native *E. coli*. However, the relatively high hypersensitivity rate to Erwinase in that study may also be due to the intravenous administration of Erwinase. As Erwinase is administrated intramuscularly in current UK clinical practice, this study is considered to be irrelevant as input for the health economic model. Consequently, evidence about differences in hypersensitivity rate at different lines of treatment is also absent for Erwinase. Therefore, the ERG used the same rate of hypersensitivity to Erwinase for

first and second line treatment. The rate used by the ERG was 9% which was the proportion of patients requiring a treatment switch in one study.

- Different OS and EFS estimates for the three paediatric risk groups.
  The OS and EFS estimates reported by the Company could not be reproduced from the evidence of the UKALL 2003 trial. Therefore, the ERG used estimates that could be derived from the published evidence. The five year OS and EFS were considered to be similar for the standard and intermediate risk group (97.9% and 94%, respectively). The five year OS and EFS of the high risk group were 83.3% and 79%, respectively.
- Allow the OS and EFS of the different formulation to vary independently in the probabilistic sensitivity analysis.
  Although no statistical differences in EFS and OS were found, there is also no evidence for the equivalence in survival. Therefore, uncertainty about the effectiveness of pegaspargase should be incorporated in the PSA.
- Change the relative reduction in mortality for patients who discontinue asparaginase treatment due to hypersensitivity to two different formulations
  In the company's base-case analysis, a reduction of 5% was used in case patients experienced hypersensitivity to two different formulations. This percentage was an assumption and not supported by any clinical evidence. The ERG found one study reporting the five year EFS for patients who discontinued asparaginase treatment versus those who continued asparaginase for more than 25 weeks. The difference between these estimates was 19% and this percentage was used in the ERG-base case as the reduction in OS and EFS for patients who discontinue asparaginase treatment.
- Change the mortality risk for patients in the R/ST state
  The mortality increase of 90% for patients in the R/ST is too optimistic since the background mortality rate for children is very low. Therefore, the ERG estimated the yearly mortality risk needed to obtain a 12% OS 5-year after having a relapse, as reported in Fielding 2007.[87] This yearly mortality risk was 35% and was used in the ERG base-case analysis.
- Estimating the EFS in the PSA dependent on OS
  In the company's submission, the EFS was independently estimated from the OS. Consequently, it was possible that in some runs of the PSA, the EFS was higher than the OS. Since this is impossible as all events of the OS are also included in the EFS, thus leading to a negative percentage of patients in R/ST, the ERG corrected this in the ERG base case analysis. In the PSA, the difference between OS and EFS is randomly drawn from a beta distribution and this difference is subtracted from the randomly drawn OS.
- Change the timing of the different treatment phases
  The start of the different treatment phases in the health economic model was not always according to treatment protocol. This has been adjusted in the ERG base-case analysis.
- Change the standard errors used in the PSA
  We have implemented the following standard errors in the PSA:

Table 5.19: Definition standard error per type of input variable

Type of variable	Percentage of mean value used as SE
Risk group distribution	Source
% paediatric patients	5%
% Adults <40 years	10%
Age children	10%
Age adults	5%
Utility decrements	10%
Hypersensitivity rates	Source
Disutility Hypersensitivity	20%
5-year outcome OS	5%
Decrease 5-year EFS	20%
RR for OS and EFS when discontinued	5%
R/ST utility decrement	20%
Mortality R/ST	10%
Costs	10%

Results of the ERG base-case

The summary of the ERG base-case ICER is reported in Table 5.20; the impact of individual changes on the ICER is shown in Table 6.1. Changes in the hypersensitivity rate for pegaspargase and Erwinia and a larger reduction in OS and EFS in case of discontinuation of asparaginase treatment had the largest impact on the ICER. According to the ERG base-case, pegaspargase-Erwinase is dominant over all three comparators with slightly better quality of life and fewer costs.

The results of the PSA show the uncertainty around the effectiveness of pegaspargase in comparison with the other formulations (Figure 5.11). The chance that pegaspargase is more effective than the other formulations is more or less equal to the chance that it is less effective. However, pegaspargase-Erwinase is almost always less expensive than the other treatment sequences causing all iterations to be situated in the two southern quadrants. The multiple cost-effectiveness acceptability curves show that at a threshold of £20,000, there is 50% probability that the pegaspargase-Erwinase is cost-effective. This probability decreases with higher thresholds as almost all iterations are situated in the two southern quadrants. When the threshold is high enough, all four treatment options have the same probability of being the most cost-effective, which is explained by the fact that for all options, the QALYs are almost the same, and as the threshold increases, the monetary value of the QALYs also increase, to such extend that the differences in costs become inconsequential.

Table 5.20: Deterministic results of the ERG base-case cost effectiveness analysis

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG-Asp.—Erwinase	**£7,329**	**17.5787**	—	—	—
Native Asp.—Erwinase	£11,083	17.5607	-£3,754	0.0179	Dominated
Erwinase—PEG-Asp.	£35,513	17.5787	-£28,184	0.0000	Dominated
Erwinase—Native Asp.	£35,447	17.5608	-£28,118	0.0179	Dominated

Figure 5.11: CE-plane for the ERG base-case analysis

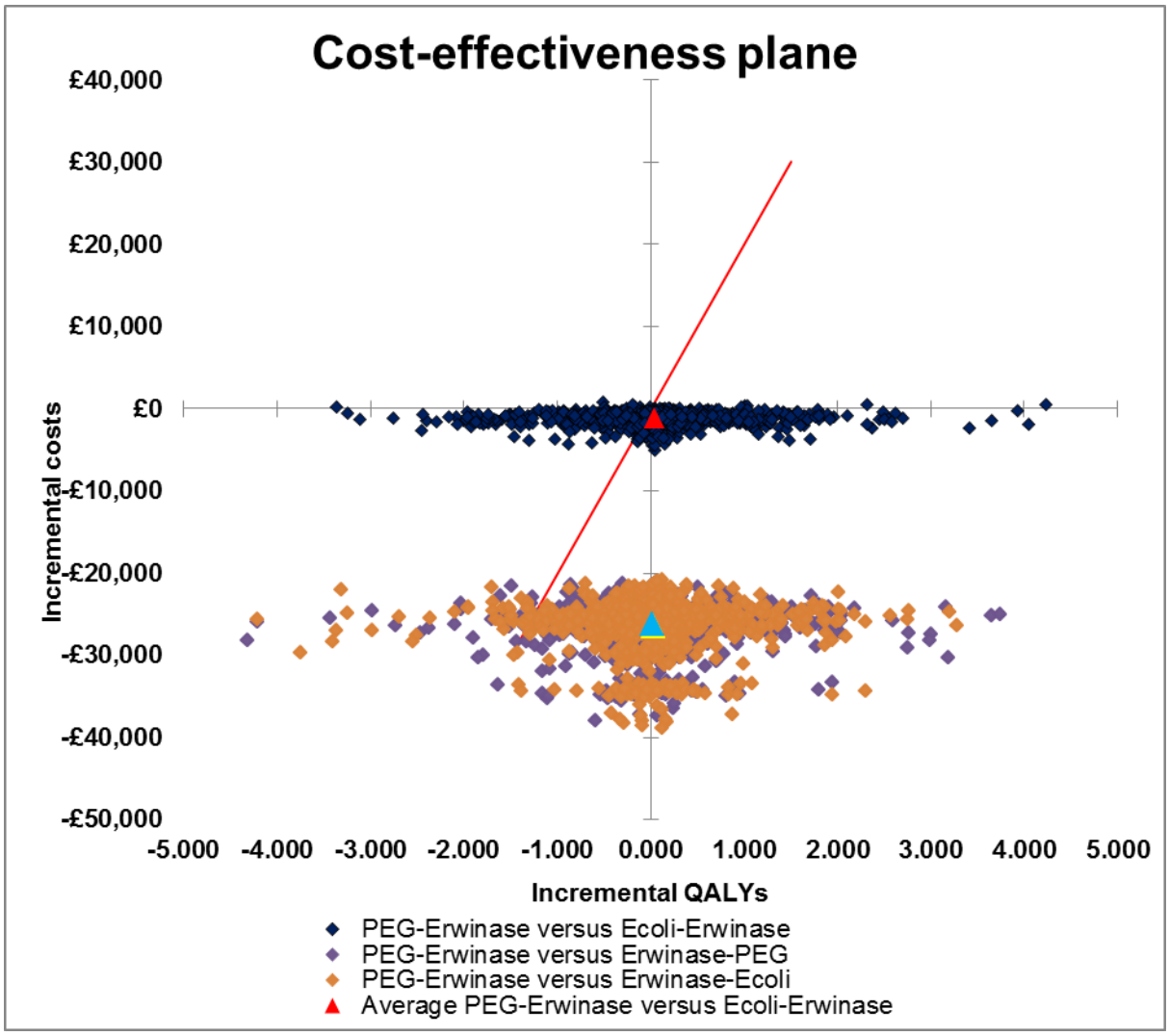
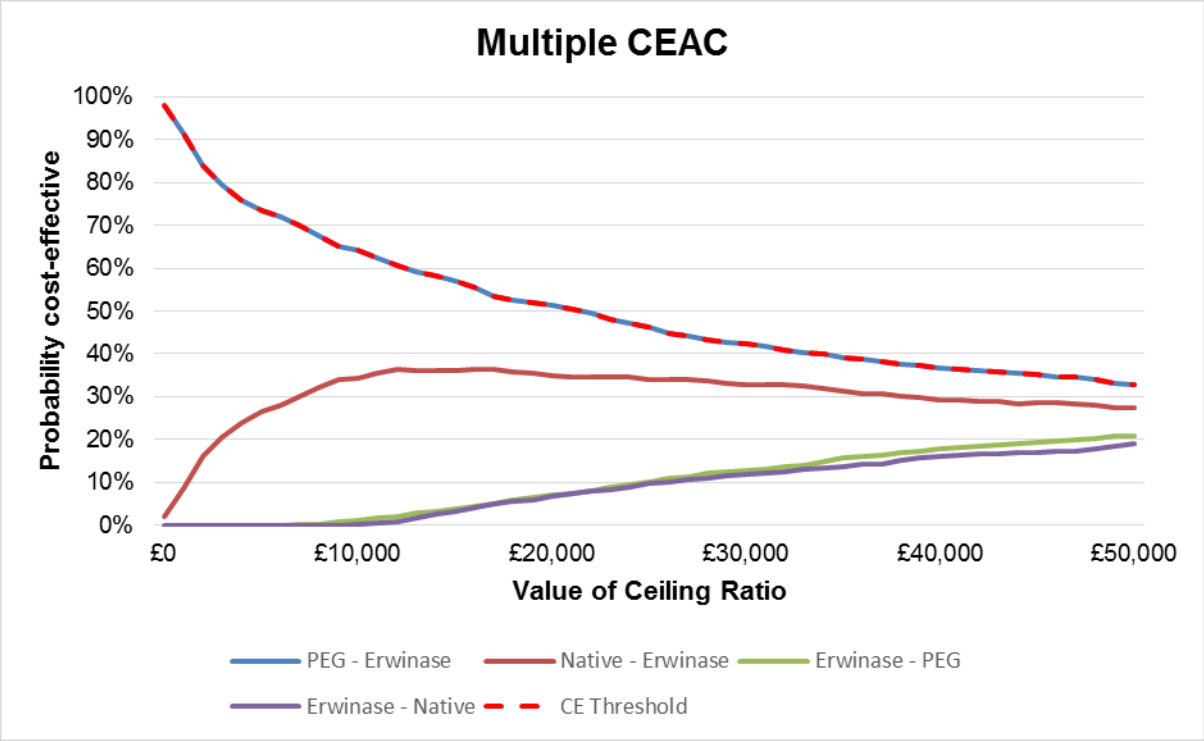


Figure 5.12: Multiple CEAC including all comparators



In addition to the adjustments to the base-case analysis, the ERG also applied a few additional scenarios on input parameters with substantial uncertainty. Some of these scenarios were also applied by the company to their base-case.

1. *Dosage pegaspargase 2,500 IU/m^2*
   Most evidence about the effectiveness of pegaspargase is based upon a dosage of 2,500. Therefore, a scenario analysis has been performed to assess the cost effectiveness of pegaspargase if given at the higher dosage of 2,500 IU/m^2
2. *Best-case scenario with better EFS and OS for pegaspargase*
   This scenario is based upon the results of the CCG-1961 trial in which the EFS and OS were numerically, but not statistical significant, better for pegaspargase in comparison with native *E. coli*.[31] Since no direct comparison of pegaspargase with Erwinase exists, it was assumed that the OS and EFS of Erwinase were similar to native *E. coli*. Furthermore, this study was performed in children and comparative evidence for adults is lacking. It was therefore also assumed that the relative improvement in survival as observed in children is also apparent in adults.
3. *Worst-case scenario with worse EFS for pegaspargase*
   This scenario is based upon the evidence from the DFCI-91-01 trial in which the EFS was lower for pegaspargase in comparison with native *E. coli*.[34] Since OS was not separately reported for the two formulations, no difference in OS was modelled. Similar to the best-case scenario, it was assumed that Erwinase had similar EFS as *E. coli* and that the relative difference between pegaspargase and *E. coli* also applies to the adult population.

4. *Quality of life utilities based upon an algorithm to map HUI3 on EQ-5D*
   Recently, a mapping algorithm has been developed that enables the estimation of EQ-5D utilities from other generic quality of life questionnaires such as the HUI3.[96] This algorithm was used as a different approach to estimate EQ-5D utilities from the evidence in the Furlong study.[89]
5. *Change utility decrement for the R/ST health state*
   The 20% decrease in utility for patients in the R/ST health state was based upon assumption without any scientific evidence supporting this assumption. This scenario uses a decrease of 68% since that would lead to a utility value of about 0.30 for the R/ST health. In a recent study, the general UK public has valued progression for ALL with a utility of 0.30.[97]
6. *Apply four doses of native E. coli or Erwinase for each dose of pegaspargase*
   The assumption that six native *E. coli* and Erwinase correspond to one dose pegaspargase is based upon expert opinion and common practice in UK clinical trials. However, no scientific evidence proves that this is the best ratio of the different formulations. For example, in the Netherlands, it is considered that four doses of native *E. coli* and Erwinase correspond with one dose of pegaspargase. Therefore, an additional scenario has been performed when applying only four doses of native *E. coli* or Erwinase for each dose of pegaspargase.

The impact of these scenarios is shown in Table 5.21. It can be seen that differences in utilities have almost no impact, which can be explained by the fact that is assumed that both OS and EFS are identical between the different formulations. The only difference in QALYs between the comparators is the rate of hypersensitivity and the subsequent proportion of patients who discontinue asparaginase treatment. The use of a higher dose of pegaspargase has also minimal impact on the ICER, because one vial contains 3,750 IU which is also sufficient for children given a dose of 2,500 IU/m^2. Substantial differences in incremental QALYs are observed for both the best and worst case scenario. For the worst case scenario, the incremental QALYs of pegaspargase-Erwinase in comparison with the other treatment sequences is about -0.86. Consequently, the ICER is located in the South West quadrant for all three comparisons. Given the UK threshold of £20,000, pegaspargase-Erwinase will not be cost effective in comparison with native *E. coli*-Erwinase if pegaspargase had a worse EFS than native *E. coli*. Another scenario with an impact on the ICER is the use of only four doses of native *E. coli* and Erwinase. Pegaspargase –Erwinase becomes even more costly than native *E. coli*-Erwinase resulting in an ICER of £36,499.

Table 5.21: Results scenario analyses in addition to the ERG base-case analysis

	Pegasparagase-Erwinia vs native *E coli*-Erwinia			**Pegasparagase-Erwinia vs Erwinia-Pegaspargase**			**Pegasparagase-Erwinia vs Erwinia-native *E. coli***		
Scenario	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Base Case	-£4,099	0.02	Dominant	-£28,526	0.01	Dominant	-£28,462	0.02	Dominant
Oncaspar Dose per SmPC (2500)	-£3,306	0.02	Dominant	-£27,842	0.01	Dominant	-£27,670	0.02	Dominant
Best case scenario	-£4,039	1.45	Dominant	-£28,309	1.45	Dominant	-£28,244	1.45	Dominant
Worst case scenario	-£4,141	-0.86	£4,810 (SW)	-£28,626	-0.87	£32,907 (SW)	-£28,562	-0.86	£33,179 (SW)
Utilities based on Mapping	-£4,099	0.02	Dominant	-£28,526	0.01	Dominant	-£28,462	0.02	Dominant
Utility R/ST state 68% reduction	-£4,099	0.02	Dominant	-£28,526	0.01	Dominant	-£28,462	0.02	Dominant
4 doses *E. coli* or Erwinase for each dose PEG	£739	0.02	£36,499 (NE)	-£17,213	0.01	Dominant	-£17,155	0.02	Dominant

NE = North-east quadrant, PEG = Pegaspargase, SW = South-west quadrant

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a fair extent, and the impact of deviations was found to be small. The ERG confirmed that there was no existing cost effectiveness model for pegaspargase for the current indication.

One point of concern was found by the ERG with respect to how well the treatment implementation in the model reflects clinical practice, as in the most recent treatment protocol for children, only one interim maintenance and delayed intensification course will be administered to the patients. The ERG base-case will incorporate only one delayed intensification course as this best reflects current clinical practice in the UK.

The ERG assessment indicated that the model was presented and reported somewhat imprecise at times, e.g. some discrepancies between the CS and the electronic model were found. Also, a few issues regarding the electronic model were identified that altered the cost effectiveness results. By correcting the errors and adjusting various input parameters (based on alternative data sources), an ERG base-case was defined. The company's base-case outcome for pegaspargase vs native *E. coli* asparaginase (both followed by Erwinase if hypersensitive) was that pegaspargase dominates native *E. coli* asparaginase with a cost saving of £4,741 and a gain in QALYs of 0.0504, whilst the corresponding ERG base-case found a cost saving of £3,754 and a gain in QALYs of 0.0179.

For the comparison of pegaspargase (Erwinase) versus Erwinase (native *E. coli*) the company base-case was a cost saving of £40,277 whilst gaining 0.0035 QALYs and the ERG base-case showed cost savings of £28,118 whilst gaining 0.0179 QALYs. The sequence comparison of pegaspargase (Erwinase) versus Erwinase (pegaspargase) showed a trade-off between costs and effects in the company base-case with cost savings at £40,362 while losing 0.0047 QALYs, leading to an ICER of £8,627,243, which is deemed acceptable given the common threshold of £20,000 to £30,000. In the ERG base case, pegaspargase (Erwinase) was dominant, with a cost saving of £28,184 and no difference in QALYs. In general, the results were not very different if only the adult or the paediatric population was considered.

The input for the model was derived from sources that included observational data, an RCT and literature. For many input values clinical expert opinion was used. However, the ERG is concerned about the approach of the company to seek expert opinion as only two experts were able to give their expert opinion, of the total of four who were approached. From the response to the clarification letter it is clear that more than four clinicians were deemed eligible, but the exact number was not stated. Given the strong reliance of the model on expert opinion, the ERG would have expected that a greater effort would have been made to consult with experts from the UK.

Additionally, the ERG was concerned about the great reliance of the model on single arm studies and observational data, rather than comparative studies. It is well possible that values

for the three formulations in the model come from different settings, with different patient populations and different treatment regimens for ALL. Thus, all reported outcomes should be interpreted with care.

Regarding the many clinical parameters in the model, the ERG questioned the source for many of those, most importantly the rate of hypersensitivity for the three formulations of asparaginase.

It was unclear to the ERG whether all hypersensitivity rates reflect the proportion of patients who require a treatment switch due to hypersensitivity. With respect to the hypersensitivity to native *E. coli*, the ERG agrees that 20% can be considered as a reliable and conservative estimate. However, there is no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinase also reflect the proportion of patients who require a treatment switch. The rate of hypersensitivity to pegaspargase is based on a paper that lists that rate in a table with adverse event rates, suggesting that it reflects the proportion of patients with a grade 3 or 4 adverse event. The ERG found another paper reporting hypersensitivity to pegaspargase given at a dosage of 1,000 IU/m^2. In that study, the proportion of patients with a treatment switch has explicitly been reported and was 13.2%. Similarly, for Erwinase it was also not clear if the rate used in the CS was based on treatment switching. The ERG found an additional study which explicitly stated that 9% discontinued Erwinase due to an allergic reaction. The ERG used these percentages as rates for both first and second line treatment with pegaspargase and Erwinase in the ERG base-case.

The cost effectiveness results were generally robust under the scenario analyses conducted, although a few scenarios impacted the outcome noticeably.

To test the impact of the assumption of equal OS and equal EFS across the three formulations a best case and worst case scenario were assessed on top of the ERG base-case, the first where pegaspargase has both a better OS and EFS (based on CCG-1961) and one where pegaspargase has both a worse OS and EFS (based on DFCI-91-01). In the best case scenario, pegaspargase clearly stays dominant, but now with a much larger gain in QALYs, 1.45 instead of 0.02. In the worst case, pegaspargase would no longer be acceptable compared to native *E. coli*, with an ICER in the south-west quadrant (saving per QALY lost) of £4,810. Compared to Erwinase (pegaspargase) and Erwinase (native *E. coli*) the ICERs are £32,907 (SW) and £33,179 (SW), respectively, just above the common threshold of £20,000 to £30,000, which indicates that pegaspargase as first line treatment would be acceptable in those comparisons.

Another scenario with noticeable impact on the outcome concerns the number of dosages of native *E. coli* and Erwinase for each dosage of pegaspargase. In the model this was assumed to be 6:1, based on expert opinion. However, other ratios also occur in practice, e.g. in the Netherlands a more common ratio is 5:1 or 4:1. Thus, the latter ratio was applied in a scenario. We now observe that for pegaspargase vs native *E. coli* asparaginase (both followed by Erwinase if hypersensitive), pegaspargase is no longer cost-saving. Instead the additional

costs are £739, yielding an ICER of £36,499 (NE), which is above the common thresholds. In both other comparisons, pegaspargase remains dominant, though with a smaller cost-saving.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Chapter 5.3 the ERG base case was presented, which was based on various changes compared to the manufacturer base case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously.

Table 6.1: Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG

	PEG-Erw vs Ecoli-Erw			**PEG-Erw vs Erw-PEG**			**PEG-Erw vs Erw-Ecoli**		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Base-case	-£4,741	0.050	PEG dominant	-£40,362	-0.005	£8,627,245 (SW)	-£40,277	0.003	PEG dominant
Corrections in the model	-£4,384	0.051	PEG dominant	-£37,218	-0.005	£7,921,590 (SW)	-£37,142	0.004	PEG dominant
Mean age for paediatric population	-£4,741	0.050	PEG dominant	-£40,362	-0.005	£8,718,463 (SW)	-£40,277	0.003	PEG dominant
No second interim maintenance and delayed intensification course + correction timing treatment	-£3,980	0.050	PEG dominant	-£32,768	-0.005	£ 6,996,189 (SW)	-£32,705	0.003	PEG dominant
Hypersensitivity rate pegaspargase 13.2%	-£3,096	0.019	PEG dominant	-£38,688	-0.031	£1,249,290 (SW)	-£38,632	-0.028	£1,385,524 (SW)
Hypersensitivity rate Erwinase 9%	-£7,022	0.012	PEG dominant	-£39,048	0.000*	PEG dominant	-£38,920	0.012	PEG dominant
OS estimates based upon evidence from UKALL2003 trial	-£4,741	0.052	PEG dominant	-£40,362	-0.005	£8,314,504 (SW)	-£40,277	0.004	PEG dominant
EFS estimates based upon evidence from UKALL2003 trial	-£4,750	0.051	PEG dominant	-£40,451	-0.005	£8,548,844 (SW)	-£40,366	0.004	PEG dominant
Reduction OS and EFS in case of discontinuation asparaginase = 19%	-£4,741	0.192	PEG dominant	-£40,363	-0.018	£2,260,256 (SW)	-£40,278	0.013	PEG dominant
Yearly mortality rate in the R/ST state = 35%	-£4,741	0.049	PEG dominant	-£40,362	-0.005	£8,941,672 (SW)	-£40,277	0.003	PEG dominant
ERG Base-case	-£3,754	0.018	PEG dominant	-£28,184	0.000**	£2,492,445,178 (SW)	-£28,118	0.018	PEG dominant

PEG = Pegaspargase, SW = South-west quadrant, *Greater than zero, **Less than zero

7. OVERALL CONCLUSIONS

Overall, the ERG agrees with the company that there is no evidence to suggest that there is a difference in effectiveness or toxicity between pegaspargase and the main comparator: native *E. coli*-derived asparaginase. However, it is unclear whether there actually is a lack of a difference in effect. None of the included RCTs was powered to assess equivalence and it was not possible to pool results from different studies.

There is no evidence for the relative effectiveness of pegaspargase versus other asparaginases in adult populations.

It is important to note that the UKALL protocols use a dose of 1,000 IU/m^2 for pegaspargase. However, the SmPC recommended dose is higher (2,000-2,500 IU/m^2). Moreover, there is no comparative evidence for this lower dose of pegaspargase versus other types of asparaginase. All trials comparing pegaspargase with *E. coli* asparaginase compared 2,500 IU/m^2 pegaspargase with 6,000 IU/m^2 *E. coli* asparaginase. In addition, there are no studies that provide a head-to-head comparison of pegaspargase used at 1,000 IU/m2 and 2,500 IU/m2 doses.

All the above directly influences the reliability of the health economic outcomes. Given the assumption of equal effectiveness and reduced toxicity, treatment with pegaspargase is the dominant choice. But clearly, if in reality there *are* differences in effectiveness, the outcome might become less favourable for pegaspargase.

7.1 Implications for research

Randomised controlled trials assessing the relative effectiveness of pegaspargase versus other asparaginases are warranted, especially in adult populations. In addition, a head-to-head comparison of pegaspargase used at 1,000 IU/m2 and 2,500 IU/m2 doses is warranted.

In the interest of all future health economic studies in ALL, UK based utilities, derived from the EQ-5D, and a good insight in resource use for each of the treatment phases would be valuable. These data could be collected in various ways, i.e. alongside clinical studies or separately, either prospectively or from a cross-sectional analysis.

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Appendix 1: Further critique of searches

Redundant lines were common in all of the search strategies for SR2, cost effectiveness and HRQoL searches. For example, in the MEDLINE search strategy in Appendix 2, line 5 of the strategy "lymphoblastic leukemia OR lymphoblastic leukaemia" will also find everything searched for in line 3, "acute lymphoblastic leukemia OR acute lymphoblastic leukaemia" making line 3 redundant. In the Ovid interface used for Embase and the Cochrane Library searches, truncation could have been used to search for more possibilities. For example leuk?emia would have found both leukaemia and leukemia; lympho$ would have found both lymphocytic and lymphoblastic. The use of proximity operators would have also improved the search strategies. For example, in the Embase search strategy in Appendix 6, 'cost adj2 (illness OR living OR health care)' would have identified the records found by line 18 (cost of illness), line 19 (cost of living) and line 21 (health care cost).

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pegaspargase for acute lymphoblastic leukaemia [ID863]

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 23 May 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ERG disagrees with the company on relevance for the decision problem of the two trials in the CS marked as pivotal studies for this assessment.

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report critiqued in section 1.3 and 4.2 on pages 9 and 33, respectively, that: "*ERG disagrees with the company that the two trials in the CS are the most important studies for this assessment. CCG-1962 compares pegaspargase with native E-coli asparaginase in children aged 1 to 9 years (N=59 in both groups). Therefore, it is a small study in very young children, covering only a small group of the total population of interest for this appraisal: people with ALL. UKALL 2003 does not include a relevant*	Baxalta suggest the following amendment to the ERG report: To the below paragraph (from ERG report section 1.3 and 4.2): *"ERG disagrees with the company that the two trials in the CS are the most important studies for this assessment. CCG-1962 compares pegaspargase with native E-coli asparaginase in children aged 1 to 9 years (N=59 in both groups). Therefore, it is a small study in very young children, covering only a small group of the total population of interest for this appraisal: people with ALL. UKALL 2003 does not include a relevant comparator and is therefore less relevant for this appraisal."* Baxalta would ask for the following to be added: However, the CS provides justifications for the relevance of both studies in the UK in section 4.2: • CCG-1962 is the only trial available that provides direct randomised comparative evidence for pegylated versus E. coli-derived asparaginase when given during the induction phase of treatment, and treatment continued through subsequent phases with the randomly assigned asparaginase. • UKALL 2003, although not providing comparative evidence versus other asparaginases, does provide pivotal evidence for the use of pegaspargase in UK and Ireland clinical practice, since the enrolled population of >3,200 patients represents	1. The ERG report fails to highlight the evidence limitations for ALL that the manufacturer has faced throughout the submission process, yet these limitations are clearly outlined in the STA dossier. An opening statement by ERG to reflect this would be appreciated. 2. As expanded on by ERG throughout the ERG report, identifying evidence that would inform the decision problem was challenging, yet no balanced view was applied by ERG on stating the relevance of the ERG identified studies for the decision problem, as done with criticising the presented studies in the CS. The ERG only states "Therefore, we present an overview of all comparative studies relevant for this appraisal in Chapter 4.5 of this report", on page 33,	Not a factual error.

comparator and is therefore less relevant for this appraisal."	97% of the eligible ALL population in the UK and Ireland aged 1 to<25 years. In addition, the CS (Section 4.8) identified the following studies as supportive studies for first line use of pegaspargase, from which evidence was used to inform the decision problem: CCG-1961, DFCI-91-01, DFCI ALL 05-001, DFCI-87-01, DFCI ALL 05-01, AALL07P4, COG AALL0232, COG AALL0331, NOPHO ALL2008 (NCT00819351), POG 9006, POG 9406, CCG-1961m/CCG-1991, GMALL 07/03, MDACC BFM augmented, INTERFANT-06, CoALL 08-09, NR, NCT00184041 and CALGB 9511.	with no further explanation provided on why these studies are more applicable to the decision problem at hand.	

Issue 2 Suggested limitation due to study design search filters

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report critiqued in section 4.1.1 and 5.1.1 on page 28 and 60, respectively, that: "*The company did not use a validated study design search filter to find cost effectiveness studies and*	Baxalta suggest either the removal of these paragraphs or a change in the wording to: The company used acceptable study design search filters to find cost effectiveness and health related quality of life studies.	The ERG statement is viewed as misleading, since the Embase filter in the search outlined in the CS contains the search terms 'cost.ti,ab' OR 'costs.ti,ab' that comprise the economic filter developed by McMaster University Health Information Research Unit. Admittedly, this wasn't explicitly covered in the responses to the ERG questions on 14 April, as it was felt not to be a major restriction or limitation in widening the searches, especially with no requirements on validated study design search filters provided by NICE or other published guidance (see below). Published guidance regarding search filters for economic reviews: • NICE guide to TA: ○ No mention of requirements regarding search filters • NICE TSDs (http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm):	We agree that the company did use a validated filter to find cost effectives studies although they did not specify this in their response to the clarification letter. They have also provided reasons why they didn't use a validated filter for the health-related quality of life searches – again this wasn't clear in their response to the clarification letter – but the explanation here is acceptable. Therefore, we have changed the wording on page 28 to: "The company used acceptable

health related quality of life; instead relied on "common knowledge and internal expertise"."		○ No mention of economic SRs in any of the TSDs • CRD York (https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf): ○ No requirement for a validated filter mentioned. ○ However, a number of potential/recommended search filters/sources are mentioned (McMaster, ISSG [including CRD NHS EED filter]) • Cochrane handbook - clinical SRs only, so no guidance on filters for economic or HSUV searches Published guidance regarding search filters for HSUV reviews: • NICE guide to TA: ○ No mention of requirements regarding search filters • NICE TSD (9 http://www.nicedsu.org.uk/TSD9%20HSUV%20values_FINAL.pdf): ○ No requirement for a validated filter mentioned, in fact: '*standard methods for identifying HSUVs do not exist…simply creating a validated filter may not be useful since it is unlikely that this will solve the problems in searching electronic databases with acceptable sensitivity and specificity for HSUVs'*. ○ Some suggested/frequently used MeSH and free text terms reported, many of which were included in the CS searches • CRD York: ○ No mention of HSUV SRs	study design search filters to find cost effectiveness and health related quality of life studies." And removed this sentence on page 60.

Issue 3 Only English language searched for in the SR (pg30)

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report states on page 14, 30 and 60 (sections 1.6.2,	To state, in the summary, that there were no	Most journals are in English and it would be more balanced to show	Not a factual error.

4.1.2, 5.1.1 respectively): Overall, the limitations of the SR are highlighted, but the fact that the ERG did not find any additional studies is not pointed out in the summary.	new studies found by the ERG	that there were no new studies found by the ERG in this section.	The ERG maintains that limiting search strategies to English introduces a language bias. As we did not run additional searches, we cannot amend the description to say that no new studies were found.

Issue 4 Page 32 states

“[redacted]

Description of problem	Description of proposed amendment	Justification for amendment	
[redacted]	[redacted]	[redacted]	Not a factual error.

[redacted]	[redacted]	[redacted]	

Issue 5 Pages 35–39: Summary of clinical evidence identified by ERG = 7 studies

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report appears to present the ERG identified evidence in a biased way and omits important quality	Baxalta request the following statements to be inserted into the document: 1. A supporting statement highlighting which ERG studies have also been	1. The ERG presents an unbalanced view of the evidence by exploring the CS pivotal studies, yet only	Not a factual error.

assessment and justifications on why these studies are preferred over the CS identified evidence. Specific section of the ERG report: Section 4.5 “Additional work on clinical effectiveness undertaken by the ERG”, presents the evidence the ERG views as relevant for the decision problem.	identified and used by the manufacturer in the CS, regardless of whether classed pivotal or supportive. 2. In table format and as a summary, a quality and risk of bias assessment of the ERG listed studies, equivalent in the structure the ERG used to critique the CS studies.	briefly mentioning the supportive studies used in the submission as *“Details of most of the other included studies are reported in section 4.8 of the CS (CS, Tables 22-29, pages 76-103)”,* without further detail. The ERG report should address this by comparing their findings of the clinical evidence to the findings presented in the CS, whether presented as pivotal or supportive. A table or a paragraph listing these studies would suffice. 2. The ERG critiques the CS on multiple accounts, markedly in section 4.1.4 (p31) of the report, that the risk of bias is “considerable” for the identified studies. The ERG did not present a quality assessment of the ERG identified studies, nor discusses the risk of bias of these studies in their report. This omission of this may lead to publication bias within the ERG report, where the lay reader is not only being presented with 7 (ERG) vs 2 (CS) studies,	

		but also is led to believe that only the CS studies have a high risk of bias attached.	

Issue 6 Figure not in report (page 76)

Description of problem	Description of proposed amendment	Justification for amendment	
On page 76 (section 5.2.3), the ERG report has referred to a revised figure that they have used to obtain updated information from, but this was not included in the report	Please include the figure in the report	Transparency of data	The company has misinterpreted our text here. Figure 2 in Vora 2013 was corrected in 2014 and now the numbers in that figure no longer match the numbers in Table 5. As Figure 2 was corrected, we assume those numbers are correct and those in Table 5 incorrect (with regards to the distribution over risk groups). We have amended the text a bit to make this more clear.

Issue 7 Repetition (page 84)

Description of problem	Description of proposed amendment	Justification for amendment	
On page 84 (section 5.2.6) The “small error” in using female rather than weighted male/ female	Please remove the repetition on page 84	Word for word repetition from page 83	We have deleted the suggested part

distribution is stated more than once in this section			

Issue 8 Rate of hypersensitivity for Pegaspargase (page 84)

Description of problem	Description of proposed amendment	Justification for amendment	
There is a noticeable difference in hypersensitivity rates between what has been assumed in the CS vs what ERG is inferring. Page 84: The company has utilised the UK-specific Vora 2013 paper as the main source of data given it is relevant to UK practice (protocols), in a large sample of patients (>3,200 patients). The ERG appears to favour the Nordic study (Henriksen, 2015), which uses a protocol not representative of UK clinical practice (e.g. differing total dose & age range) on a much smaller sample of patients (615 patients) Baxalta therefore questions this being an accurate representation of the hypersensitivity rate for pegaspargase for use in the model for decision-making	Revert back to the Vora paper as the main source of data relevant to the UK population and include the Nordic (Henriksen publication) data as a scenario analysis to assessing cost effectiveness in this setting. The ERG would then also need to highlight the key differences between these protocols.	The Henriksen cumulative allergy of 13.2% is taken from a Nordic protocol which uses a higher amount of pegaspargase than that given in the majority of UK patients. This is a possible driver for the higher allergy rates in the Nordic population. The age range in the protocol is also very different (UK study (Vora) includes patients under 25 years of age, whilst the Nordic (Henriksen) protocol includes patients under 45 years of age). For context, the current UK adult protocol stratifies treatment protocols to adult patients over and under 41 years of age. Hypersensitivity rate is a key driver of the model, and it is therefore important that a balanced view is represented, and Baxalta believe this would give a more balanced view across the 2 publications.	This is not a factual error, and the ERG disagrees with the proposed change by the Company. Firstly, the Nordic study incorporated 615 patients ranging from 1-17 years which is not very different from the range in the Vora study (1-24 years). The median white blood cell count and the immunophenotype distribution were also comparable between studies. In addition, the dosage use per administration was the same in both studies, i.e. 1.000 IU/m^2 i.m. though the number of administrations differed. However, in the Nordic study PEG hypersensitivity developed after a median of 2 doses, so it is unlikely that the different dosing schedule would have a great impact.

purposes, and is concerned that a non-representative study seems to be favoured over the data available for the UK.			Moreover, as clearly stated in the ERG report, the Vora study does not present the % of switches due to hypersensitivity, but only grade 3 and 4 adverse events. Also, the protocol of UKALL2003 states that patients should switch formulation when hypersensitivity occurs at grade 2, 3 and 4. Thus, it is clear that basing the switch rate on the Vora 2013 publication will lead to an underestimation of the percentage of switches.

Issue 9 Number of doses of native asparaginase or Erwinase used

Description of problem	Description of proposed amendment	Justification for amendment	
Page 15 states *"Another scenario with noticeable impact on the outcome concerns the number of dosages of native E. coli and Erwinase for each dosage of pegaspargase. In the model this was assumed to be 6:1, based on expert opinion. However, other ratios also occur in practice so a 4:1 ratio was*	Baxalta requests to remove reference to other doses, or acknowledge that the dose ratios (5:1 or 4:1) are listed in other countries' protocols, as these use different dosing regimens, patients have different age stratifications, etc. and are therefore not reflective of UK practice.	The 6:1 ratio is reflective of UK practice, and stating the ratios used as "in practice" could be misconstrued as being "UK practice". Erwinase is stipulated to be given as a ratio of 6:1 in the UK trial protocols. Page 189 of the UKALL trial protocol version 3 states: Each dose of pegaspargase (Oncaspar) should be replaced with 6	We agree with the Company that the wording used by the ERG could potentially be interpreted as relating to UK practice, rather than common practice in some other countries. Thus we have replaced the wording "in practice" by "in other countries"

applied in a scenario." The other studies whose dosing regimens are referred to are not reflective of current UK practice (e.g. use different doses per administration and different age ranges). The source of dosing regimens for Erwinase was also taken from the UK protocols		doses of 20,000 Units/m^2. For background info, dosing (Rowe et al, 2005): the previous UK trial using native asaparaginase, UKALL XII, had L-asparaginase administered intravenously or intramuscularly on days 17 to 28 in induction (i.e. in a ratio of native 6 doses: to 1 pegaspargase dose in the new trial).	

Issue 10 Statement of lower efficacy of lower dose – this has not been demonstrated in the literature and misrepresents what we presented in our submission and clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	
On page 78 (section 5.2.6), the ERG report disjointed the information, leading to an unbalanced presentation of the ERG conclusion vs the CS and the company's responses to the ERG questions. The ERG report states: *"They argued that it may be reasonable to assume a lower efficacy and fewer side effects at the lower dosage"*, which is incorrect given our statement on page 25 of the CS. In addition, further clarification	Baxalta request to please amend the report to reflect the assumptions made more clearly, especially as the language is felt to be misrepresentative by using "they argued". Please delete the ERG text: "*They argued that it may be reasonable to assume a lower efficacy and fewer side effects at the lower dosage"* on page 78. Please add a supporting statement to acknowledge Baxalta's rationale.	CS, page 25 and clarification letter provided further rationales on the assumption made, which is not outlined by the ERG in the current context of the ERG report. CS page 25 states: *"The use of pegaspargase at the reduced dose and UKALL specified dosing frequency is currently supported by clinical efficacy and safety data from >3,000 children, adolescents and young adults from UKALL 2003 (see CS section* ***Error! Reference source not found.*** *for further detail). The evidence for the reduced dose demonstrates no loss of*	The ERG agrees that the information provided in the response to the clarification was presented inaccurately, due to a misunderstanding about the message of the text. We have amended the text as follows: "In their response to the clarification letter, the Company mentioned that no head-to-head comparisons exist of pegaspargase used at 1,000 IU/m^2 and 2,500 IU/m^2. They indicated that a priori ~~argued that~~

on this assumption was provided in the clarification letter to the ERG, which is presented in the next paragraph on page 78 of the ERG report.		*efficacy and a broadly comparable safety profile to the SmPC recommended dose."* In addition, the language used to present the assumptions made is viewed as inappropriate by Baxalta.	it may be reasonable to assume a lower efficacy and fewer side effects at the lower dosage. <u>However,</u> ~~S~~<u>s</u>ince the EFS and OS of the UKALL2003 (using a dose of 1,000 IU/m^2) were at least as good as that of studies using the 2,500 IU/m^2, the Company considered it to be reasonable to use these survival estimates for all formulations."

Issue 11 Page 117 states: "But clearly, if in reality there are differences in effectiveness, the outcome might become less favourable for pegaspargase".

Description of problem	Description of proposed amendment	Justification for amendment	
On page 117 (Section 7) of the ERG report, the closing statement implies that further evidence gathered <u>will</u> be less favourable for pegaspargase, but fails to account for the fact that additional data could also positively support the cost-effectiveness of pegaspargase even further.	Baxalta proposes a change of the closing statement on page 117 4th paragraph to: "But clearly, if in reality there are differences in effectiveness, the outcome might become less or even more favourable for pegaspargase."	Only listing the "less favourable" aspect in the closing statement by ERG could be seen as coercive and potentially be a leading statement with negative connotation, especially as the conclusion statements usually have high impact on the reader in shaping their opinions on the decision problem. Although the existing evidence has its limitations, further emerging evidence could equally support the cost-effectiveness argument on pegaspargase even further and not as ERG implies,	Not a factual error.

		make it "less favourable" only.	

Issue 12 The ERG has not included all the relevant commercial in confidence aspects

Description of problem	Description of proposed amendment	Justification for amendment	
The ERG report does not account for all the areas of commercial in confidence in their report	Please amend per the highlights submitted by Baxalta in the CS, for both the ERG report and our responses to the ERG report	Commercial in confidence	We are awaiting further advice from NICE.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Pegaspargase for acute lymphoblastic leukaemia

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
15	"in practice" replaced by "in other countries"
28, 29	Changed wording on 28 to: "The company used acceptable study design search filters to find cost effectiveness and health related quality of life studies."
60, 65	Removed sentence
76	Text added: ", and the model uses the numbers as reported in Table 5. However," Text removed: "that" Text added ", and in Table 5 incorrect"
78	"argued that" replaced by "indicated that a priori" and "S" replaced by "However, s"
84	Paragraph removed

According to the ERG base-case, pegaspargase-Erwinase is dominant over all three comparators with slightly better quality of life and fewer costs.

Comparing pegaspargase vs native *E. coli* asparaginase (both followed by Erwinase if hypersensitive) showed a cost-saving of £3,754 and a gain in QALYs of 0.0179. For the comparison of pegaspargase (Erwinase) versus Erwinase (native *E. coli*) cost savings of £28,118 were found whilst gaining 0.0179 QALYs. The sequence comparison of pegaspargase (Erwinase) versus Erwinase (pegaspargase) showed cost saving of £28,184 and no difference in QALYs.

Of all the adjustments made, the changes in the hypersensitivity rate for pegaspargase and Erwinia and a larger reduction in OS and EFS in case of discontinuation of asparaginase treatment had the largest impact on the outcomes.

A number of scenarios were explored to study how various assumptions about input values impact the outcomes. These revealed that the outcomes are sensitive to changes in the assumption of equal OS and equal EFS across the three formulations. However, the scenarios explored represented a best case and worst case scenario so these may be unlikely to represent reality in the UK.

Another scenario with noticeable impact on the outcome concerns the number of dosages of native *E. coli* and Erwinase for each dosage of pegaspargase. In the model this was assumed to be 6:1, based on expert opinion. However, other ratios also occur in other countries so a 4:1 ratio was applied in a scenario.

possible that some relevant evidence may not have been identified as a consequence of the study design limits.

Cost effectiveness

The CS states that a comprehensive search of the peer-reviewed literature was conducted to identify and select cost effectiveness studies relevant to decision-making in England on clinical efficacy, safety and toxicity of pegaspargase in all age groups of patients with newly diagnosed ALL.[3]

The searches were conducted on 31 January 2016 in the same databases as searched for in the clinical effectiveness searches: MEDLINE, Embase, CDSR, CENTRAL, ACP Journal Club, DARE, HTA and NHS EED. The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were also provided. Detailed search strategies for the database searches were reported in Appendix 6. In addition, the company manually searched ClinicalTrials.gov, ASH, ASPHO, CALGB, Google, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), NHS Choices, National Institute for Health and Clinical Care Excellence (NICE) and Scottish Medicines Consortium (SMC).

The company translated the decision problem into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into clinical condition and economic outcomes. In the MEDLINE search strategy (Appendix 6) the economic outcomes were combined from line 24 to line 27, instead of line 9 to line 32. This is thought to be a reporting error, rather than a consequential error as the search results suggest the latter. The company used acceptable study design search filters to find cost effectiveness and health related quality of life studies..[39] A language limit for English only was used which the ERG felt introduced language bias.

Web addresses and the date of searching for manual searching was provided, but the details of the search strategy were not sufficient to assess the effectiveness of this strategy.

A search of other economic resources, such as the CEA Registry and ScHARRHUD, for cost-utility analyses might have been a useful addition to the literature searches.

The ERG requested a flowchart/schematic diagram detailing the results of the cost-effectiveness searches. These were provided in the response to the ERG clarification letter but did not include results from the Cochrane Library.[39] This was thought to be a transcription error.

Search strategy for measurement and valuation of health effects

The CS states that a search was conducted to identify and select relevant health related quality of life (HRQoL) studies in line with the objectives of gathering data relevant to decision-making in England on clinical efficacy, safety and toxicity of pegaspargase in all age groups of patients newly diagnosed with ALL.

Searches were conducted on 31 January 2016 in the same databases as were searched for clinical and cost effectiveness studies: MEDLINE, Embase, CDSR, CENTRAL, Cochrane Methodology Register, ACP Journal Club, DARE, HTA and NHS EED. The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were also provided. In addition, the company manually searched ClinicalTrials.gov, ASH, ASPHO, CALGB, Google, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), NHS Choices, National Institute for Health and Clinical Care Excellence (NICE) and Scottish Medicines Consortium (SMC). Detailed search strategies for the database searches were reported in Appendix 8.[3]

The company translated the decision problem into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into clinical condition and HRQoL outcomes and were correctly combined using Boolean operators. The company did not use a validated study design search filter to find HRQoL studies and relied on "common knowledge and internal expertise".[39] An English language limit was used which the ERG felt introduced language bias.

A detailed search strategy for manual searching was not provided so it was not possible to assess the effectiveness of this strategy. Web addresses and the date of manual searching were provided in the response to the ERG clarification letter.[39]

The ERG requested a flowchart/schematic diagram detailing searches for measurement and valuation of health effects. These were provided but did not include results from the Cochrane Library. This was thought to be a transcription error.

Summary of searching

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional supplementary searches of relevant websites and databases were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[41]

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for SR1 and SR2 are shown in Tables 5 and 6 of the CS (CS, pages 42 and 44). These two tables are combined in Table 4.1 below.

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

A comprehensive search of the literature was conducted to identify all relevant cost-effectiveness studies. The CS reported searches for Medline, Embase, the Cochrane Database of Systematic Reviews, and NHS Economic Evaluation. All searches were conducted on 31 January 2016. The search was restricted to English language articles and to studies that were performed in humans. In addition, only articles that contained an abstract were selected and several date restrictions were applied i.e. Medline and Embase was searched for the period 1946 (database inception) to 31 December 2015 and the Cochrane Database was searched for the period 2005-2015. The date restriction applied for the Cochrane Database was not further justified.

Measurement and valuation of health effects

A comprehensive search of the literature was conducted to identify and select relevant health related quality of life studies. This search used the same databases and restrictions as the cost effectiveness search. In addition, search terms were well reported and validated study design filters were applied.

Resource identification, measurement and valuation studies

The search conducted for the cost effectiveness studies was also used to identify studies reporting resource use. This search included search terms related to resource utilisation and costs (e.g. 'resource utilisation', 'resource costs' and 'costs').

ERG comments: The search strategy was limited to English only which the ERG believes introduces a language bias. In addition, the search was reported inaccurately and there were typing errors and discrepancies between the company submission and Appendix 6. For a more detailed critique, see Section 4.1.1.

5.1.2 Inclusion/exclusion criteria used in the study selection

The reviews on cost effectiveness, resource use and health outcomes as reported in the company submission started with a screening on title by one single reviewer. The exclusion criteria for this first screening were not clearly specified; only a rather vague description for this phase of screening was given i.e. 'obviously irrelevant studies (such as animal studies, case reports etc.) were excluded'.

The second stage of the cost effectiveness, health effects and resource use reviews consisted of screening based on abstract. This screening was performed by two reviewers. When there was uncertainty about the relevance of an article, it was included for full text reading. Final

5.1.4 Conclusions of the cost effectiveness review

None of the identified cost effectiveness studies were deemed relevant to decision-making in England.

ERG comment: The ERG is concerned about the quality of the cost effectiveness reviews for several reasons. The results of the searches were not clearly reported in the company submission. Discrepancies were observed between the PRISMA results and results reported in the company submission appendices. Typing errors (i.e. the ERG assumes these were typing errors) were observed in the description of the searches (CS Appendices 6 and 8). Lastly, the first screening was done by one reviewer only despite the fact that this is clearly not a recommended method. Despite these concerns, the ERG does not expect that the company missed relevant studies. After reading several studies and performing some ad-hoc searches, the ERG did not find any relevant publications that were not identified by the company searches.

Overall, the ERG shares the opinion of the company that the development of a *de novo* model was required.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3 presents a summary of the de novo economic model developed by the manufacturer. The ERG has assessed the company's economic evaluation and their critique is presented in the following sections.

Even in the case that the risk classification from the UKALL 2003[19, 20] is still in use in clinical practice, there is some inconsistency in the distribution of patients over the three risk groups. Figure 2 and Table 5 of Vora et al.[19] report slightly different number of patients in the three risk groups, and the model uses the numbers as reported in Table 5. However, as a corrected version of Figure 2 has been published on 30 June 2014, it is expected that the numbers in Figure 2 are correct, and in Table 5 incorrect. Therefore, in the ERG base-case analysis, the distribution of paediatric patients in the three risk groups will be based upon the numbers reported in the corrected Figure 2 instead of Table 5.
The ERG doubts whether the median age of the UKALL 2003 trial[19, 20] is more reliable than data from the CRUK since the inclusion of patients in the UKALL 2003[19, 20] trial has been expanded over time. At the start of the study only patients up to 18 years were eligible, but the upper age limit was increased to 20 years in February 2006 and to 24 years in August 2007. It is therefore possible that the age of the paediatric patients is slightly underestimated since older patients were only eligible in the last five years. Furthermore, health economists aim to use means instead of medians for all estimates used in a model. Therefore, in the ERG base-case analysis, the starting age of paediatric patients is considered to be 7.3 years instead of five years.

5.2.4 Interventions and comparators

The intervention under study is the use of pegaspargase as first line treatment and Erwinase as second line treatment for patients developing hypersensitivity to pegaspargase. This treatment sequence is compared with three alternative treatment sequences (see Table 5.6). Although Erwinase is only used as second line treatment after hypersensitivity to first line asparaginase in current UK practice (UKALL 2003[19, 20] and UKALL 14[16]), its use as first line treatment is considered in two alternatives because Erwinase was listed as a comparator in the NICE scope and its UK indication is not limited to a specific line of asparaginase treatment. Since the administration of *E. coli* after pegaspargase or vice versa is considered unsuitable due to the risk of cross reactivity and subsequent hypersensitivity, these treatment sequence alternatives have not been modelled.

Table 5.1: Treatment alternatives in the cost effectiveness analysis

	1st line Asparaginase	**2nd line Asparaginase (in case of hypersensitivity 1st line treatment)**
Intervention	Pegaspargase	Erwinase
Comparator 1	*E. coli*	Erwinase
Comparator 2	Erwinase	Pegaspargase
Comparator 3	Erwinase	*E. coli*

Asparaginase (either pegaspargase, *E. coli* or Erwinase) is administered in different phases of ALL treatment. Table 5.7 shows when asparaginase is administered. Note that the weeks represent the timing of the treatment from start of induction treatment (i.e. induction treatment takes five weeks and subsequently, consolidation treatment starts in week six). The total dosage of asparaginase per treatment phase is reported in Section 5.2.8.

However, the ERG considers a mortality increase of 90% for patients in the R/ST state as far too small. Given that at the age of 10 years the mortality rate in the general population is extremely small, increasing this probability by 90% is a very limited impact on life expectancy. The percentage of R/ST patients still being alive would be 99.78%. The company motivated the 90% reduction in mortality by referring to two studies reporting five year OS of 7-10% in relapsed patients.[86, 87] As the paper by Oriol et al.[86] only pertains to the adult population, the ERG used the Fielding et al study,[87] which reported a 5-year OS of 12% in patients aged below 20 years. In order to arrive at the survival percentage of 12%, it would be necessary to assume a yearly mortality rate of approximately 35%. Thus, we use in our ERG base case an estimate of 35% for the probability of death per year.

The survival in adult patients is modelled according to a Weibull function and the assumption that all patients have been died after 40 years. Due to a lack of data, the company was unable to explore alternative parametric survival functions. The ERG did not explore other parametric functions, as indeed no data was available for this. We did vary the year that 0% was reached with the survival curve, and those changes had no visible impact on the ICER. The ERG considers it unlikely that alternative survival functions would substantially impact the ICER since equal effectiveness is assumed between the different formulations.

Hypersensitivity rate

The ERG questions whether all hypersensitivity rates used as input for the cost effectiveness analysis reflect the proportion of patients who require a treatment switch due to hypersensitivity to asparaginase. With respect to the hypersensitivity to native *E. coli*, the ERG agrees that 20% can be considered as a reliable and conservative estimate. However, there is no evidence that the percentages used for hypersensitivity to pegaspargase and Erwinase also reflect the proportion of patients who require a treatment switch. The rate of hypersensitivity to pegaspargase is based on the estimate of hypersensitivity in Vora et al. 2013.[19] However, no definition of that rate has been provided and from the reported information it appears most reasonable to assume that the reported percentage reflects the proportion of patients with a grade 3 or 4 adverse event. The ERG found another paper reporting hypersensitivity to pegaspargase given at a dosage of 1,000 IU/m^2.[49] In that paper, the proportion of patients with a treatment switch has explicitly been reported and was 13.2%. The ERG has used this estimate in the ERG base case analysis.

It was also not defined in the original studies[55, 84] that the rates of hypersensitivity to Erwinase reflect the proportion of patients switching treatment. The ERG found an additional study which explicitly stated that 9% discontinued Erwinase due to an allergic reaction.[88] The ERG used this percentage as rate for both first and second line Erwinase. The ERG decided to not distinguish in the hypersensitivity rate between first and second line for Erwinase,

will therefore incorporate only one delayed intensification course as this best reflects current clinical practice in the UK.

5.2.5 Perspective, time horizon and discounting

A time horizon of five years post treatment initiation and a life time horizon were chosen. The five years post treatment initiation was chosen because five year EFS and OS estimates are usually reported in the literature and clinical protocols. Costs are considered from the NHS and PSS perspective. A discount rate of 3.5% was applied for both the costs and effects.

ERG comment: The ERG concludes that the discount rate and perspective are in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

In the CS, it is assumed that the OS and EFS of the different asparaginase agents are equivalent. This assumption is based upon clinical data demonstrating non-significant differences in OS and PFS between pegylated and native *E. coli* asparaginase as first line treatment (Section 4.14 of the CS). All available studies evaluating long-term outcome of Erwinia-derived asparaginase compared to native *E. coli* asparaginase used lower dosages of Erwinia than common in current clinical practice (10,000 IU/m^2 twice weekly or 25,000 IU/m^2 weekly versus 60,000 IU/m^2 weekly in UKALL protocols). In these studies, long-term outcome was significantly worse for patients treated with Erwinase.[24, 55, 56] However, according to the CS, it is expected by the company that the higher dose of Erwinase is as effective as pegaspargase and *E. coli* asparaginase. This assumption has been confirmed by clinical experts.

Likewise, the comparative clinical evidence regarding pegaspargase used higher dosages than common in current clinical practice in the UK (2,500 IU/m^2 in all comparative studies versus 1,000 IU/m^2 in UK clinical practice). In their response to the clarification letter, the company mentioned that no head-to-head comparisons exist of pegaspargase used at 1,000 IU/m^2 and 2,500 IU/m^2. They indicated that a priori it may be reasonable to assume a lower efficacy and fewer side effects at the lower dosage. However, since the EFS and OS of the UKALL 2003 (using a dose of 1,000 IU/m^2) were at least as good as that of studies using the 2,500 IU/m^2, the company considered it to be reasonable to use these survival estimates for all formulations.

In the clarification letter, the ERG indicated that the absence of any significant difference in OS and EFS does not mean that these can be assumed to be equal for all treatment strategies. In their response, the Company reported that they did not find any robust comparative evidence on potential OS and EFS differences between the different asparaginase formulations. The absence of any difference was also confirmed by clinical experts. Finally, it was indicated that it is very difficult to isolate the effect of asparaginase on OS and EFS, since asparaginase is used with different dosing/frequency within multi-treatment regimens.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Pegaspargase for acute lymphoblastic leukaemia

ERRATUM

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Table 5.21 on page 122 of the ERG report should be replaced by the table below.

Table 5.1: Results scenario analyses in addition to the ERG base-case analysis

	Pegasparagase-Erwinia vs native *E coli*-Erwinia			**Pegasparagase-Erwinia vs Erwinia-Pegaspargase**			**Pegasparagase-Erwinia vs Erwinia-native *E. coli***		
Scenario	**Incr. costs**	**Incr. QALYs**	**ICER**	**Incr. costs**	**Incr. QALYs**	**ICER**	**Incr. costs**	**Incr. QALYs**	**ICER**
Base Case ERG	-£3,754	0.02	Dominant	-£28,184	0.00	Cost-saving	-£28,118	0.018	Dominant
Oncaspar Dose per SmPC (2500)	-£3,017	0.02	Dominant	-£27,625	0.01	Cost-saving	-£27,381	0.018	Dominant
Best case scenario EFS/OS	-£3,694	1.45	Dominant	-£28,037	1.45	Dominant	-£27,901	1.45	Dominant
Worst case scenario EFS/OS	-£3,796	-0.86	£4,400 (SW)	-£28,354	-0.87	£32,907 (SW)	-£28,218	-0.86	£33,179 (SW)
Utilities based on Mapping	-£3,754	0.02	Dominant	-£28,184	0.00	Cost-saving	-£28,118	0.018	Dominant
Utility R/ST state 68% reduction	-£3,754	0.02	Dominant	-£28,184	0.00	Cost-saving	-£28,118	0.018	Dominant
4 doses *E. coli* or Erwinase for each dose PEG	£357	0.02	£36,499 (NE)	-£19,719	0.00	Cost-saving	-£19,702	0.018	Dominant
Worst case EFS/OS + Oncaspar dose per SmPC (2500) + 4 doses *E. coli* or Erwinase for each dose PEG	£1,290	-0.86	Dominated	-£16,300	-0.87	£18,537 (SW)	-£16,213	-0.86	£18,791 (SW)

NE = North-east quadrant (ICERS should be below threshold), PEG = Pegaspargase, SW = South-west quadrant (ICERs should be above threshold)