South African National Department of Health
Brief Report of NEMLC Limited Review[1]
PEGASPARGASE for Acute Lymphoblastic Leukaemia
SEPTEMBER 2025

Medicine details:

Medicine Class	Antineoplastic and Immunomodulating Agents	
Medicine/s name **-INN/South African name** (if differs from INN)	Pegaspargase *(Pegylated L-asparaginase)*	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	L01XX24	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	Acute lymphoblastic leukaemia (ALL) (C91.0)	*https://www.health.gov.za/icd-10-master-industry-table/*
SAHPRA Approved	Section 21	SAHPRA registered health products *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Injection	
Route of administration/s	Intramuscular/ Intravenous	
Patient population	Paediatric and adult patients with Acute lymphoblastic leukaemia (ALL)	
Prevalence and/or incidence of condition	The National Cancer Registry 2023 reports leukaemia collectively, with 0.83 adjusted cases per 100 000/year.[1] ALL is the most common childhood cancer in South Africa. South Africa recorded an estimated crude mean annual incidence rate of 76 new cases of cancer per million children aged below 15 years for the period 1986 – 1991.[2,3]	
Level of Care	Tertiary	
Prescriber level	Specialist	

[1] This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Current Standard of Care

- E-coli derived L-asparaginase injections

Current standard of care for ALL in children and the adolescent and young adult population is multi-agent chemotherapy given as intensive treatment blocks for 6-8 months, followed by 2-year maintenance therapy. This standard of care has been put in place by international cross-continental collaborative treatment groups such as the Children's Oncology Group (COG).[4] The current standard of care is per standardised treatment protocol. On these international treatment protocols delivering asparaginase treatment in its pegylated form is the current standard of care.

Executive Summary

- E-coli derived asparaginase is approved on the Tertiary and Quaternary Essential Medicines List for Acute lymphoblastic leukaemia (ALL).
- There is currently (2025) only one supplier for this product within South Africa, and there have been signals that this supplier is likely going to discontinue supply in the future. In such a situation, only supply via section 21 will be possible. Pegaspargase or Pegylated (PEG) asparaginase is a long-acting form of L-asparaginase has been proposed as a possible alternative.
- A literature search was conducted, and 2 randomised trials, and one meta-analysis were included in the assessment.

- <u>Effectiveness and safety results:</u>
- **Comparison: Pegaspargase vs L-Asparaginase:**
  - ***Disease-free survival/Event-free survival/Relapse Rate:***
    - » 5-year disease-free survival was found to be similar between IV pegaspargase [90% (95% CI 86 to 94)] and IM L-asparaginase [89% (95% CI 85 to 93)], p = 0.58. (*Place et.al.)*
    - » There were no significant differences found between groups using pegaspargase (7 of 59 patients) and L-asparaginase (8 of 59 patients). (*Avramis et.al.)*
  - ***Overall survival***
    - » 5-year overall survival was found to be similar with use of IV pegaspargase [96% (95% CI 93 to 98)] and IM L-asparaginase [94% (95% CI 89 to 96)]; p = 0.3. (*Place et.al.)*
  - ***Complete remission rate:***
    - » A randomised study and a meta-analysis in Chinese children found that complete remission rate and complete response respectively showed no significant differences between pegaspargase and L-asparaginase groups. (*Avramis et.al. and Dai et.al.)*
  - ***Serum asparaginase trough level***
    - » A randomised trial demonstrated that the median trough serum asparaginase activity was significantly higher in patients who received IV pegaspargase than in those who received IV L-asparaginase; p< 0.0001 at each time point. (*Place et.al.)*
    - » Another randomised study reported notably higher percentage of samples from children in the pegaspargase group having asparaginase activity on day 21 of therapy in delayed intensification (DI) 1 and DI 2. (*Avramis et.al.)*
  - ***Overall rate of asparaginase related toxicities: pancreatitis, hepatic injury, thrombosis, bleeding, allergic reactions***
    - » Two randomised trials found that the overall all frequency of pegaspargase and L-asparaginase did not differ significantly (*Avramis et.al. and Place et.al.)*

- » The meta-analysis in Chinese children reported a lower hepatic injury rate (risk ratio [RR] = 0.45; 95% CI, 0.27 to 0.75; p = 0.002) and a lower hypersensitivity rate (RR = 0.63, 95% CI, 0.40 to 1.01; p = 0.05) in the pegaspargase group compared to the L-asparaginase group. (*Dai et.al.)*

- ***Quality of Life***
  - » A randomised study reported on an optional health-related quality of life assessment (n=202) In both the parent-proxy report and the patient report; there was significantly more anxiety reported in the IM L-asparaginase group. Scores for emotional functioning, pain and hurt, general fatigue, and sleep or rest fatigue, were similar between the groups on both parent and patient reports. (*Place et.al.)*
  - » Length of hospital stay was reported in a meta-analysis in Chinese children and found that it was significantly less in patients in the pegaspargase group than the L-asparaginase group (mean difference = –7.04, 95% CI, –8.06 to –6.02; P<0.00001). Inversely, the frequency of administration/lower number of doses was less for pegaspargase compared to L-asparaginase. *(Dai et.al.)*

➡ Pegaspargase and L-asparaginase are shown to be equally effective with similar toxicities. Pegaspargase has the benefit of less immunogenicity compared as to L-Asparaginase and additionally has the benefit of reduced hospitalisation and dosing.

➡ Both items currently need to be procured via section 21. Pricing is thus not stable, however pegaspargase results in 7 days less hospitalisation which should be considered when comparing regimen prices.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	**X**	☐

High level summary of conclusions	Pegaspargase can be used as an alternative to L-asparaginase for the management of ALL in adults and children. Pegaspargase has been shown to have similar safety and efficacy compared to L-asparaginase, however it has the benefit of less immunogenicity and reduced dosing. This also translates to reduced hospitalisation and less discomfort of injections for patients. If there is price parity, pegaspargase would be preferred.					
NEMLC Ratification	**Date:**		**Comments**			
	16 October 2025		NEMLC ratified the recommendation as described.			
Therapeutic Interchange Considerations (if applicable)	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
		Pegaspargase L-asparaginase	No	Injections	See protocol – appendix 3	☐
Trigger for review	Registration of products in South Africa, price changes.					

Background and rationale

E-coli derived asparaginase (L-asparaginase) is approved on the Tertiary and Quaternary Essential Medicines List for Acute lymphoblastic leukaemia (ALL). There is currently (2025) only one supplier for this product within South Africa, and there have been signals that this supplier is likely going to discontinue supply in the future. In such a situation, only supply via section 21 will be possible. Pegaspargase is a long-acting form of L-asparaginase has been proposed as a possible alternative. Pegaspargase has been shown to be equally effective with similar toxicities as L-asparaginase when given as a single intramuscular dose of 2,500 international units/m 2 replacing the 9 L-asparaginase doses of 6,000 international units/m 2 during induction, as well as the 6 doses during delayed intensification, on Children's Cancer Group Study (CCG) -1962 *(Avramis et. al.)*.

Purpose/Objective i.e., PICO question (if relevant):

Population Subgroups	Acute lymphoblastic leukaemia (ALL) in children and adults
Intervention(s)	Pegylated E-coli derived asparaginase
Comparator(s)	E-coli derived asparaginase (L-Asp) / Native
Outcome(s)	1. Disease free survival/Event free survival or relapse rate 2. Overall-survival 3. Complete remission rate 4. Serum asparaginase-trough levels 5. Overall rate of Asparaginase related toxicities: pancreatitis, thrombosis, bleeding, allergic reactions 6. Quality of life
Study types	Clinical Practice Guidelines initially, then Meta-analyses and systematic reviews; and Randomised controlled trials

Methods

1. Data Sources

An initial search was undertaken for Clinical Practice Guidelines; however, none were identified, and only protocol type guides were found. Thus, the search was moved to meta-analyses, systematic reviews and randomised controlled trials.

We searched the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Epistemonikos databases for meta-analyses, systematic reviews and randomised controlled trials on 8 August 2025.

2. Search Strategy

JR developed and conducted the search strategy without language or publication restrictions, in consultation with clinical expert (LdP). Search strategy and findings documented in appendix 1.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The eligibility criteria for the review were developed a priori and comprised the components as indicated above in the PICO elements. Titles identified were loaded to Rayyan for screening. Screening of titles and abstracts was undertaken by one reviewer (JR). Studies identified for full-text screening was undertaken independently and in duplicate by two reviewers (JR, LdP) and selection of studies were done independently and in duplicate by two reviewers (JR, LdP). We summarised the selection process graphically in a PRISMA flow diagram (Figure 1). Data extraction (JR and LdP) was conducted independently and in duplicate (JR, LdP), and disagreements were resolved through discussion. Appraisal was conducted by YW (meta-analyses/systematic review) and JR (randomised trials).

4. Assessment of methodological quality

AMSTAR 2[5] was used to assess quality of meta-analyses/systematic review, and the NIH (National Institute for Health) Quality Assessment of Controlled Intervention Studies tool[6] was used for randomised studies.

Results

Describe as appropriate based on the methodology outlined

1. Result of the search

An electronic search of the databases, with no language or publication date restrictions, retrieved 97 records. Following removal of duplicates (16 records), 81 records were screened, of which 10 were identified for full-text screening. From full-text screening 3 were identified for inclusion. *See Figure 1 for the PRISMA flow diagram.*

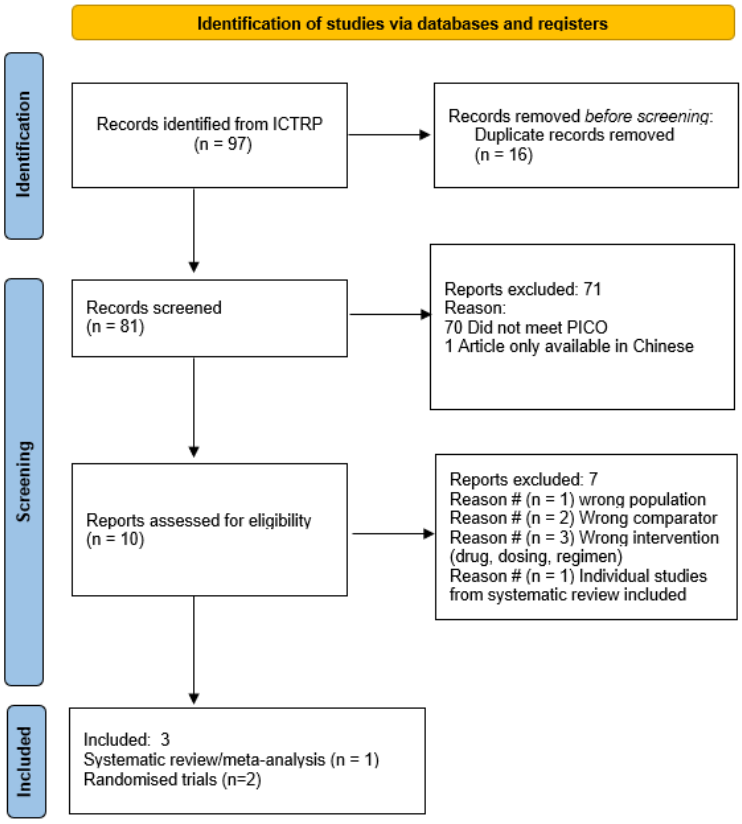

Figure 1: PRISMA diagram – included studies

2. Description of included studies:

2.1. Meta-analysis and/or Systematic reviews

We included one meta-analysis, which investigated the efficacy and safety of pegaspargase versus L-asparaginase in Chinese children with ALL, *Dai et al. 2021*[7].

2.2. Randomised trials

We included two randomised trials. One was a randomised comparison of L-asparaginase versus pegaspargase in children with newly diagnosed ALL, a Children's Cancer Group study (*Avramis et al. 2002*[8]); and a randomised, open-label phase 3 trial comparing IV PEG-asparaginase and IM L-asparaginase in newly diagnosed children with ALL (*Place et al. 2015*[9]).

3. Methodological quality of included studies

Randomised studies (JR assessed)

See appendix 4

- Avramis et.al. All criteria were met except there was no blinding, and method of randomisation and allocation concealment was not reported, and there was no mention of prespecified subgroups.
- Place et.al. met all the criteria except there was no blinding in this study.

Meta-analysis

(duplicate assessed: YW and JR)

Dai et.al. was found to be Low quality: list of excluded studies that went through full text review not included AND no trial registry/expert consultation/grey literature.

4. Effectiveness and/or safety

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of included studies
1. Pegaspargase vs L-asparaginase	3

Comparison: Pegaspargase vs L-asparaginase:

- **Outcome 1: Disease free survival/event-free survival/relapse rate**

  Two randomised studies reported on disease free survival/event free survival or relapse rate.

  » Place et.al. evaluated disease free survival as a predefined secondary endpoint. They reported that 5-year disease-free survival was 90% (95% CI 86 to 94) for patients using IV pegaspargase and 89% (95% CI 85 to 93) for those assigned to IM L-asparaginase; p = 0.58. See figure 2 below. No differences in disease free survival between groups were noted within patient subsets defined by baseline characteristics, risk group classification or residual disease.

  » Avramis et.al. reported relapse for 7 of 59 patients in the pegaspargase arm and 8 of 59 patients in the L-asparaginase arm (not significant). The event-free survival rate was shown to be 85% for pegaspargase and 78% for L-asparaginase (not significant).

- **Outcome 2: Overall-survival**

  » Place et.al. reported 5-year overall survival as 96% (95% CI 93 to98) for patients assigned to intravenous pegaspargase, and 94% (95% CI 89 to 96) for those randomly assigned to IM L-asparaginase; p = 0.3, see figure 2 below.

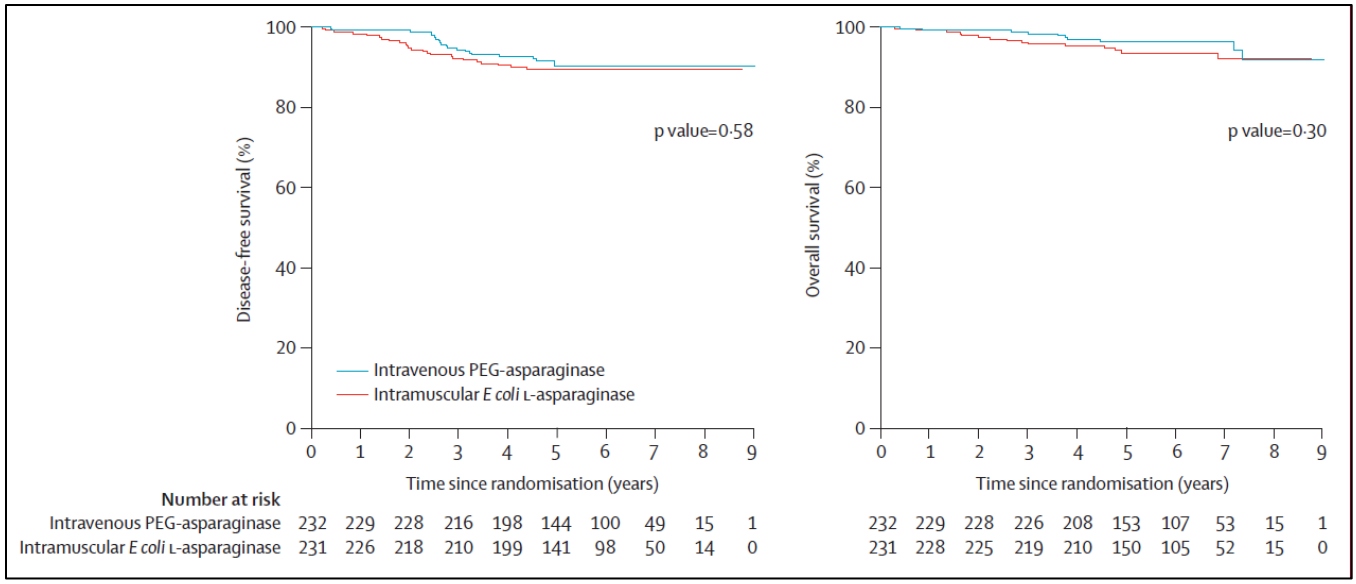

Figure 2: Disease free survival and Overall-survival

- **<u>Outcome 3: Complete remission rate</u>**
  - » Avramis et.al. defined remission as the presence of lymphoblasts less than or equal to 5% of cells found in the bone marrow. This study found complete remission was achieved in 52 patients (96% of analysed sample and 88% of total randomised) in the pegaspargase group; and 43 patients (83% of analysed sample and 73% of total randomised) in L-asparaginase group. Children treated with pegaspargase had more rapid clearance of lymphoblasts from day 7 and day 14 bone marrow aspirates than L-asparaginase patients. See figure 3 below.

	Pegaspargase		Native ASNase	
BM status	Day 7	Day 14	Day 7	Day 14
M1	36 (63)	52* (96)	26 (47)	43† (83)
M2	13 (23)	2 (4)	13 (24)	5 (10)
M3	8 (14)	0	16 (29)	4 (8)
Total patients	57 (100)	54 (100)	55 (100)	52 (100)

Entries are numbers of patients; parentheticals are percentages. Two patients were excluded from analysis: one had Philadelphia chromosome and one received both asparaginase preparations.
BM indicates bone marrow.
*This number includes 34 patients with M1 bone marrow on day 7 and day 28 who did not have a bone marrow aspirate on day 14.
†This number includes 24 patients with M1 bone marrow on day 7 and day 28 who did not have a bone marrow aspirate on day 14.

Figure 3: Bone marrow status on day 7 and day 14

  - » Dai et.al where all 15 studies (1194 patients) reported complete response. The pooled analysis showed that there was no significant difference in complete response under the fixed effect model between pegaspargase and L-asparaginase (RR = 1.01; 95% CI, 0.96 to 1.08, p = 0.64. See figure 4 below.

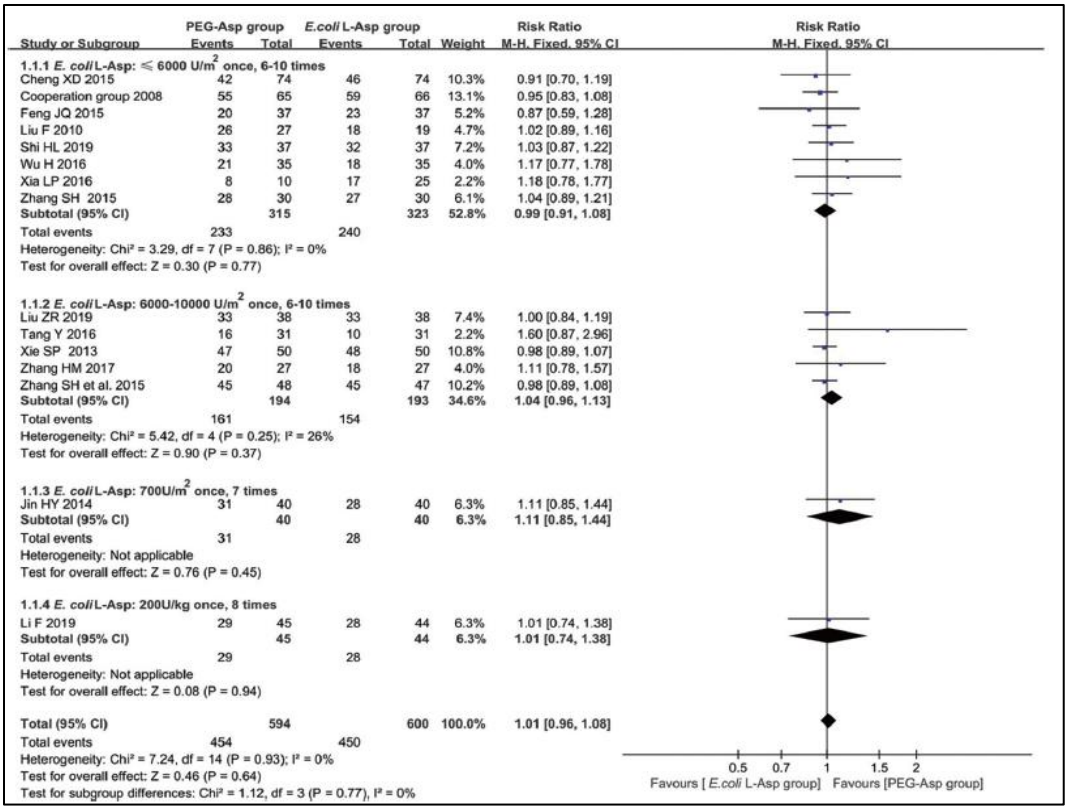

Figure 4: Forest plot of complete remission for pegaspargase vs L-asparaginase.

- **<u>Outcome 4: Serum asparaginase trough level (ASNase activity level)</u>**
  The internationally accepted standard trough asparaginase activity level is ≥ 0.1 IU/ml. This level indicates sufficient asparagine depletion for therapeutic benefit and can also assist to identify silent inactivation of asparaginase. If the trough level is below the target, it may signal immune-mediated inactivation.[10]

  » Place et.al. demonstrated that the median nadir serum asparaginase activity was significantly higher in patients who received IV pegaspargase than in those who received IV L-asparaginase; p< 0.0001 at each time point. See figure 5 and 6.

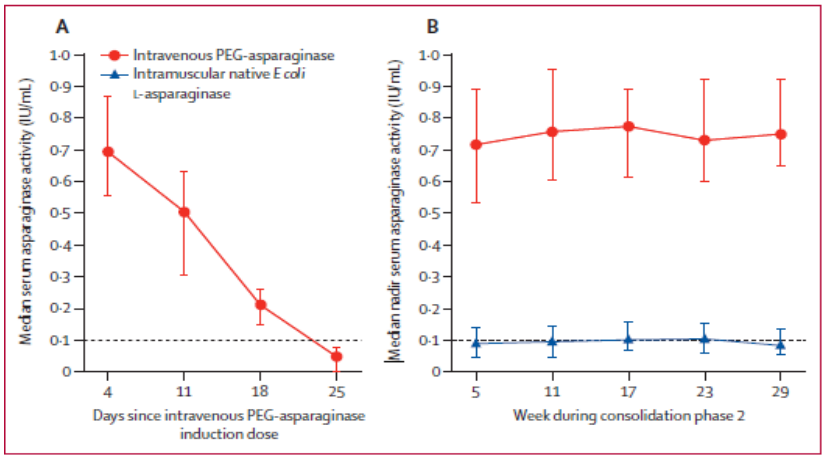

Figure 5: Serum asparaginase activity

	Patients (n)	Serum asparaginase activity (IU/mL)		Patients (%) with each level of serum asparaginase activity		
		Median (IQR)	Mean (SD)†	≥0·025 IU/mL	≥0·10 IU/mL	≥0·20 IU/mL
Day 4	317	0·694 (0·556–0·868)	0·737 (0·282)	97%	97%	94%
Day 11	348	0·505 (0·306–0·632)	0·502 (0·222)	97%	96%	89%
Day 18	294	0·211 (0·150–0·259)	0·254 (0·164)	97%	87%	56%
Day 25	298	0·048 (<0·025–0·076)	0·092 (0·125)	73%	12%	5%

*Intravenous PEG-asparaginase administered during induction on day 7. †Excludes samples with an enzyme activity below the 0·025 IU/mL lower limit of quantification.

Table 5*: Induction serum asparaginase activity after one dose of intravenous PEG-asparaginase, by day post-administration

Figure 6: Serum asparaginase activity

» Avramis et.al. reported ASNase activity data during delayed intensification (DI) 1 and 2 to compare the percentage of samples with activity levels of more than 0.03 and 0.1 IU/mL, between the children receiving pegaspargase and L-asparaginase. Figure 7 indicates that a notably higher percentage of samples from children in the pegaspargase group had ASNase activity of more than 0.03 IU/mL and 0.1 IU/mL on day 21 of therapy in DI 1 and DI 2.

	Day 21 DI no. 1		Day 21 DI no. 2	
ASNase activity	PEG	Native	PEG	Native
Above 0.03 IU/mL	95%	31%	91%	39%
Above 0.1 IU/mL	95%	19%	91%	22%

DI indicates delayed intensification; PEG, pegaspargase.

Figure 7: Percentage of samples with adequate ASNase activity

- **<u>Outcome 5: Overall rate of asparaginase related toxicities: pancreatitis, hepatic injury, thrombosis, bleeding, allergic reactions</u>**
  - » Place et. al. found that the overall frequency of asparaginase-related toxicities did not differ significantly between the two groups, 65 of 232 (28%) patients in the IV pegaspargase group versus 59 of 231 (26%) of patients in IM L-asparaginase group. See figure 8 below.

	Intramuscular native *Escherichia coli* L-asparaginase (n=231)	Intravenous PEG-asparaginase (n=232)	p value
Asparaginase toxicity	59 (26%)	65 (28%)	0·60
Pancreatitis, grade ≥2	22 (10%)	27 (12%)	0·55
Mild/moderate	16 (7%)	14 (6%)	0·71
Severe	8 (3%)	13 (6%)	0·37
Allergy (all grades)*	21 (9%)	28 (12%)	0·36
Grades 1 and 2	13 (6%)	14 (6%)	0·99
Grades 3 and 4	6 (3%)	14 (6%)	0·10
Thrombosis or bleeding, grade ≥2	24 (10%)	17 (7%)	0·26
CNS	3 (1%)	6 (3%)	0·50
Non-CNS	21 (9%)	12 (5%)	0·11
Infection (bacterial/fungal), grade ≥3	51 (22%)	47 (20%)	0·65
Hyperbilirubinaemia, grade ≥4	1 (<1%)	2 (<1%)	0·99
5-year cumulative incidence of grade ≥2 osteonecrosis (95% CI)†	9% (6–13)	9% (5–13)	0·85
5-year cumulative incidence of grade ≥1 bone fracture (95% CI)†	23% (18–28)	21% (16–27)	0·60

Data are n (%) unless otherwise indicated. Toxicity was continually monitored during treatment and was graded using the Common Terminology Criteria for Adverse Events version 3.0. *Two additional patients in the intramuscular *E coli* L-asparaginase group experienced an unknown grade of allergy. These patients were not included in the analysis. †The 5-year cumulative incidence of osteonecrosis and fracture was calculated from the date of randomisation using the competing risk regression package in R and compared with the Gray test, with relapse and death in remission as competing risks.

Table 2: **Adverse events in randomly assigned patients during post-induction treatment phases**

Figure 8: Adverse events in randomly assigned patients during post-induction treatment phases.

» Avramis et. al. reported no toxicity-related deaths in either the pegaspargase or L-asparaginase (native) groups, and the incidence and type of toxic events were similar between the two groups during IND (induction) and DI (delayed intensification 1 & 2). See table below for reported toxicity.

Table 5. Grade 3 and grade 4 toxicity during asparaginase-containing courses

Event type	Pegaspargase			Native		
	IND	DI no. 1	DI no. 2	IND	DI no. 1	DI no. 2
CNS thrombosis	1	1	—	2	—	—
Other CNS complications*	—	3	3	—	2	2
Life-threatening infections†	—	1	1	—	—	1
Bacteremia	1	6	10	6	2	9
Hyperglycemia	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	—	—	—
Hemorrhagic cystitis	—	—	—	—	1	—
Constipation	—	—	1	—	—	—
Diarrhea	—	—	1	—	—	—
Allergy to asparaginase	—	1	—	—	—	—
Assessable patients	59	54	48	59	53	53

IND indicates 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.

Figure 9: Grade 3 and 4 toxicity during asparaginase -containing courses.

» Meta-analysis by Dai et.al. reported a lower hepatic injury rate (risk ratio [RR] = 0.45; 95% CI, 0.27 to 0.75; p = 0.002) and a lower hypersensitivity rate (RR = 0.63, 95% CI, 0.40 to 1.01; p = 0.05) in the pegaspargase group than in the L-asparaginase group. In terms of gastrointestinal symptoms and coagulation abnormalities, both the pegaspargase and L-asparaginase groups had similar findings.

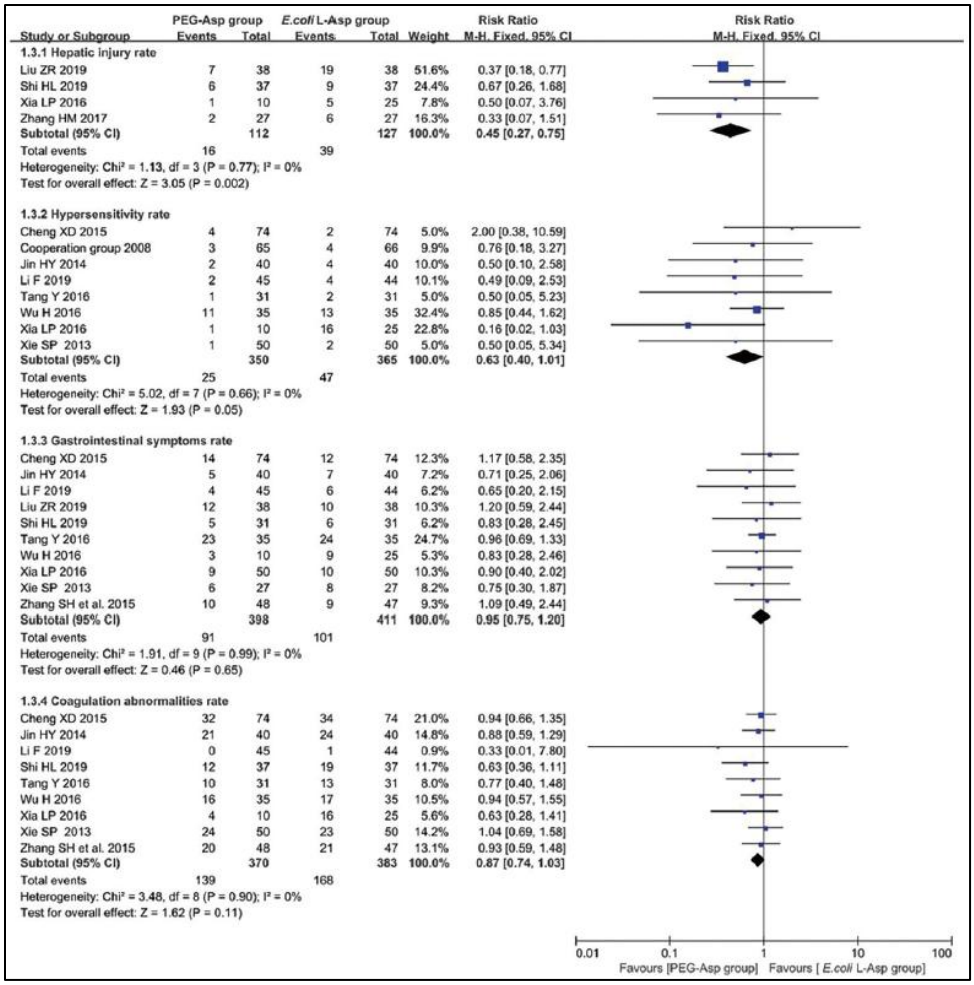

Figure 10: Forest plot of adverse events for the pegaspargase group vs L-asparaginase group.

- **<u>Outcome 6: Quality of Life</u>**
  - » Place et.al. reported on an optional health-related quality of life assessment which 202 patients participated in (97 patients in IM L-asparaginase group and 105 patients in the pegaspargase group – patient characteristics did not differ significantly between groups). In both the parent-proxy report and the patient report, there was significantly more anxiety reported in the IM L-asparaginase group. Scores for emotional functioning, pain and hurt, general fatigue, and sleep or rest fatigue, were similar between the groups on both parent and patient reports.
  - » Dai et.al. reported that length of hospital stay of patients in the pegaspargase group was significantly less than for patients in the L-asparaginase group (mean difference = –7.04, 95% CI, –8.06 to –6.02; P<0.00001); this is likely linked to the frequency of administration/lower number of doses which is less for pegaspargase compared to L-asparaginase. See figure 11 below:

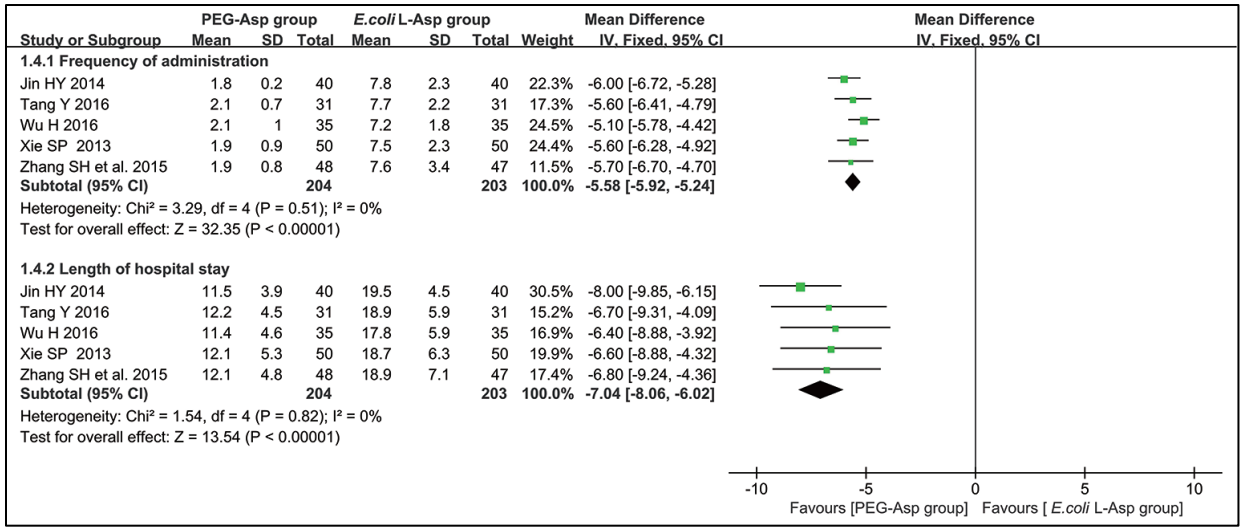

Figure 11: Forest plot of frequency of administration and length of hospital say for pegaspargase versus L-asparaginase.

Route of administration: IV and IM dosing

Route of administration should be determined by patient preference and the treating physician's level of comfort, considering a higher rate of hypersensitivity in patients receiving asparaginase intravenously.

A meta-analysis by Hasan et.al.11 reported that pooled hypersensitivity rates were 23.5% (95% CI 14.7 to 33.7) and 8.7% (95% CI 5.4 to 12.8) for IV and IM, respectively. Odds ratios were computed for each study and the pooled fixed effects odds ratio, unadjusted for publication bias, was 2.99 (95% CI 1.86 to 4.80). IM administration is however associated with more pain and anxiety.

Costs

The prices of pegaspargase and asparaginase are currently unstable. There is a registered asparaginase product in South Africa, that provinces were buying out (not on contract). The single exit price (SEP) and buy-out price are shown below in table 1. The continued supply of this registered asparaginase is however in question, and a short-term section 21 is being put in place (price for this section 21 acquisition is still being investigated).

Pegaspargase is only available through section 21 (no registered product). A quote for a specific supplier has been received, and this price is reflected in table 1.

Table 1: Asparaginase and Pegaspargase prices

Source	Active	Supplier	Medicine Proprietary Name	Strength	PRICE
SEP 24 July 2025	Asparaginase	Pharmacare Limited	Laspar	10000 IU	R1,863.60
State buy-out Aug 2025	Asparaginase	Pharmacare Limited	Laspar	10000 IU	R1,600.00
Sec 21 (quote - Aug 25)	Pegaspargase	Gennova (Emcure) sec 21	Hamsyl	3750 IU	R16,500.00

Based on these prices, and protocols outlined in appendix 3, the following price comparisons were calculated, see

Table 2: Estimated cost of total course for L-asparaginase compared to pegaspargase at various patient body surface area.

Total dose per m^2 category*	Product	Standard risk B-cell ALL		High-risk b cell ALL		T-cell ALL	
		Total cost (Vial sharing)	Total cost (NO vial sharing)	Total cost (Vial sharing)	Total cost (NO vial sharing)	Total cost (Vial sharing)	Total cost (NO vial sharing)
TOTAL $0.75m^2$	**L-asparaginase**	R10,800.00	R24,000.00	R23,760.00	R52,800.00	R32,400.00	R72,000.00
	Pegaspargase	R16,500.00	R33,000.00	R41,250.00	R82,500.00	R57,750.00	R115,500.00
TOTAL $1m^2$	**L-asparaginase**	R14,400.00	R24,000.00	R31,680.00	R52,800.00	R43,200.00	R72,000.00
	Pegaspargase	R22,000.00	R33,000.00	R55,000.00	R82,500.00	R66,520.00	R115,500.00
TOTAL $1.3m^2$	**L-asparaginase**	n/a**	n/a **	R41,184.00	R52,800.00	R56,160.00	R72,000.00
	Pegaspargase	n/a**	n/a **	R71,500.00	R82,500.00	R100,100.00	R115,500.00

**Estimated doses using Children's Oncology Group (COG) Protocol*

*** all patients older than 10 years are considered high risk*

Hospitalisation

Dai et.al. reported the use of pegaspargase reduced the hospital stay by 7 days. This cost was estimated in table 3 below:

Table 3: Estimated additional hospitalisation expenditure for asparaginase as compared to pegaspargase

	Inpatient general ward fee	**Duration (days)**	**Total cost for 7 days hospitalisation**
Regional hospital*	R1,339.00	7	R9,373.00
Tertiary hospital*	R2,534.00	7	R17,738.00

Uniform Patient Fee Schedule (UPFS) 2025

Note: No other costs incorporated.

By off-setting the differences with the cost of hospitalisation averted with pegaspargase, the costs are somewhat comparable, however L-asparaginase is still the more affordable option based on current pricing of registered product.

The section 21 price of L-asparaginase attained for 6-months from October 2025 is reported to be R340.00/vial. At this temporary price point the L-asparaginase would be the far more affordable oprion. See table 4 below:

		Standard risk B-cell ALL		High-risk b cell ALL		T-cell ALL	
		Total cost (Vial sharing)	Total cost (NO vial sharing)	Total cost (Vial sharing)	Total cost (NO vial sharing)	Total cost (Vial sharing)	Total cost (NO vial sharing)
TOTAL 0.75m2	**L-asparaginase**	R2,295.00	R5,100.00	R5,049.00	R11,220.00	R6,885.00	R15,300.00
	Peg-aspargase	R16,500.00	R33,000.00	R41,250.00	R82,500.00	R57,750.00	R115,500.00
TOTAL 1m2	**L-asparaginase**	R3,060.00	R5,100.00	R6,732.00	R11,220.00	R9,180.00	R15,300.00
	Peg-aspargase	R22,000.00	R33,000.00	R55,000.00	R82,500.00	R66,520.00	R115,500.00
TOTAL 1.3m2	**L-asparaginase**			R8,751.60	R11,220.00	R11,934.00	R15,300.00
	Peg-aspargase			R71,500.00	R82,500.00	R100,100.00	R115,500.00

Discussion

Pegaspargase is a long-acting form of E. coli asparaginase that has been shown to be equally effective with similar toxicities as L-asparaginase (Avramis et. al.). It is an enzyme conjugated to polyethylene glycol (PEG) molecules, and in addition to the unaffected biological activity of asparaginase, pegaspargase greatly diminishes unappreciated immunogenicity. The half-life of pegaspargase (7±2 days) is significantly longer than that of L-asparaginase (20 hours), indicating that pegaspargase can reduce the frequency of administration (Dai et.al.)

In the South African public health sector, there is limited access to the immunologically distinct asparaginase, Erwinia chrysanthemi, that is considered an effective alternative for patients developing a hypersensitivity reaction to L-asparaginase. Due to high cost and access barriers (unregistered in South Africa) this leaves patients at higher risk for leukemic relapse, as the assigned asparaginase doses cannot be completed. Gupta et al. (2020)[12] retrospectively assessed treatment outcomes for children and young adults treated on COG AALL0331 for National Cancer Institute (NCI) standard risk patients and COG AALL0232 for NCI high-risk patients. The key objective was to evaluate the impact of Erwinia non-availability on risk for ALL relapse. For the high-risk patients who did not receive all asparaginase doses, a significantly poorer disease-free survival was noted, compared to those receiving all prescribed doses, with a hazard risk of 1.5 for disease relapse.

Pegaspargase has demonstrated a substantially lower incidence of immunogenicity. This reduced likelihood of allergic response decreases the need for an alternative agent such as Erwinase, making pegaspargase a clinically advantageous option for maintaining treatment continuity and improving outcomes in this vulnerable patient population.

EVIDENCE TO DECISION FRAMEWORK

Assessment

Desirable Effects ***How substantial are the desirable anticipated effects (i.e., benefits)?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
X Trivial *o Small* *o Moderate* *o Large* *o Varies (if so, why?)* *o Don't know*	Generally show to have similar effects in terms of outcomes of: • *Disease-free survival/Event-free survival/Relapse Rate:* • *Overall survival* • *Complete remission rate:* *Moderate benefits were seen with use of pegaspargase in terms of quality of life.*	*Clinically determined to be similar*
Undesirable Effects ***How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
o Large *X Moderate* *o Small* *o Trivial* *o Varies (if so, why?)* *o Don't know*	Benefits of pegaspargase seen in terms of outcomes: • *Less immunogenicity* • *Serum asparaginase trough level* Generally show to have similar effects in terms of outcomes of: • *Asparaginase related toxicities: pancreatitis, hepatic injury, thrombosis, bleeding.*	*Certain benefits seen with IV pegaspargase*
Certainty of evidence[2] ***What is the overall certainty of the evidence of effects (across all critical outcomes)?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
o Very low *o Low* *X Moderate* *o High* *o No included studies*	*Although quality of evidence was not strong for comparisons investigated, the direction of effects was similarly reported for all included studies.*	
Values ***Is there important uncertainty in how people with conditions, caregivers, healthcare providers or decision-makers value the main outcomes?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
o Important uncertainty *o Possibly important uncertainty* *X Probably no important uncertainty* *o No important uncertainty*	*Outcomes were determined by practicing clinicians. There is no reason to expect affected population to have differing values.*	*The ERC judged that there was no reason to suspect varying values among the affected population/healthcare providers/others from that identified in the evidence.*
Balance of effects ***Does the balance of effects favour the medicine being considered an essential medicine? Does the desirable effects outweigh the undesirable effects?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***

X Yes *○ Probably Yes* *○ Probably No* *○ No* *○ Varies (if so, why?)* *○ Don't know*	*Yes – there is no reason to suspect different balance of health effects.*	• *The ERC judged that there was no reason to suspect different balance of health effects from that presented in the evidence.*
Resources required ***How large are the resource requirements (costs)?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
O Large costs *O Moderate costs* *O Negligible costs or savings* *O Moderate savings* *O Large savings* *O Varies* *X Don't know*	*See Cost discussions sections.*	*Due to the lack of a registered product true resource requirements is difficult to determine.*
Equity* ***What would be the impact on health equity?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
O Reduced *O Probably reduced* *O Probably no impact* *O Probably increased* *O Increased* *O Varies* *X Don't know*	*There is no reason to suspect differences, however with no registered product of either the comparator or the intervention, aspects of equity are hard to determine – equitable accessibility.*	*The ERC judged that there was no reason to suspect differences in the impact on health equity from that presented in the evidence.*
Acceptability* ***Is the option acceptable to recommend as an essential medicine to key stakeholders?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
O No *O Probably no* *O Probably yes* *X Yes* *O Varies (if so, why?)* *O Don't know*	*Presented evidence indicates that pegaspargase has benefits that may enhance acceptability: decreased doses, decreased length of stay*	
Feasibility* ***Is the option feasible to implement?***		
Judgement	***Research evidence***	***Additional considerations (by committee)***
O No *O Probably no* *O Probably yes* *O Yes* *O Varies (if so, why?)* *X Don't know*	*Due to a lack of a registered product (comparator or intervention drug), feasibility is difficult to determine.*	

Summary of judgements

	Judgement						
Desirable effects	***Trivial***	*Small*	*Moderate*	*Large*		*Varies*	*Don't know*
Undesirable effects	*Large*	***Moderate***	*Small*	*Trivial*		*Varies*	*Don't know*
Certainty of evidence	*Very low*	*Low*	***Moderate***	*High*			*No included studies*
Values	*Important uncertainty or variability*	*Possibly important uncertainty or variability*	***Probably no important uncertainty or variability***	*No important uncertainty or variability*			
Balance of effects	*Favors the comparison*	*Probably favors the comparison*	*Does not favor either the intervention or the comparison*	***Probably favors the intervention***	*Favors the intervention*	*Varies*	*Don't know*
Resources required	*Large costs*	*Moderate costs*	*Negligible costs and savings*	*Moderate savings*	*Large savings*	*Varies*	***Don't know***
Equity	*Reduced*	*Probably reduced*	*Probably no impact*	*Probably increased*	*Increased*	*Varies*	***Don't know***
Acceptability	*No*	*Probably no*	*Probably yes*	***Yes***		*Varies*	*Don't know*
Feasibility	*No*	*Probably no*	*Probably yes*	*Yes*		*Varies*	***Don't know***

Conclusion and Recommendation

Pegaspargase and L-asparaginase are shown to be equally effective with similar toxicities. Pegaspargase has the benefit of less immunogenicity compared as to L-Asparaginase and additionally has the benefit of reduced hospitalisation and dosing.

Review Team

The following people were involved in this review:

Name	Affiliation(s)	Role and Contribution	Interest declaration
Liezl du Plessis	Paediatric Oncologist · Robert Mangaliso Sobukwe Hospital	PICO development, article screening, data extraction, formulation of recommendations	No specific conflicts
Jane Riddin	National Department of Health (NDoH)	Search strategy, quality assessments, data screening and extraction, cost analysis.	None
Alicia Sheriff	Head of Department Oncology, University of the Free State; Head Clinical Unit, Depart Oncology: Free State Health	General review of content	No specific conflicts
Derusha Frank	Clinton Health Access Initiative (CHAI), seconded to NDoH	General review of content	None
Ya-Ying Wang	Eastern Cape Department of Health	Quality assessment - AMSTARS	None

Expert Review Committee Members

General review by ERC. No specific conflicts declared relating to this review.

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Appendix 1: Search Strategy

PubMed (conducted 8 August 2025)

Search	Query	Search details	Results
#2	Limited to meta-analyses; systematic-reviews; randomised controlled trials	(("Asparaginase"[Mesh] AND "pegaspargase" [Supplementary Concept]) NOT "asparaginase erwinia chrysanthemi recombinant" [Supplementary Concept]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	46
#1	Asparaginase and Pegaspargase	("Asparaginase"[Mesh] AND "pegaspargase" [Supplementary Concept]) NOT "asparaginase erwinia chrysanthemi recombinant" [Supplementary Concept]	367

Additional titles identified in Pub Med

Titles shared by clinical experts not picked up in original search above	3

Cochrane Library (conducted 8 August 2025)

Query	Search details	Results
#1	MeSH descriptor: [Asparaginase] explode all trees	380
#2	Pegylated asparaginase	58
#3	#1 AND #2	25
#4	#3 PLUS Cochrane review limit	2
#5	#3 PLUS Trials	23

Epistamonikus (conducted 8 August 2025)

Query	Search details	Results
#1	(title:((title:(asparaginase) OR abstract:(asparaginase)) AND (title:(pegaspargase) OR abstract:(pegaspargase)) OR (title:(pegylated asparaginase) OR abstract:(pegylated asparaginase)) AND (title:(Acute lymphoblastic leukaemia) OR abstract:(Acute lymphoblastic leukaemia))) OR abstract:((title:(asparaginase) OR abstract:(asparaginase)) AND (title:(pegaspargase) OR abstract:(pegaspargase)) OR (title:(pegylated asparaginase) OR abstract:(pegylated asparaginase)) AND (title:(Acute lymphoblastic leukaemia) OR abstract:(Acute lymphoblastic leukaemia))))	23

Appendix 2: Excluded studies

	Study	Reason excluded
1	**Brigitha, 2021** et.al. Hypersensitivity to Pegylated *E. coli* asparaginase as first line treatment in contemporary paediatric acute lymphoblastic leukaemia protocols: a meta-analysis of the Ponte di Legno Toxicity working group.	• Only evaluating pegaspargase hypersensitivity, with no comparison to L-asparaginase. • The administration on some of the study protocols was very different from more recent protocols.
2	**Henriksen, 2015** et.al. PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol.	• Only evaluating pegaspargase allergy, with no comparison to L-asparaginase. • Dosing schedule is different from what is currently used.
3	**Ko, 2015**. Et.al. Allergic Reactions and Antiasparaginase Antibodies in Children with High-Risk Acute Lymphoblastic Leukemia: A Children's Oncology	• All participants got L-asparaginase during induction and were them randomised; thus, sensitization most likely already occurred during the first injections which was not PEG-asparaginase related.
4	**Kurtzberg 2011**, et.al. Polyethylene Glycol-Conjugated L-Asparaginase Versus Native L-Asparaginase In Combination with Standard Agents for Children with Acute Lymphoblastic Leukemia in Second Bone Marrow Relapse: A Children's Oncology Group	• This population is children with relapsed ALL. • Some has had allergic reactions to L-asparaginase during their initial treatment and were then assigned to received PEG-asparaginase with their "salvage therapy".
5	**Lynggaard, 2023**, et.al. Treatment regimens for acute lymphoblastic leukaemia in children: a network meta-analysis (Cochrane Review)	• None of the 3 RCTs included are that applicable to the way therapy is currently being delivered. • One study is in low-risk patients, a classification we don't really use. • Another study is for low intermittent / continuous dosing which is not used. • One study is a comparison with calaspargase.
6	**Hasan, 2017,** et. al. Comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic leukemia: A meta-analysis and systematic review.	• Not a comparison of pegaspargase to L-asparaginase. • Used in general text to outline IM and IV use.
7	**Medawar, 2020** et.al. PEG-asparaginase and native Escherichia coli L-asparaginase in acute lymphoblastic leukemia in children and adolescents: a systematic review.	• Included 2 studies included in this review (Avramis et.al. and Place et.al. – however other studies included were excluded in full text review as they did not meet the PICO. Thus only the applicable randomised trials Avramis and Place were included.

Appendix 3: Childnren's Oncology Group (COG) Protocol

Standard risk B-cell ALL (COG AALL0934)

Total Laspar usage : 15 doses IM
Total Peg-aspargase usage: 2 doses IM / IV

Induction:

L-asparaginase: 9 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 1 dose IM (2500IU/m^2 per dose)

Delayed Intensification:

L-asparaginase: 6 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 1 doses IM (2500IU/m^2 per dose

High risk B-cell ALL (COG AALL1131)

**** all patients older than 10 years are considered high risk****
Total asparaginase usage: Laspar 33 doses IM or
Total Peg-aspargase usage: 5 doses IM / IV

Induction:

L-asparaginase: 9 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 1 dose IM / IV (2500IU/m^2 per dose)

Consolidation:

L-asparaginse: 12 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 2 doses IM /IV (2500IU/m^2 per dose)

Delayed Intensification:

L-asparaginse: 12 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 2 doses IM / IV (2500IU/m^2 per dose)

T-cell ALL (COG AALL0434)

Total L-asparaginase usage : 45 doses IMI or
Total Pegasparaginase usage : 7 doses IM / IV

Induction:

L-asparaginase: 9 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 1 dose IM (2500IU/m^2 per dose)

Consolidation:

L-asparaginse: 12 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 2 doses IM (2500IU/m^2 per dose)

Interim Maintenance:

L-asparaginse: 12 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 2 doses IM (2500IU/m^2 per dose)

Delayed Intensification:

L-asparaginse: 12 doses IM (6000IU/m^2 per dose)
Peg-aspargase : 2 doses IM (2500IU/m^2 per dose)

Appendix 4 :

Avramis et.al.

Criteria	Yes	No	Other (CD, NR, NA*)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	X		
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			NR
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			NR
4. Were study participants and providers blinded to treatment group assignment?		X	
5. Were the people assessing the outcomes blinded to the participants' group assignments?		X	
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	X		
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	X		
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	X		
9. Was there high adherence to the intervention protocols for each treatment group?	X		
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	X		
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X		
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	X		But not for EFS
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			NR
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	X		

*CD – cannot determine; NA – not applicable; NR – not reported

Place et.al.

Criteria	Yes	No	Other (CD, NR, NA*)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	x		
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	x		
3. Was the treatment allocation concealed (so that assignments could not be predicted)?		x	
4. Were study participants and providers blinded to treatment group assignment?		x	
5. Were the people assessing the outcomes blinded to the participants' group assignments?		x	
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	x		
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	x		
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	x		
9. Was there high adherence to the intervention protocols for each treatment group?	x		
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	x		

11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	x		
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	x		
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	x		
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	x		

*CD – cannot determine; NA – not applicable; NR – not reported