Evidence review for a decision aid in adults with severe/very severe aplastic anaemia

For Fülöp Scheibler

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Abbreviations

1L	First-line
AA	Aplastic anaemia
AE	Adverse event
AGREE II	Appraisal of Guidelines, Research and Evaluation
Allo SCT	Allogeneic stem cell transplant
AML	Acute myelogenous leukaemia
ATG	Anti-thymocyte globulin
BID	Twice a day
BMT	Bone marrow transfer
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CMV	Cytomegalovirus
CR	Complete response
CRD	Centre for Research and Dissemination
CsA	Cyclosporin A
Cy	Cyclophosphamide
DARE	Database of Abstracts of Reviews of Effects
dC	Degrees celsius
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
ECRI	Emergency Care Research Institute
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – 30-items
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue scale
FAQ	Frequently asked question
FDA	Food and Drug Administration
FluCy	Fludarabine and cyclophosphamide
g	Grams
G-BA	Gemeinsamer Bundesausschuss
G-CSF	Granulocyte-colony stimulating factor
GFFS	GVHD-free, failure-free survival
G-I-N	Guidelines International Network
GVHD	Graft-versus-host disease
Haplo-HSCT	Haploidentical - haematopoietic stem cell transplant
hATG	Horse anti-thymocyte globulin
Hb	Haemoglobin
HLA	Human leucocyte antigen
HRQoL	Health-related quality of life
HSC	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplant
HTA	Health technology agency
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IST	Immunosuppressive therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
Kg	Kilograms

mg	Milligrams
MI	Myocardial infarction
MINORS	Methodological Index for Non-Randomised Studies
NA	Not applicable
MDS	Myelodysplastic syndrome
M-H	Mantel-Haenzel
Mismatched UD-HSCT	Mismatched unrelated donor haematopoietic stem cell transplant
MTX	Methotrexate
MSD-HSCT	Matched sibling donor - haematopoietic stem cell transplant
MUD-HSCT	Matched unrelated donor - haematopoietic stem cell transplant
NED	No evidence of a difference
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OS	Overall survival
pALG	Porcine anti-lymphocyte globulin
PO	Orally
PNH	Paroxysmal noctural haemoglobinuria
PR	Partial response
pRBC	Packed red blood cells
PRISMA	Preferred reporting items in systematic reviews and meta-analyses
PTLD	Post-transplant lymphoproliferative disorder
QD	Once a day
QLQ-AA/PNH-54	Quality of life questionnaire for aplastic anaemia/paroxysmal noctural haemoglobinuria – 54-items
QoL	Quality of life
rATG	Rabbit anti-thymocyte globulin
RBC	Red blood cell
RCT	Randomised controlled trial
RD	Risk difference
RoB	Risk of bias
ROBIS	Risk of bias in systematic reviews
RR	Risk ratio
SAA	Severe aplastic anaemia
SD	Standard deviation
SDM	Shared decision making
SE	Standard error
SEM	Standard error of the mean
SOC	Standard-of-care
SQ	Subcutaneous
SR	Systematic review
TBI	Total body irradiation
Ti, ab	Title and abstract
UK	United Kingdom
USA	United States of America
UTI	Urinary tract infection
VSAA	Very severe aplastic anaemia

1. Introduction

The Share To Care team are working on an ongoing research project to create interactive websites to provide patients with shared decision-making (SDM) decision aids.

This decision aid is focussed on generating the best available evidence to inform a series of research questions to support the development of a new SDM aid for adults with severe/very severe aplastic anaemia (SAA/VSAA).

2. Objectives and research questions

The overall aim of this project is to answer seven research questions pertaining to the treatment, effectiveness/efficacy and safety of treatments for adults with SAA/VSAA.

The seven pre-specified research questions include:

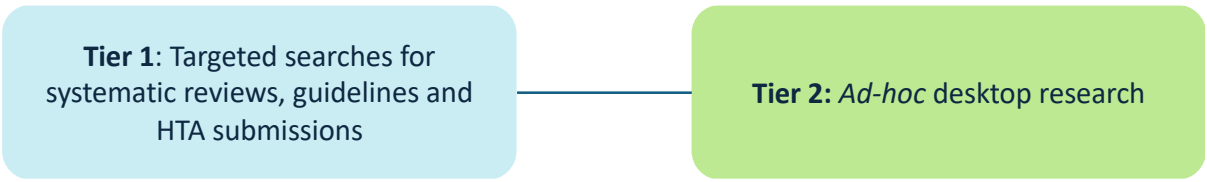
- FAQ1: What does the treatment involve?
- FAQ2: Will the therapy affect [efficacy outcomes, including: how much I bleed; how often I need transfusions]?
- FAQ3: Will the treatment impact how long I live?
- FAQ4: How will the treatment impact my quality of life?
- FAQ5: What are the risks or side effects [for drug therapies vs. stem cell transplants]?
- FAQ6: Are there any long-term negative effects of treatment?
- FAQ7: Where can I get additional information and/or a second opinion?

The research questions will also be supplemented with a standalone section introducing the disease and treatment options.

3. Methodology

A two-tiered approach was taken to identify evidence in support of the decision aid. The first tier of the process involved performing targeted database searches to identify systematic reviews, guidelines and HTA submissions in aplastic anaemia. Additional *ad-hoc* desktop research formed the second tier to inform the decision aid. An overview of this approach is provided in Figure 1.

Figure 1: Overview of the process



Eligibility Criteria

The inclusion and exclusion criteria applied in this review are provided in Table 1.

Table 1: Eligibility criteria for the review

Facet	Inclusion criteria	Exclusion criteria
Population	Adults ≥18 years with severe or very severe acquired aplastic anaemia¶ *Note that patients with moderate AA were tagged during screening to fill any evidence gaps in the severe/very severe population*	• Children or young adults <18 years • Mild or moderate AA* • Inherited AA (e.g. Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia) • Mixed AA/PNH syndrome

Intervention	• **Immunosuppressive drug therapy**:
	  ○ Equine anti-thymocyte globulin (ATG) or IVIg (IV Ig) plus cyclosporin A plus eltrombopag; plus infection prophylaxis†
	  ○ Equine ATG plus cyclosporin A†
	  ○ Eltrombopag†, a thrombopoietin receptor agonist
		• Porcine or rabbit ATG***

Comparator	• **Stem cell transplant** (comparative studies):
	  ○ Allogeneic stem cell transplant (family or unrelated donor); plus infection prophylaxis
	  ○ Haematopoietic stem cell transplant; plus infection prophylaxis
	• **No comparison** (single arm studies)
		-

Outcomes	**<u>Efficacy/effectiveness:</u>** • All-cause mortality • Cause-specific mortality • Bleeding events • Anaemia • Need for transfusions • Recurrence/therapy failure • Duration of treatment response‡ **<u>HRQoL:</u>** • By any HRQoL measure (e.g. constitutional symptoms, fatigue, …) **<u>Safety:</u>** ***Stem cell transplant:*** • Graft-versus-host disease ***Immunosuppressive drug therapy:*** • Lymphomas/malignant tumours • Renal insufficiency ***Other risks/side effects of any therapy:***	• Haematological abnormalities • Immunogenicity

Facet	Inclusion criteria	Exclusion criteria
	• Fever • Anorexia‡ • Malaise • Headache • Weakness • Fatigue • Infections	
Study design	**Core focus:** • Systematic reviews • Guidelines • HTA assessments **If additional evidence is needed to fill evidence gaps:** • Randomised clinical studies • Non-randomised clinical studies • Comparative or single-arm observational studies (retrospective or prospective)	• Review/opinion pieces • Letters to the editor • Animal/*in vivo* studies • Case studies • Case series • Commentaries • News articles • Studies with <10 patients • Conference abstracts pre-2022
Subgroups	Disease-induced AA (e.g. hepatitis-induced AA)	-
Language	Any language is included	-
Geography	Any geographical location is included	-
Date limit	Last 10 years (2014 onwards)**	-

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; HRQoL, health-related quality-of-life; HTA, Health Technology Assessment.
*Note that patients with moderate AA were tagged during screening to fill any evidence gaps in the severe/very severe population
† Note that any combination of ATG/cyclosporin A/eltrombopag was included
‡ For cyclosporin A only
¶ Note that mixed populations of patients that included non-severe AA were included if >80% of patients were SAA/VSAA
**Note that no date limit was applied for primary studies
***See protocol amendments section for rabbit ATG

Searches

Database searches were conducted from 2014 to 28th October 2024 to identify the most up-to-date and relevant systematic reviews, guidelines and health technology agency (HTA) assessments. Searches were conducted across multiple databases to identify relevant studies. The search strategies were developed for each database and were not limited by language or publication type. Searches were limited based on date (2014 onwards) and study design (to focus on systematic reviews, guidelines and HTA assessments).

Searches were conducted in the following databases:

- **Systematic reviews:**
  - Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk)
  - Epistemonikos (Internet) (www.epistemonikos.org)
- **Guidelines**:
  - Guidelines International Network (G-I-N) (www.g-i-n.net
  - ECRI Guidelines Trust (https://guidelines.ecri.org/)

- **HTAs**:
    - HTA database (www.crd.york.ac.uk)
    - International Network of Agencies for Health Technology Assessment (INAHTA) (https://database.inahta.org/)
    - National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
    - Gemeinsamer Bundesausschuss (G-BA) (https://www.g-ba.de/)
    - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) (https://www.iqwig.de/en/)
- **Other databases**:
    - Embase® (Ovid)
    - MEDLINE® (PubMed)

Search strategies and results per data source are provided in Appendix A.

Grey literature searches were conducted by searching the reference lists of priority studies for extraction to identify additional records. *Ad-hoc* desktop research was also performed to fill any evidence gaps. Searches were de-duplicated in EndNote™.

Screening

Screening was performed in Microsoft® Excel®. Two reviewers independently screened records in line with Cochrane guidance.[1] Any disagreements were resolved through discussion or the intervention of a third reviewer.

Data Extraction

Data extraction was conducted by a single reviewer and 20% of data were checked by a second reviewer in line with Cochrane rapid review guidance.[2] Data extraction was conducted directly into the report (i.e. a standalone data extraction workbook was not produced). The final list of included studies to extract was agreed with the Share To Care team before data extraction began.

Risk of Bias Assessment

Risk of bias (RoB) was assessed using a tool matched to the study design. Guidelines were assessed using the AGREE II RoB tool.[3] Systematic reviews were assessed using the ROBIS tool.[4] Randomised controlled trials were assessed using the Cochrane RoB tool (version 1)[5] and non-randomised studies were assessed using the MINORS tool.[6] A risk of bias assessment sheet was designed in Microsoft® Excel® for each tool. Quality assessments were performed by a single reviewer.

Data Synthesis

An evidence hierarchy was used to identify the best available evidence for each research question. Where multiple relevant studies were identified, the best available evidence was defined based on:

- Date (prioritising the most recent studies)
- Closeness of population match (prioritising studies in patients who represent the target population; however, for example, moderate severity AA patients would be considered where no studies of severe/very severe patients are identified)

- Risk of bias (prioritising studies rated at low risk of bias)

For primary studies, only those that exclusively recruited adult patients were considered for inclusion; those that included both paediatric and adult patients or only reported age subgroup data were not considered further.

For studies reporting on different types of HSCT (e.g. matched sibling donor HSCT (MSD-HSCT), matched unrelated donor HSCT (MUD-HSCT), mismatched unrelated donor HSCT (mismatched UD-HSCT), haploidentical HSCT (haplo-HSCT)), these treatments were assessed separately rather than as a group as it was considered that the type of donor source would result in important clinical differences. Of note, this differed from the approach taken by some key guidelines,[7] where studies for any type of alternate donor HSCT (including MUD-HSCT and haplo-HSCT) were pooled.

Where data permitted, risk ratios and 95% confidence intervals were plotted using RevMan 5.4.0 for Mac to graphically represent the data.[1] Dichotomous data were plotted using the Mantel-Haenszel method with random effects. Allogeneic BMT comparative studies were not included in the forest plots as the type of donor was unclear (e.g. matched sibling, matched unrelated, mismatched unrelated etc.). However, no formal meta-analysis or quantitative synthesis was performed. Figures were drawn in GraphPad Prism for Mac (version 10.3.0).

Numerical values within 1% point or effect estimates between 0.9 and 1.1 were considered to show no evidence of a difference.

Protocol Amendments

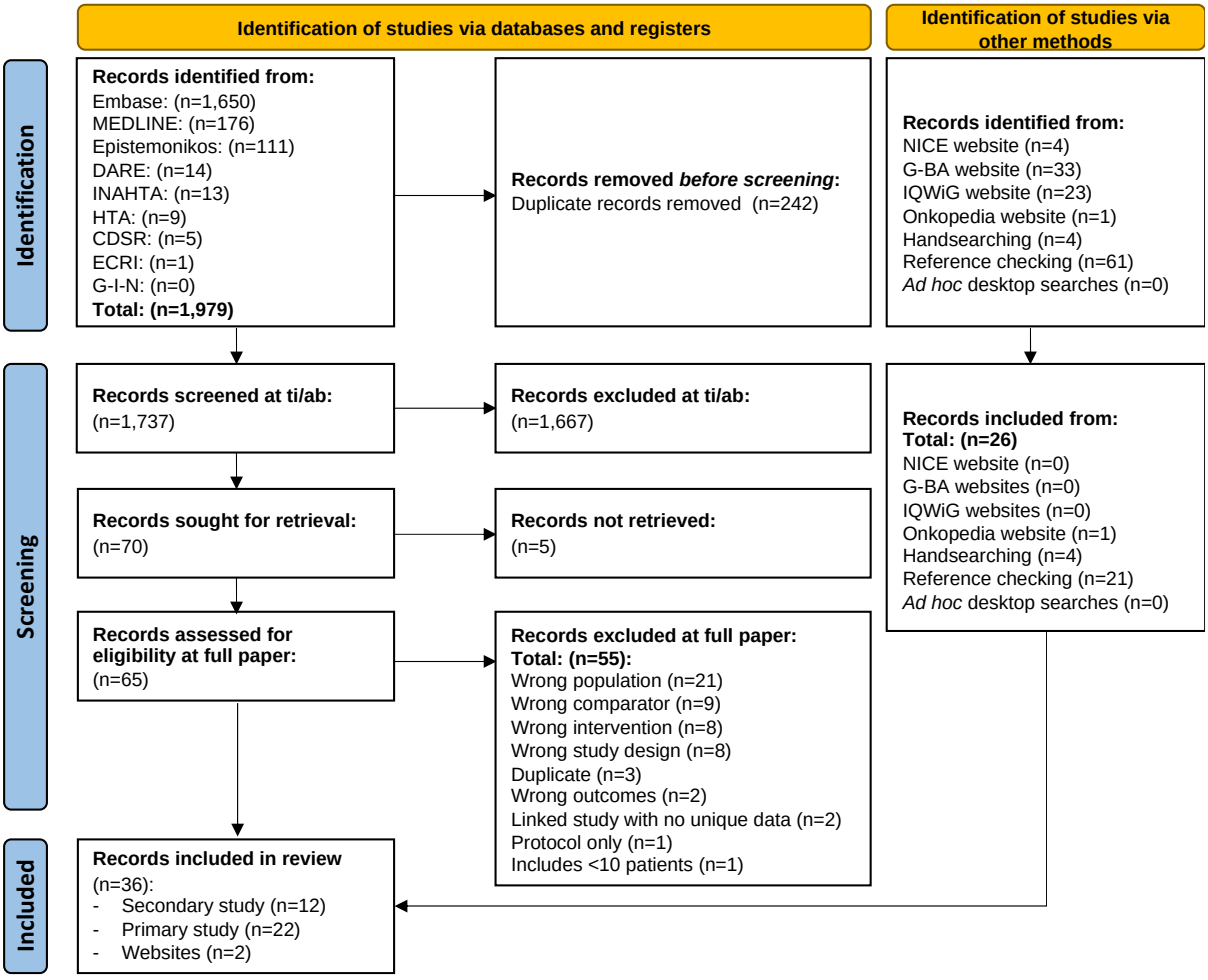
Rabbit ATG was tagged during screening rather than immediately excluded in case of a lack of evidence for horse ATG. Disease-induced AA was added as a subgroup of interest during title/abstract screening. Conference abstracts pre-2022 were added as an exclusion criterion during title/abstract screening.

4. Results

Literature searches

A total of 1,979 records were retrieved from database searches. After de-duplication, 1,737 records were screened at the title/abstract stage. A total of 70 records were identified as potentially relevant and taken through to full paper screening; full papers were not obtainable for 5 records so 65 were finally screened. At the full paper screening stage, a total of 55 records were excluded: 21 for wrong population, 9 for wrong comparator, 8 for wrong intervention, 8 for wrong study design, 3 duplicates, 2 for wrong outcomes, 2 linked studies with no unique data, 1 protocol only and one study including fewer than 10 patients. The list of studies excluded during full paper screening is provided in Appendix B. Grey literature searches included an additional 26 records. Overall, a total of 35 studies (with 36 records) were included. A summary of the study flow is provided in Figure 2.

Figure 2: PRISMA flow diagram



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; ECRI, Emergency Care Research Institute; G-I-N, Guidelines International Network; INAHTA, International HTA database; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; PRISMA, preferred reporting items in systematic reviews and meta-analyses; ti/ab, title/abstract.

Overview of included studies

Seven frequently asked questions of key relevance to shared decision-making in adults with SAA/VSAA were compiled and eligibility criteria were created to reflect consultations with the commissioner and clinical expert. Among the 36 included records, 12 were classified as secondary records, 22 as primary records and 2 were websites.

The 12 relevant systematic reviews or guidelines or HTA sources (secondary records) were identified through the database searches, from the commissioner or through handsearching. Five of the 12 secondary records were systematic reviews, five were guidelines, one was a Delphi study and one was an HTA record. Of the five guidelines, only one was identified in adults alone (from the UK: a British Society for Haematology Guideline),[8] and four guidelines were identified in mixed age groups but with specific adult-only recommendations included.[7 9-11]

Since only one of the 12 secondary records identified through database searches/commissioner/handsearching was exclusively in an adult-only population (the population of interest for this project),[8] these 12 secondary records were reference checked plus additional handsearching was performed to identify relevant primary adult-only studies and to provide data for any evidence gaps. After this process, an additional 21 primary studies (22 records; some studies had more than one record associated with them) plus 2 websites were identified as key sources of evidence. An overview of the included primary and secondary studies is provided in Table 2; and the FAQs that the studies informed are summarised in Table 3.

Of the 21 primary studies, 1 was a randomised controlled trial, 1 was a non-randomised comparative interventional study, 12 were comparative cohorts, 2 were non-randomised single arm studies, 4 were single-arm cohort studies, and 1 was a cross-sectional single arm study.

The study sample size ranged from 8 to 499 patients (Table 2).

Almost all primary studies recruited adult-only patients; the lowest age inclusion criterion was 12 years;[12 13] most studies recruited patients ≥18 years. Only one study recruited exclusively younger adults (14-30 years).[14]

Aplastic anaemia severity was mixed severe or very severe in most primary studies (14 studies) followed by severe alone (4 studies) or a mix of moderate/non-severe, severe and very severe with a majority of severe/non-severe (3 studies).

Most primary studies were conducted in Asia (7 in China, 4 in South Korea) followed by North America (4 studies, USA), Europe (4 studies; 1 each in France, Germany, Netherlands, UK) and 2 multinational studies (Table 2).

Across the 21 primary studies:

- 5 studies compared different types of HSCT (including matched sibling donor, matched unrelated donor, haploidentical and unmatched unrelated donor)
- 5 studies compared HSCT vs IST

- 4 studies compared eltrombopag plus IST vs IST alone
- 3 studies reported on haploidentical HSCT in a single arm study
- 2 studies reported on eltrombopag in a single arm study
- 2 studies reported on IST in a single arm study

An overview of the treatment evidence network is provided in Figure 3.

Table 2: Overview of relevant studies

Study ID	Intervention	Comparator	Population	# patients	Design	Country	Source	RoB rating
Secondary studies								
Elgohary 2020[15]	Haploidentical HSCT	NA	SAA and VSAA	NA	SR and MA	Europe	Database searches	High
Groth 2017[16]	NA	NA	AA	NA	Development of new disease-specific HRQoL tool (Delphi)	NA		NA
Iftikhar 2024[7]	Allogeneic HSCT	IST	Newly diagnosed adults with SAA	NA	Guideline	USA		132/168
Kulasekararaj 2024[8]	NA	NA	Adults with AA	NA	Guideline	UK		135/168
Mihailova 2020[9]	NA	NA	AA	NA	Guideline	Russia		100/168
Peinemann 2010[17]	Matched related donor HSCT	IST	SAA	NA	SR and MA	NA		High
Piekarska 2024[10]	NA	NA	SAA	NA	Guideline	NR		91/168
Yang 2021[18]	Haploidentical HSCT	Eltrombopag plus IST	1L SAA	NA	SR	NA		High
Zhao 2023[19]	Haploidentical HSCT	MRD-HSCT; MUD-HSCT; IST	AA	NA	SR and MA	NA		High
Zhu 2019[20]	Allogeneic HSCT	IST	1L AA	NA	SR and MA	NA		High
Onkopedia 2024[11]	NA	NA	AA	NA	Guideline	Germany	Commissioner	102/168
EMA 2022[21]	NA	NA	NA	NA	HTA record	Europe	Handsearching	NA
Websites								
DKMS 2025[22]	NA	NA	NA	NA	Website	UK	Hand-searching	NA
Dana-Farber 2025[23]	NA	NA	NA	NA	Website	USA		NA

Study ID	Intervention	Comparator	Population	# patients	Design	Country	Source	RoB rating
Comparative primary studies								
Miao Chen 2020[14]	Haploidentical HSCT	IST (rATG/pALG plus CsA)	Young adults (14-30 years) with SAA or VSAA	55	Comparative cohort	China	Zhao 2023[19]	15/24
Xu 2019[24]	Haploidentical HSCT	IST (rATG plus CsA)	Adults with SAA or VSAA	113	Comparative cohort	China	Multiple	19/24
Ahn 2003[25]	Allogeneic BMT	IST (ATG with or without CsA)	Adults with SAA or VSAA	220	Comparative cohort	South Korea	Peineman n 2010[17] & Zhu 2019[20]	9/24
Paquette 1995[26]	Allogeneic BMT	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA	201	Comparative cohort	USA	Peineman n 2010[17]	12/24
Kim 2003[27]	Matched sibling donor HSCT (BM source)	IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA	22	Comparative cohort	South Korea	Peineman n 2010[17] & Zhu 2019[20]	12/24
Niu 2022[28]	Matched sibling donor HSCT	Haploidentica l HSCT	Adults (≥15 years) with SAA or VSAA	44	Comparative cohort	China	Zhao 2023[19]	18/24
Rice 2019[29]	Matched sibling donor HSCT	Matched unrelated donor HSCT	Adults >50 years with severe AA	499	Comparative cohort	Multinatio nal	Handsearc hing	17/24
Zhang 2020[30]	Matched sibling donor HSCT	Matched unrelated donor HSCT; haploidentical HSCT	Adults (≥40 years) with SAA or VSAA	85	Comparative cohort	China	Zhao 2023[19]	19/24
Park 2021[31]	Haploidentical HSCT	Matched unrelated donor HSCT; mismatched	Adults with SAA or VSAA	153	Comparative cohort	South Korea	Zhao 2023[19]	19/24

Study ID	Intervention	Comparator	Population	# patients	Design	Country	Source	RoB rating
		unrelated donor HSCT						
Kim 2016[32]	Haploidentical HSCT	Alternative donor (matched unrelated or partially matched)	Adults (>18 years) with SAA	64	Comparative cohort	South Korea	Zhao 2023[19]	11/24
Assi 2018[33]	Eltrombopag plus IST	IST alone	Adults with newly diagnosed SAA	38	Non-randomised interventional trial	USA	Yang 2021[18]	18/24
Jin 2022[34]	Eltrombopag plus IST	IST alone	Adults with newly diagnosed SAA or VSAA	121	Comparative cohort	China	Handsearching	19/24
Peffault de Latour 2022[35]	Eltrombopag plus IST	IST alone	Adults (≥15 years) with SAA or VSAA	197	RCT	Multinational	Handsearching	High
Shinn 2023[36]	Eltrombopag plus IST	IST alone	Adults with SAA or VSAA	82	Comparative cohort	USA	Handsearching	19/24
Single arm primary studies								
Clay 2014[37]	Haploidentical HSCT	NA	Adults with refractory SAA/VSAA	8	Single arm cohort	UK	Elgohary 2020[15]	5/16
Gao 2014[38]	Haploidentical HSCT	NA	Adults with refractory severe/very severe AA	26	Single arm cohort	China	Elgohary 2020[15]	12/16
Xu 2018[39]	Haploidentical HSCT	NA	Adults with severe/very severe AA	51	Single arm cohort	China	Elgohary 2020[15]	12/16
Alashkar 2019[40]	IST (ATG plus CsA)	NA	Adults with AA (81% SAA/ VSAA)	71	Single arm cohort	Germany	Handsearching	8/16
Lommerse 2024[41]	IST (CsA or ATG)	NA	Adults with AA who had been successfully treated with IST (CR or PR)	36	Single arm cohort	Netherlands	Groth 2017[16]	13/16

Study ID	Intervention	Comparator	Population	# patients	Design	Country	Source	RoB rating
Lengline 2018[42]	Eltrombopag	NA	Adults with SAA or VSAA	46	Cross-sectional	France	Handsearching	11/16
Desmond 2014[12]	Eltrombopag	NA	Adults (18-77 years) with refractory SAA or VSAA	26	Non-randomised interventional	USA	Handsearching	14/16
Olnes 2012[13]				43				

Abbreviations: 1L, first-line; AA, aplastic anaemia; CsA, cyclosporin A; HRQoL, health-related quality of life; HSCT, haemotopoietic stem cell transplant; IST, immunosuppressive therapy; MRD, matched related donor; MUD, matched unrelated donor; NA, not applicable; pALG, porcine anti-lymphocyte globulin; rATG, rabbit anti-thymocyte globulin; RCT, randomised controlled trial; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia; UK, United Kingdom.

Table 3: Overview of included study sources

Study ID	Record type	Key treatment comparisons	Key patient populations	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my efficacy outcomes?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?
Primary comparative studies										
Miao Chen 2020[14]	Full paper	Haploidentical HSCT vs IST (rATG/pALG plus CsA	Young adults (14-30 years) with SAA or VSAA		✓	✓		✓		
Xu 2019[24]	Full paper	Haploidentical HSCT vs IST (rATG plus CsA)	Adults with SAA or VSAA		✓	✓		✓		
Ahn 2003[25]	Full paper	Allogeneic BMT vs IST (ATG with or without CsA)	Adults with SAA or VSAA		✓	✓		✓		
Paquette 1995[26]	Full paper	Allogeneic BMT vs IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA		✓	✓		✓		
Kim 2003[27]	Full paper	Matched sibling donor HSCT (BM source) vs IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA		✓	✓	✓	✓		

Study ID	Record type	Key treatment comparisons	Key patient populations	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my efficacy outcomes?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?
Niu 2022[28]	Full paper	Matched sibling donor HSCT vs haploidentical HSCT	Adults (≥15 years) with SAA or VSAA		✓	✓		✓		
Rice 2019[29]	Full paper	Matched sibling donor HSCT vs matched unrelated donor HSCT	Adults >50 years with severe AA			✓		✓		
Zhang 2020[30]	Full paper	Matched sibling donor HSCT vs matched unrelated donor HSCT vs haploidentical HSCT	Adults (≥40 years) with SAA or VSAA		✓	✓		✓		
Park 2021[31]	Full paper	Haploidentical HSCT vs matched unrelated donor HSCT vs mismatched unrelated donor HSCT	Adults with SAA or VSAA		✓	✓		✓		
Kim 2016[32]	Full paper	Haploidentical HSCT vs alternative donor	Adults (>18 years) with SAA		✓	✓		✓		

Study ID	Record type	Key treatment comparisons	Key patient populations	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my efficacy outcomes?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?
		(matched unrelated or partially matched)								
Assi 2018[33]	Full paper	Eltrombopag plus IST vs IST alone	Adults with newly diagnosed SAA		✓	✓		✓		
Jin 2022[34]	Full paper	Eltrombopag plus IST vs IST alone	Adults with newly diagnosed SAA or VSAA		✓	✓		✓		
Peffault de Latour 2022[35]	Full paper	Eltrombopag plus IST vs IST alone	Adults (≥15 years) with SAA or VSAA		✓	✓	✓	✓		
Shinn 2023[36]	Full paper	Eltrombopag plus IST vs IST alone	Adults with SAA or VSAA		✓	✓				
Primary single arm studies										
Clay 2014[37]	Full paper	Haploidentical HSCT	Adults with refractory SAA or VSAA		✓	✓		✓		
Gao 2014[38]	Full paper	Haploidentical HSCT	Adults with refractory severe/very severe AA		✓	✓		✓		

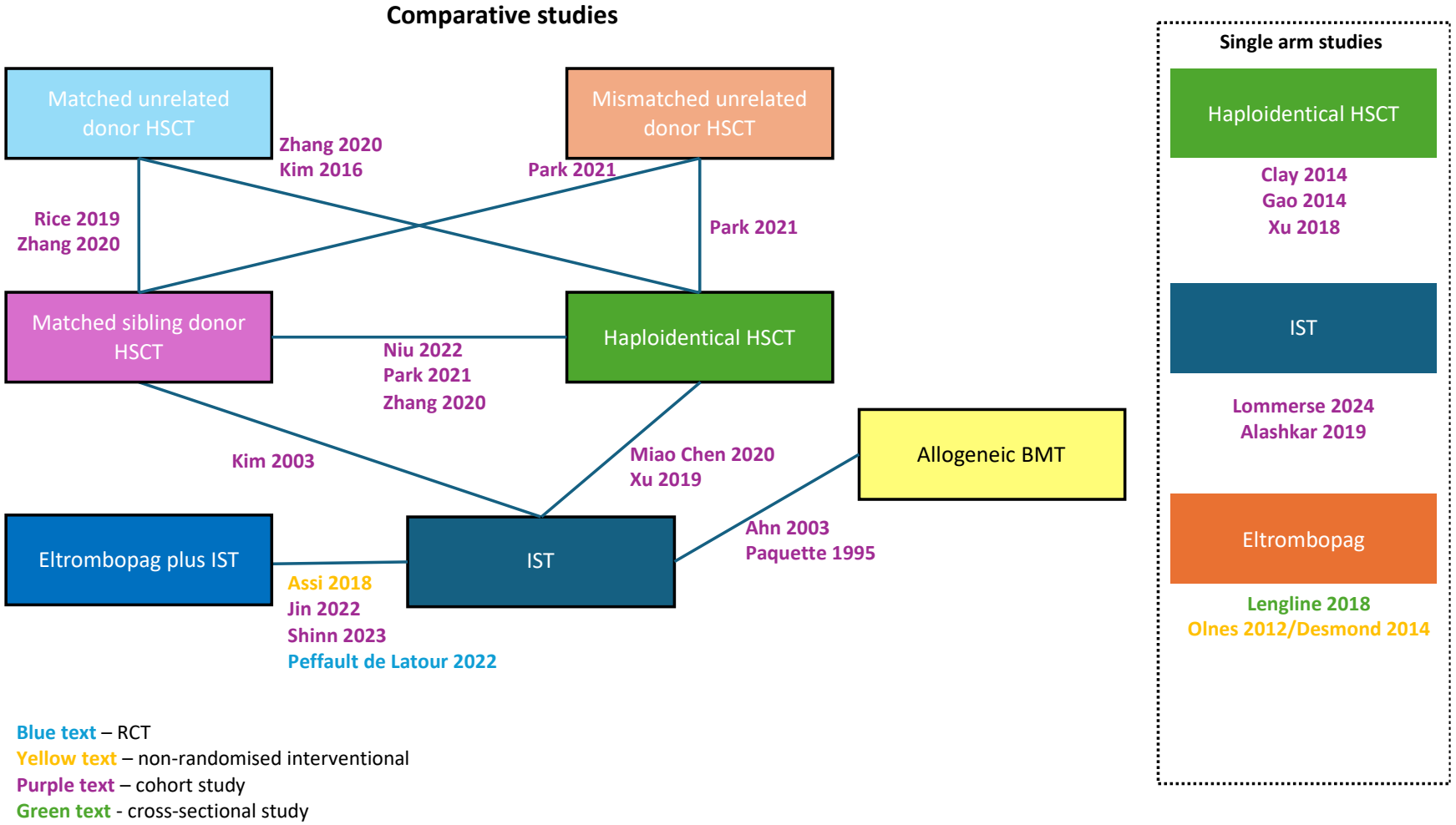
Study ID	Record type	Key treatment comparisons	Key patient populations	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my efficacy outcomes?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?
Xu 2018[39]	Full paper	Haploidentical HSCT	Adults with SAA or VSAA		✓	✓		✓		
Desmond 2014[12] **Olnes 2012**[13]	Full paper	Eltrombopag	Adults (18-77 years) with refractory SAA or VSAA		✓		✓	✓		
Lengline 2018[42]	Full paper	Eltrombopag	Adults with SAA or VSAA		✓			✓		
Alashkar 2019[40]	Full paper	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)		✓	✓		✓		
Lommerse 2024[41]	Full paper	IST (CsA or ATG)	Adults with AA who had been successfully treated with IST (CR or PR)				✓			
Secondary studies*										
Kulasekararaj 2024[8]	Full paper	Mixed	Adults with AA	✓						✓
Onkopedia 2024[11]	Full paper	Mixed	AA	✓						✓
Piekarska 2024[10]	Full paper	Mixed	SAA	✓						
EMA 2022[21]	HTA record	NA	AA	✓						
Websites										
DKMS 2025[22]	Website	NA	AA	✓						

Study ID	Record type	Key treatment comparisons	Key patient populations	FAQ1: What does treatment involve	FAQ2: Will the therapy affect my efficacy outcomes?	FAQ3: Will the treatment impact how long I live?	FAQ4: How will the treatment impact my QoL?	FAQ5: What are the risks or side effects?	FAQ6: Are there any long-term negative effects of treatment?	FAQ7: Where can I get additional information?
Dana-Farber 2025[23]	Website	NA	AA	✓						

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; CR, complete response; CsA, cyclosporin A; FAQ, frequenctly asked question; HSCT, haematopoietic stem cell transplant; HTA, health technology assessment; IST, immunosuppressive therapy; NA, not applicable; pALG, porcine anti-lymphocyte globulin; PR, partial response; QoL, quality of life; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

*Note that other secondary study sources that did not directly inform a FAQ were used to cross-check and include primary studies in adult-only SAA/VSAA populations.

Figure 3: Primary study evidence network for adults with severe/very severe AA



Blue text – RCT
Yellow text – non-randomised interventional
Purple text – cohort study
Green text - cross-sectional study

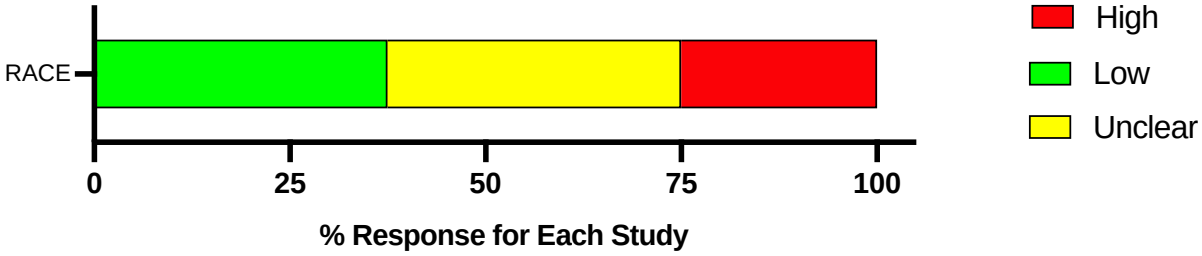
Abbreviations: AA, aplastic anaemia; BMT, bone marrow transplant; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; RCT, randomised controlled trial. Note that included secondary sources (e.g. systematic reviews, guidelines) are not included in the figure.

Risk of bias

The risk of bias in each included primary study was assessed with a RoB tool matched to the study design. A single randomised controlled trial was assessed with the Cochrane RoB1 tool at the study level,[5] and the 20 non-randomised studies were assessed with the MINORS tool at the study level.[6]

One randomised controlled trial (RACE[35]) was assessed using the Cochrane RoB1 tool (Figure 4). This study was rated at an overall high risk of bias, which was driven by the open-label nature of the trial where neither the participants nor the study personnel were blinded.

Figure 4: Risk of bias across the included randomised controlled trials



A total of 20 non-randomised studies were assessed using the MINORS tool (Figure 5). Thirteen of these were comparative studies and rated out of a total of 24 potential points; and seven of these were single arm studies and rated out of a total of 16 potential points.

The highest rated comparative studies considered at the lowest risk of bias were Jin 2022, Park 2021, Shinn 2023, Xu 2019 and Zhang 2020 (all 19/24) and the lowest rated comparative study considered at the highest risk of bias was Ahn 2003 (9/24)

The highest rated single arm study considered at the lowest risk of bias was Lommerse 2024 (13/16) and the lowest rated single arm study considered at the highest risk of bias was Clay 2014 (5/16).

A full summary of the risk of bias assessments, including those for secondary study sources (e.g. systematic reviews, guidelines), is provided in Appendix C.

Figure 5: Risk of bias across the included single arm studies

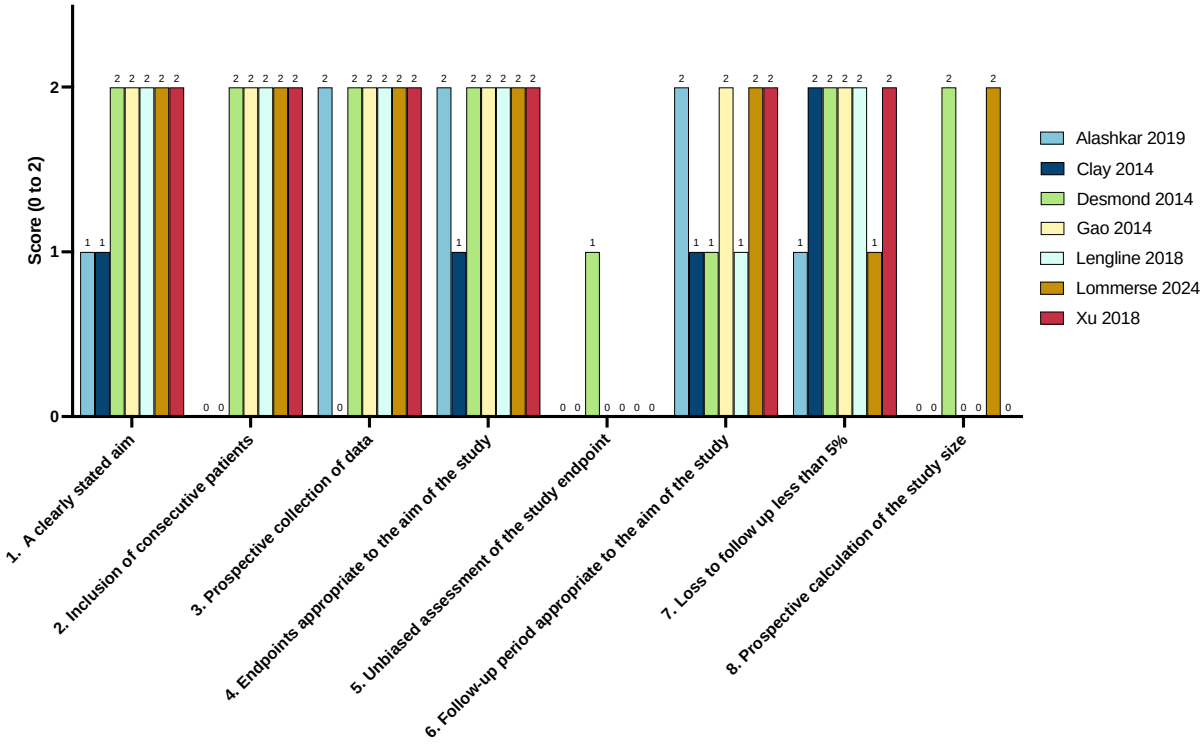
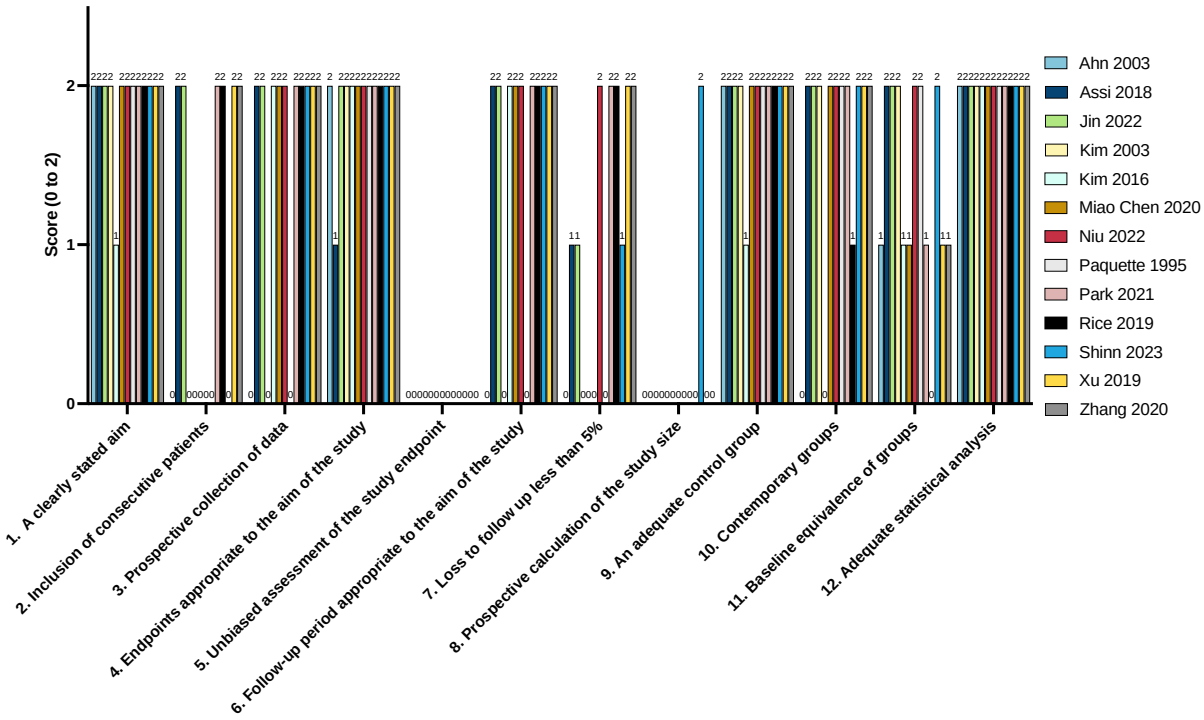


Figure 6: Risk of bias across the included comparative studies



Research questions

Introduction to the disease

Acquired aplastic anaemia (AA) is a rare and complex disease that develops when the haematopoietic stem cells in the bone marrow become damaged and can no longer produce enough blood cells, establishing a condition known as pancytopenia. This drop in the numbers of blood cells, including red blood cells, platelets and neutrophils, can lead to severe, life-threatening issues, including uncontrolled bleeding and susceptibility to infection, as well as symptoms such as fatigue, bruising, bleeding and petechiae.[43]

The initial damage to the bone marrow can be caused by other immune diseases, as well as infections (such as hepatitis) or exposure to certain chemicals, drugs or radiation. However, it is also quite common for the cause of AA to remain unclear: this is referred to as idiopathic acquired AA.

AA is typically diagnosed in two peaks: one between the ages of 10 to 25 years, and one over 60 years.[8 11] The incidence of AA in Europe has been estimated at between 2-3 cases per million individuals per year,[44-46] and is higher in East Asia.[8]

AA can affect people across a range of different severities, which are defined based on Camitta criteria; these criteria are based on several factors, including: bone marrow cellularity, neutrophil counts, platelet counts, and reticulocyte counts. Severe and very severe AA, which are the core populations of interest for this SDM project, are typically defined as:[8 11]

- **Severe AA**: bone marrow cellularity <25% (or 25%–50% with <30% residual haematopoietic cells), plus at least two of:
    - (a) neutrophil count <0.5x10^9/L;
    - (b) platelet count <20x10^9/L;
    - (c) reticulocyte count <60x10^9/L
- **Very severe AA**: as for severe AA but with a neutrophil count <0.2x10^9/L.

Treatment options

For severe and very severe AA, active treatment (rather than watchful waiting) is always recommended.[11]

There are two key goals for the treatment of AA: addressing the symptoms of the disease through supportive management, and treating the bone marrow failure itself.[43] Supportive management aims to boost the numbers of blood cells and includes blood transfusions of platelets and red blood cells. Treatment of the bone marrow failure aims to achieve normal blood counts through either a one-off curative procedure (such as haematopoietic stem cell transplant [HSCT], which replaces the defective bone marrow with healthy tissue) or longer-term treatment (such as immunosuppressive therapy [IST] or eltrombopag plus IST, which aims to reduce the number of lymphocytes in the blood and reactivate the bone marrow to restart blood cell production).

An overview of the currently recommended treatment options for adults with severe or very severe AA is provided in Figure 7 based on the most up-to-date guidelines from the UK, Europe, Russia and the USA.[7-10]

The typical treatment recommended for newly diagnosed SAA or VSAA patients is either IST or matched sibling donor HSCT (MSD-HSCT). For adults, HSCT is a one-off curative procedure that was at one time contraindicated as it required an intense pre-conditioning regimen that was poorly tolerated (and often lethal). However, the age limit for considering up-front HSCT in low-risk adult patients has continued to increase as pre-conditioning regimens have become more tolerable.[8] Indeed, current USA and German guidelines recommend that adult patients with SAA should be considered to receive HSCT up to the age of 50 years and even beyond due to improvements in supportive care and conditioning regimens,[7 11] especially in older adults with a low likelihood of responding to IST (i.e. those with the absence of PNH clone, very severe aplastic anemia or the presence of myeloid mutations).

In adults younger than 40 or 50 years, MSD-HSCT is usually the recommended first-line treatment option.[7-10] If a suitable matched sibling donor is not available, most guidelines recommend immunosuppressive therapy as the next treatment of choice - unless the transplant is urgent, in which case a matched unrelated donor HSCT can be considered)[8-10] (of note, US guidelines currently recommend matched unrelated donor HSCT over IST in younger adults based on the long-term risk of disease relapse and secondary myelodysplastic syndrome (MDS)/acute myelogenous leukaemia (AML) after IST - a strong recommendation based on moderate quality evidence[7]). IST typically includes treatment with horse anti-thymocyte globulin (hATG) plus cyclosporin A (CsA), and can be given with or without eltrombopag. German Onkopedia guidelines recommend that eltrombopag is given alongside IST in SAA/VSAA[11]; in other guidelines, eltrombopag is currently only recommended for patients who are refractory to IST or heavily pre-treated and unsuitable for HSCT,[8] and approvals are still pending in most countries for the use of eltrombopag together with IST as a first-line treatment option.

In adults older than 40 or 50 years, IST (hATG plus CsA) with or without eltrombopag is typically recommended as the first-line treatment of choice.[8-10] However, HSCT may still represent a valid treatment option in this age group, and an individual patient assessment is

recommended based on the patient's unique profile of comorbidities and performance status, the expertise of the transplant centre, and the speed at which a sibling donor could be available.[8] In US guidelines, MRD-HSCT is recommended as the first-line treatment for newly diagnosed adults with SAA up to 50 years and beyond over IST - a strong recommendation based on moderate quality evidence.[7]

In both age groups, if patients fail to respond to IST (hATG plus CsA) with or without eltrombopag, the recommended treatment options are either:

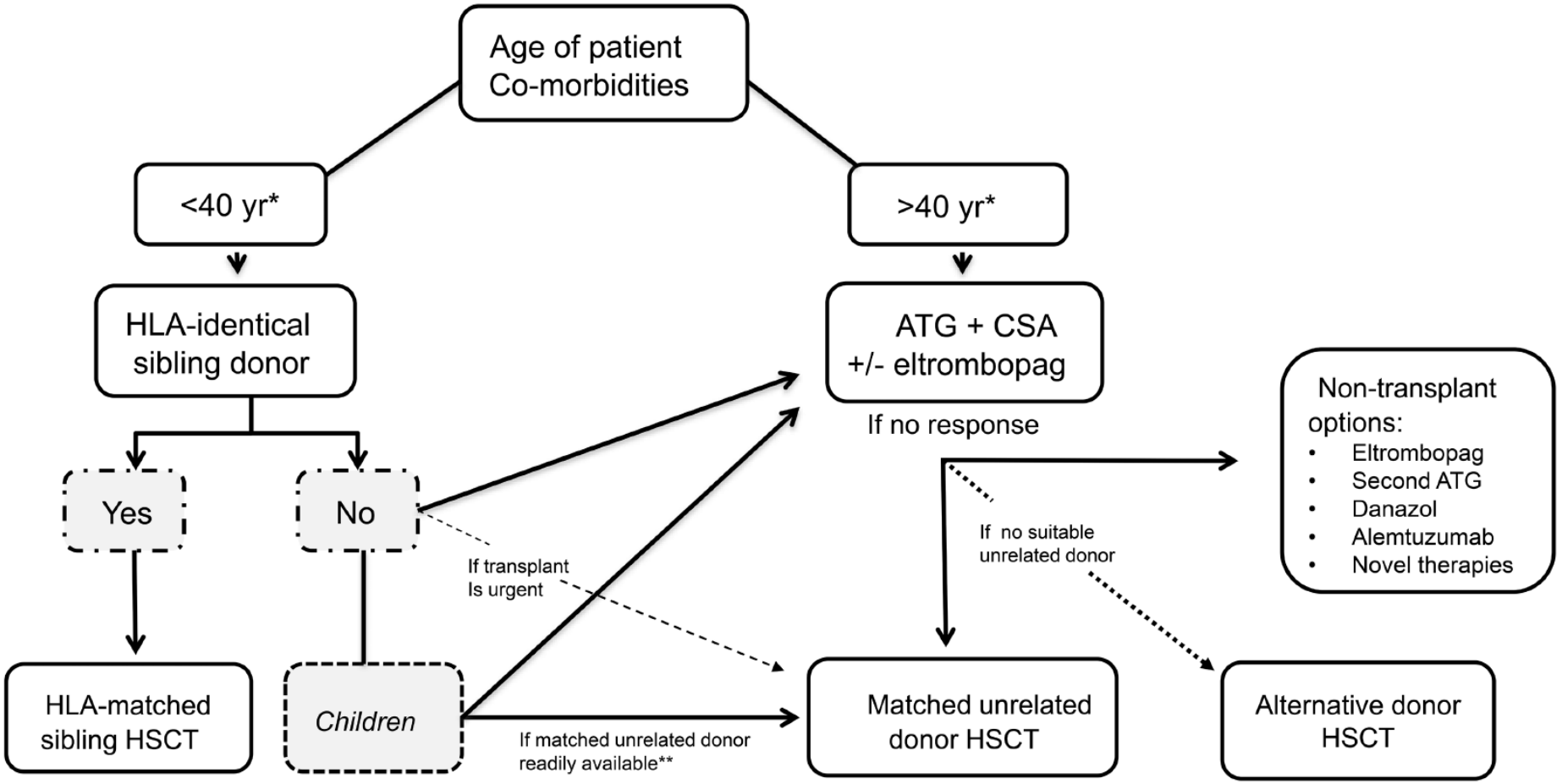
- **Transplant therapy:**
    - Matched unrelated donor haematopoietic stem cell transplant (MUD-HSCT) in the first instance
    - Alternative donor HSCT if no suitable unrelated donor can be found – including either haploidentical HSCT (haplo-HSCT; from a family member donor) or mismatched unrelated HSCT (mismatched UD-HSCT from an unrelated donor)
- **Non-transplant therapy:**
    - Eltrombopag alone
    - A second round of ATG, usually with rabbit ATG instead of horse ATG
    - Although outside the scope of this SDM project, other potential non-transplant options mentioned in guidelines include danazol, alemtuzumab or other novel treatments

In adults over 60 years, guidelines note that a careful assessment is needed before patients receive IST as increased levels of cardiovascular side effects together with increased mortality from infection and bleeding can occur.[8] HSCT is not typically recommended as a first-line treatment in this age group, although certain patients who fail to respond to IST can still be considered. Patients who cannot receive IST would typically be offered best supportive care.[8]

Best supportive care, which includes blood and platelet transfusions, and iron chelation therapy along with infection prevention and prompt management of any infections that do arise, typically remains a key and ongoing part of care for most AA patients.

Since most adults with acquired AA will still be working and will have a long life expectancy, it can be a challenge to integrate their chronic illness into their lives. Psychological support is therefore also recommended.[8 11]

Figure 7: Current UK recommended treatment pathway options for adults with SAA



Reproduced from Kulasekararaj 2024[8]

Abbreviations: ATG, anti-thymocyte globulin; CSA, cyclosporin; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; MSD, matched sibling donor; SAA, severe aplastic anaemia.

* For patients aged between 40 and 50 years, an individual patient assessment based on comorbidities, performance status, expertise of transplant centre and rapid availability of sibling donor can be made to help decide whether to treat with first line IST or MSD HSCT. **Within 8 weeks.

FAQ1: What does the treatment involve?

A **haematopoietic stem cell transplant (HSCT)** replaces the patient's faulty bone marrow with healthy donated tissue. This tissue can be donated from either an HLA-matched sibling donor (MSD), a matched unrelated donor (MUD) or a haploidentical (half match) donor (haplo; e.g. a parent or a child). Patients undergo a preparatory pre-conditioning regime of chemotherapy and immune suppression to reduce the likelihood of them rejecting the donated bone marrow. In younger adults <30 years with a matched sibling donor, the pre-conditioning regime typically consists of cyclophosphamide (at a dose of 200mg/kg given as 4 doses on consecutive days) together with ATG.[11] Cyclosporin plus methotrexate is subsequently given as a standard regimen to prevent graft versus host disease (GVHD).[11] Different options for pre-conditioning are provided in Figure 8.

The haematopoetic stem cells themselves can be sourced from either the donor's bone marrow or their peripheral blood, which largely depends on the type of pre-conditioning regime that the patient needs to undergo.[8] Typically, fewer side effects are experienced using bone marrow as the HSCT source, especially GVHD.[11] For bone marrow donation, the donor undergoes a general or spinal anaesthetic and a needle is used to collect around 1L of a blood-bone marrow mixture from the iliac crest of the pelvis, which regenerates a few weeks later.[22] For peripheral blood donation, the donor receives a series of injections with a drug called granulocyte-colony stimulating factor (G-CSF), which encourages their stem cells to move from the bone marrow into the bloodstream, where they can be collected through a needle in the arm.[23]

The HSCT transplant itself is given like a blood transfusion through an intravenous needle. Usually, only a single transplant is needed. After the transplant, it is typically necessary for patients to stay in hospital for a few weeks to give the bone marrow time to engraft and prevent infections.[43]

Immunosuppressive therapy (IST) typically consists of horse anti-thymocyte globulin (ATG) plus cyclosporin (CsA) with or without eltrombopag. These drugs are designed to stimulate the bone marrow to restart producing blood cells. IST is typically a long-term treatment. Horse ATG is administered intravenously at a dose of 40mg/kg per day for 4 days as part of a hospital inpatient stay. The patient is normally in hospital for around 1-3 weeks providing no infections or other complications arise.[8] During ATG treatment, platelet counts are checked daily, and blood counts are subsequently checked every 1-2 weeks during recovery, as needed.[11]

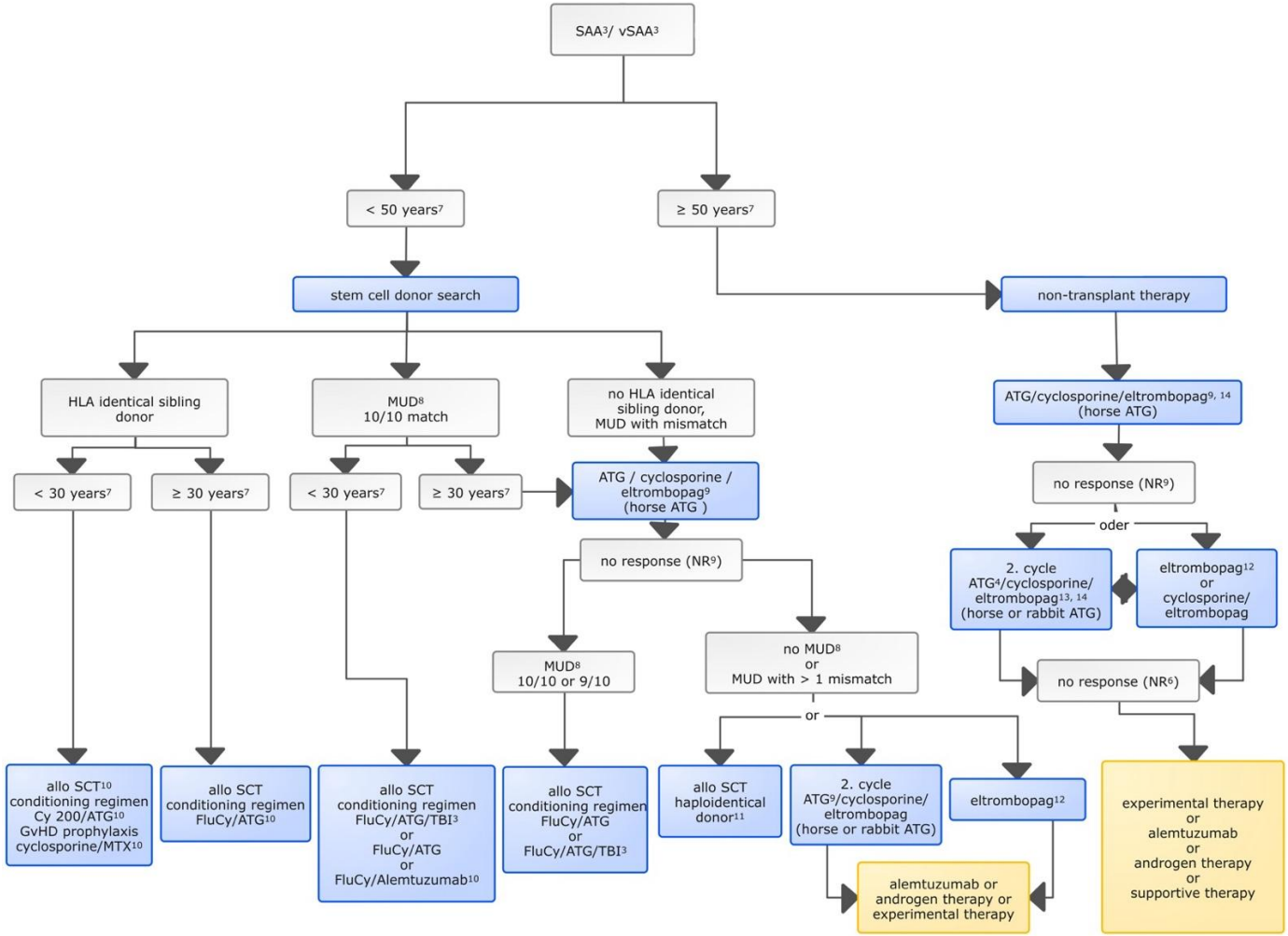
CsA is given orally at a dose of 2.5mg/kg or 5mg/kg twice daily,[8 11] and this treatment continues for at least 4 months and usually more than 12 months.[11] Eltrombopag is also administered orally at an initial dose of 50 mg once daily, which can be increased to a maximum dose of 150 mg per day for 3-6 months depending on how well the patient responds. Prednisolone is often given alongside IST through intravenous infusion at a dose of 1mg/kg per day to treat infusion-related side effects and prevent serum sickness;[8 11] this is rapidly tapered off if no serum sickness symptoms present. A typical treatment timeline for IST (ATG plus CsA) plus eltrombopag is provided in Figure 9.

Eltrombopag can also be given on its own (without ATG and CsA), usually in patients who are refractory to IST. It is initially administered at a dose of 50 mg once daily, and the dose is subsequently adjusted to achieve a platelet count of 50x10e9/litre or more to a maximum dose of 150 mg per day.[21]

The response to ATG does not typically happen before 3-4 months, so **supportive therapy** is continued as needed until blood counts begin to improve. This typically includes blood transfusions (platelets and red blood cells) together with iron overload treatment, and infection prophylaxis and treatment.[11] Patients receiving IST would typically receive prophylactic antibiotics and anti-mycotics, plus air filtration if possible,[11] and anti-viral prophylaxis is also recommended during and after treatment with ATG plus CsA.[8]

After treatment completion, regular check-ins at least once every 3 months are usually needed to track progress.[9]

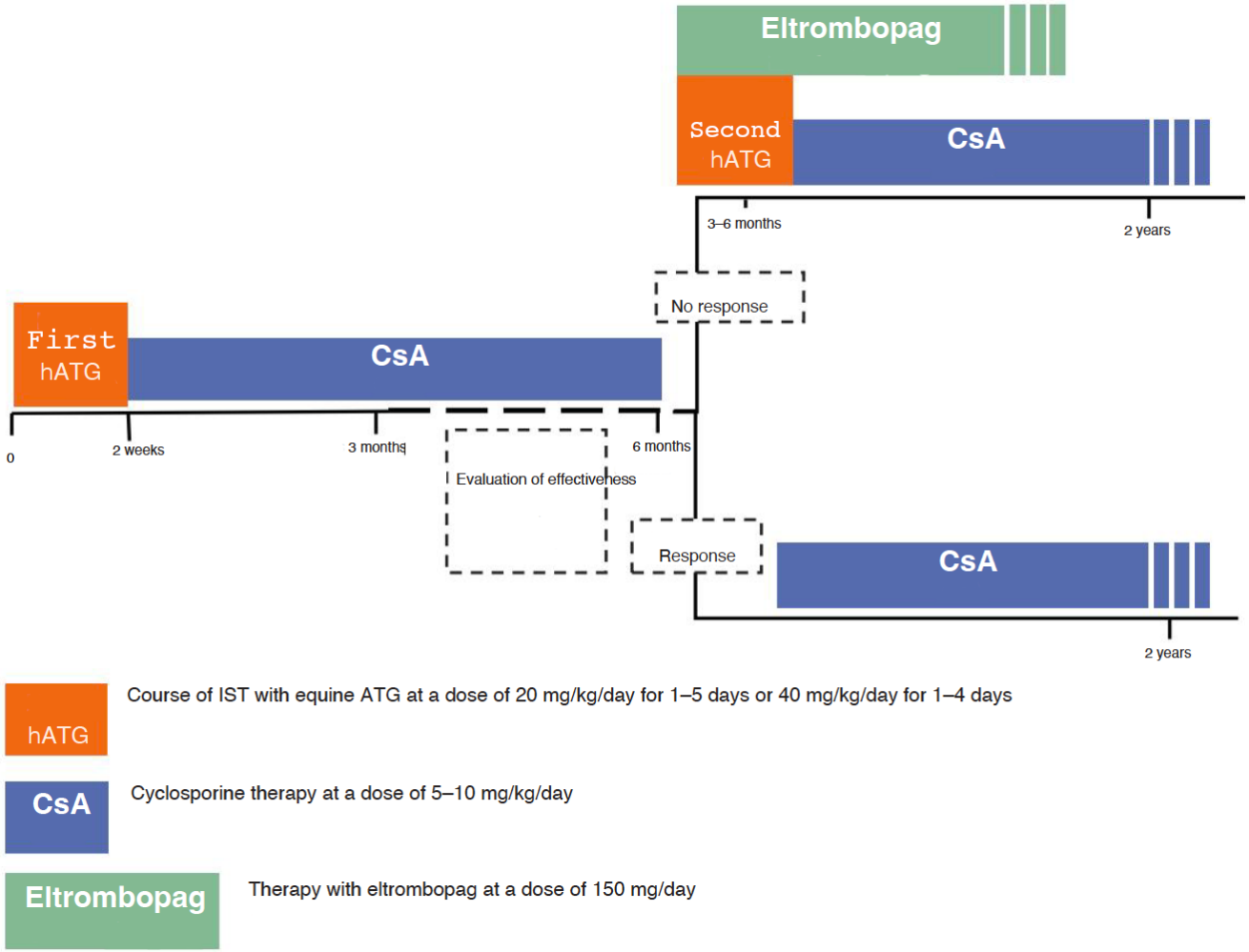
Figure 8: Pre-conditioning regimen options



Reproduced from Onkopedia 2024[11]

Abbreviations: Allo SCT, allogeneic stem cell transplant; ATG, anti-thymocyte globulin; Cy, cyclophosphamide; FluCy, fludarabine and cyclophosphamide; HLA, human leucocyte antigen; GVHD, graft-versus-host disease; MUD, matched unrelated donor; MTX, methotrexate; TBI, total body irradiation. Blue represents established therapies; yellow represents experimental therapies.

Figure 9: Typical treatment timelines for IST with or without eltrombopag



Reproduced from Mihailova 2020.[9]
Abbreviations: CsA, cyclosporin A; hATG, horse anti-thymocyte globulin; IST, immunosuppressive therapy; kg, kilograms; mg, milligrams.

FAQ2: Will the therapy affect efficacy outcomes?

All-cause mortality

A total of seven studies provided comparative evidence on all-cause mortality (Table 4). This included one RCT and six cohort studies. Comparisons included: MSD-HSCT vs IST (1 study), MSD-HSCT vs haplo-HSCT (1 study), haplo-HSCT vs IST (2 studies), allogeneic BMT vs IST (1 study) and eltrombopag plus IST vs IST (2 studies). Risk of bias ranged from 12/24 to 19/24 in the cohort studies, and was rated high in the RCT.

An overview of the comparative evidence for mortality is provided in Figure 10.

For MSD-HSCT vs IST, one study (Kim 2003) reported fewer deaths following treatment with MSD-HSCT compared to IST; however, this was not a statistically significant result.

For haplo-HSCT vs IST, 2 studies (Miao Chen 2020, Xu 2019) reported more deaths following treatment with haplo-HSCT compared to IST; however, this was not a statistically significant result.

For MSD-HSCT vs haplo-HSCT, one study (Niu 2022) reported fewer deaths following treatment with MSD-HSCT compared to haplo-HSCT; however, this was not a statistically significant result.

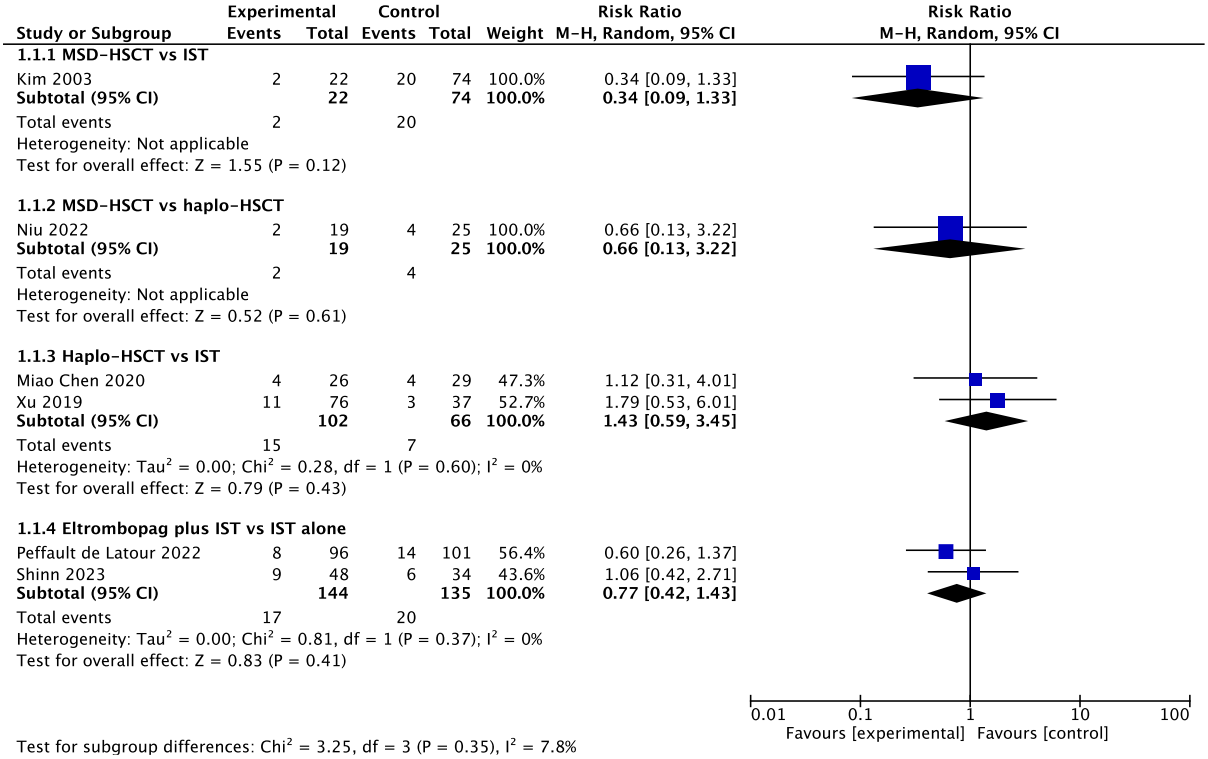
For allogeneic BMT vs IST, 1 study (Ahn 2003) reported fewer deaths following treatment with allogeneic BMT compared to IST; however, this was not a statistically significant difference.

For eltrombopag plus IST vs IST, 2 studies (Peffault de Latour 2022, Shinn 2023) reported either a lower rate of death with eltrombopag plus IST compared to IST alone;[35] or a similar rate of death for both treatment arms.[36]

Single arm evidence was also provided from 5 studies: 3 haplo-HSCT, 1 eltrombopag and 1 IST.

Conclusion for the decision aid: death occurs in between 9 to 11 out of 100 patients receiving MSD-HSCT, approximately 20 out of 100 patients receiving allogeneic BMT, between 15 to 38 out of 100 patients receiving haplo-HSCT, between 8 to 27 out of 100 patients receiving IST, between 8 to 19 out of 100 patients receiving eltrombopag plus IST, and in approximately 13 out of 100 patients receiving eltrombopag alone (12 studies, moderate to high risk of bias).

Figure 10: Comparative data for mortality



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant. Note that 1 comparative study (allogeneic BMT vs IST) is not included in the forest plot.

Table 4: All-cause mortality

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Death due to any cause	30 (12 to 71) months	4/26 (15.4%)	NR	NR	Comparative cohort	Numerically favours IST	15/24
	IST (rATG/ pALG plus CsA)				4/29 (13.8%)					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA		Median 24.7 (range 6.1 to 103.0) months	11/76 (14.5%)	NR	NR	Comparative cohort	Numerically favours IST	19/24
	IST (rATG plus CsA)			Median 20.2 (range 3.2 to 96.0) months	3/37 (8.1%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA		NR	13/64 (20.3%)	NR	P=0.584	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				37/156 (23.7%)					
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	2/22 (9%)	NR	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or				20/74 (27%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	without CsA)									
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA		24.7 (range 6.8 to 30.4) months	2/19 (10.5%)	NR	NR	Comparative cohort	Numerically favours matched sibling donor HSCT	18/24
	Haploidentical HSCT				4/25 (16%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	8/96 (8.3%)	NR	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone				14/101 (13.9%)					
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA	Death rate	6 months	19%	NR	P=0.90	Comparative cohort	NED	19/24
	IST alone				19%					
	Eltrombopag plus IST			24 months	9/48 (19%)		NR		NED	
	IST alone				6/34 (18%)					
	Eltrombopag plus IST			At full follow-up (18 months)	9/48 (19%)				Numerically favours eltrombopag plus IST	
	IST alone			At full follow-up (49 months)	8/34 (24%)					
Single arm evidence										
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Death due to any cause	12.2 (range 3.2 to 40.4) months	3/8 (37.5%)	NR	NR	Single arm cohort	NA	5/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA		43.2 (24.3 to 65.9) months	4/26 (15.4%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	8/51 (15.7%)	NR	NR	Single arm cohort	NA	12/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA		9 to 13 months	6/46 (13.0%)	NR	NR	Single arm cohort	NA	11/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)		23.2 (range 6 to 173) months	7/67 (10.1%)	NR	NR	Single arm cohort	NA	8/16

Abbreviations: AA, aplastic anaemia; ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; BMT, bone marrow transplant; CsA, cyclosporin A; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; rATG, rabbit anti-thymocyte globulin; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Cause-specific mortality

A wide range of cause-specific mortalities were reported. The three main causes were: infection- or sepsis-related mortality, bleeding-related mortality and transplant-related mortality.

Infection- or sepsis-related mortality

For **infection- or sepsis-related mortality**, a total of six studies provided comparative evidence (Table 5). This included one RCT, one non-randomised interventional study and four cohort studies. Comparisons included: MSD-HSCT vs IST (1 study), haplo-HSCT vs IST (2 studies), eltrombopag plus IST vs IST (2 studies) and allogeneic BMT vs IST (1 study). Risk of bias ranged from 9/24 to 19/24, and was rated high in the RCT.

An overview of the comparative evidence for infection- or sepsis-related mortality is provided in Figure 11.

For MSD-HSCT vs IST, one study (Kim 2003) reported fewer infection-related deaths with MSD-HSCT compared IST (0% vs to 55%, respectively); however, this was not a statistically significant result.

For haplo-HSCT vs IST, one study (Xu 2019) reported more infection-related deaths following haplo-HSCT compared to IST, and 1 study (Miao Chen 2020) reported no evidence of a difference.

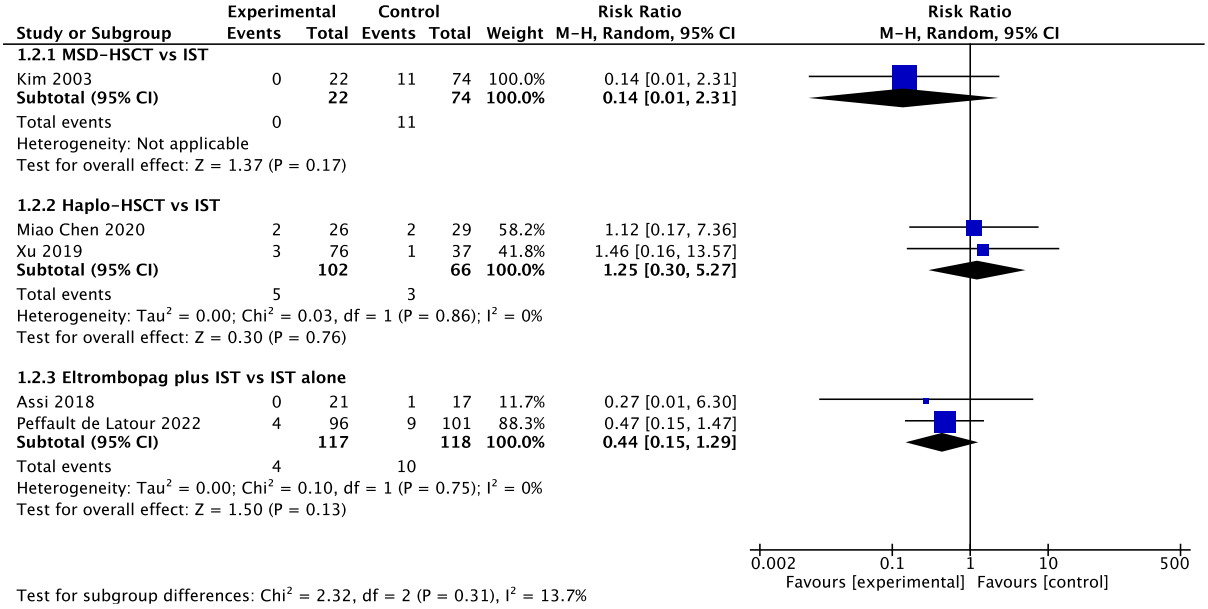
For allogeneic BMT vs IST, 1 study (Ahn 2003) reported more sepsis-related deaths following allogeneic BMT compared to IST; however, this was not a statistically significant result.

For eltrombopag plus IST vs IST, two studies (Assi 2018, Peffault de Latour 2022) reported fewer sepsis- or infection-related deaths following treatment with eltrombopag plus IST compared to IST alone; however, this was not a statistically significant result.

Single arm evidence was also provided from 6 studies: 3 haplo-HSCT, 1 eltrombopag, 1 IST and 1 MSD-HSCT.

Conclusion for the decision aid: sepsis- or infection-related death occurs in between 0 to 11 out of 100 patients receiving MSD-HSCT, approximately 14 out of 100 patients receiving allogeneic BMT, between 4 to 25 out of 100 patients receiving haplo-HSCT, between 3 to 55 out of 100 patients receiving IST, between 0 to 4 out of 100 patients receiving eltrombopag plus IST and approximately 2 out of 100 patients receiving eltrombopag alone (12 studies, moderate to high risk of bias).

Figure 11: Comparative data for infection- or sepsis-related mortality



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant. Note that 1 comparative study (allogeneic BMT vs IST) is not included in the forest plot.

Malignancy-related mortality

For **malignancy-related mortality**, a total of two studies provided comparative evidence (Table 5). This included one RCT and one cohort study. Comparisons included: MSD-HSCT vs IST (1 study) and eltrombopag plus IST vs IST (1 study). Risk of bias was 12/24 (cohort study) and was rated high in the RCT.

An overview of the comparative evidence for malignancy-related mortality is provided in Figure 12.

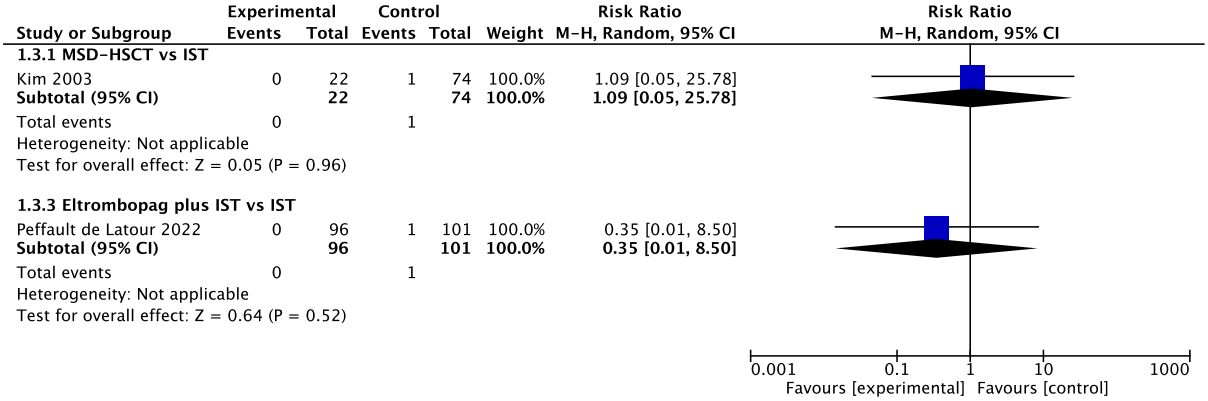
For MSD-HSCT vs IST, one study (Kim 2003) reported fewer deaths due to secondary malignancies with MSD-HSCT compared to IST (0% vs 5%, respectively); however, this was not a statistically significant result.

For eltrombopag plus IST vs IST, one RCT (Peffault de Latour 2022) reported no evidence of a difference in deaths due to lung cancer for eltrombopag plus IST compared to IST alone (0% vs 1%, respectively).

Single arm evidence was also provided from 3 studies: 1 haplo-HSCT, 1 eltrombopag and 1 IST.

Conclusion for the decision aid: malignancy-related death occurs in approximately zero out of 100 patients receiving MSD-HSCT, approximately 4 out of 100 patients receiving haplo-HSCT, between 1 to 5 out of 100 patients receiving IST, approximately zero out of 100 patients receiving eltrombopag plus IST and approximately 2 out of 100 patients receiving eltrombopag alone (5 studies, moderate to high risk of bias).

Figure 12: Comparative data for malignancy-related mortality



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant.

Transplant-related mortality

For **transplant-related mortality**, a total of two studies provided comparative evidence (Table 5). This included one RCT and one cohort study. Comparisons included: haplo-HSCT vs MUD-HSCT vs mismatched unrelated donor HSCT (1 study) and eltrombopag plus IST vs IST (1 study). Risk of bias was 19/24 (cohort study) and was rated high in the RCT.

An overview of the comparative evidence for transplant-related mortality is provided in Figure 13.

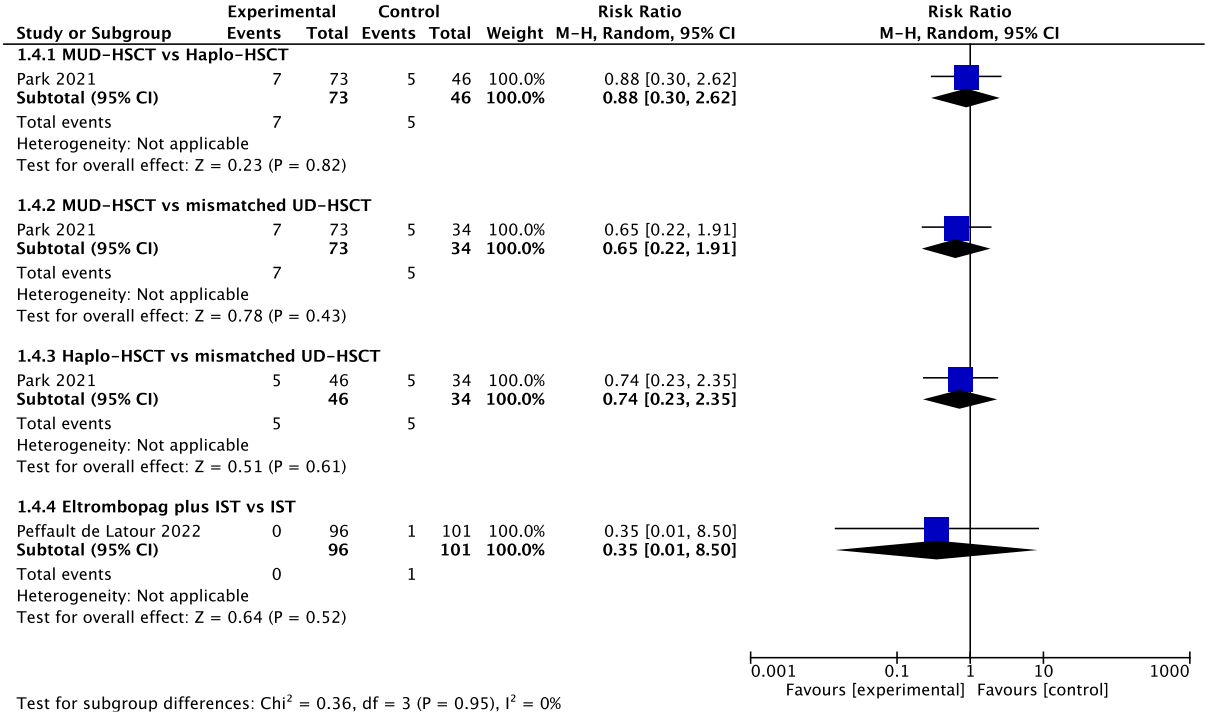
For haplo-HSCT vs MUD-HSCT vs mismatched unrelated donor HSCT, one study (Park 2021) reported a lower rate of transplant-related deaths with MUD-HSCT compared to haplo-HSCT or mismatched unrelated donor HSCT (9.8% vs 11.2% vs 14.7%, respectively); however, this was not a statistically significant result.

For eltrombopag plus IST vs IST, one RCT (Peffault de Latour 2022) reported no evidence of a difference in transplant-related mortality for eltrombopag plus IST compared to IST alone (0% vs 1%, respectively).

No single arm evidence was provided on transplant-related mortality.

Conclusion for the decision aid: transplant-related mortality occurs in approximately 10 out of 100 patients receiving MUD-HSCT, approximately 11 out of 100 patients receiving haplo-HSCT, approximately 15 out of 100 patients receiving mismatched unrelated donor HSCT, approximately zero out of 100 patients receiving eltrombopag plus IST, and approximately 1 out of 100 patients receiving IST alone (2 studies, moderate to high risk of bias). No evidence was identified for transplant-related mortality in MSD-HSCT.

Figure 13: Comparative data for transplant-related mortality



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Table 5: Cause-specific mortality

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Death due to sepsis	NR	9/64 (14.1%)	NR	NR	Comparative cohort	Numerically favours IST	9/24
	IST (ATG with or without CsA)				16/156 (10.3%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA		21 months	0/21 (0%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				1/17 (5.9%)					
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Death due to infection	30 (12 to 71) months	2/26 (7.7%)	NR	NR	Comparative cohort	Numerically favours IST	15/24
	IST (rATG/pALG plus CsA				2/29 (6.9%)					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA		Median 24.7 (range 6.1 to 103.0) months	3/76 (3.9%)	NR	NR	Comparative cohort	Numerically favours IST	19/24
	IST (rATG plus CsA)			Median 20.2 (range 3.2 to 96.0) months	1/37 (2.7%)					
Kim 2003[27]	Matched sibling donor	Adults with SAA or VSAA		NR	0/22 (0%)	NR	NR	Comparative cohort	Numerically favours	12/24

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	HSCT (BM source)								MSD-HSCT (BM source)	
	IST (equine ATG/ALG with or without CsA)				11/74 (55%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	4/96 (4.2%)	NR	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone				9/101 (8.9%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Death due to haemorrhage/ bleeding	NR	2/64 (3.1%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				8/156 (5.1%)					
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	0/22 (0%)	NR	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or without CsA)				8/74 (40%)					
Peffault de	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	0/96 (0%)	NR	NR	RCT	Numerically favours	High
	IST alone				2/101 (2%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Latour 2022[35]									eltrombopag plus IST	
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA	Death due to secondary malignant conditions	NR	0/22 (0%)	NR	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or without CsA)				1/74 (5%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	Death due to lung cancer	24 (95% CI 23 to 24) months	0/96 (0%)	NR	NR	RCT	NED	High
	IST alone				1/101 (1%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Death due to adult respiratory distress syndrome	NR	1/64 (1.6%)	NR	NR	Comparative cohort	Numerically favours IST	9/24
	IST (ATG with or without CsA)				1/156 (0.6%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	1/96 (1%)	NR	NR	RCT	Numerically favours IST alone	High
	IST alone				0/101 (0%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	Death due to encephalopathy	24 (95% CI 23 to 24) months	0/96 (0%)	NR	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone				1/101 (1%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	Death due to aortic valve disease, cardiac tamponade or thrombosis	24 (95% CI 23 to 24) months	3/96 (3.1%)	NR	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone				0/101 (0%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	Transplant-related mortality	3 years	5/46 (11.2% [95% CI 4.0 to 22.5%])	NR	P=0.655	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				7/73 (9.8% [95% CI 4.3 to 18.0%])					
	Mismatched unrelated donor HSCT				5/34 (14.7% [95% CI 5.3 to 28.7%])					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	0/96 (0%)	NR	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone				1/101 (1%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA	Lethal organ toxicity	17.6 months	0/38 (0%)	NR	NR	Comparative cohort	NED	19/24
	Matched unrelated				0/12 (0%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	donor HSCT									
	Haploidentical HSCT				0/35 (0%)					
Single arm evidence										
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Death due to sepsis	12.2 (range 3.2 to 40.4) months	2/8 (25%)	NR	NR	Single arm cohort	NA	5/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Death due to septic shock	9 to 13 months	1/46 (2.2%)	NR	NR	Single arm cohort	NA	11/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	Death due to septicemia as a consequence of neutropenia	23.2 (range 6 to 173) months	4/69 (5.8%)	NR	NR	Single arm cohort	NA	8/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Death due to infection	43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	4/51 (7.8%)	NR	NR	Single arm cohort	NA	12/16
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA	Death due to pulmonary infection	24.7 (range 6.8 to 30.4) months	2/19 (10.5%)	NR	NR	Single arm cohort	NA	10/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA	Death due to haemorrhage	Median 20.2 (range 3.2 to 96.0) months	1/37 (2.7%)	NR	NR	Single arm cohorrt	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA		9 to 13 months	2/46 (4.4%)	NR	NR	Single arm cohort	NA	11/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Death due to AML	9 to 13 months	1/46 (2.2%)	NR	NR	Single arm cohort	NA	11/16
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Death due to PTLD	Median 24.7 (range 6.1 to 103.0) months	3/76 (4%)	NR	NR	Single arm cohorrt	NA	12/16
Miao Chen 2020[14]	IST (rATG/pALG plus CsA	Young adults (14-30 years) with SAA or VSAA	Death due to transformation to M5	30 (12 to 71) months	1/29 (3.5%)	NR	NR	Single arm cohort	NA	8/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	Death due to cerebral metastasis from breast cancer	23.2 (range 6 to 173) months	1/69 (1.5%)	NR	NR	Single arm cohort	NA	8/16
Miao Chen 2020[14]	IST (rATG/pALG plus CsA	Young adults (14-30 years) with SAA or VSAA	Death due to relapse	30 (12 to 71) months	1/29 (3.5%)	NR	NR	Single arm cohort	NA	8/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Death due to graft failure	43.2 (24.3 to 65.9) months	2/26 (7.7%)	NR	NR	Single arm cohort	NA	12/16
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Death due to secondary graft failure	Median 24.7 (range 6.1 to	2/76 (2.6%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
				103.0) months						
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Death due to GVHD	NR	1/64 (1.6%)	NR	NR	Single arm cohort	NA	4/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA		43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA		30 (12 to 71) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	8/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	1/51 (2%)	NR	NR	Single arm cohort	NA	12/16
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA		Median 24.7 (range 6.1 to 103.0) months	2/76 (2.6%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Death due to organ toxicity	43.2 (24.3 to 65.9) months	0/26 (0%)	NR	NR	Single arm cohort	NA	12/16
Ahn 2003[25]	IST (ATG with or without CsA)	Adults with SAA or VSAA	Death due to brain death	NR	1/156 (0.6%)	NR	NR	Single arm cohort	NA	4/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Death due to cardiotoxicity	21.1 (range 3.2 to 71.1) months	2/51 (3.9%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Ahn 2003[25]	IST (ATG with or without CsA)	Adults with SAA or VSAA	Death due to congestive heart failure	NR	1/156 (0.6%)	NR	NR	Single arm cohort	NA	4/16
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Death due to thrombotic microangiopathy	30 (12 to 71) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	8/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA	Death due to cerebral infarction	Median 20.2 (range 3.2 to 96.0) months	1/37 (2.7%)	NR	NR	Single arm cohort	NA	12/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	Death due to MI	23.2 (range 6 to 173) months	1/69 (1.5%)	NR	NR	Single arm cohort	NA	8/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Death due to pulmonary embolism	9 to 13 months	1/46 (2.2%)	NR	NR	Single arm cohort	NA	11/16
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA	Death due to hepatic veno-occlusive disease		1/22 (4.6%)	NR	NR	Single arm cohort	NA	4/16
			Treatment-related mortality (death by causes other than relapse)		2/22 (8%)	NR	NR		NA	
Gao 2014[38]	Haploidentical HSCT			100 days	1/26 (3.8%)	NR	NR		NA	12/16
				1 year	3/26 (11.5%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		Adults with refractory SAA/VSAA	Transplant-related mortality	2 years	4/26 (15.4%)			Single arm cohort		
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	7/51 (13.7%)	NR	NR	Single arm cohort	NA	12/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Death following cord blood transplant	9 to 13 months	1/46 (2.2%)	NR	NR	Single arm cohort	NA	11/16
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Death due to suicide	Median 24.7 (range 6.1 to 103.0) months	1/76 (1.3%)	NR	NR	Single arm cohorrt	NA	12/16

Abbreviations: AA, aplastic anaemia; ALG, anti-lymphocyte globulin; AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; BMT, bone marrow transplant; CI, confidence interval; CsA, cyclosporin A; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplant; MI, myocardial infarction; NA, not applicable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit anti-thymocyte globulin; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Bleeding events

One cohort study provided comparative evidence on bleeding events comparing haplo-HSCT with MUD-HSCT and mismatched unrelated HSCT (Table 6). Risk of bias was 19/24.

For HSCT, comparative evidence indicated a lower rate of severe haemorrhagic cystitis in patients receiving MUD-HSCT vs haplo-HSCT or mismatched unrelated donor HSCT (9.6% vs 13.1% vs 14.7%, respectively); however, these were not statistically significant changes (Table 6).

One single arm study reported that the rate of severe gingival bleeding was 4% with eltrombopag (Table 6).

Conclusion for the decision aid: haemorrhage occurs in approximately 9 out of 100 patients receiving MUD-HSCT, approximately 13 out of 100 patients receiving haplo-HSCT, approximately 15 out of 100 patients receiving mismatched unrelated donor HSCT, and approximately 4 out of 100 patients receiving eltrombopag (2 studies, low RoB).

Anaemia

One cohort study provided comparative evidence on anaemia comparing haplo-HSCT with IST (Table 7). Risk of bias was 19/24.

Comparative evidence indicated a higher proportion of patients achieving complete recovery of blood counts to within a normal range after treatment with haplo-HSCT compared to IST (83.1% vs 38.2%, respectively); this was a statistically significant difference.

Single arm evidence from two studies reporting on eltrombopag alone indicated that 24% of patients had improved Haemoglobin (Hb) levels following treatment with eltrombopag (with a median increase of 4.4g/dL) after >6 months in one study while ATG-naïve adults had a higher increase in Hb levels following treatment with eltrombopag compared to ATG-experienced patients (median 5.0 vs median 2.75, respectively) in a second study.

Conclusion for the decision aid: a reduction in anaemia occurs in approximately 83 out of 100 patients receiving haplo-HSCT, approximately 38 out of 100 patients receiving IST, and around 24 out of 100 patients receiving eltrombopag alone (3 studies, moderate or low RoB).

Table 6: Bleeding events

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	Haemorrhagic cystitis (≥grade II)	3 years	13.1% (95% CI 5.2 to 24.6%)	NR	P=0.751	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				9.6% (95% CI 4.2 to 17.7%)					
	Mismatched unrelated donor HSCT				14.7% (95% CI 5.3 to 28.7%)					
Single arm evidence										
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	Gingival bleeding of grade 2 or higher	NR	1/26 (4%)	NR	NR	Non-randomised interventional	NA	14/16

Abbreviations: CI, confidence interval; HSCT, haemoatopoietic stem cell transplant; NA, not applicable; NR, not reported; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Table 7: Anaemia

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA (alive patients)	Complete recovery of blood counts to within normal range	Median 24.7 (range 6.1 to 103.0) months	54/65 (83.1%)	NR	P<0.001	Comparative cohort	Significantly favours haploidentical HSCT	19/24
	IST (rATG plus CsA)				13/NR (38.2%)					
Single arm evidence										
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	Improvement in Hb levels (by ≥1.5 g/dL without transfusion or a reduction in # units transfused)	12 weeks	2/25 (8%)	NR	NR	Non-randomised interventional	NA	14/16
				Most recent FU	6/25 (24%)	Median increase 4.4g/dL				
Lengline 2018[42]	Eltrombopag	ATG naïve adults with SAA or VSAA	Hb levels (g/dL)	Baseline	NR	Median 8.0 (IQR 7.3 to 8.3) g/dL	NA	Single arm cohort	NA	11/16
		ATG experienced daults with SAA or VSAA				Median 8.0 (IQR 7.0 to 9.0) g/dL				
		ATG naïve adults with SAA or VSAA		Last follow-up (>6 months)		Median 9.8 (IQR 8.2 to 11.5) g/dL	Median variation +5.0 (IQR 3.3 to 6.0) g/dL			

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		ATG experienced daults with SAA or VSAA				Median 9.4 (IQR 8.0 to 12.0) g/dL	Median variation +2.75 (IQR 1.1 to 4.3) g/dL			

Abbreviations: ATG, anti-thymocyte globulin; CsA, cyclosporin A; dL, decilitre; FU, follow-up; g, grams; Hb, haemoglobin; IQR, interquartile range; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; rATG, rabbit anti-thymocyte globulin; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Need for transfusions

A total of six studies provided comparative evidence on overall response rate (ORR) (defined as complete response (CR) or partial response (PR), usually based on normalised Hb/platelet/neutrophil levels or reaching transfusion independence). Comparisons included: haplo-HSCT vs IST (1 study), allogeneic BMT vs IST (1 study) and eltrombopag plus IST vs IST (4 studies). Risk of bias ranged from 9/24 to 19/24 in the non-randomised studies and was rated high in the RCT.

An overview of the comparative evidence for ORR is provided in Figure 14.

For haplo-HSCT vs IST, one study (Miao Chen 2020) reported a significantly higher ORR for patients treated with haplo-HSCT compared with IST at early timepoints (3 months, 6 months) but not at 12 months or at the end of the follow-up period (34 to 28.5 months depending on the treatment arm (Figure 14)).

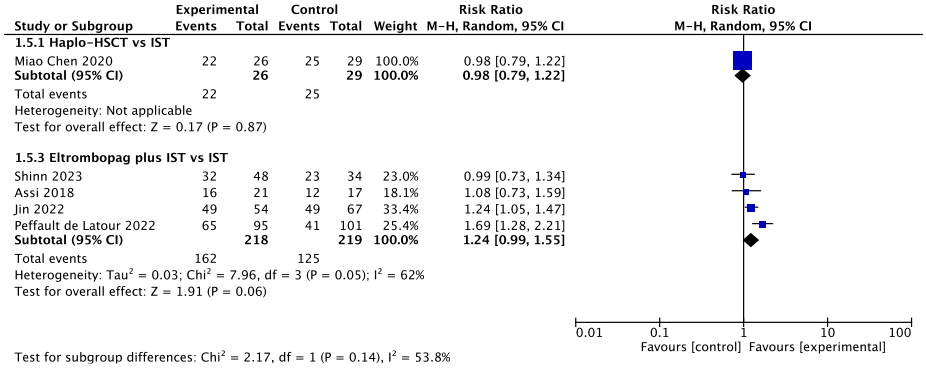
For allogeneic BMT vs IST, one study (Ahn 2003) reported a higher ORR for patients treated with allogeneic BMT compared with IST; however, this was not a statistically significant result.

For eltrombopag plus IST vs IST, three of four studies (Assi 2018, Jin 2022, Peffault de Latour 2022) reported a higher ORR for patients treated with eltrombopag plus IST vs IST alone; one of four studies (Shinn 2023) reported no evidence of a difference. In the three studies reporting a higher ORR, this was a statistically significant difference at early timepoints (1, 3 or 6 months) but generally not at later timepoints.

Single arm evidence was also provided from 5 studies: 1 eltrombopag and 4 IST.

Conclusion for the decision aid: ORR occurs in approximately 85 out of 100 patients receiving haplo-HSCT, between 41 to 86 out of 100 patients receiving IST, approximately 83 out of 100 patients receiving allogeneic BMT, between 67 to 91 out of 100 patients receiving eltrombopag plus IST and approximately 40 out of 100 patients receiving eltrombopag alone (11 studies, moderate to high risk of bias).

Figure 14: Comparative data for overall response rate



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel. ORR defined as complete response or partial response (usually defined as transfusion independence). Note that the data are plotted for the latest timepoint reported for each study, which ranged from 6 to 28.5 months. Note that 1 comparative study (allogeneic BMT vs IST) is not included in the forest plot.

Table 8: Need for transfusions

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	ORR (CR or PR)	3 months	26/26 (100.0%), P<0.001	NR	NR	Comparative cohort	**Statistically favours haploidentical HSCT**	15/24
	IST (rATG/pALG plus CsA				18/29 (62.1%)					
	Haploidentical HSCT			6 months	25/26 (96.2%), P<0.05	NR	NR		**Statistically favours haploidentical HSCT**	
	IST (rATG/pALG plus CsA				21/29 (72.4%)					
	Haploidentical HSCT			12 months	23/26 (88.5%)	NR	NR		Numerically favours haploidentical HSCT	
	IST (rATG/pALG plus CsA				23/29 (79.3%)					
	Haploidentical HSCT			34 (17 to 68) months	22/26 (84.6%)	NR	NR		Numerically favours IST	
	IST (rATG/pALG plus CsA			28.5 (12 to 71) months	25/29 (86.2%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA		NR	53/64 (82.8%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				73/156 (46.8%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA		21 months	16/21 (76%)	NR	P=0.72	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				12/17 (71%)					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		1 month	19/54 (35%)	NR	P=0.002	Comparative cohort	**Statistically favours eltrombopag plus IST**	19/24
	IST alone				8/67 (12%)					
	Eltrombopag plus IST			3 months	35/54 (64%)	NR	P=0.028		**Statistically favours eltrombopag plus IST**	
	IST alone				30/67 (44%)					
	Eltrombopag plus IST			6 months	46/54 (85%), P=0.006	NR	OR 3.600 (95% CI 1.345 to 9.638)		**Statistically favours eltrombopag plus IST**	
	IST alone				41/67 (61%)					
	Eltrombopag plus IST			12 months	49/54 (91%)	NR	P=0.031		**Statistically favours eltrombopag plus IST**	
	IST alone				49/67 (73%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		3 months	57/96 (59%)	NR	OR 3.2 (95% CI 1.3 to 7.8), P=0.01	RCT	**Statistically favours eltrombopag plus IST**	High
	IST alone				31/101 (31%)					
	Eltrombopag plus IST			6 months	65/95 (68%)		NR		Numerically favours eltrombopag plus IST	
	IST alone				41/101 (41%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA		6 months	28/48 (58%)	NR	P=0.56	Comparative cohort	Numerically favours IST alone	19/24
	IST alone				22/34 (65%)					
	Eltrombopag plus IST			12 months	32/48 (67%)	NR	P=0.93		NED	
	IST alone				23/34 (68%)					
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	CR (defined as Hb in normal range, Nt >1.5e9/L and Pt >150e9/L)	3 months	100.0%, P<0.001	NR	NR	Comparative cohort	**Statistically favours haploidentical HSCT**	15/24
	IST (rATG/pALG plus CsA				10.3%					
	Haploidentical HSCT			6 months	96.2%, P<0.001	NR	NR		**Statistically favours haploidentical HSCT**	
	IST (rATG/pALG plus CsA				27.6%					
	Haploidentical HSCT			12 months	88.5%, P<0.001	NR	NR		**Statistically favours haploidentical HSCT**	
	IST (rATG/pALG plus CsA				34.5%					
	Haploidentical HSCT			34 (17 to 68) months	84.6%, P<0.05	NR	P=0.034		**Statistically favours haploidentical HSCT**	
	IST (rATG/pALG plus CsA			28.5 (12 to 71) months	58.6%					
Ahn 2003[25]	Allogeneic BMT		CR (defined as granulocytes	NR	48/64 (75.0%)	NR	P=0.000	Comparative cohort	**Statistically favours**	9/24

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	IST (ATG with or without CsA)	Adults with SAA or VSAA	>2000/mm3, Pt>120,000/mm3 and Hb>12g/dL without transfusion)		36/156 (23.1%)				**allogeneic BMT**	
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA	CR (defined as ANC >1e9/L, Hb>10g/dL and Pt>100e9/L)	1 month	0%	NR	NR	Comparative cohort	NED	19/24
	IST alone				0%					
	Eltrombopag plus IST			3 months	17.0%	NR	P=0.069		Numerically favours eltrombopag plus IST	
	IST alone				7.0%					
	Eltrombopag plus IST			6 months	27.0%	NR	P=0.11		Numerically favours eltrombopag plus IST	
	IST alone				14.0%					
	Eltrombopag plus IST			12 months	32.0%	NR	P=0.92		NED	
	IST alone				33.0%					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	CR (defined as Hb>10g/dL, ANC >1000/mm3, Pt>100,000/mm3 without transfusion)	3 months	21/96 (22%)	NR	OR 3.2 (95% CI 1.3 to 7.8), P=0.01	RCT	**Statistically favours eltrombopag plus IST**	High
	IST alone				10/101 (10%)					
	Eltrombopag plus IST			6 months	30/95 (32%)		NR		Numerically favours eltrombopag plus IST	
	IST alone				20/101 (20%)					
Shinn 2023[36]	Eltrombopag plus IST		CR (defined as ANC	6 months	14/48 (29%)	NR	P=0.06	Comparative cohort	Numerically favours	19/24

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	IST alone	Adults with SAA or VSAA	>1000/mm3, Pt>100,000/mm3 and Hb >10g/dL)		4/34 (12%)				eltrombopag plus IST	
	Eltrombopag plus IST			12 months	23/48 (48%)		P=0.005		**Statistically favours eltrombopag plus IST**	
	IST alone				6/34 (18%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	PR (defined as granulocytes >500/mm3, Pt>30,000/mm3 or resolution of all RBC transfusions)	NR	5/64 (7.8%)	NR	P=0.000	Comparative cohort	**Statistically favours allogeneic BMT**	9/24
	IST (ATG with or without CsA)				37/156 (23.7%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	PR (defined as transfusion independence)	21 months	8/21 (38%)	NR	NR	Non-randomised interventional	Numerically favours IST alone	18/24
	IST alone				7/17 (42%)					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA	PR (defined as ANC >0.5e9/L, Hb>80g/dL and Pt>20e9/L without meeting criteria for CR without transfusion)	1 month	35.0%	NR	P=0.002	Comparative cohort	**Statistically favours eltrombopag plus IST**	19/24
	IST alone				12.0%					
	Eltrombopag plus IST			3 months	47.0%	NR	NR		Numerically favours eltrombopag plus IST	
	IST alone				37.0%					
	Eltrombopag plus IST			6 months	58.0%	NR	NR		Numerically favours eltrombopag plus IST	
	IST alone				47.0%					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	Eltrombopag plus IST			12 months	32/54 (59.0%)	NR	NR		Numerically favours eltrombopag plus IST	
	IST alone				27/67 (40.0%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	PR (defined as transfusion independence; both RBC and Pt)	3 months	36/96 (38%)	NR	OR 3.2 (95% CI 1.3 to 7.8), P=0.01	RCT	**Statistically favours eltrombopag plus IST**	High
	IST alone				21/101 (21%)					
	Eltrombopag plus IST			6 months	35/95 (37%)		NR		Numerically favours eltrombopag plus IST	
	IST alone				21/101 (21%)					
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA	PR (defined as no longer meeting the criteria for SAA)	6 months	28/48 (58%)	NR	NR	Comparative cohort	Numerically favours IST alone	19/24
	IST alone				22/34 (65%)					
	Eltrombopag plus IST			12 months	32/48 (67%)				NED	
	IST alone				23/34 (68%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	Time to Pt transfusion independence	24 (95% CI 23 to 24) months	NR	40 days (IQR 20 to 80)	NR	RCT	Numerically favours eltrombopag plus IST	High
	IST alone					68 days (IQR 34 to 151)				
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with	Time to RBC transfusion independence	24 (95% CI 23 to	NR	51 days (IQR 23 to 122)	NR	RCT	Numerically favours	High

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	IST alone	SAA or VSAA		24) months		140 days (IQR 62 to 252)			eltrombopag plus IST	
Single arm evidence										
Kim 2003[27]	IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA	ORR (including PR and CR)	NR	33/74 (45%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA		NR	74/155 (47.7%)	NR	NR	Single arm cohort	NA	4/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA		3 months	15/37 (40.5%)	NR	NR	Single arm cohort	NA	12/16
				6 months	21/32 (65.6%)					
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)		23.2 (range 6 to 173) months	45/67 (67.2%)	NR	NR	Single arm cohort	NA	8/16
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA		NR	17/43 (40%)	NR	NR	Non-randomised interventional	NA	14/16
Kim 2003[27]	IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA	CR (defined as Ht ≥35%, ANC ≥1e9/L and Pt 100e9/L without transfusion	NR	16/74 (22%)	NR	NR	Single arm cohort	NA	4/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA	CR (defined as granulocytes >2.0e3/uL, Pt >120e3/uL and Hb >12g/dL without transfusion)	NR	19/155 (12.3%)	NR	NR	Single arm cohort	NA	4/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA	CR (defined as ANC >1e9/L, Hb>100g/L and Pt>100e9/L)	3 months	1/37 (2.7%)	NR	NR	Single arm cohort	NA	12/16
				6 months	6/32 (18.7%)					
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	CR (defined as min Hb 2g/dL, Nt >1.5e9/L, Pt >150e9/L)	23.2 (range 6 to 173) months	16/67 (23.9%)	NR	NR	Single arm cohort	NA	8/16
Kim 2003[27]	IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA	PR (defined as Nt≥0.5e9/L, Pt ≥30e9/L or no need for RBC transfusion)	NR	17/74 (23%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA	PR (defined as granulocytes ≥0.5e3/uL, Pt ≥30e3/uL or resolution or all RBC transfusions)	NR	55/155 (35.5%)	NR	NR	Single arm cohort	NA	4/16
Xu 2019[24]	IST (rATG plus CsA)			3 months	14/37 (37.8%)	NR	NR		NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		Adults with SAA or VSAA	PR (defined as transfusion independence)	6 months	15/32 (46.9%)			Single arm cohort		
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	PR (defined as transfusion independence or no longer meeting the criteria for SAA)	23.2 (range 6 to 173) months	29/67 (43.3%)	NR	NR	Single arm cohort	NA	8/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Transfusion independence	9 to 13 months	21/46 (45.7%)	NR	NR	Single arm cohort	NA	11/16
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	No need for platelet transfusion	Baseline	1/43 (2.3%)	NR	NR	Non-randomised interventional	NA	14/16
				16 weeks	11/43 (25.6%)					
				Most recent FU	12/43 (27.9%)					
			No need for RBC transfusion	Baseline	3/43 (7.0%)					
				16 weeks	4/43 (9.3%)					
				Most recent FU	11/43 (25.6%)					

Abbreviations: ANC, absolute neutrophil count; BMT, bone marrow transplant; CI, confidence interval; CR, complete response; CsA, cyclosporin A; FU, follow-up; Hb, haemoglobin; HSCT, haematopoietic stem cell transplant; Ht, haematocrit; IQR, interquartile range; IST, immunosuppressive therapy; Nt, neutrophils; OR, odds ratio; ORR, overall response rate; pALG, porcine anti-lymphocyte globulin; PR, partial response; Pt, platelets; rATG, rabbit anti-thymocyte globulin; RBC, red blood cell; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Recurrence/therapy failure

Recurrence

Recurrence/relapse

A total of four studies provided comparative evidence for relapse (Table 9). This included one RCT and three cohort studies. Comparisons included: haplo-HSCT vs IST (1 study) and eltrombopag plus IST vs IST (3 studies). Risk of bias ranged from 15/24 to 19/24 in the cohort studies and was rated high in the RCT.

An overview of the comparative evidence for relapse is provided in Figure 15.

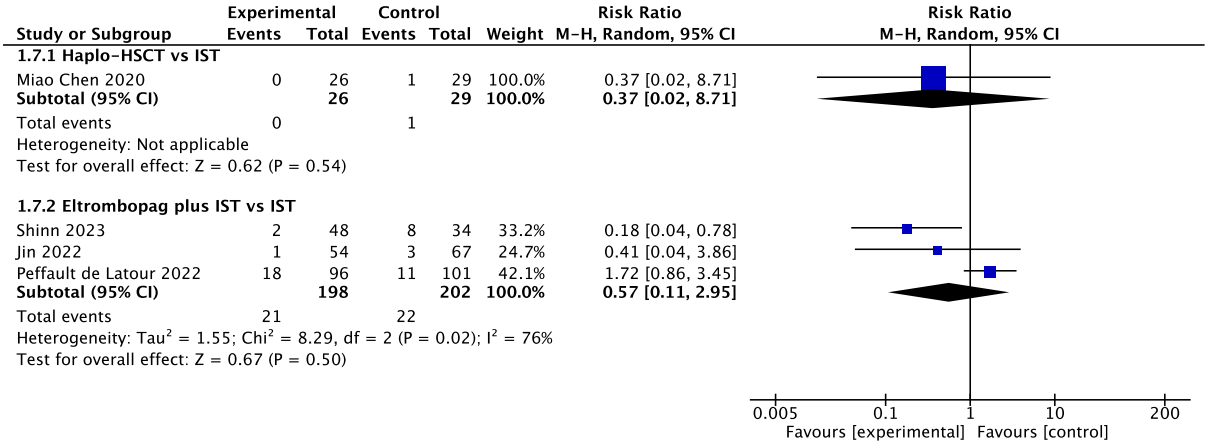
For haplo-HSCT vs IST, one study (Miao Chen 2020) reported a lower risk of relapse for patients treated with haplo-HSCT compared with IST (0% vs 3.4%, respectively); however, this was not a statistically significant difference.

For eltrombopag plus IST vs IST, two of three studies (Jin 2022, Shinn 2023) reported a lower rate of relapse for patients treated with eltrombopag plus IST vs IST alone; one of three studies (Peffault de Latour 2022) reported a higher rate of relapse for patients treated with eltrombopag plus IST vs IST alone. None of these were statistically significant differences.

Single arm evidence was also provided from 6 studies: 1 haplo-HSCT and 5 IST.

Conclusion for the decision aid: relapse occurs in approximately zero out of 100 patients receiving haplo-HSCT, between 3 to 24 out of 100 patients receiving IST and between 2 to 19 out of 100 patients receiving eltrombopag plus IST (10 studies, moderate to high risk of bias).

Figure 15: Comparative data for relapse



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel.

Failure-free survival

A total of six studies provided comparative evidence for failure-free survival (Table 9). One was a non-randomised interventional study and five were cohort studies. Comparisons included: haplo-HSCT vs IST (1 study), MSD-HSCT vs haplo-HSCT (2 studies), MSD-HSCT vs MUD-HSCT (1 study), MUD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs mismatched UD-HSCT (1 study), haplo-HSCT vs mismatched UD-HSCT (1 study) and eltrombopag plus IST vs IST (2 studies). Risk of bias ranged from 18/24 to 19/24.

An overview of the comparative dichotomous evidence for failure-free survival is provided in Figure 16.

For haplo-HSCT vs IST, one study (Xu 2019) reported a statistically significant improvement in failure-free survival following treatment with haplo-HSCT compared to IST (HR 4.275, 95% CI 1.957 to 9.338, P<0.001) (Figure 16).

For MSD-HSCT vs haplo-HSCT, 2 studies (Niu 2022, Zhang 2020) reported no evidence of a difference in failure-free survival following treatment with MSD-HSCT compared to haplo-HSCT; however, this was not a statistically significant difference.

For MSD-HSCT vs MUD-HSCT, 1 study reported no evidence of a difference in failure-free survival following treatment with MSD-HSCT compared to MUD-HSCT; however, this was not a statistically significant difference.

For MUD-HSCT vs haplo-HSCT, 2 studies (Park 2021, Zhang 2020) reported no evidence of a difference in failure-free survival following treatment with MUD-HSCT compared to haplo-HSCT.

For haplo-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported no evidence of a difference in failure-free survival following treatment with haplo-HSCT compared to mismatched UD-HSCT.

For MUD-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported no evidence of a difference in failure-free survival following treatment with MUD-HSCT vs mismatched UD-HSCT.

Single arm evidence was also provided from 1 study (for haplo-HSCT).

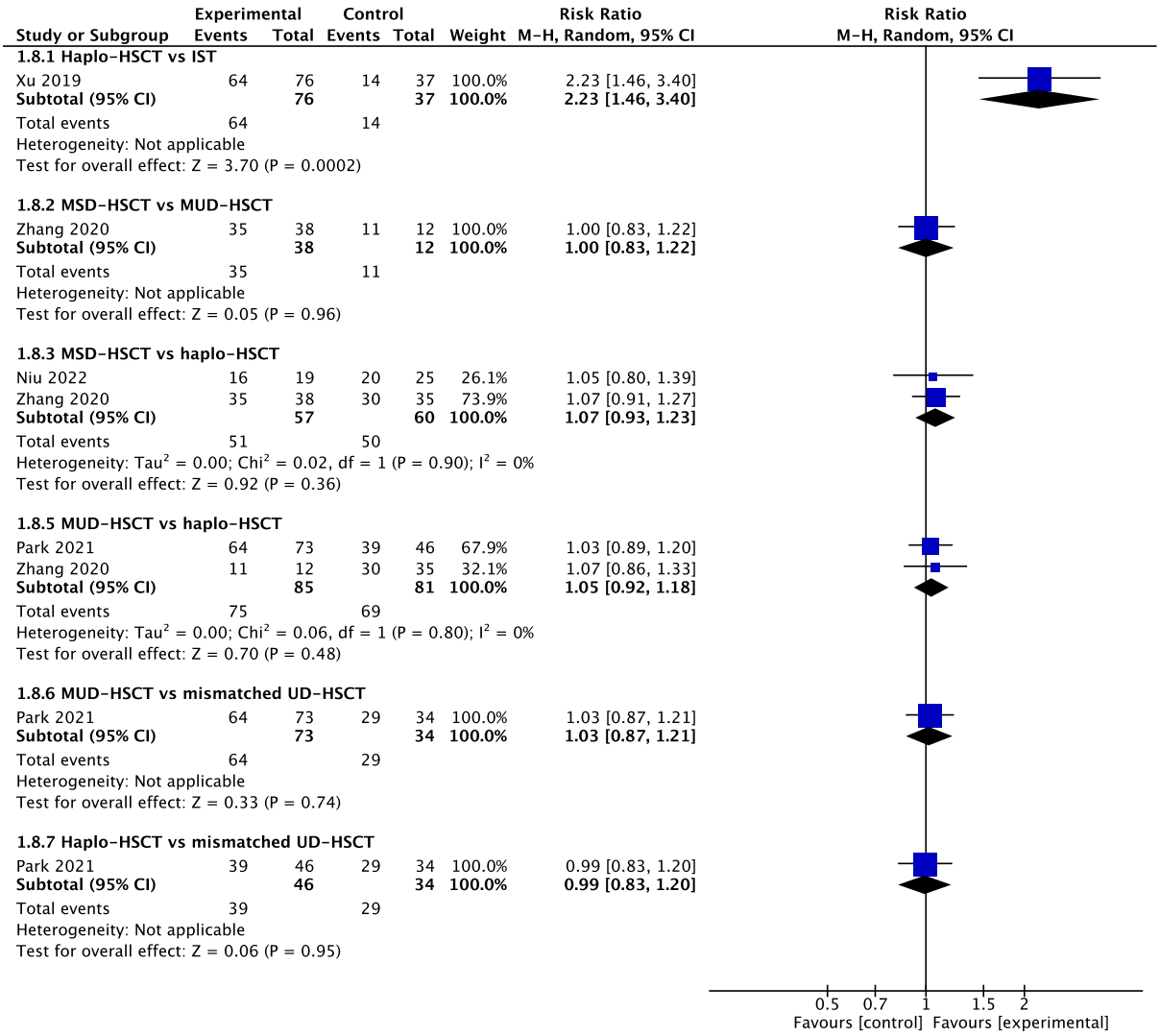
Data from a secondary source (the Iftikhar 2024 guideline[7]) provided additional evidence indicating that matched related donor HSCT or alternative donor transplant (either MUD-HSCT or haplo-HSCT) was associated with significant improvements in FFS compared to IST (Figure 17, Figure 18). The same secondary source reported similar outcomes for FFS for matched related donor transplant compared to alternate donor transplant (either MUD-HSCT or haplo-HSCT) (Figure 19).

Finally, two studies reported on median relapse-free or failure-free survival (Assi 2018, Shinn 2023) for eltrombopag plus IST vs IST. One study (Assi 2018) reported an worsening in relapse-free survival for eltrombopag plus IST compared to IST; and one study (Shinn 2023)

reported an improvement in disease-free survival for eltrombopag plus IST compared to IST; however, neither of these were statistically significant differences.

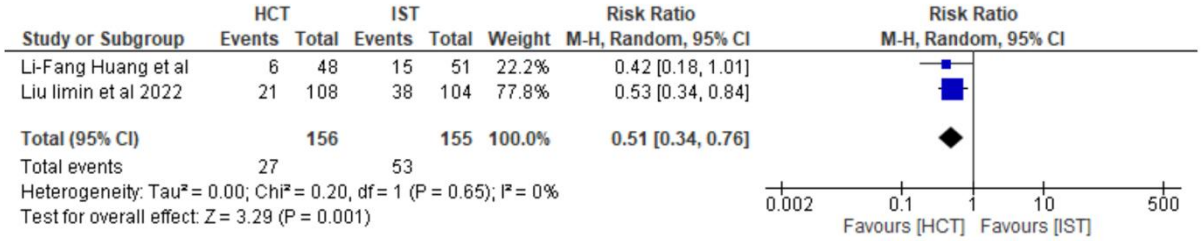
Conclusion for the decision aid: failure-free survival occurs in between 84 to 92 out of 100 patients receiving MSD-HSCT, between 80 to 87 out of 100 patients receiving haplo-HSCT, approximately 88 out of 100 patients receiving MUD-HSCT, approximately 85 out of 100 patients receiving mismatched UD-HSCT and approximately 39 out of 100 patients receiving IST (5 studies, moderate to high risk of bias).

Figure 16: Comparative data for failure-free survival – primary studies



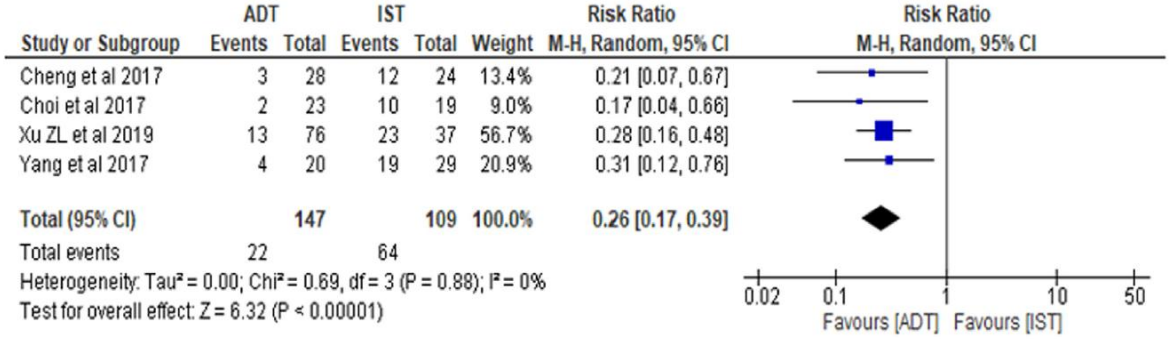
Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Figure 17: Comparative data for failure-free survival in adults who have a matched related donor – secondary source



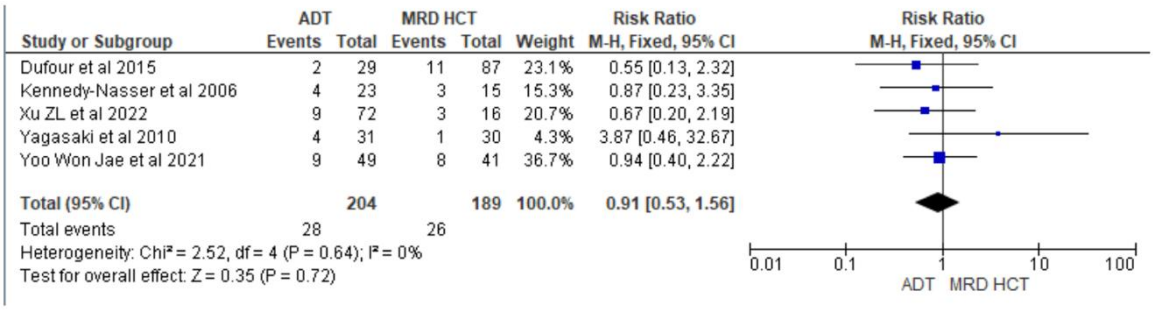
Reproduced from Iftikhar 2024[7]
Abbreviations: CI, confidence interval; HCT, allogeneic haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel.

Figure 18: Comparative data for failure-free survival in adults who lack a matched related donor - secondary source



Reproduced from Iftikhar 2024[7]
Abbreviations: ADT, alternative donor transplant (defined as either MUD-HSCT or haplo-HSCT); CI, confidence interval; haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Figure 19: Comparative data for failure-free survival in adults who have matched or alternate donor options - secondary source



Reproduced from Iftikhar 2024[7]
Abbreviations: ADT, alternative donor transplant (defined as either MUD-HSCT or haplo-HSCT); CI, confidence interval; haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MRD-HSCT, mnatched related donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Therapy failure (graft failure)

A total of four studies provided comparative evidence on therapy failure, including graft failure, primary graft failure or secondary graft failure (Table 9). All four studies were cohorts. Comparisons included: MSD-HSCT vs MUD-HSCT (1 study), MSD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs haplo-HSCT (3 studies), MUD-HSCT vs mismatched UD-HSCT (1 study) and haplo-HSCT vs mismatched UD-HSCT (1 study). Risk of bias ranged from 11/24 to 19/24.

An overview of the comparative evidence for therapy failure is provided in Figure 20.

For MSD-HSCT vs MUD-HSCT, 1 study (Zhang 2020) reported lower rates of secondary graft failure for patients treated with MSD-HSCT compared to MUD-HSCT (0% vs 8.3%, respectively); however, this was not a statistically significant difference.

For MSD-HSCT vs haplo-HSCT, 1 study (Niu 2022) reported a lower rate of graft failure for patients treated with MSD-HSCT compared to haplo-HSCT (although this was not a statistically significant difference), and one study (Zhang 2020) reported no evidence of a difference in secondary graft failure (0% in both treatment arms).

For MUD-HSCT vs haplo-HSCT, 2 studies (Park 2021, Kim 2016) reported a lower rate of graft failure for patients treated with MUD-HSCT (or a mix of MUD-HSCT and partially matched HSCT for Kim 2016) compared to haplo-HSCT, and one study (Zhang 2020) reported a higher rate of secondary graft failure for patients treated with MUD-HSCT compared to haplo-HSCT; none of these were statistically significant differences

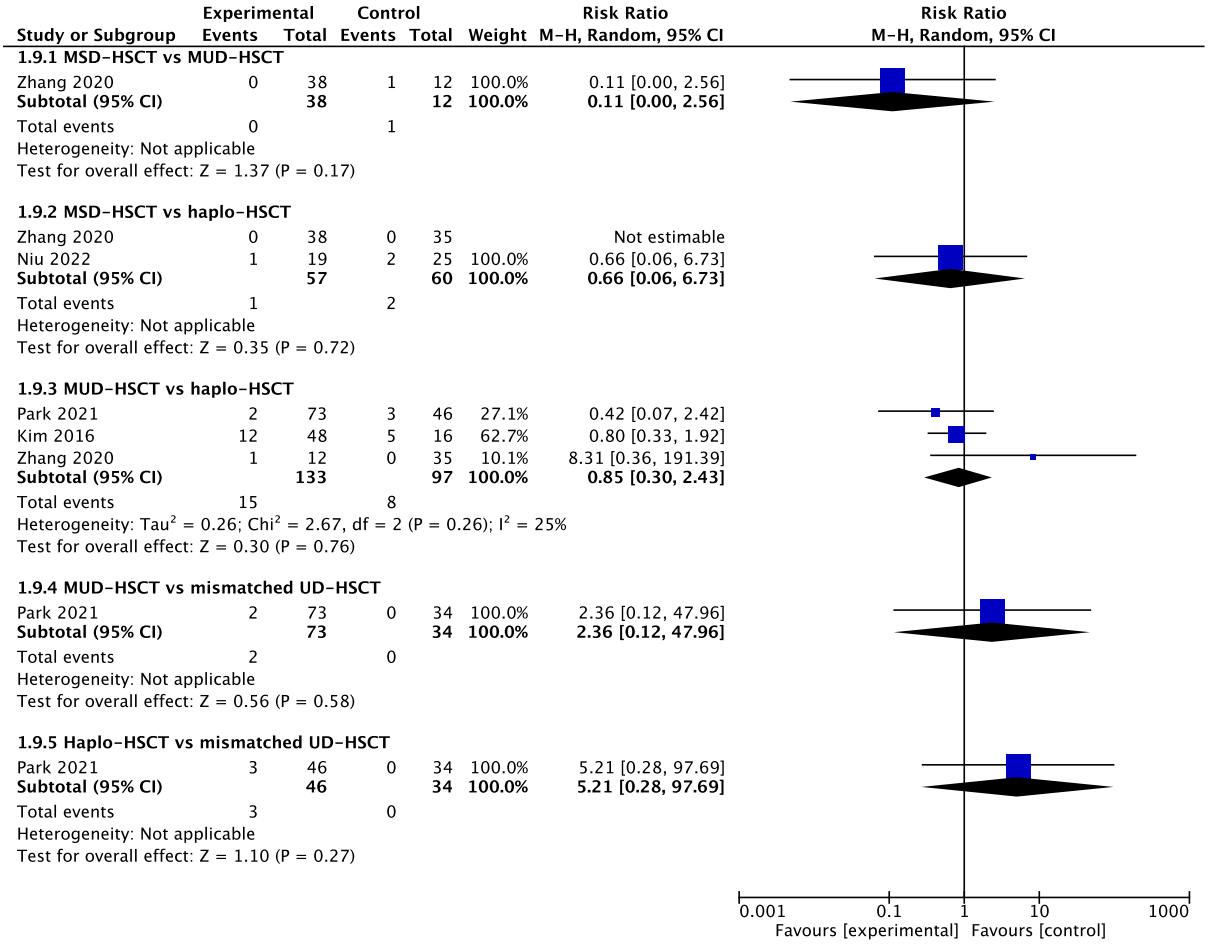
For MUD-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a higher rate of graft failure for patients treated with MUD-HSCT compared to mismatched UD-HSCT (2.7% vs 0%, respectively); however, this was not a statistically significant difference.

For haplo-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a higher rate of graft failure for patients treated with haplo-HSCT compared to mismatched UD-HSCT (6.5% vs 0%, respectively); however, this was not a statistically significant difference.

Single arm evidence was also provided from 8 studies: 1 MSD-HSCT, 2 allogeneic BMT and 5 haplo-HSCT.

Conclusion for the decision aid: therapy failure (graft failure) occurs in between 0 to 5 out of 100 patients receiving MSD-HSCT, between 3 to 25 out of 100 patients receiving MUD-HSCT, between 0 to 31 out of 100 patients receiving haplo-HSCT, approximately zero of 100 patients receiving mismatched UD-HSCT and between 9 to 13 out of 100 patients receiving allogeneic BMT (12 studies, moderate to high risk of bias).

Figure 20: Comparative data for therapy failure



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Table 9: Recurrence/therapy failure

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Recurrence – comparative evidence										
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Relapse	30 (12 to 71) months	0%	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				3.4%					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		14 (1 to 79) months	1/54 (2%)	NR	P=0.77	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			16 (1 to 79) months	3/67 (5%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		18 months after response	19% (95% CI 9 to 29%)	NR	HR 1.32 (95% CI 0.55 to 3.21)	RCT	Numerically favours IST alone	High
	IST alone				11% (95% CI 2 to 20%)					
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA		2 years	2/48 (4.2%)	NR	NR	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone				8/34 (23.5%)					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Failure-free survival (defined as survival with response)	8 years	83.7% ± 4.8% (n=76), P=0.001	NR	HR 4.275 (95% CI 1.957 to 9.338), P<0.001	Comparative cohort	**Statistically favours haploidentical HSCT**	19/24
	IST (rATG plus CsA)				38.5% ± 13.2% (n=37)					
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA		24.7 (range 6.8 to 30.4) months	84.2 ± 3.9%	NR	P=0.965	Comparative cohort	Numerically favours matched sibling donor HSCT	18/24
	Haploidentical HSCT				80.0 ± 3.5%					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA		3 years	35/38 (92.1% ± 4.4%)	NR	P=0.866	Comparative cohort	Numerically favours matched sibling donor HSCT	19/24
	Matched unrelated donor HSCT				11/12 (87.5% ± 11.7%)					
	Haploidentical HSCT				30/35 (86.7% ± 6.4%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA		3 years	82.3% (95% CI 67.6 to 90.7%)	NR	P=0.8	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				87.5% (95% CI 77.3 to 93.3%)					
	Mismatched unrelated donor HSCT				85.3% (95% CI 68.2 to 93.6%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Relapse-free survival	2 years	NR	Not reached	95% CI 0.015 to 1.432, P=0.10	Non-randomised interventional	Numerically favours IST alone	18/24
	IST alone					Not reached				
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA	Disease-free survival (defined as time from day of therapy initiation to relapse or death from any cause)	18 months	NR	Not reached	P=0.20	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			49 months		13.3 (95% CI 1.9 to 24.7) months				
Recurrence – single arm evidence										

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Relapse	21.1 (range 3.2 to 71.1) months	0/51 (0%)	NR	NR	Single arm cohort	NA	12/16
Ahn 2003[25]	IST (ATG with or without CsA)	Adults with SAA or VSAA	Relapse	NR	11/73 (15.0%)	NR	NR	Single arm cohort	NA	4/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA	Relapse	5.7 or 5.0 years	2/37 (5.4%)	NR	NR	Single arm cohort	NA	12/16
Kim 2003[27]	IST (equine ATG/ALG with or without CsA)	Adults with SAA or VSAA	Recurrent aplasia	NR	4/74 (5.4%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA who were responders	Recurrent AA	NR	8/74 (10.8%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA	Relapse risk	3 years	12% ± 4%	NR	NR	Single arm cohort	NA	4/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Failure-free survival	21.1 (range 3.2 to 71.1) months	83.5 ± 5.4%	NR	NR	Single arm cohort	NA	12/16
Therapy failure – comparative evidence										
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA	Graft failure	24.7 (range 6.8 to 30.4) months	1/19 (5.26%) (95% CI 0.03 to 0.12)	NR	P=0.196	Comparative cohort	Numerically favours matched sibling donor HSCT	18/24
	Haploidentical HSCT				2/25 (8.00%) (95% CI 0.05 to 0.17)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA		3 years	6.5% (95% CI 1.7 to 16.2%)	NR	NR	Comparative cohort	Numerically favours mismatched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				2.7% (95% CI 0.5 to 8.6%)					
	Mismatched unrelated donor HSCT				0%					
Kim 2016[32]	Haploidentical HSCT	Adults (>18 years) with SAA	Engraftment failure	NR	5/16 (31.3%)	NR	P=0.745	Comparative cohort	Numerically favours alternative donor HSCT	11/24
	Alternative donor HSCT (matched unrelated or partially matched)				12/48 (25.0%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA	Secondary graft failure	17.6 months	0/38 (0%)	NR	NR	Comparative cohort	Numerically favours matched sibling donor HSCT and haploidentical HSCT	19/24
	Matched unrelated donor HSCT				1/12 (8.3%)					
	Haploidentical HSCT				0/35 (0%)					
Therapy failure – single arm evidence										
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA	Graft rejection	NR	1/22 (4.6%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA		NR	5/55 (9%)	NR	NR	Single arm cohort	NA	4/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Graft failure	NR	8/64 (12.5%)	NR	NR	Single arm cohort	NA	4/16
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Engraftment failure	12.2 (range 3.2 to 40.4) months	2/8 (25%)	NR	NR	Single arm cohort	NA	5/16
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA		34 (17 to 68) months	2/26 (7.7%)	NR	NR	Single arm cohort	NA	8/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	0/51 (0%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Primary graft failure	43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	0/50 (0%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Secondary graft failure	43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	0/50 (0%)	NR	NR	Single arm cohort	NA	12/16
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Late graft failure	NR	3/53 (5.7%)	NR	NR	Single arm cohort	NA	4/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	GFFS (defined as free of grade 3-4 acute GVHD, extensive chronic GVHD and treatment failure)	Median 24.7 (range 6.1 to 103.0) months	72.4% ± 5.7%	NR	NR	Single arm cohort	NA	12/16

Abbreviations: AA, aplastic anaemia; ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; BMT, bone marrow transplant; GFFS, GVHD-free, failure-free survival; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplant; NA, not applicable, NR, not reported; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Duration of treatment response (cyclosporin A only)

No formal evidence was found for duration of treatment response. One cohort study provided comparative evidence on duration of treatment (as a proxy for duration of treatment response) (Table 10) and compared eltrombopag plus IST vs IST. The risk of bias was rated at 19/24.

Shinn 2023 reported that the duration of cyclosporin therapy was longer for patients receiving eltrombopag plus IST compared to IST alone (11 vs 7.4 months); however, this was not a statistically significant difference.

Two single arm studies also reported evidence for treatment duration for eltrombopag plus IST or eltrombopag alone.

Conclusion for the decision aid: a shorter duration of cyclosporin A treatment (<6 months) is seen in approximately 35 out of 100 patients receiving eltrombopag plus IST and approximately 44 out of 100 patients receiving IST (1 study, moderate risk of bias).

Table 10: Duration of response

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA	Median duration of CsA therapy	18 months	NR	11 (range 0.1 to 70) months	NR	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			49 months		7.4 (range 0.3 to 79) months				
	Eltrombopag plus IST		Duration of CsA therapy <6 months	18 months	17/48 (35%)	NR	P=0.63		Numerically favours eltrombopag plus IST	
	IST alone			49 months	15/34 (44%)					
Single arm evidence										
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA	Median duration of eltrombopag therapy	18 months	NR	7 (range 0.1 to 51) months	NR	Single arm cohort	NA	11/16
			Duration of eltrombopag therapy <6 months		17/48 (35%)	NR	NR		NA	
			Duration of eltrombopag therapy <3 months		8/48 (17%)	NR	NR		NA	
Lengline 2018[42]	Eltrombopag	ATG naïve adults with SAA or VSAA	Treatment duration	9 to 13 months	NR	Median 5.3 (IQR 3.5 to	NR	Single arm cohort	NA	11/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
						10.4) months				
		ATG experienced daults with SAA or VSAA				Median 6.1 (IQR 4.4 to 11.5) months				

Abbreviations: ATG, anti-thympocyte globulin; CsA, cyclosporin A; DoR, duration of response; IQR, interquartile range; IST, immunosuppressive therapy; NR, not reported; SAA, severe aplastic anaemia; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

FAQ3: Will the treatment impact how long I live?

A total of 14 studies provided comparative evidence on OS (Table 11). This included one RCT, one non-randomised interventional study and 12 cohort studies. Comparisons included: MSD-HSCT vs IST (1 study), haplo-HSCT vs IST (2 studies), MSD-HSCT vs MUD-HSCT (2 studies), MSD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs haplo-HSCT (3 studies), MUD-HSCT vs mismatched/partially matched UD-HSCT (2 studies), haplo-HSCT vs mismatched/partially matched UD-HSCT (2 studies) and eltrombopag plus IST vs IST (3 studies). Risk of bias ranged from 9/24 to 19/24 in the non-randomised studies, and was rated high in the RCT.

An overview of the comparative evidence for OS is provided in Figure 21.

For MSD-HSCT vs IST, 1 study (Kim 2003) reported improved OS for patients treated with MSD-HSCT compared to IST; this was a statistically significant difference.

For haplo-HSCT vs IST, 1 study (Xu 2019) reported a numerical improvement in OS for patients treated with haplo-HSCT compared to IST, and 1 study (Miao Chen 2020) reported no evidence of a difference.

For MSD-HSCT vs MUD-HSCT, 1 study (Rice 2019) reported improved OS for patients treated with MSD-HSCT compared to MUD-HSCT, and 1 study (Zhang 2020) no evidence of a difference.

For MSD-HSCT vs haplo-HSCT, 2 studies (Niu 2022, Zhang 2020) reported no evidence of a difference for OS in patients treated with MSD-HSCT compared to haplo-HSCT.

For MUD-HSCT vs haplo-HSCT, 2 studies (Kim 2016, Zhang 2020) reported improved OS for patients treated with MUD-HSCT (or a mix of MUD-HSCT/partially matched HSCT for Kim 2016) compared to haplo-HSCT, and 1 study (Park 2021) reported no evidence of a difference.

For MUD-HSCT vs mismatched/partially matched UD-HSCT, 1 study (Kim 2016) reported improved OS for patients treated with MUD-HSCT compared to mismatched/partially matched UD-HSCT, and 1 study (Park 2021) reported no evidence of a difference.

For haplo-HSCT vs mismatched/partially matched UD-HSCT, 1 study (Kim 2016) reported improved OS for haplo-HSCT compared to partially matched UD-HSCT, and 1 study (Park 2021) reported no evidence of a difference.

For allogeneic BMT vs IST, 2 studies (Ahn 2003, Paquette 1995) reported better OS for patients treated with allogeneic BMT compared to IST; however, these were not statistically significant differences.

For eltrombopag plus IST vs IST, 1 study (Jin 2022) reported improved OS for eltrombopag plus IST compared to IST alone (a statistically significant difference), 1 study (Peffault de Latour 2022) reported no evidence of a difference, and 1 study (Assi 2018) reported worse

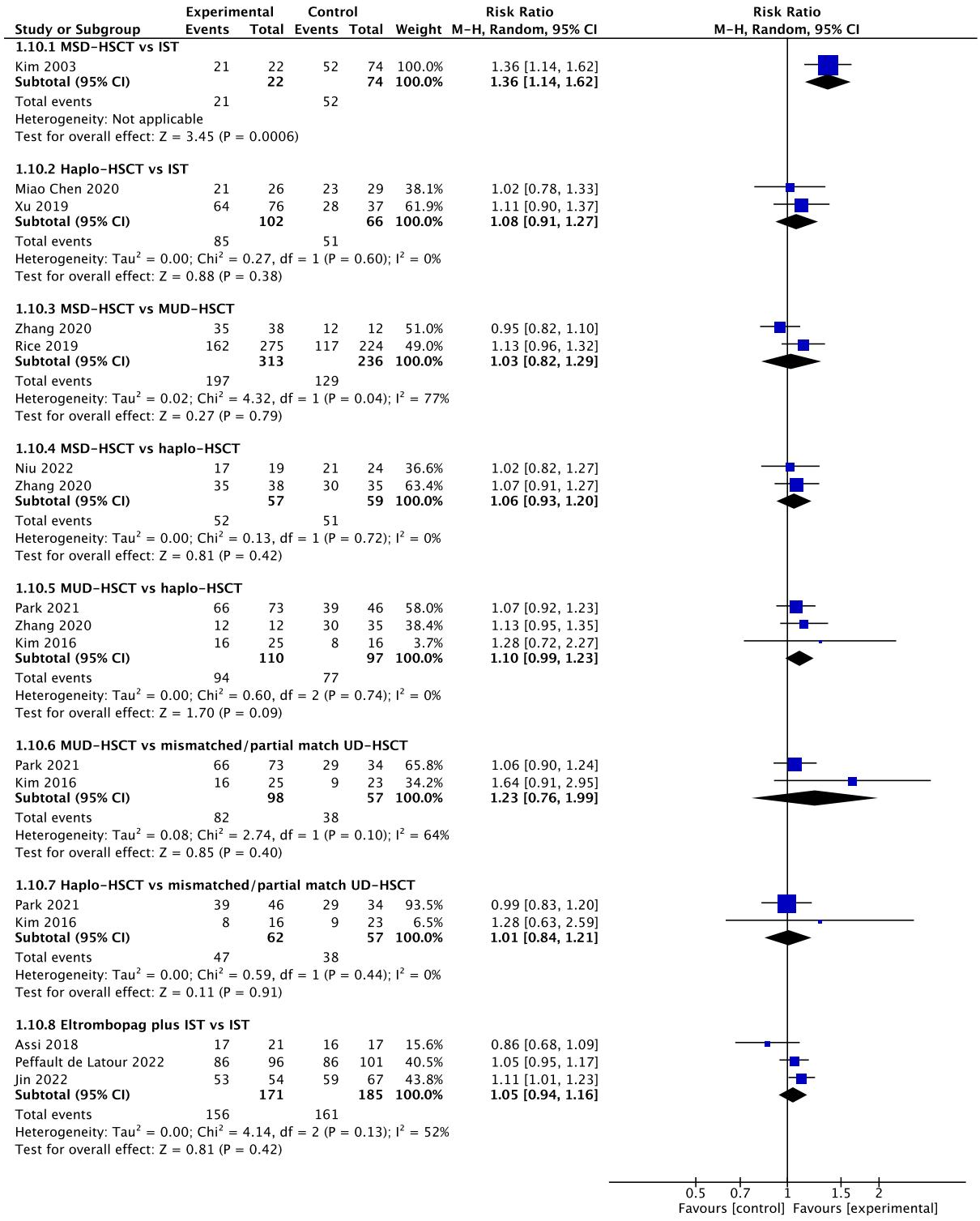
OS for eltrombopag plus IST compared to IST alone (this was not a statistically significant difference).

Single arm evidence was also provided from 4 studies: 3 haplo-HSCT and 1 IST.

The overall trend of HSCT achieving improved OS in adults compared to IST was supported by pooled data from a secondary source (the Iftikhar 2024 guideline[7]), which indicated that matched related donor HSCT achieved significant improvements in OS compared to IST (Figure 22) and that alternative donor transplant (either MUD-HSCT or haplo-HSCT) also had a trend towards improved OS compared to IST (Figure 23). The same secondary source reported a small improvement for matched related donor transplant compared to alternate donor transplant (either MUD-HSCT or haplo-HSCT) (Figure 24).

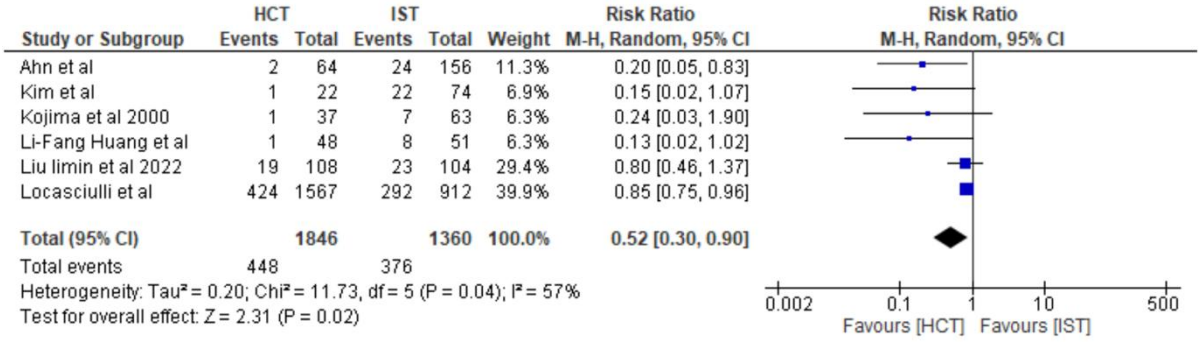
Conclusion for the decision aid: overall survival occurs in between 59 to 95 out of 100 patients receiving MSD-HSCT, between 52 to 100 out of 100 patients receiving MUD-HSCT, between 48 to 87 out of 100 patients receiving haplo-HSCT, between 52 out of 79 patients receiving allogeneic BMT, between 41 to 85 out of 100 patients receiving mismatched/ partially matched UD HSCT, between 49 to 91 out of 100 patients receiving IST and between 82 to 98 out of 100 patients receiving eltrombopag plus IST (17 studies, moderate to high risk of bias).

Figure 21: Comparative data for OS – primary studies



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

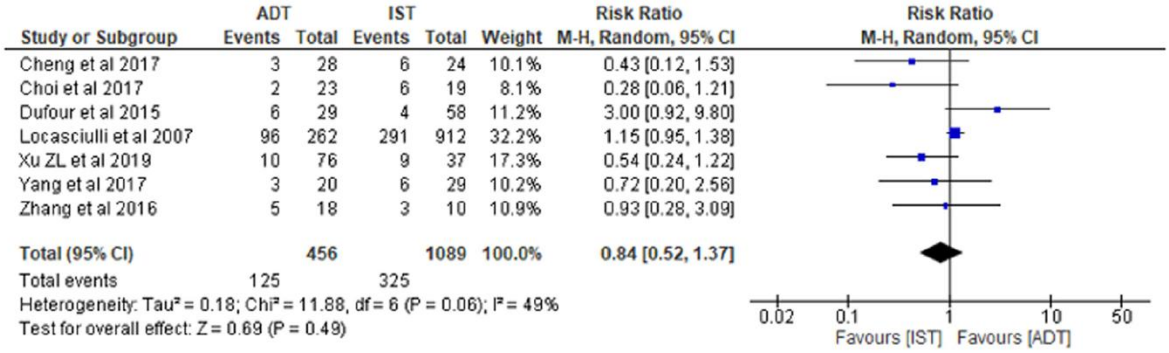
Figure 22: Comparative data for OS in adults who have a matched related donor – secondary source



Reproduced from Iftikhar 2024[7]

Abbreviations: CI, confidence interval; HCT, allogeneic haematopoietic stem cell transplant (matched related donor); IST, immunosuppressive therapy; M-H, Mantel-Haenzel.

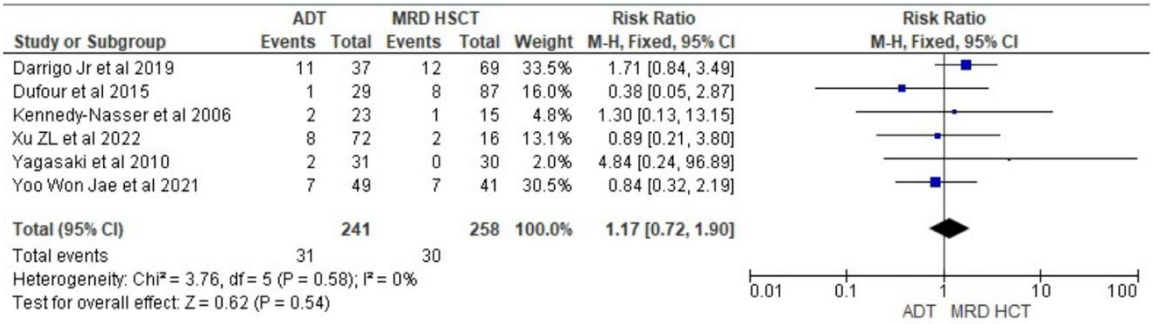
Figure 23: Comparative data for OS in adults who lack a matched related donor - secondary source



Reproduced from Iftikhar 2024[7]

Abbreviations: ADT, alternative donor transplant (defined as either MUD-HSCT or haplo-HSCT); CI, confidence interval; haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Figure 24: Comparative data for OS in adults who have matched or alternate donor options - secondary source



Reproduced from Iftikhar 2024[7]

Abbreviations: ADT, alternative donor transplant (defined as either MUD-HSCT or haplo-HSCT); CI, confidence interval; haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MRD-HSCT, mnatched related donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Table 11: Survival

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	OS	5 years	82.1% ± 8.4%	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				77.9% ± 11.7%					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA		8 years	83.7% ± 4.8% (n=76), P=0.328	NR	HR 1.269 (95% CI 0.320 to 5.040), P=0.735	Comparative cohort	Numerically favours haploidentical HSCT	19/24
	IST (rATG plus CsA)				75.6% ± 17.2% (n=37)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA		6 years	50/64 (78.8%)	Mean 95.16 months	P=0.8307	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				108/156 (69.3%)	Mean 96.01 months				
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA		6 years	52% ± 7%	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				49% ± 4	Median 5.6 years				
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		5 years	95%	NR	P=0.04	Comparative cohort	**Statistically favours MSD-HSCT (BM source)**	12/24
	IST (equine ATG/ALG				70%					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
	with or without CsA)									
Rice 2019[29]	Matched sibling donor HSCT	Adults >50 years with severe AA		3 years	59% (53 to 66%)	NR	HR 1.47 (95% CI 1.00 to 2.16), P=0.05	Comparative cohort	Numerically favours matched sibling donor HSCT	17/24
	Matched unrelated donor HSCT				52% (45 to 60%)					
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA		2 years	17/19 (89.5% ± 3.50%)	NR	P=0.664	Comparative cohort	Numerically favours matched sibling donor HSCT	18/24
	Haploidentical HSCT				21/24 (84.0% ± 4.31%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA		3 years	35/38 (92.1% ± 4.4%)	NR	P=0.481	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				12/12 (100%)					
	Haploidentical HSCT				30/35 (86.7% ± 6.4%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA		3 years	84.4% (95% CI 70.0 to 92.3%)	NR	P=0.659	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				90.3% (95% CI 80.6 to 95.2%)					
	Mismatched unrelated donor HSCT				85.3% (95% CI 68.2 to 93.6%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Kim 2016[32]	Haploidentical HSCT	Adults (>18 years) with SAA		5 years	48.2%	NR		Comparative cohort	Numerically favours alternative donor HSCT	11/24
	Alternative donor HSCT (matched unrelated or partially matched)				52%					
	Haploidentical HSCT				48.2%	NR	P=0.526		Numerically favours matched unrelated HSCT	
	Matched unrelated HSCT				61.8%					
	Partially matched unrelated HSCT				40.8%					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA		2 years	82%	NR	HR 0.78 (95% CI 0.09 to 6.69), P=0.82	Non-randomised interventional	Numerically favours IST alone	18/24
	IST alone				91%					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		2 years	98%	NR	P=0.0078	Comparative cohort	**Statistically favours eltrombopag plus IST**	19/24
	IST alone				88%					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		6 months	96.9% (95% CI 93.4 to 100.0%)	NR	NR	RCT	Numerically favours	High

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
	IST alone				93.1% (95% CI 88.1 to 98.0%)				eltrombopag plus IST	
	Eltrombopag plus IST			12 months	95.7% (95% CI 91.6 to 99.8%)		NR		Numerically favours eltrombopag plus IST	
	IST alone				88.9% (95% CI 82.8 to 95.1%)					
	Eltrombopag plus IST			2 years	89.5% (95% CI 82.4 to 96.6%)		HR 0.57 (95% CI 0.24 to 1.37)		Numerically favours eltrombopag plus IST	
	IST alone				85.0% (95% CI 77.7 to 92.4%)					
Shinn 2023[36]	Eltrombopag plus IST	Adults with SAA or VSAA		2 years	NR	Not reached	NR	Comparative cohort	NED	19/24
	IST alone					Not reached				
Single arm evidence										
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Survival	12.2 (range 3.2 to 40.4) months	5/8 (62.5%)	NR	NR	Single arm cohort	NA	5/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA		43.2 (24.3 to 65.9) months	22/26 (84.6%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Probability of 1- and 3-year OS	21.1 (range 3.2 to 71.1) months	83.5 ± 5.4%	NR	NR	Single arm cohort	NA	12/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	OS	5 years	79.5% (n=69)	NR	NR	Single arm cohort	NA	8/16

Abbreviations: ATG, anti-thymocyte globulin; BMT, bone marrow transplant; CI, confidence interval; CsA, cyclosporin A; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NED, no evidence of a difference; NR, not reported; OS, overall survival; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

FAQ4: How will the treatment impact my quality of life?

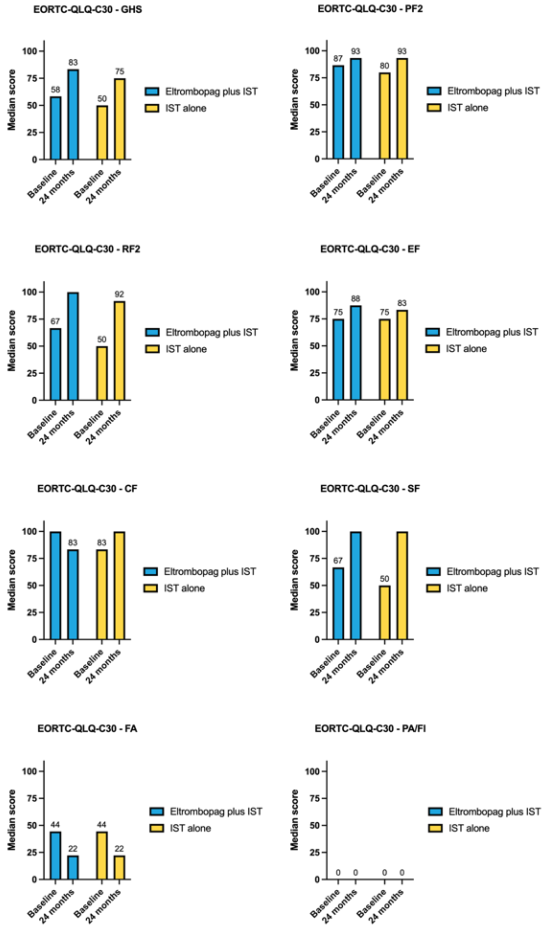
A total of three studies provided comparative evidence on health-related quality of life (HRQoL) (Table 12). This included one RCT and two cohort studies. Comparisons included: MSD-HSCT vs IST (1 study), haplo-HSCT vs IST (1 study) and eltrombopag plus IST vs IST (1 study). Risk of bias ranged from 12/24 to 19/24 in the cohort studies, and was rated high in the RCT.

For MSD-HSCT vs IST, 1 study (Kim 2003) reported an improvement in HRQoL (based on Karnofsky performance score) for MSD-HSCT compared to IST; however, this was not a statistically significant difference (Table 12).

For haplo-HSCT vs IST, 1 study (Xu 2019) reported a statistically significant improvement in HRQoL (based on Karnofsky performance score) for haplo-HSCT compared to IST (Table 12).

For eltrombopag plus IST vs IST, 1 study (Peffault de Latour 2022) reported no evidence of a difference in HRQoL (based on EORTC QLQ-C30 GHS) for eltrombopag plus IST compared to IST (Table 12). This multinational RCT also reported similar improvements for HRQoL subscales including: physical scale, role scale, emotional scale, cognitive scale, social scale and fatigue scale from baseline to 24 months. No evidence of a difference was seen in pain scale or financial difficulties due to treatment/illness scale; no between-group statistical comparisons were presented (Figure 25).

Figure 25: EORTC-QLQ-C30 after treatment with eltrombopag plus IST vs IST alone



Data sourced from Peffault de Latour 2022[35]
Abbreviations: QL2, Global health status; PF2, physical scale; RF2, role scale; CF, cognitive scale; EF, emotional scale; SF, social scale; FA, fatigue scale; PA, pain scale; FI, financial difficulties due to treatment/illness scale. For the first 5 scales, higher scores indicate better quality of life status, while for FA, PA and FI, higher scores indicate worse status.

Single arm evidence was also provided from 2 studies: 1 IST and 1 eltrombopag. These studies reported on QLQ-AA/PNH-54 or SF-36 tools, respectively.

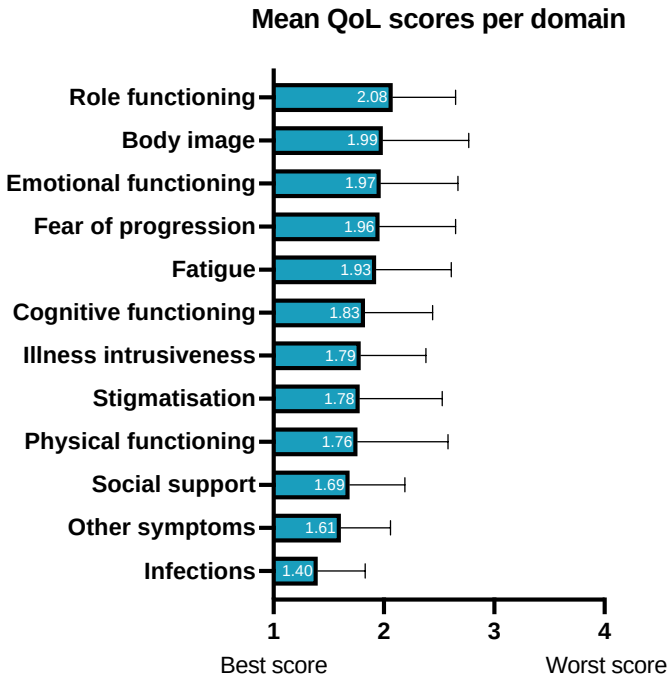
A single arm Dutch cohort (Lommerse 2024) reported that the highest mean scores (a negative outcome) per question following treatment with IST were observed in domains 'Role functioning' (2.08), 'Body image' (1.99), 'Emotional functioning' (1.97) and 'Fear of progression' (1.96). The lowest mean score (a positive outcome) was observed in the domain, 'Infections' (1.40) (Figure 26).

This study also reported that age had a weak inverse correlation ($R2 = 0.112$, $\beta = -0.63$, $p = 0.05$) with the mean total QLQ-AA/PNH-54 score after treatment with IST. The number of years after treatment did not appear to influence total scores, nor did the current level of haemoglobin or thrombocyte counts. Response to IST impacted HRQoL with patients who experienced complete responses reporting improved HRQoL compared to patients experiencing partial responses (data not shown).

A single arm US cohort (Desmond 2014) reported that physical health scores for adult AA patients at baseline were significantly lower than those of the US general population although mental health scores did not differ. A total of 27 patients completed surveys after 3-4 months of treatment with eltrombopag, and reported no significant change for pre- vs post-eltrombopag physical or mental scores (data not shown).

Conclusion for the decision aid: HRQoL is improved in between 80 to 100 out of 100 patients receiving MSD-HSCT, between 20 to 100 out of 100 patients receiving haplo-HSCT and between 20 to 100 out of 100 patients receiving IST. Eltrombopag plus IST and IST are likely associated with similar improvements in HRQoL (2 studies, moderate to high risk of bias).

Figure 26: QLQ-AA/PNH-54 scores across domains after treatment with IST



Data taken from Lommerse 2024[41]
Abbreviations: IST, immunosuppressive therapy; QoL, quality of life.

Table 12: HRQoL

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA (survivors)	Karnofsky PS	Median 24.7 (range 6.1 to 103.0) months	NR	100 (20 to 100)	P=0.002	Comparative cohort	**Statistically favours haploidentical HSCT**	19/24
	IST (rATG plus CsA)			Median 20.2 (range 3.2 to 96.0) months		90 (20 to 100)				
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	NR	Median 100% (range 80 to 100); n=21	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or without CsA)					Median 80% (range 50 to 100); n=54				
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	EORTC QLQ-30 – GHS – change from baseline	24 months	NR	NR	25	RCT	NED	High
	IST alone						25			
Single arm evidence										
Lommerse 2024[41]	IST (CsA or ATG)	Adults with AA who had been successfully	QLQ-AA/PNH-54*	NR	NR	Mean 99 (range 63 to 165)	NR	Cohort	NA	13/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
		treated with IST (CR or PR)								
		Adults with AA who had a CR to IST				Mean 92 (range 65 to 142)				
		Adults with AA who had a PR to IST				Mean 105 (range 63 to 165)				
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	SF-36 QoL	3-4 months	NR	"No significant change in pre- vs post-tx physical or mental scores"	NR	Non-randomised interventional	NA	14/16

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; CR, complete response; CsA, cyclosporin A; GHS, global health status; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; PNH, paroxysmal nocturnal haemoglobinuria; PR, partial response; PS, performance score; QoL, quality of life; RoB, risk of bias; SAA, severe aplastic anaemia; SF-36, short-form 36 items; VSAA, very severe aplastic anaemia.
*The total score of the QLQ-AA/PNH-54 questionnaire can range between 54 (best QoL) and 216 (worst QoL).

FAQ5: What are the risks or side effects?

Evidence was sought for the following side effects: GVHD, lymphomas/malignant tumours, renal insufficiency, fever, anorexia, malaise, headache, weakness, fatigue and infections.

GVHD

Acute GVHD

A total of five studies provided comparative evidence on acute GVHD (Table 13). All five studies were cohorts. Comparisons included: MSD-HSCT vs MUD-HSCT (2 studies), MSD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs haplo-HSCT (3 studies), MUD-HSCT vs mismatched UD-HSCT (1 study) and haplo-HSCT vs mismatched UD-HSCT (1 study). Risk of bias ranged from 11/24 to 19/24.

An overview of the comparative evidence for acute GVHD is provided in Figure 27.

For MSD-HSCT vs MUD-HSCT, 2 studies (Rice 2019, Zhang 2020) reported a lower rate of acute GVHD for patients treated with MSD-HSCT compared to MUD-HSCT; one of these was a statistically significant difference.

For MSD-HSCT vs haplo-HSCT, 2 studies (Niu 2022, Zhang 2020) reported a lower rate of acute GVHD for patients treated with MSD-HSCT compared to haplo-HSCT; one of these was a statistically significant difference.

For MUD-HSCT vs haplo-HSCT, 2 studies (Park 2021, Zhang 2020) reported a higher rate of acute GVHD for patients treated with MUD-HSCT compared to haplo-HSCT, and 1 study (Kim 2016) reported no evidence of a difference.

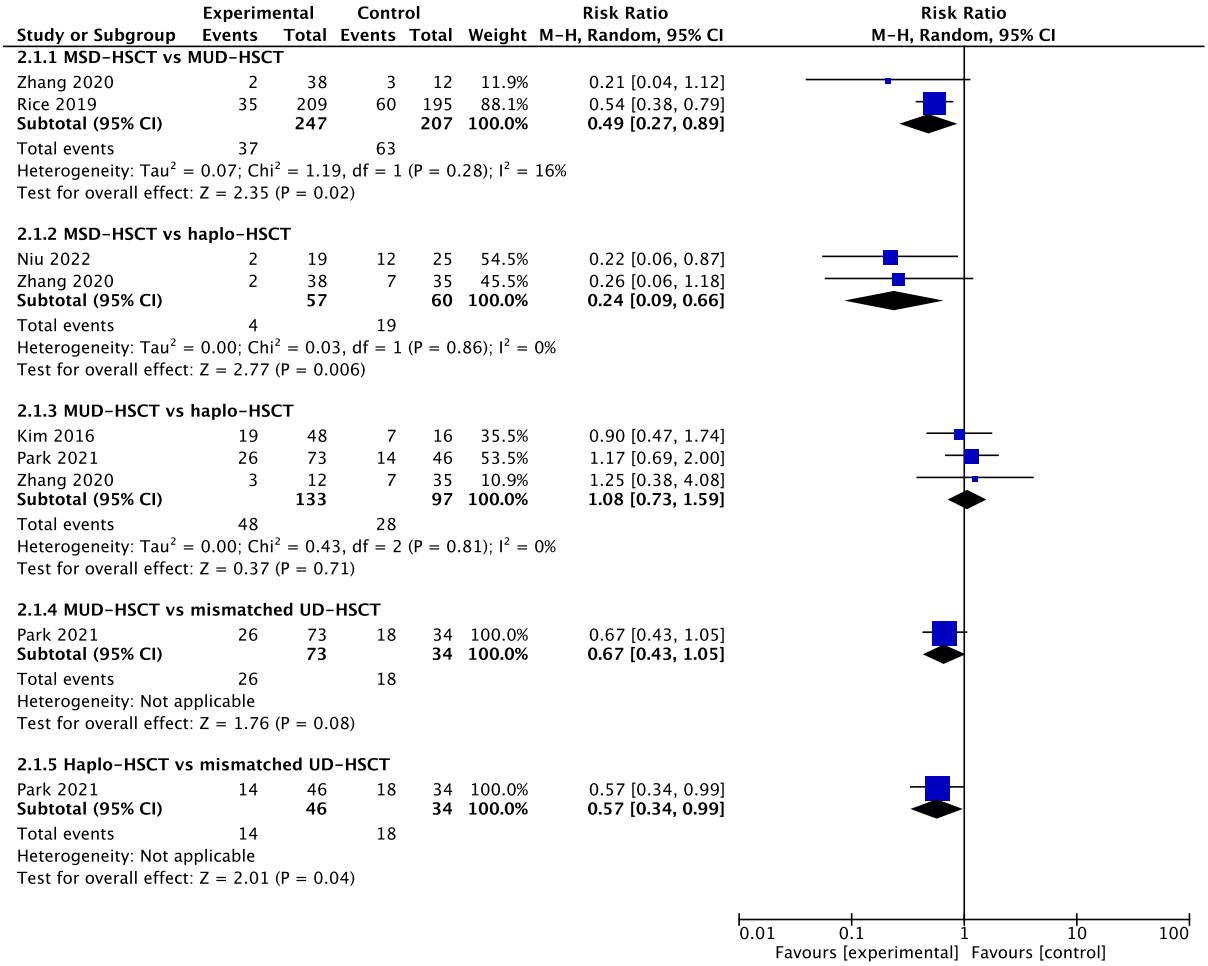
For MUD-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a lower rate of acute GVHD for patients treated with MUD-HSCT compared to mismatched UD-HSCT; however, this was not a statistically significant difference.

For haplo-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a lower rate of acute GVHD for patients treated with haplo-HSCT compared to mismatched UD-HSCT; however, this was not a statistically significant difference.

Single arm evidence was also provided from 8 studies: 2 allogeneic BMT, 1 MSD-HSCT and 5 haplo-HSCT.

Conclusion for the decision aid: acute GVHD occurs in between 5 to 23 out of 100 patients receiving MSD-HSCT, between 25 to 40 out of 100 patients receiving MUD-HSCT, between 13 to 56 out of 100 patients receiving haplo-HSCT, between 31 to 59 out of 100 patients receiving allogeneic BMT and approximately 53 out of 100 patients receiving mismatched UD-HSCT (13 studies, moderate to high risk of bias).

Figure 27: Comparative data for acute GVHD



Abbreviations: CI, confidence interval; GVHD, graft-versus-host disease; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Chronic GVHD

A total of five studies provided comparative evidence on chronic GVHD (Table 13). All five studies were cohorts. Comparisons included: MSD-HSCT vs MUD-HSCT (2 studies), MSD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs haplo-HSCT (3 studies), MUD-HSCT vs mismatched UD-HSCT (1 study) and haplo-HSCT vs mismatched UD-HSCT (1 study). Risk of bias ranged from 11/24 to 19/24.

An overview of the comparative evidence for chronic GVHD is provided in Figure 28.

For MSD-HSCT vs MUD-HSCT, 1 study (Zhang 2020) reported a significantly lower rate of chronic GVHD for patients treated with MSD-HSCT compared to MUD-HSCT, and 1 study (Rice 2019) reported no evidence of a difference.

For MSD-HSCT vs haplo-HSCT, 2 studies (Niu 2022, Zhang 2020) reported a lower rate of chronic GVHD for patients treated with MSD-HSCT compared to haplo-HSCT; both of these were statistically significant differences.

For MUD-HSCT vs haplo-HSCT, 2 studies (Kim 2016, Zhang 2020) reported a lower rate of chronic GVHD for patients treated with MUD-HSCT/partially matched-HSCT compared to haplo-HSCT (one of these was a statistically significant difference), and 1 study (Park 2021) reported a higher rate of chronic GVHD for patients treated with MUD-HSCT compared to haplo-HSCT (this was not a statistically significant difference).

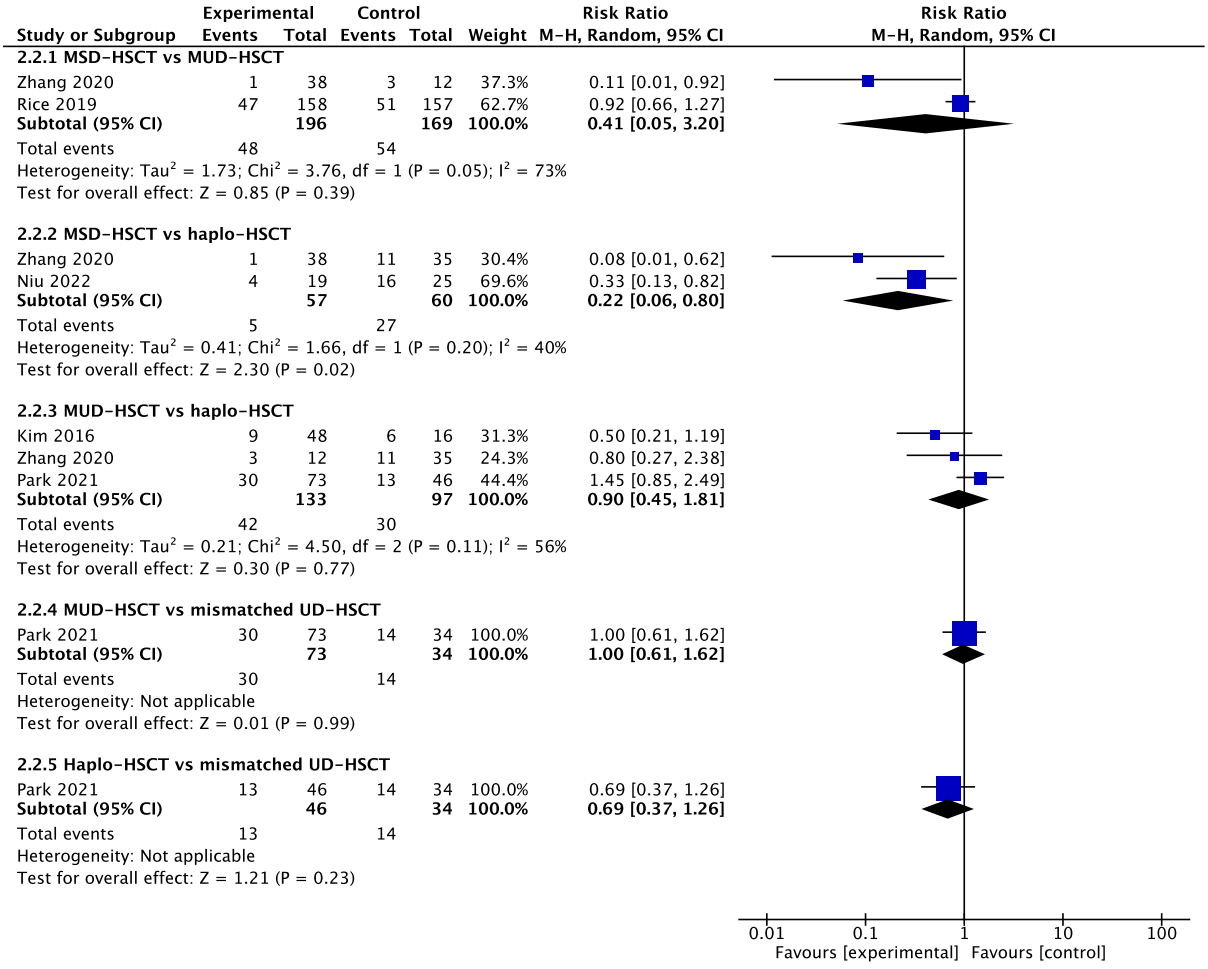
For MUD-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported no evidence of a difference in the rate of chronic GVHD for patients treated with MUD-HSCT compared to mismatched UD-HSCT.

For haplo-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a lower rate of chronic GVHD for patients treated with haplo-HSCT compared to mismatched UD-HSCT; however, this was not a statistically significant difference.

Single arm evidence was also provided from 8 studies: 2 allogeneic BMT, 1 MSD-HSCT and 5 haplo-HSCT.

Conclusion for the decision aid: chronic GVHD occurs in between 3 to 33 out of 100 patients receiving MSD-HSCT, between 19 to 41 out of 100 patients receiving MUD-HSCT, between 0 to 64 out of 100 patients receiving haplo-HSCT, between 19 to 39 out of 100 patients receiving allogeneic BMT and approximately 41 out of 100 patients receiving mismatched UD-HSCT (13 studies, moderate to high risk of bias).

Figure 28: Comparative data for chronic GVHD



Abbreviations: CI, confidence interval; GVHD, graft-versus-host disease; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Table 13: GVHD

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Acute GVHD – comparative evidence										
Rice 2019[29]	Matched sibling donor HSCT	Adults >50 years with severe AA	Acute GVHD	NR	35/209 (16.8%)	NR	HR 2.01 (95% CI 1.18 to 3.42), P=0.011	Comparative cohort	**Statistically favours matched sibling donor HSCT**	17/24
	Matched unrelated donor HSCT				60/195 (30.8%)					
Kim 2016[32]	Haploidentical HSCT	Adults (>18 years) with SAA	Acute GVHD (any)	NR	7/16 (43.8%)	NR	P=0.769	Comparative cohort	Numerically favours alternative donor HSCT	11/24
	Alternative donor HSCT (matched unrelated or partially matched)				19/48 (39.6%)					
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA	Acute GVHD (grades II to IV)	NR	2/19 (10.5%)	NR	P=0.034	Comparative cohort	**Statistically favours matched sibling donor HSCT**	18/24
	Haploidentical HSCT				12/25 (48.0%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA		100 days	5.3% ± 0.1%	NR	P=0.068	Comparative cohort	Numerically favours matched sibling donor HSCT	19/24
	Matched unrelated donor HSCT				25.0% ± 1.7%					
	Haploidentical HSCT				21.4% ± 0.5%					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA		180 days	30.4% (95% CI 17.8 to 44.0%), P=0.076	NR	NA	Comparative cohort	Numerically favours haploidentical HSCT	19/24
	Matched unrelated donor HSCT				35.6% (95% CI 24.8 to 46.6%)		HR 0.65 (95% CI 0.28 to 1.493), P=0.31			
	Mismatched unrelated donor HSCT				52.9% (95% CI 34.7 to 68.3%)		HR 1.4 (95% CI 0.61 to 3.213), P=0.43			
Acute GVHD – single arm evidence										
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Acute GVHD	NR	20/64 (31.3%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA who engrafted	Acute GVHD (any grade)	NR	19/32 (59%)	NR	NR	Single arm cohort	NA	4/16
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	5/22 (23%)	NR	NR	Single arm cohort	NA	4/16
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Acute GVHD	12.2 (range 3.2 to 40.4) months	1/8 (12.5%)	NR	NR	Single arm cohort	NA	5/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Acute GVHD (any grade)	43.2 (24.3 to 65.9) months	3/25 (12%)	NR	NR	Single arm cohort	NA	12/16
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Acute GVHD (any grade)	30 (12 to 71) months	5/26 (19.2%)	NR	NR	Single arm cohort	NA	8/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Acute GVHD (any grade)	21.1 (range 3.2 to 71.1) months	10/49 (20.4%)	NR	NR	Single arm cohort	NA	12/16
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Acute GVHD (any grade)	Median 24.7 (range 6.1 to 103.0) months	42/75 (56.0%)	NR	NR	Single arm cohort	NA	12/16
Chronic GVHD – comparative evidence										
Rice 2019[29]	Matched sibling donor HSCT	Adults >50 years with severe AA	Chronic GVHD	NR	47/158 (29.8%)	NR	HR 1.11 (95% CI 0.65 to 1.88), P=0.71	Comparative cohort	Numerically favours matched sibling donor HSCT	17/24
	Matched unrelated donor HSCT				51/157 (32.5%)					
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with	Chronic GVHD (any)	NR	4/19 (21.1%)	NR	P=0.026	Comparative cohort	**Statistically favours matched**	18/24

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	Haploidentical HSCT	SAA or VSAA			16/25 (64.0%)				**sibling donor HSCT**	
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA		3 years	2.9% ± 0.1%	NR	P=0.030	Comparative cohort	**Statistically favours matched sibling donor HSCT**	19/24
	Matched unrelated donor HSCT				27.3% ± 2.0%					
	Haploidentical HSCT				30.2% ± 1.1%					
Kim 2016[32]	Haploidentical HSCT	Adults (>18 years) with SAA		NR	6/16 (37.5%)	NR	P=0.173	Comparative cohort	Numerically favours alternative donor HSCT	11/24
	Alternative donor HSCT (matched unrelated or partially matched)				9/48 (18.8%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	Chronic GVHD (mild to severe)	180 days	28.5% (95% CI 16.2 to 42.2%), P=0.425	NR	Reference	Comparative cohort	Numerically favours haploidentical HSCT	19/24
	Matched unrelated donor HSCT				41.1% (95% CI 29.7 to 52.2%)		HR 1.097 (95% CI 0.319 to 3.772)			
	Mismatched unrelated donor HSCT				41.2% (95% CI 24.4 to 57.2%)		HR 1.441 (95% CI 0.376 to 5.528)			
Chronic GVHD – single arm evidence										

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Chronic GVHD	NR	12/64 (18.8%)	NR	NR	Single arm cohort	NA	4/16
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA who engrafted	Chronic GVHD	NR	15/39 (38.5%)	NR	NR	Single arm cohort	NA	4/16
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA	Chronic GVHD (any extent)	NR	7/21 (33%)	NR	NR	Single arm cohort	NA	4/16
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Chronic GVHD	12.2 (range 3.2 to 40.4) months	0/8 (0%)	NR	NR	Single arm cohort	NA	5/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Chronic GVHD (any extent)	43.2 (24.3 to 65.9) months	10/25 (40%)	NR	NR	Single arm cohort	NA	12/16
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Chronic GVHD (any extent)	30 (12 to 71) months	4/26 (15.4%)	NR	NR	Single arm cohort	NA	8/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	Chronic GVHD (any grade)	21.1 (range 3.2 to	8/45 (17.8%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
				71.1) months						
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Chronic GVHD (any extent)	Median 24.7 (range 6.1 to 103.0) months	14/73 (19.2%)	NR	NR	Single arm cohort	NA	12/16

Abbreviations: ATG, anti-thymocyte globulin; BMT, bone marrow transplant; CI, confidence interval; CsA, cyclosporin A; GVHD, graft-versus-host disease; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Lymphomas/malignant tumours

A wide range of lymphoma/malignant tumour outcomes were reported. The three most commonly reported malignancy-related outcomes were: leukaemia/acute myeloid leukaemia (AML)/non-Hodgkin lymphoma (NHL), myelodysplastic syndrome (MDS) and post-transplant lymphoproliferative disorder (PTLD).

Leukaemia/AML/NHL

A total of five studies provided comparative evidence on leukaemia/AML/NHL (Table 14). All five studies were cohorts. Comparisons included: MSD-HSCT vs IST (1 study), haplo-HSCT vs IST (1 study), allogeneic BMT vs IST (2 studies) and eltrombopag plus IST vs IST (1 study). Risk of bias ranged from 9/24 to 19/24.

An overview of the comparative evidence for leukaemia/AML/NHL is provided in Figure 29.

For MSD-HSCT vs IST, 1 study (Kim 2003) reported no evidence of a difference in the rate of AML for patients treated with MSD-HSCT compared to IST.

For haplo-HSCT vs IST, 1 study (Miao Chen 2020) reported a lower rate of AML for patients treated with haplo-HSCT compared to IST (0% vs 6.9%, respectively); however, this was not a statistically significant difference.

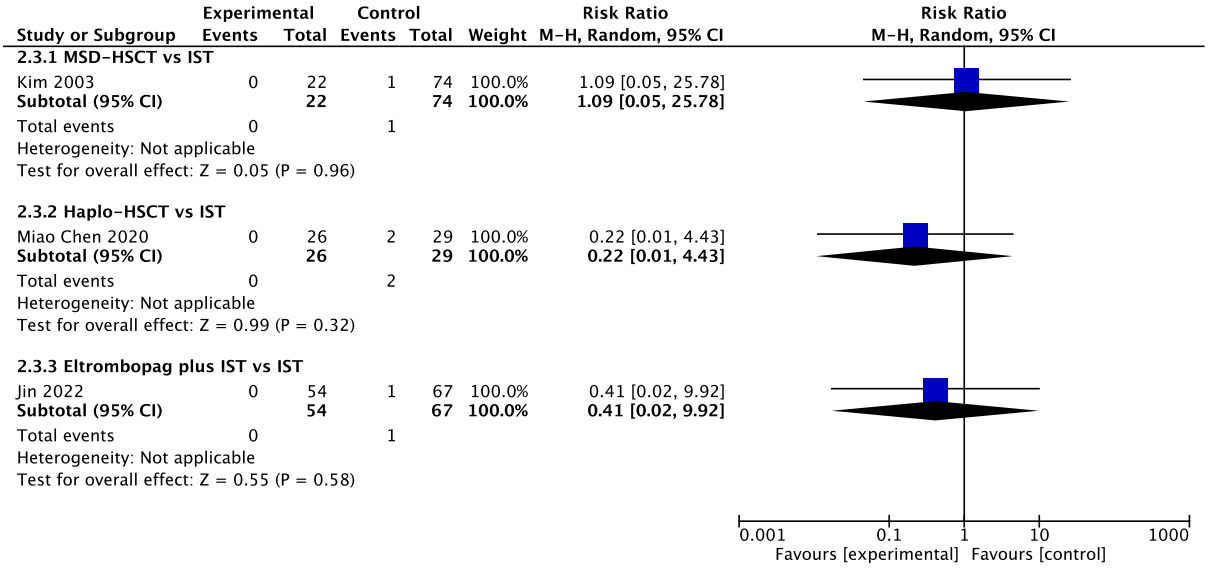
For allogeneic BMT vs IST, 2 studies (with 3 datasets; Ahn 2003, Paquette 1995) reported a lower rate of leukaemia, NHL or AML for patients treated with allogeneic BMT compared to IST; however, these were not statistically significant differences.

For eltrombopag plus IST vs IST, 1 study (Jin 2022) reported a lower rate of AML for patients treated with eltrombopag plus IST compared to IST; however, this was not a statistically significant difference.

Single arm evidence was also provided from 2 studies: 1 IST and 1 eltrombopag.

Conclusion for the decision aid: leukaemia/AML/NHL occurs in approximately zero out of 100 patients receiving MSD-HSCT, haplo-HSCT, allogeneic BMT or eltrombopag plus IST, between 0 to 7 out of 100 patients receiving IST and approximately 4 out of 100 patients receiving eltrombopag (7 studies, moderate to high risk of bias).

Figure 29: Comparative data for leukaemia/AML/NHL



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant. Note that 2 comparative studies (with 3 datasets; allogeneic BMT vs IST) are not included in the forest plot.

Myelodysplastic syndrome

A total of five studies provided comparative evidence on MDS (Table 14). Four studies were cohorts and one was a RCT. Comparisons included: MSD-HSCT vs IST (1 study), allogeneic BMT vs IST (2 studies) and eltrombopag plus IST vs IST (2 studies). Risk of bias ranged from 9/24 to 19/24 in the cohort studies, and was rated high in the RCT.

An overview of the comparative evidence for MDS is provided in Figure 30.

For MSD-HSCT vs IST, 1 study (Kim 2003) reported no evidence of a difference in the rate of MDS for patients treated with MSD-HSCT compared to IST.

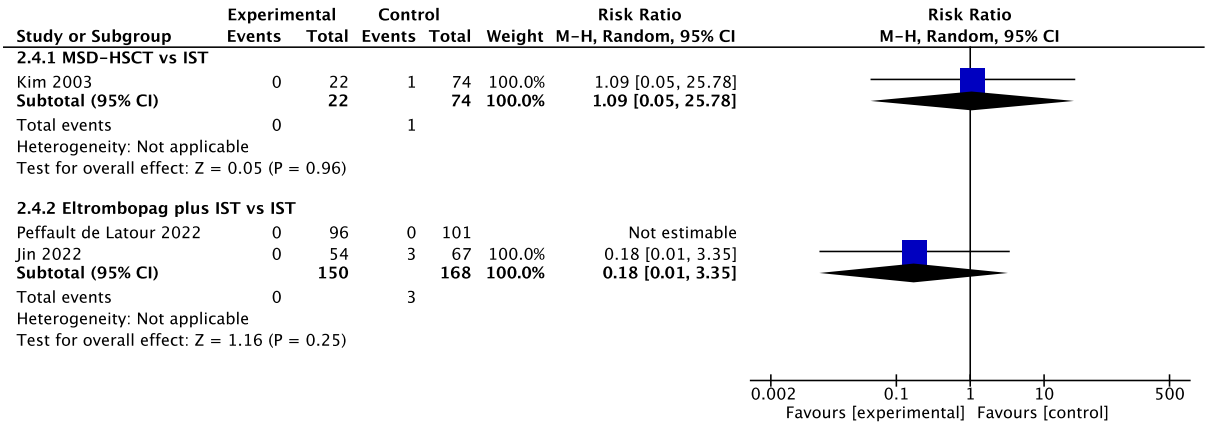
For allogeneic BMT vs IST, 2 studies (Ahn 2003, Paquette 1995) reported a lower rate of MDS for patients treated with allogeneic BMT compared to IST; however, these were not statistically significant differences.

For eltrombopag plus IST vs IST, 1 study (Jin 2022) reported a lower rate of MDS for patients treated with eltrombopag plus IST compared to IST, and 1 study (Peffault de Latour 2022) reported no evidence of a difference in MDS rates for patients treated with eltrombopag plus IST compared to IST.

Single arm evidence was also provided from 1 study (IST).

Conclusion for the decision aid: MDS occurs in approximately zero out of 100 patients receiving MSD-HSCT, allogeneic BMT or eltrombopag plus IST and between 0 to 5 out of 100 patients receiving IST (6 studies, moderate to high risk of bias).

Figure 30: Comparative data for MDS



Abbreviations: CI, confidence interval; IST, immunosuppressive therapy; M-H, Mantel-Haenzel; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant. Note that 2 comparative studies (allogeneic BMT vs IST) are not included in the forest plot.

PTLD

A total of three studies provided comparative evidence on PTLD (Table 14). All three studies were cohorts. Comparisons included: MSD-HSCT vs haplo-HSCT (2 studies), MSD-HSCT vs MUD-HSCT (1 study), MSD-HSCT vs haplo-HSCT (1 study), MUD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs mismatched UD-HSCT (1 study) and haplo-HSCT vs mismatched UD-HSCT (1 study). Risk of bias ranged from 18/24 to 19/24.

An overview of the comparative evidence for PTLD is provided in Figure 31.

For MSD-HSCT vs haplo-HSCT, 1 study (Niu 2022) reported a higher rate of PTLD for patients treated with MSD-HSCT compared to haplo-HSCT (5.26% vs 4.00%, respectively) and 1 study (Zhang 2020) reported a lower rate of PTLD for patients treated with MSD-HSCT compared to haplo-HSCT (0% vs 2.9%, respectively); these were not statistically significant differences.

For MSD-HSCT vs MUD-HSCT, 1 study (Zhang 2020) reported no evidence of a difference in PTLD rates for patients treated with MSD-HSCT compared to MUD-HSCT (zero events in both arms).

For MUD-HSCT vs haplo-HSCT, 1 study (Park 2021) reported a lower rate of PTLD for patients treated with MUD-HSCT compared to haplo-HSCT (although this was not a statistically significant difference), and 1 study (Zhang 2020) reported no evidence of a difference.

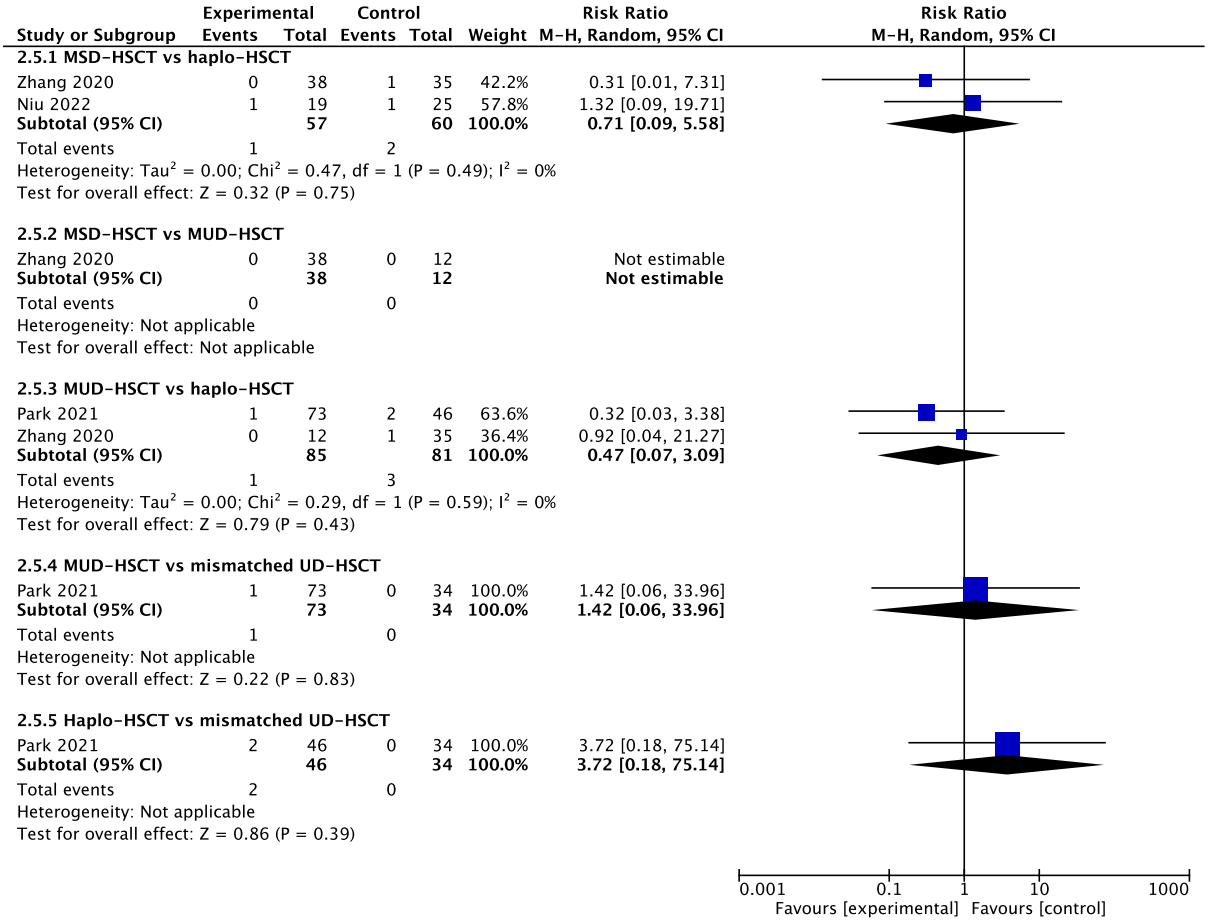
For MUD-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a higher rate of PTLD for patients treated with MUD-HSCT compared to mismatched UD-HSCT (1.4% vs 0%, respectively); however, this was not a statistically significant difference.

For haplo-HSCT vs mismatched UD-HSCT, 1 study (Park 2021) reported a higher rate of PTLD for patients treated with MUD-HSCT compared to mismatched UD-HSCT (4.3% vs 0%, respectively); however, this was not a statistically significant difference.

No single arm evidence was identified.

Conclusion for the decision aid: PTLD occurs in between 0 to 5 out of 100 patients receiving MSD-HSCT, between 3 to 4 out of 100 patients receiving haplo-HSCT, between 0 to 1 out of 100 patients receiving MUD-HSCT and approximately zero out of 100 patients receiving mismatched UD-HSCT (3 studies, moderate risk of bias).

Figure 31: Comparative data for PTLD



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; M-H, Mantel-Haenzel; mismatched UD HSCT, mismatched unrelated donor haematopoietic stem cell transplant; MSD-HSCT, matched sibling donor haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor haematopoietic stem cell transplant.

Table 14: Lymphomas/malignant tumours

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Leukaemia	NR	0/64 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				1/156 (0.6%)					
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA	NHL	NR	0/55 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				1/155 (0.7%)					
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA	AML	NR	0/55 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				2/155 (1.3%)					
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	0/22 (0%)	NR	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or without CsA)				1/74 (1.4%)					
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA		30 (12 to 71) months	0/26 (0%)	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				2/29 (6.9%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		14 (1 to 79) months	0/54 (0%)	NR	NR	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			16 (1 to 79) months	1/67 (1.5%)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Myelodysplastic syndrome	NR	0/64 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				1/156 (0.6%)					
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA		NR	0/55 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				4/155 (2.6%)					
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		NR	0/22 (0%)	NR	NR	Comparative cohort	Numerically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG with or without CsA)				1/74 (1.4%)					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		14 (1 to 79) months	0/54 (0%)	NR	NR	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			16 (1 to 79) months	3/67 (5%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA		24 (95% CI 23 to 24) months	0/96 (0%)	NR	NR	RCT	NED	High
	IST alone				0/101 (0%)					
Niu 2022[28]	Matched sibling donor HSCT	Adults (≥15 years) with SAA or VSAA	PTLD	24.7 (range 6.8 to 30.4) months	1/19 (5.26%)	NR	P=0.226	Comparative cohort	Numerically favours haploidentical HSCT	18/24
	Haploidentical HSCT				1/25 (4.00%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA		17.6 months	0/38 (0%)	NR	NR	Comparative cohort	Numerically favours matched sibling donor HSCT or matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				0/12 (0%)					
	Haploidentical HSCT				1/35 (2.9%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA		3 years	4.3% (95% CI 0.8 to 13.2%)	NR	P=0.336	Comparative cohort	Numerically favours mismatched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				1.4% (95% CI 0.1 to 6.6%)					
	Mismatched unrelated donor HSCT				0%					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA	Solid tumours	NR	0/64 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				0/156 (0%)					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA		NR	0/55 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				2/155 (1.3%)					
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA	HCC	NR	0/55 (0%)	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				1/155 (0.7%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	Secondary malignancy	3 years	2.2% (95% CI 0.2 to 10.1%)	NR	P=0.105	Comparative cohort	Numerically favours mismatched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				5.5% (95% CI 1.8 to 12.5%)					
	Mismatched unrelated donor HSCT				0%					
Single arm evidence										
Paquette 1995[26]	IST (ATG with or without CsA)	Adults with MAA, SAA or VSAA	Squamous cell carcinoma of the lung	NR	1/155 (0.7%)	NR	NR	Single arm cohort	NA	4/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	AML	23.2 (range 6 to 173) months	0/67 (0%)	NR	NR	Single arm cohort	NA	8/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change / effect estimate	Study type	Favours?	RoB rating
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	Myeloid leukaemia	NR	1/25 (4%)	NR	NR	Non-randomised interventional	NA	14/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	MDS	23.2 (range 6 to 173) months	0/67 (0%)	NR	NR	Single arm cohort	NA	8/16
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Lung cancer	9 to 13 months	1/46 (2.2%)	NR	NR	Single arm cohort	NA	11/16

Abbreviations: ALG, anti-lymphocyte globulin; AML, acute myelogenous leukaemia; ATG, anti-thymocyte globulin; BMT, bone marrow transplant; CI, confidence interval; CsA, cyclosporin A; HCC, hepatocellular carcinoma; IST, immunosuppressive therapy; MAA, moderate aplastic anaemia; MDS, hypoplastic myelodysplastic syndrome; NA, not applicable; NED, no evidence of a difference; NHL, Non-Hodgkin's Lymphoma; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Renal insufficiency

A total of two studies provided comparative evidence on renal insufficiency (Table 15). One study was a RCT, and one was a non-randomised interventional study. Both studies compared eltrombopag plus IST vs IST. Risk of bias was rated as 18/24 in the non-randomised study and high in the RCT.

Both studies (Assi 2018, Peffault de Latour 2022) reported a lower rate of renal failure (any grade) or a lower number of renal and urinary disorder events (any grade) for patients treated with eltrombopag plus IST compared with IST alone; however, these were not statistically significant differences.

Both studies also reported the same outcomes specifically focussed on grade ≥3 events. One study (Assi 2018) reported no evidence of a difference in grade ≥3 renal failure (zero events in both arms), and one study (Peffault de Latour 2022) reported a numerically lower number of grade ≥3 renal and urinary disorder events for patients treated with eltrombopag plus IST compared with IST alone.

Single arm evidence was also provided from 4 studies: 1 IST and 3 haplo-HSCT.

Conclusion for the decision aid: renal insufficiency occurs in between 0 to 39 out of 100 patients receiving haplo-HSCT, between zero and potentially up to 64 out of 100 patients receiving eltrombopag plus IST and between 12 and potentially up to 68 out of 100 patients receiving IST (6 studies, moderate to high risk of bias).

Table 15: Renal insufficiency

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Assi 2018[33]	Eltrombopag plus IST IST alone	Adults with newly diagnosed SAA	Renal failure (any grade)	21 months	0/21 (0%) 2/17 (12%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
Peffault de Latour 2022[35]	Eltrombopag plus IST IST alone	Adults (≥15 years) with SAA or VSAA	Renal and urinary disorders (# events)	6 months	NR	64 68	NR	RCT	NC	High
Assi 2018[33]	Eltrombopag plus IST IST alone	Adults with newly diagnosed SAA	Grade ≥3 renal failure	21 months	0/21 (0%) 0/17 (0%)	NR	NR	Non-randomised interventional	NED	18/24
Peffault de Latour 2022[35]	Eltrombopag plus IST IST alone	Adults (≥15 years) with SAA or VSAA	Grade ≥3 renal and urinary disorders (# events)	6 months	NR	6 10	NR	RCT	NC	High
Single arm evidence										
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Haemorrhagic cystitis	12.2 (range 3.2 to 40.4) months	0/8 (0%)	NR	NR	Single arm cohort	NA	5/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to	20/51 (39.2%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
				71.1) months						
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Renal toxicity	43.2 (24.3 to 65.9) months	0/26 (0%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Frequent micturition and urgent urination	43.2 (24.3 to 65.9) months	2/26 (7.7%)	NR	NR	Single arm cohort	NA	12/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	Indicators of acute renal failure	23.2 (range 6 to 173) months	13/67 (19.4%)	NR	NR	Single arm cohort	NA	8/16

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; BMT, bone marrow transplant; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NC, not calculable; NED, no evidence of a difference; NR, not reported; RCT, randomised controlled trial; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Fever

A total of two studies provided comparative evidence on fever/pyrexia (Table 16). One study was a non-randomised interventional study and one was a cohort. Both studies compared eltrombopag plus IST vs IST. Risk of bias ranged from 18/24 to 19/24.

One study (Assi 2018) reported on fever of any grade and reported a lower rate for patients treated with eltrombopag plus IST compared with IST alone; however, this was not a statistically significant difference.

Both studies reported on grade ≥3 fever. One study (Assi 2018) reported no evidence of a difference in grade ≥3 fever (zero events in both arms), and one study (Peffault de Latour 2022) reported a numerically lower number of patients experiencing grade ≥3 fever following treatment with eltrombopag plus IST compared with IST alone (although this was not a statistically signficiant difference).

Single arm evidence was also provided from 3 studies: 1 haplo-HSCT, 1 IST and 1 eltrombopag.

Conclusion for the decision aid: fever (any grade or grade ≥2 or grade ≥3) occurs in approximately 39 out of 100 patients receiving haplo-HSCT, between 0 to 15 out of 100 patients receiving eltrombopag plus IST, between 0 to 39 out of 100 patients receiving IST, and approximately 24 out of 100 patients receiving eltrombopag (5 studies, moderate to high risk of bias).

Table 16: Fever

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Fever (any grade)	21 months	1/21 (5%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				3/17 (18%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Grade ≥3 fever	21 months	0/21 (0%)	NR	NR	Non-randomised interventional	NED	18/24
	IST alone				0/17 (0%)					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA		14 (1 to 79) months	8/54 (14.8%)	NR	NR	Comparative cohort	Numerically favours eltrombopag plus IST	19/24
	IST alone			16 (1 to 79) months	11/67 (16.4%)					
Single arm evidence										
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Fever	43.2 (24.3 to 65.9) months	10/26 (38.5%)	NR	NR	Single arm cohort	NA	12/16
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	Pyrexia (≥38dC)	23.2 (range 6 to 173) months	27/69 (39.1%)	NR	NR	Single arm cohort	NA	8/16
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	Fever of grade 2 or higher	NR	6/26 (24%)	NR	NR	Non-randomised interventional	NA	14/16

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; CsA, cyclosporin A; dC, degrees celsius; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NED, no evidence of a difference; NR, not reported; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Anorexia

No evidence was found for anorexia.

Malaise

No evidence was found for malaise.

Headache

One non-randomised interventional study provided comparative evidence on headache (Table 17) and compared eltrombopag plus IST vs IST. The risk of bias was rated at 18/24.

Assi 2018 reported fewer headaches of any grade for patients receiving eltrombopag plus IST compared to IST alone (5% vs 12%, respectively); however, this was not a statistically significant difference.

The same study reported more grade ≥3 headaches for patients receiving eltrombopag plus IST compared to IST alone (5% vs 0%, respectively); however, this was not a statistically significant difference.

No single arm evidence was identified.

Conclusion for the decision aid: headaches are seen in between 0 to 12 out of 100 patients receiving IST and approximately 5 out of 100 patients receiving eltrombopag plus IST (1 study, moderate risk of bias).

Weakness

No comparative evidence was identified for weakness.

One single arm study (Desmond 2014) reported that 1 out of 26 patients (4%) experienced grade ≥2 weakness following treatment with eltrombopag.

Conclusion for the decision aid: weakness was seen in approximately 4 out of 100 patients receiving eltrombopag (1 study, low risk of bias).

Table 17: Headache

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Headache (any grade)	21 months	1/21 (5%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				2/17 (12%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Grade ≥3 headache	21 months	1/21 (5%)	NR	NR	Non-randomised interventional	Numerically favours IST alone	18/24
	IST alone				0/17 (0%)					
Single arm evidence										
No evidence identified										

Abbreviations: ATG, anti-thymocyte globulin; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; RoB, risk of bias.; SAA, severe aplastic anaemia.

Table 18: Weakness

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
No evidence identified										
Single arm evidence										
Desmond 2014[12] and Olnes 2012[13]	Eltrombopag	Adults with refractory SAA or VSAA	Weakness of grade 2 or higher	NR	1/26 (4%)	NR	NR	Non-randomised interventional	NA	14/16

Abbreviations: ATG, anti-thymocyte globulin; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Fatigue

A total of two studies provided comparative evidence on fatigue (Table 19). One study was a non-randomised interventional study and one was a RCT. Both studies compared eltrombopag plus IST vs IST. Risk of bias was 18/24 in the non-randomised study and was rated high in the RCT.

One study (Assi 2018) reported a lower rate of fatigue (any grade or grade ≥3) for patients treated with eltrombopag plus IST compared with IST alone; however, this was not a statistically significant difference.

One study (Peffault de Latour 2022) reported no evidence of a difference in fatigue measured using the EORTC-QLQ-C30 tool in patients treated with eltrombopag plus IST compared with IST alone. Both treatment arms reported the same level of improvement in fatigue from baseline.

Single arm evidence was also provided from 1 study (IST).

Conclusion for the decision aid: fatigue (any grade or grade ≥3) occurs in between 12 to 83 out of 100 patients receiving IST and between 0 to 14 out of 100 patients receiving eltrombopag plus IST (2 studies, moderate to high risk of bias).

Table 19: Fatigue

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Fatigue (any grade)	21 months	3/21 (14%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				4/17 (24%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Grade ≥3 fatigue	21 months	0/21 (0%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				2/17 (12%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	EORTC-QLQ-C30 – fatigue scale	Baseline	NR	Median 44.44 (Q1, Q3: 22.22 to 66.67)	NR	RCT	NED	High
	IST alone					Median 44.44 (Q1, Q3: 22.22 to 55.56)				
	Eltrombopag plus IST			24 months	NR	Median 22.22 (Q1, Q3: 11.11 to 33.33)				
	IST alone					Median 22.22 (Q1, Q3: 11.11 to 33.89)				
Single arm evidence										

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Lommerse 2024[41]	IST (CsA or ATG)	Adults with AA who had been successfully treated with IST (CR or PR)	QLQ-AA/PNH-54 - Fatigue	NR	30/36 (83%)	NR	NR	Single arm cohort	NA	13/16

Abbreviations: ATG, anti-thymocyte globulin; CsA, cyclosporin A; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – 30 items; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; QLQ-AA/PNH-54, quality of life questionnaire for aplastic anaemia/paroxysmal noctural haemoglobinuria – 54-items; RoB, risk of bias; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

Infections

A total of six studies provided comparative evidence on infections across all treatments of interest (Table 20). Four studies were cohorts, one was a non-randomised interventional study and one study was a RCT. Comparisons included: eltrombopag plus IST vs IST (3 studies), haplo-HSCT vs IST (1 study), MSD-HSCT vs MUD-HSCT (1 study), MSD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs haplo-HSCT (2 studies), MUD-HSCT vs mismatched UD-HSCT (1 study) and haplo-HSCT vs mismatched UD-HSCT (1 study). Risk of bias ranged from 15/24 to 19/24 in the non-randomised studies and was rated high in the RCT.

Evidence was captured for several infection outcomes, including: adenovirus viraemia, CMV infection/reactivation/DNAemia/viraemia requiring hospitalisation/PTLD/pneumonia, EBV infection/viraemia/PTLD, any infections/infestations, grade ≥3 infections/infestations, viraemia, bacterial infections/bacteriaemia, fungal infections/invasive fungal disease, mixed infection (bacterial and CMV), grade ≥3 UTI requiring hospitalisation, grade ≥2 upper respiratory tract infection, grade ≥2 shingles, grade ≥2 *Clostridium difficile* colitis or grade ≥2 viral hepatitis.

Most evidence was identified for CMV infections (4 comparative studies), any infections/infestations or grade ≥3 infections/infestations (4 comparative studies) and fungal infections/invasive fungal disease (2 comparative studies).

For **CMV infections**, four comparative studies reported on CMV infection/reactivation/ DNAemia/viraemia requiring hospitalisation. The risk of bias ranged from 15/24 to 19/24:

- Rates of CMV infection were reported to be higher for patients receiving haplo-HSCT compared to IST (19.2% vs 3.5%); however, this was not a statistically significant difference
- Rates of CMV viraemia/reactivation were reported to be lower for patients receiving MSD-HSCT compared to MUD-HSCT or haplo-HSCT (55.3% vs 66.7% vs 80.0%, respectively)
- Rates of CMV DNAemia were reported to be lower for patients receiving MUD-HSCT compared to haplo-HSCT or mismatched UD-HSCT (41.1% vs 45.7% vs 52.9%, respectively)
- Rates of CMV viraemia requiring hospitalisation were reported to be lower for patients receiving eltrombopag plus IST vs IST alone (0% vs 5.9%, respectively)
- 3 single arm studies provided additional evidence for haplo-HSCT

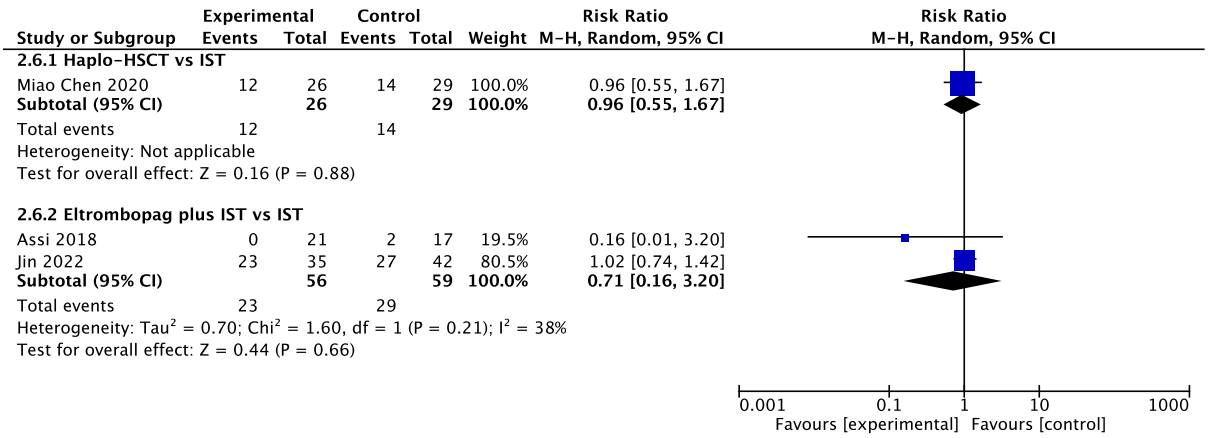
For **general infections**, four comparative studies reported on any infections/infestations or grade ≥3 infections/infestations. The risk of bias ranged from 15/24 to 19/24 or high:

- An overview of the comparative evidence for any infection is provided in Figure 32
- One study (Miao Chen 2020) reported similar rates of any infections for haplo-HSCT vs IST
- One study (Assi 2018) reported that rates of any grade or grade ≥3 other infections were lower for eltrombopag plus IST compared with IST (0% vs 12%, respectively), and one study (Jin 2022) reported similar rates of infections for eltrombopag plus IST compared with IST (65% vs 65%)
- One study reported that the absolute number of adverse events that were infections or infestations was lower for eltrombopag plus IST compared to IST (177 vs 215,

respectively); a similar trend was reported for grade ≥3 infections and infestations (63 vs 76, respectively)

- 2 single arm studies provided additional evidence for haplo-HSCT or eltrombopag

Figure 32: Comparative data for any infection



Abbreviations: CI, confidence interval; Haplo-HSCT, haploidentical haematopoietic stem cell transplant; M-H, Mantel-Haenzel; IST, immunosuppressive therapy.

For **fungal infections**, two comparative studies reported on fungal infections or invasive fungal disease. The risk of bias ranged from 15/24 to 19/24:

- One study (Miao Chen 2020) reported a lower rate of fungal infections for haplo-HSCT compared to IST (3.9% vs 6.9%, respectively)
- One study (Park 2021) reported a lower rate of invasive fungal disease for mismatched UD-HSCT compared to MUD-HSCT or haplo-HSCT (8.8% vs 9.6% vs 10.9%)
- 1 single arm study provided additional evidence for haplo-HSCT

Conclusion for the decision aid: CMV infection or reactivation or viraema/DNAemia occurs in approximately 55 out of 100 patients receiving MSD-HSCT, between 41 to 67 out of 100 patients receiving MUD-HSCT, between 0 to 84 out of 100 patients receiving haplo-HSCT, approximately 53 out of 100 patients receiving mismatched UD-HSCT, approximately zero out of 100 patients receiving eltrombopag plus IST and between 4 to 6 out of 100 patients receiving IST (4 studies, moderate to high risk of bias).

Any infections occur in between 8 to 46 out of 100 patients receiving haplo-HSCT, between 12 to 65 out of 100 patients receiving IST, between 0 to 65 out of 100 patients receiving eltrombopag plus IST and approximately 28 out of 100 patients receiving eltrombopag (6 studies, moderate to high risk of bias).

Fungal infections occur in approximately 10 out of 100 patients receiving MUD-HSCT, approximately 4 out of 100 patients receiving haplo-HSCT, approximately 9 out of 100 patients receiving mismatched UD-HSCT and approximately 7 out of 100 patients receiving IST (3 studies, moderate to high risk of bias).

Table 20: Infections

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Grade ≥3 UTI requiring hospitalisation	21 months	0/21 (0%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				1/17 (5.9%)					
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	CMV infections	30 (12 to 71) months	5/26 (19.2%)	NR	NR	Comparative cohort	Numerically favours IST	15/24
	IST (rATG/pALG plus CsA				1/29 (3.5%)					
Zhang 2020[30]	Matched sibling donor HSCT	Adults (≥40 years) with SAA or VSAA	CMV viraemia/ reactivation	17.6 months	21/38 (55.3% ± 0.7%)	NR	P=0.046	Comparative cohort	**Statistically favours matched sibling donor HSCT**	19/24
	Matched unrelated donor HSCT				8/12 (66.7% ± 2.2%)		P=0.506			
	Haploidentical HSCT				28/35 (80.0% ± 5.8%)		Reference			
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	CMV DNAemia	3 years	45.7% (95% CI 30.7 to 59.4%)	NR	P=0.337	Comparative cohort	Numerically favours matched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				41.1% (95% CI 29.7 to 52.1%)					
	Mismatched unrelated donor HSCT				52.9% (95% CI 34.7 to 68.2%)					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly		21 months	0/21 (0%)	NR	NR	Non-randomis	Numerically favours	18/24

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	IST alone	diagnosed SAA	CMV viraemia requiring hospitalisation		1/17 (5.9%)			ed interventional	eltrombopag plus IST	
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Infections	30 (12 to 71) months	46.2%	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				48.3%					
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Infections, other (any grade)	21 months	0/21 (0%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				2/17 (12%)					
Jin 2022[34]	Eltrombopag plus IST	Adults with newly diagnosed SAA or VSAA	Infections	14 (1 to 79) months	23/35 (65%)	NR	NR	Comparative cohort	NED	19/24
	IST alone			16 (1 to 79) months	27/42 (65%)					
Peffault de Latour 2022[35]	Eltrombopag plus IST	Adults (≥15 years) with SAA or VSAA	Infections and infestations (# Aes)	6 months	NR	177	NR	RCT	ND	High
	IST alone					215				
Assi 2018[33]	Eltrombopag plus IST	Adults with newly diagnosed SAA	Grade ≥3 infections, other	21 months	0/21 (0%)	NR	NR	Non-randomised interventional	Numerically favours eltrombopag plus IST	18/24
	IST alone				2/17 (12%)					
Peffault de	Eltrombopag plus IST	Adults (≥15 years) with		6 months	NR	63	NR	RCT	Numerically favours	High

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Latour 2022[35]	IST alone	SAA or VSAA	Grade ≥3 infections and infestations (# Aes)			76			eltrombopag plus IST	
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Bacterial infections	30 (12 to 71) months	6/26 (23.1%)	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				11/29 (37.9%)					
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	Fungal infections	30 (12 to 71) months	1/26 (3.9%)	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				2/29 (6.9%)					
Park 2021[31]	Haploidentical HSCT	Adults with SAA or VSAA	Invasive fungal disease	3 years	10.9% (95% CI 3.9 to 21.8%)	NR	P=0.94	Comparative cohort	Numerically favours mismatched unrelated donor HSCT	19/24
	Matched unrelated donor HSCT				9.6% (95% CI 4.2 to 17.7%)					
	Mismatched unrelated donor HSCT				8.8% (95% CI 2.2 to 21.4%)					
Single arm evidence										
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Adenovirus viremia	12.2 (range 3.2 to 40.4) months	0/8 (0%)	NR	NR	Single arm cohort	NA	5/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	CMV infection	21.1 (range 3.2 to	42/50 (84%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
				71.1) months						
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	CMV viremia	12.2 (range 3.2 to 40.4) months	2/8 (25%)	NR	NR	Single arm cohort	NA	5/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	CMV viremia	43.2 (24.3 to 65.9) months	6/26 (23.1%)	NR	NR	Single arm cohort	NA	12/16
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	CMV PTLD	12.2 (range 3.2 to 40.4) months	0/8 (0%)	NR	NR	Single arm cohort	NA	5/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	CMV pneumonia	43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	CMV disease	21.1 (range 3.2 to 71.1) months	1/50 (2%)	NR	NR	Single arm cohort	NA	12/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA	EBV infection	21.1 (range 3.2 to 71.1) months	8/50 (16%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	EBV viremia	12.2 (range 3.2 to 40.4) months	5/8 (62.5%)	NR	NR	Single arm cohort	NA	5/16
Clay 2014[37]	Haploidentical HSCT	Adults with refractory SAA/VSAA	EBV PTLD	12.2 (range 3.2 to 40.4) months	0/8 (0%)	NR	NR	Single arm cohort	NA	5/16
Xu 2018[39]	Haploidentical HSCT	Adults with SAA/VSAA		21.1 (range 3.2 to 71.1) months	1/50 (2%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Viremia (any)	43.2 (24.3 to 65.9) months	6/26 (23.1%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Bacteriemia (any)	43.2 (24.3 to 65.9) months	7/26 (26.9%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Invasive fungal infection	43.2 (24.3 to 65.9) months	1/26 (3.9%)	NR	NR	Single arm cohort	NA	12/16
Gao 2014[38]	Haploidentical HSCT	Adults with refractory SAA/VSAA	Mixed infection (bacterial and CMV)	43.2 (24.3 to	2/26 (7.7%)	NR	NR	Single arm cohort	NA	12/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
				65.9) months						
Lengline 2018[42]	Eltrombopag	Adults with SAA or VSAA	Infection (any)	9 to 13 months	13/46 (28.3%)	NR	NR	Single arm cohort	NA	11/16
Desmond 2014[12] **and Olnes 2012**[13]	Eltrombopag	Adults with refractory SAA or VSAA	Upper respiratory infection of grade 2 or higher	NR	3/26 (12%)	NR	NR	Non-randomised interventional	NA	14/16
			Shingles of grade 2 or higher		1/26 (4%)					
			Clostridium difficile colitis of grade 2 or higher		1/26 (4%)					
			Viral hepatitis of grade 2 or higher		1/26 (4%)					

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; CMV, cytomegalovirus; CsA, cyclosporin A; EBV, Epstein-Barr virus; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; ND, not determinable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; RoB, risk of bias; SAA, severe aplastic anaemia; UTI, urinary tract infection; VSAA, very severe aplastic anaemia.

FAQ6: Are there any long-term negative effects of treatment?

Several studies that contributed data for this report only followed up patients for a limited period. For example, the RACE trial comparing eltrombopag plus IST vs IST only reported most outcomes up to 6 months, and while a long-term follow-up is planned, it has not yet been published. This means that long-term data are lacking for most non-survival-related outcomes.

For all drugs and outcomes of interest, any data from 48 months/4 years or longer was compiled to assess longer-term evidence (Table 21). This provided information from six comparative studies and three single arm studies. OS was the most widely reported outcome beyond 48 months/4 years. No long-term evidence beyond 48 months/4 years was identified for eltrombopag plus IST or eltrombopag alone, and limited evidence was identified for MSD-HSCT and MUD-HSCT (1 study each).

Six comparative studies reported on longer-term **OS/survival/mortality** between 5 to 8 years after study treatment. OS rates were approximately 95% for MSD-HSCT (based on 1 study), approximately 62% for MUD-HSCT (based on 1 study), approximately 41% for partially matched UD-HSCT (based on 1 study), between 48% to 84% for haplo-HSCT (based on 3 studies), between 52% to 79% for allogeneic BMT (based on 2 studies) and between 49% to 78% for IST (based on 5 studies). One single arm study also reported an OS of 79.5% at 5 years for IST; and one single arm study reported a death rate of 24% at 49 months for IST.

One comparative study reported on longer-term **failure-free survival** at 8 years. This study reported a higher rate of long-term failure-free survival for patients receiving haplo-HSCT compared to IST (93.7% vs 38.5%, respectively); this was a statistically significant difference. One single arm study also reported a disease-free survival of 13.3 months (95% CI 1.9 to 24.7 months) for IST.

One single arm study reported a **relapse** rate of 5.4% at between 5.0 to 5.7 years of follow-up for patients treated with IST.

One single arm study reported a median **duration of CsA therapy** of 7.4 months (range 0.3 to 79 months) for patients treated with IST.

Table 21: All long-term outcomes – ≥48 months/4 years

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Comparative evidence										
Miao Chen 2020[14]	Haploidentical HSCT	Young adults (14-30 years) with SAA or VSAA	OS/survival	5 years	82.1% ± 8.4%	NR	NR	Comparative cohort	Numerically favours haploidentical HSCT	15/24
	IST (rATG/pALG plus CsA				77.9% ± 11.7%					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA		8 years	83.7% ± 4.8% (n=76), P=0.328	NR	HR 1.269 (95% CI 0.320 to 5.040), P=0.735	Comparative cohort	Numerically favours haploidentical HSCT	19/24
	IST (rATG plus CsA)				75.6% ± 17.2% (n=37)					
Ahn 2003[25]	Allogeneic BMT	Adults with SAA or VSAA		6 years	50/64 (78.8%)	Mean 95.16 months	P=0.8307	Comparative cohort	Numerically favours allogeneic BMT	9/24
	IST (ATG with or without CsA)				108/156 (69.3%)	Mean 96.01 months				
Paquette 1995[26]	Allogeneic BMT	Adults with MAA, SAA or VSAA		6 years	52% ± 7%	NR	NR	Comparative cohort	Numerically favours allogeneic BMT	12/24
	IST (ATG with or without CsA)				49% ± 4	Median 5.6 years				
Kim 2003[27]	Matched sibling donor HSCT (BM source)	Adults with SAA or VSAA		5 years	95%	NR	P=0.04	Comparative cohort	Statistically favours MSD-HSCT (BM source)	12/24
	IST (equine ATG/ALG				70%					

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
	with or without CsA)									
Kim 2016[32]	Haploidentical HSCT	Adults (>18 years) with SAA		5 years	48.2%	NR NR		Comparative cohort	Numerically favours alternative donor HSCT	11/24
	Alternative donor HSCT (matched unrelated or partially matched)				52%					
	Haploidentical HSCT				48.2%		P=0.526		Numerically favours matched unrelated HSCT	
	Matched unrelated HSCT				61.8%					
	Partially matched unrelated HSCT				40.8%					
Xu 2019[24]	Haploidentical HSCT	Adults with SAA or VSAA	Failure-free survival (defined as survival with response)	8 years	83.7% ± 4.8% (n=76), P=0.001	NR	HR 4.275 (95% CI 1.957 to 9.338), P<0.001	Comparative cohort	**Statistically favours haploidentical HSCT**	19/24
	IST (rATG plus CsA)				38.5% ± 13.2% (n=37)					
Single arm evidence										
Alashkar 2019[40]	IST (ATG plus CsA)	Adults with AA (81% SAA/ VSAA)	OS	5 years	79.5% (n=69)	NR	NR	Single arm cohort	NA	8/16

Study ID	Treatments	Patient description	Outcome	Timepoint	Dichotomous data (n/N (%))	Continuous data	Change/ effect estimate	Study type	Favours?	RoB rating
Shinn 2023[36]	IST alone	Adults with SAA or VSAA	Death rate	49 months	8/34 (24%)	NR	NR	Single arm cohort	NA	11/16
Shinn 2023[36]	IST alone	Adults with SAA or VSAA	Disease-free survival (defined as time from day of therapy initiation to relapse or death from any cause)	49 months	NR	13.3 (95% CI 1.9 to 24.7) months	NR	Single arm cohort	NA	11/16
Xu 2019[24]	IST (rATG plus CsA)	Adults with SAA or VSAA	Relapse	5.7 or 5.0 years	2/37 (5.4%)	NR	NR	Single arm cohort	NA	12/16
Shinn 2023[36]	IST alone	Adults with SAA or VSAA	Median duration of CsA therapy	49 months	NR	7.4 (range 0.3 to 79) months	NR	Single arm cohort	NA	11/16

Abbreviations: ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; BMT, bone marrow transfer; CI, confidence interval; CMV, CytomegalovirusCsA, cyclosporin A; GVHD, graft-versus host disease; HSCT, haematopoietic stem cell transplant; IST, immunosuppressive therapy; NA, not applicable; NR, not reported; OS, overall survival; rATG, rabbit anti-thymocyte globulin; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

FAQ7: Where can I get additional information and/or a second opinion?

ORPHAnet provides additional patient-centred resources and information on AA. This includes links to patient organisations and clinical trials:
https://www.orpha.net/en/disease/detail/88?name=aplastic%20anemia&mode=name

In Germany, treatment guidelines for AA are available through the onkopedia website:
https://www.onkopedia.com/de/onkopedia/guidelines/aplastische-anaemie/@@guideline/html/index.html

Further, the Aplastische Anamie and PNH e.V. organisation provides information and advice to AA patients and their families and friends:
https://aa-pnh.org/category/aplastische-anaemie-aa/

Finally, the Lichterzellen (light cells) Foundation for the relief of PNH and aplastic anaemia provides support for adults affected by these diseases and their families:
https://www.lichterzellen.de/

5. Discussion

Summary of main findings

This evidence review captures outcomes for key drugs available to severe or very severe adult AA patients. Key findings from the evidence review are summarised in Table 22.

Overall, MSD-HSCT and eltrombopag plus IST appeared to be the most useful treatments in terms of improving effectiveness and maintaining safety in adults with SAA or VSAA. While no direct comparative evidence for MSD-HSCT vs eltrombopag plus IST was identified in an adult-only population, one study (Kim 2003) compared MSD-HSCT to a common comparator to that used in eltrombopag plus IST studies: IST alone. Comparing the effect size from Kim 2003 (MSD-HSCT vs IST) with the effect size from Assi 2018, Jin 20023, Shinn 2023 and Peffault de Latour 2022 (eltrombopag plus IST vs IST), the effect size was typically bigger for Kim 2003 for OS, all-cause mortality and infection-related mortality although not for malignancy-related mortality, leukaemia / AML / NHL or MDS. However, it should be noted that this is a crude comparison, and that Kim 2003 was an older study that may have used less modern pre-conditioning regimens; further, the IST treatments provided in the Kim 2003 study were heterogeneous and included either hATG alone (51% of patients), hALG alone (26% of patients) or hATG with CsA (23% of patients), which does not reflect the modern standard-of-care IST regimen (hATG plus CsA).

Out of the different types of HSCT, MSD-HSCT typically outperformed MUD-HSCT and/or haplo-HSCT (for all-cause mortality, cause-specific mortality, OS, GVHD and CMV infections). If no matched sibling donor was available for HSCT, MUD-HSCT generally outperformed haplo-HSCT and mismatched-UD-HSCT as the next-best HSCT therapy.

Similarly, out of the different types of immunosuppressive therapy, eltrombopag plus IST typically outperformed IST alone or eltrombopag alone (for all-cause mortality, cause-specific mortality, recurrence, duration of therapy, OS, lymphomas, renal insufficiency, fever, headache, fatigue, CMV infections or any infections).

Generally, the findings from this project were in line with adult-only meta-analyses performed as part of a USA guideline published by Iftikhar in 2024.[7] This guideline recommends that adult patients of any age should be considered for upfront HSCT, and that either MSD-HSCT, MUD-HSCT or haplo-HSCT should be prioritised over IST. Of note, this guideline did not formally incorporate comparisons with eltrombopag plus IST, and due to limited evidence at the time it was published, perhaps cautiously restricted guidance for eltrombopag plus IST to patients where matched related donor HSCT was not available.

Table 22: Summary of the comparative evidence

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
FAQ1: What does the treatment involve?									
Treatment schedules and doses	Kulasekararak 2024,[8] Mihailova 2020,[9] onkopedia 2024[11]	Peripheral blood or bone marrow tissue donated from either a sibling, a relation or a stranger. Typical pre-conditioning regime includes CsA (200mg/kg QD for 4 days) plus hATG (40mg/kg IV for 4 days) but can be different depending on the patient			hATG 40mg/kg IV for 4 days, CsA PO at 2.5 or 5mg/kg BID	hATG 40mg/kg IV for 4 days, CsA PO at 2.5 or 5mg/kg BID plus elt PO 150mg* QD	Initially 50mg QD PO then uptitrated to a maximum of 150mg QD PO to achieve a platelet count of ≥50x10e9/L	Moderate to High	NA
FAQ2: Will the therapy affect all-cause mortality, cause-specific mortality, bleeding events, anaemia, need for transfusions, recurrence/therapy failure and duration of response?									
All-cause mortality	Miao Chen 2020,[14] Xu 2019,[24] Ahn 2003,[25] Kim 2003,[27] Niu 2022,[28] Peffault de Latour 2022,[35] Shinn 2023,[36]	Better than IST, better than haplo-HSCT	-	Worse than IST, worse than MSD-HSCT	Better than haplo-HSCT, worse than MSD-HSCT, slightly worse than eltrombopag plus IST	Slightly better than IST	-	12/24 to 19/24 or High	MSD-HSCT likely better than IST or haplo-HSCT, IST likely better than haplo-HSCT, IST plus elt likely slightly better than IST alone
Cause-specific mortality: infection or sepsis	Ahn 2003,[25] Assi 2018,[33] Miao Chen 2020,[14] Xu	Better than IST	-	Probably worse than IST	Worse than MSD-	Better than IST	-	9/24 to 19/24 or High	MSD-HSCT likely better than IST, IST probably better than

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	2019,[24] Kim 2003,[27]				HSCT, probably better than haplo-HSCT, worse than IST plus elt				haplo-HSCT., IST plus elt likely better than IST
Cause-specific mortality: malignancy	Kim 2003,[27] Peffault de Latour 2022[35]	Slightly better than IST	-	-	Slight worse than MSD-HSCT or IST plus elt	Slightly better than IST	-	12/24 or High	MSD-HSCT and IST plus elt likely better than IST, probably no difference between MSD-HSCT and IST plus elt
Cause-specific mortality: transplant-related	Park 2021,[31] Peffault de Latour 2022[35]	-	Slightly better than haplo-HSCT or mismatched UD-HSCT	Slightly worse than MUD-HSCT; slightly better than mismatched UD-HSCT	Slight worse than IST plus elt	Slightly better than IST	-	19/24 or High	IST plus elt likely better than IST alone, MUD-HSCT likely better than haplo-HSCT or mismatched UD-HSCT
Bleeding events	Park 2021[31]	-	Slightly better than haplo-HSCT or mismatc		-	-	-	14/16, 19/24	MUD-HSCT likely slightly better than haplo-HSCT or mismatched unrelated donor HSCT. Probably no

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
			hed donor						difference between haplo-HSCT and mismatched unrelated donor HSCT
Anaemia	Xu 2019,[24]	-	-	Much better than IST (rATG plus CsA)	-	-	-	11/16, 14/16, 19/24	Haplo-HSCT much better than IST (rATG plus CsA)
Need for transfusions: ORR	Miao Chen 2020,[14] Ahn 2003,[25] Assi 2018,[33] Jin 2022,[34] Peffault de Latour 2022,[35] Shinn 2023[36]	-	-	Better than IST at early timepoints but not later timepoints	Worse than haplo-HSCT at early timepoints but not at later timepoints; worse than IST plus elt	Better than IST	-	9/24 to 19/24 or High	IST plus elt likely better than IST; haplo-HSCT better than IST at early points but similar after 12 months
Recurrence/therapy failure: relapse	Miao Chen 2020,[14] Jin 2022,[34] Peffault de Latour 2022,[35] Shinn 2023[36]	-	-	Slightly better than IST	Slightly worse than haplo-HSCT; probably worse than IST plus elt	Probably better than IST	-	15/24 to 19/24 or High	Haplo-HSCT probably better than IST; IST plus elt probably better than IST
Recurrence/therapy failure: failure-free survival	Xu 2019,[24] Niu 2022,[28] Zhang	Much better	Similar to MSD-	Much better	Probably slightly	Probably slightly	-	18/24 to 19/24	MSD-HSCT, MUD-HSCT and haplo-HSCT

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	2020,[30] Park 2021,[31] Assi 2018,[33] Shinn 2023,[36] Iftikhar 2024[7]	than IST, similar to MUD-HSCT or haplo-HSCT	HSCT and haplo-HSCT	than IST; similar to MSD-HSCT and MUD-HSCT; slightly worse than mismatched UD-HSCT	worse than IST plus elt	better than IST			much better than IST, MSD-HSCT, MUD-HSCT and haplo-HSCT probably similar, IST plus elt probably slightly better than IST
Recurrence/therapy failure: therapy failure	Niu 2022,[28] Park 2021,[31] Kim 2016,[32] Zhang 2020[30]	Slightly better than MUD-HSCT or haplo-HSCT	Probably slightly better than haplo-HSCT	Probably slightly worse than MSD-HSCT or MUD-HSCT	-	-	-	11/24 to 19/24	MSD-HSCT likely better than MUD-HSCT or haplo-HSCT
Duration of treatment	Shinn 2023[36]	-	-	-	-	CsA taken for longer in combination with elt vs alone	-	19/24	IST plus elt likely better than IST
FAQ3: Will the treatment impact how long I live?									
OS	Miao Chen 2020,[14] Xu 2019,[24] Kim 2003,[27] Rice 2019,[29] Niu	Much better than IST, probably	Probably worse than MSD-	Probably better than IST or	Much worse than MSD-	Better than IST	-	9/24 to 19/24 or High	MSD-HSCT and haplo-HSCT better than IST, MSD-HSCT similar to haplo-HSCT and

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	2022,[28] Zhang 2020,[30] Park 2021,[31] Kim 2016,[32] Assi 2018,[33] Jin 2022,[34] Peffault de Latour 2022,[35] Iftikhar 2024[7]	better than MUD-HSCT, probably similar to haplo-HSCT	HSCT, probably better than haplo-HSCT or mismatched UD-HSCT	mismatched UD-HSCT, probably similar to MSD-HSCT	HSCT, probably worse than haplo-HSCT, worsen than IST plus elt				probably better than MUD-HSCT, MUD-HSCT better than haplo-HSCT or mismatched UD-HSCT, haplo-HSCT probably better than mismatched UD-HSCT
FAQ4: How will the treatment impact my quality of life?									
HRQoL	Xu 2019,[24] Kim 2003,[27] Peffault de Latour 2022[35]	Better than IST	-	Much better than IST	Much worse than haplo-HSCT or MSD-HSCT, same as IST plus elt	Same as IST	-	12/24 to 19/24 or High	MSD-HSCT better than IST, haplo-HSCT much better than IST, iST plus elt similar to IST
FAQ5: What are the risks or side effects?									
GVHD: Acute GVHD	Rice 2019,[29] Kim 2016,[32] Niu 2022,[28] Zhang 2020,[30] Park 2021[31]	Much better than MUD-HSCT or haplo-HSCT	Much worse than MSD-HSCT, probably worse than haplo-HSCT	Much worse than MSD-HSCT, probably better than MUD-HSCT	-	-	-	11/24 to 19/24	MSD-HSCT much better than MUD-HSCT or haplo-HSCT, MUD-HSCT worse than haplo-HSCT
GVHD: Chronic GVHD	Rice 2019,[29] Niu 2022,[28] Zhang	Better than	Worse than	Much worse	-	-	-	11/24 to 19/24	MSD-HSCT better than MUD-HSCT or

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	2020,[30] Kim 2016,[32] Park 2021[31]	MUD-HSCT or haplo-HSCT	MSD-HSCT, probably better than haplo-HSCT	than MSD-HSCT, probably worse than MUD-HSCT					haplo-HSCT, MUD-HSCT better than haplo-HSCT
Lymphomas/malignant tumours – leukaemia /AML / NHL	Ahn 2003,[25] Paquette 1995,[26] Kim 2003,[27] Miao Chen 2020,[14] Jin 2022[34]	Similar to IST	-	Better than IST	Similar to MSD-HSCT, worse than haplo-HSCT or IST plus elt	Better than IST	-	9/24 to 19/24	MSD-HSCT similar to IST, haplo-HSCT and IST plus elt better than IST
Lymphomas/malignant tumours – MDS	Ahn 2003,[25] Paquette 1995,[26] Kim 2003,[27] Jin 2022,[34] Peffault de Latour 2022[35]	Similar to IST	-	-	Similar to MSD-HSCT , probably worse than IST plus elt	Probably better than IST	-	9/24 to 19/24 or High	MSD-HSCT similar to IST, IST plus elt probably better than IST
Lymphomas/malignant tumours – PTLD	Niu 2022,[28] Zhang 2020[30], Park 2021[31]	Probably similar to haplo-HSCT and MUD-HSCT	Similar to MSD-HSCT and probably better than haplo-HSCT	Probably similar to MSD-HSCT and probably worse than	-	-	-	18/24 to 19/24	MSD-HSCT probably similar to MUD-HSCT and haplo-HSCT, MUD-HSCT probably better than haplo-HSCT

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
				MUD-HSCT					
Renal insufficiency	Assi 2018,[33] Peffault de Latour 2022[35]	-	-	-	Worse than IST plus elt	Better than IST	-	18/24 or High	IST plus elt better than IST alone
Fever	Assi 2018,[33] Jin 2022[34]	-	-	-	Worse than IST plus elt	Better than IST	-	18/24 to 19/24	IST plus elt better than IST alone
Anorexia	No comparative evidence identified								
Malaise	No comparative evidence identified								
Headache	Assi 2018[33]	-	-	-	Probably worse than IST plus elt	Probably better than IST	-	18/24	IST plus elt probably better than IST alone, although potentially not for grade ≥3 headaches
Weakness	No comparative evidence identified								
Fatigue	Assi 2018,[33] Peffault de Latour 2022[35]	-	-	-	Probably worse than IST plus elt	Probably better than IST	-	18/24 or High	IST plus elt probably better than IST alone
Infections – CMV infection / reactivation / viraemia / DNAemia	Miao Chen 2020,[14] Zhang 2020,[30] Park 2021,[31] Assi 2018[33]	Probably similar to MUD-HSCT and probably better than haplo-HSCT	Probably similar to MSD-HSCT and probably better than haplo-HSCT	Probably worse than MSD-HSCT or MUD-HSCT	Worse than IST plus elt	Better than IST	-	15/24 to 19/24	MSD-HSCT and MUD-HSCT probably similar, haplo-HSCT probably worse than MSD-HSCT or MUD-HSCT, IST plus elt better than IST
Infections - any infections	Miao Chen 2020,[14] Assi 2018,[33] Jin 2022,[34]	-	-	Similar to IST	Probably worse than IST	Probably better than IST	Probably better than IST	15/24 to 19/24 or High	IST plus elt or elt alone probably better than IST, haplo-HSCT

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	Peffault de Latour 2022[35]				plus elt or elt alone, similar to haplo-HSCT				and IST probably similar
Infections – fungal disease	Miao Chen 2020,[14] Park 2021[31]	-	Probably worse than haplo-HSCT and probably similar to mismatched UD-HSCT	Probably better than MUD-HSCT or mismatched UD-HSCT and IST	Probably worse than haplo-HSCT	-	-	15/24 to 19/24	Haplo-HSCT probably better than MUD-HSCT or mismatched UD-HSCT or IST
FAQ6: Are there any long-term negative effects of treatment?									
Long-term OS/survival/mortality	Miao Chen 2020,[14] Xu 2019,[24] Ahn 2003,[25] Paquette 1995,[26] Kim 2003,[27] Kim 2016[32]	95% at 5 years	61.8% at 5 years	48% to 84% at between 5-8 years	49% to 78% at between 5-8 years	-	-	9/24 to 19/24	MSD-HSCT probably better than MUD-HSCT, haplo-HSCT or IST
Long-term failure-free survival	Xu 2019[24]	-	-	Much better than IST	Worse than haplo-HSCT	-	-	19/24	Haplo-HSCT much better than IST (rATG plus CsA)
FAQ7: Where can I get additional information?									
Additional information sources	ORPHAnet provides additional patient-centred resources and information on AA. This includes links to patient organisations and clinical trials: https://www.orpha.net/en/disease/detail/88?name=aplastic%20anemia&mode=name In Germany, treatment guidelines for AA are available through the onkopedia website: https://www.onkopedia.com/de/onkopedia/guidelines/aplastische-anaemie/@@guideline/html/index.html								

Outcome	Source	MSD-HSCT	MUD-HSCT	Haplo-HSCT	IST	IST plus elt	Elt alone	RoB rating of evidence	Overview of evidence
	Further, the Aplastische Anamie and PNH e.V. organisation provides information and advice to patients and their families and friends: https://aa-pnh.org/category/aplastische-anaemie-aa/ Finally, the Lichterzellen (light cells) Foundation for the relief of PNH and aplastic anaemia provides support for adults affected by these diseases and their families: https://www.lichterzellen.de/								

Abbreviations: AA, aplastic anaemia; AML, acute myeloid leukaemia; BID, twice a day; CMV, cytomegalovirus; CsA, cyclosporin A; DNA, deoxyribonucleic acid; Elt, eltrombopag; GVHD, graft-versus-host disease; haplo-HSCT, haploidentical haematopoietic stem cell transplant; HRQoL, health-related quality of life; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; MSD-HSCT, matched sibling donor - haematopoietic stem cell transplant; MUD-HSCT, matched unrelated donor-haematopoietic stem cell transplant; NA, not applicable; NHL, Non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PNH, paroxysmal noctural haemoglobinuria; PO, orally; PTLD, post-transplant lymphoproliferative disorder; QD, daily; RoB, risk of bias.

* Initially 50mg QD PO then uptitrated to a maximum of 150mg QD PO to achieve a platelet count of ≥50x10e9/L.

Strengths and limitations

Our study had several key strengths. The included evidence was based on rigorous systematic review methods with two independent reviewers involved in screening and two reviewers involved in data extraction (one reviewer extracted the data, and a second reviewer checked 20% of the extracted data). Searches were conducted across a wide range of databases, including Embase, MEDLINE, CDSR, DARE, Epistemonikos, G-I-N, ECRI, HTA, INAHTA, NICE and G-BA/IQWiG.

Our systematic review also analysed the outcomes of each type of HSCT separately rather than pooling these as has been done in several other reviews. This established additional important insights into the efficacy and safety of HSCT when patients have to make a treatment choice in the absence of matched sibling donors, matched unrelated donors etc.

In terms of study limitations, most of the evidence identified was based on data from comparative observational studies supported with single-arm studies where available, and only one RCT was included. All included non-randomised studies were rated at moderate or high risk of bias, and the single RCT was rated at high risk of bias, a rating that was predominantly driven by its open-label design.

Half of the identified primary study evidence came from Asia, which may limit applicability due to differences in background treatments or conditioning regimens.

Any type of IST treatment was grouped together in the data synthesis; however, there was heterogeneity in the drug combinations used within the IST intervention arms. While most studies used horse ATG, some studies used rabbit ATG or horse ALG. For some outcomes, the only available evidence was found in IST using rATG plus CsA. Similarly, while most studies treated all patients in the IST arm with ATG plus CsA, some studies (usually earlier studies) only treated patients with either CsA alone, ATG alone or both (ATG plus CsA). Finally, the background drugs used alongside the formal IST intervention differed between studies. For example, some studies treated patients with G-CSF or prednisolone alongside IST, and this additional complexity was not captured in the description of 'IST' used in the tables to simplify the analysis.

Finally, for assessing statistically significant differences, in some studies it was unclear if statistical testing had not been conducted or if the testing had been conducted and was negative and therefore not reported, which may have introduced reporting bias.

Comparison with other reviews

A total of five systematic reviews published between 2010 and 2023 were identified as part of the searching and screening process for this project.[15 17-20] However, only one of these reviews focussed on an adult-only population and only provided a comparison between eltrombopag plus IST vs haplo-HSCT,[18] and therefore did not assess the broad range of drugs/studies captured here. Therefore, this appears to be the first study to bring together this level of evidence for exclusively adult-only studies in one assessment.

Evidence gaps

No studies describing direct comparisons of eltrombopag with or without IST vs HSCT were identified and therefore indirect evidence had to form the focus of this review.

Many of the more modern outcome definitions, including relapse and response rates, were not well reported outside of eltrombopag plus IST vs IST alone comparison, which limited comparability.

No evidence was found for transplant-related mortality for MSD-HSCT, and no evidence was found for partial response (transfusion independence) outcomes for any treatment comparisons outside of eltrombopag plus IST vs IST alone.

No information was identified for MSD-HSCT for several outcomes, including bleeding events, anaemia, need for transfusions, renal insufficiency, fever, headache, weakness and fatigue; and limited evidence (1 study) was identified for HRQoL and infections.

Similarly, no information was identified for eltrombopag plus IST for several outcomes, including bleeding events, anaemia, weakness; and limited evidence (1 study) was identified for HRQoL, headache and duration of response.

Long-term outcomes (>48 months/4 years) were almost exclusively limited to OS, with no long-term evidence identified for safety outcomes of interest.

Generally, renal insufficiency, fever, fatigue and headache were not widely reported outside of eltrombopag plus IST vs IST comparisons. No evidence was identified for anorexia or malaise.

Recommendations for further research

Direct comparative evidence for the two most promising treatments in adult patients with SAA/VSAA (MSD-HSCT vs eltrombopag plus IST) was lacking. In the absence of head-to-head trials comparing all the drugs of interest in adult SAA/VSAA patients, it would be useful to perform a network meta-analysis that provides an indirect assessment of which drugs are most useful for AA treatment. Future trials should consider applying double-blinding to reduce patient and sponsor bias, and ensuring that core patient-reported outcome sets are captured for AA patients (including general quality of life and the ability to work/activities of daily living).[47]

6. References

1. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). 2024.

2. Garritty C, Hamel C, Trivella M, et al. Updated recommendations for the Cochrane rapid review methods guidance for rapid reviews of effectiveness. *Bmj* 2024;384:e076335. doi: 10.1136/bmj-2023-076335 [published Online First: 20240206]

3. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *Cmaj* 2010;182(18):E839-42. doi: 10.1503/cmaj.090449 [published Online First: 20100705]

4. Whiting P, Savović J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016;69:225-34. doi: 10.1016/j.jclinepi.2015.06.005 [published Online First: 20150616]

5. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928. doi: 10.1136/bmj.d5928 [published Online First: 20111018]

6. Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003;73(9):712-6. doi: 10.1046/j.1445-2197.2003.02748.x

7. Iftikhar R, DeFilipp Z, DeZern AE, et al. Allogeneic Hematopoietic Cell Transplantation for the Treatment of Severe Aplastic Anemia: Evidence-Based Guidelines From the American Society for Transplantation and Cellular Therapy. *Transplantation and Cellular Therapy* 2024;20:20. doi: https://dx.doi.org/10.1016/j.jtct.2024.09.017

8. Kulasekararaj A, Cavenagh J, Dokal I, et al. Guidelines for the diagnosis and management of adult aplastic anaemia: A British Society for Haematology Guideline. *British Journal of Haematology* 2024;204(3):784-804. doi: https://dx.doi.org/10.1111/bjh.19236

9. Mihailova EA, Fidarova ZT, Troitskaya VV, et al. Clinical recommendations for the diagnosis and treatment of aplastic anemia (2019 edition). [Russian]. *Gematologiya i Transfusiologiya* 2020;65(2):208-26. doi: https://dx.doi.org/10.35754/0234-5730-2020-65-2-208-226

10. Piekarska A, Pawelec K, Szmigielska-Kaplon A, et al. The state of the art in the treatment of severe aplastic anemia: immunotherapy and hematopoietic cell transplantation in children and adults. *Frontiers in Immunology* 2024;15:1378432. doi: https://dx.doi.org/10.3389/fimmu.2024.1378432

11. onkopedia. Aplastische Anämie 2024 [Available from: https://www.onkopedia.com/de/onkopedia/guidelines/aplastische-anaemie/@@guideline/html/index.html accessed 21st March 2025.

12. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. *Blood* 2014;123(12):1818-25. doi: 10.1182/blood-2013-10-534743 [published Online First: 20131217]

13. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med* 2012;367(1):11-9. doi: 10.1056/NEJMoa1200931

14. Miao Chen YW, Zhou D, Duan M, et al. Comparison of intensive immunosuppressive therapy with haploidentical transplantation for young severe aplastic anemia. *Basic Clin Med* 2020;40(6):759-64.

15. ElGohary G, El Fakih R, de Latour R, et al. Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT). *Bone Marrow Transplantation* 2020;55(10):1906-17. doi: https://dx.doi.org/10.1038/s41409-020-0897-2

16. Groth M, Singer S, Niedeggen C, et al. Development of a disease-specific quality of life questionnaire for patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria (QLQ-AA/PNH)-report on phases I and II. *Annals of Hematology* 2017;96(2):171-81. doi: https://dx.doi.org/10.1007/s00277-016-2867-8

17. Peinemann, Grouven F, Kroger U, et al. First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia. *Plos One* 2010;6(4):e18572.

18. Yang Y, Ji J, Tang Z, et al. Comparisons Between Frontline Therapy and a Combination of Eltrombopag Plus Immunosuppression Therapy and Human Leukocyte Antigen-Haploidentical Hematopoietic Stem Cell Transplantation in Patients With Severe Aplastic Anemia: A Systematic Review. *Frontiers in Oncology* 2021;11(no pagination) doi: https://dx.doi.org/10.3389/fonc.2021.614965

19. Zhao J, Ma L, Zheng M, et al. Meta-analysis of the results of haploidentical transplantation in the treatment of aplastic anemia. *Annals of Hematology* 2023;102(9):2565-87. doi: https://dx.doi.org/10.1007/s00277-023-05339-7

20. Zhu Y, Gao Q, Hu J, et al. Allo-HSCT compared with immunosuppressive therapy for acquired aplastic anemia: Is superiority a one-sided understanding? *ResearchSquare* 2019 doi: 10.21203/rs.2.19154/v1

21. EMA. Revolade - Eltrombopag SmPC, 2022.

22. DKMS. Bone marrow donation 2025 [Available from: https://www.dkms.org.uk/donation-explained/stem-cell-donation/bone-marrow-donation accessed 21st March 2025.

23. Dana-Farber Cancer Institute. Frequently Asked Questions About Donating Bone Marrow 2025 [accessed 21st March 2025.

24. Xu ZL, Zhou M, Jia JS, et al. Immunosuppressive therapy versus haploidentical transplantation in adults with acquired severe aplastic anemia. *Bone Marrow Transplant* 2019;54(8):1319-26. doi: 10.1038/s41409-018-0410-3 [published Online First: 20190122]

25. Ahn MJ, Choi JH, Lee YY, et al. Outcome of adult severe or very severe aplastic anemia treated with immunosuppressive therapy compared with bone marrow transplantation: multicenter trial. *Int J Hematol* 2003;78(2):133-8. doi: 10.1007/bf02983381

26. Paquette RL, Tebyani N, Frane M, et al. Long-term outcome of aplastic anemia in adults treated with antithymocyte globulin: comparison with bone marrow transplantation. *Blood* 1995;85(1):283-90.

27. Kim I, Yoon SS, Park S, et al. The treatment of severe aplastic anemia: outcomes of bone marrow transplantation and immunosuppressive therapy in a single institution of Korea. *J Korean Med Sci* 2003;18(3):365-71. doi: 10.3346/jkms.2003.18.3.365

28. Niu YY, Ma LM, Wang T. Haploidentical haematopoietic stem cell transplantation for the treatment of severe aplastic anaemia patients with high-risk factors who lack an HLA-matched sibling donor. *Transfus Clin Biol* 2022;29(1):53-59. doi: 10.1016/j.tracli.2021.07.007 [published Online First: 20210731]

29. Rice C, Eikema DJ, Marsh JCW, et al. Allogeneic Hematopoietic Cell Transplantation in Patients Aged 50 Years or Older with Severe Aplastic Anemia. *Biol Blood Marrow Transplant* 2019;25(3):488-95. doi: 10.1016/j.bbmt.2018.08.029 [published Online First: 20180905]

30. Zhang YY, Mo WJ, Zuo YY, et al. Comparable survival outcome between transplantation from haploidentical donor and matched related donor or unrelated donor for severe aplastic anemia patients aged 40 years and older: A retrospective multicenter cohort study. *Clin Transplant* 2020;34(3):e13810. doi: 10.1111/ctr.13810 [published Online First: 20200220]

31. Park SS, Min GJ, Park S, et al. Comparable Outcomes Between Unrelated and Haploidentical Stem Cell Transplantation in Adult Patients With Severe Aplastic Anemia. *Transplantation* 2021;105(5):1097-105. doi: 10.1097/tp.0000000000003342

32. Kim H, Lee JH, Joo YD, et al. Comparable Allogeneic Hematopoietic Cell Transplantation Outcome of a Haplo-Identical Family Donor with an Alternative Donor in Adult Aplastic Anemia. *Acta Haematol* 2016;136(3):129-39. doi: 10.1159/000445820 [published Online First: 20160714]

33. Assi R, Garcia-Manero G, Ravandi F, et al. Addition of eltrombopag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia. *Cancer* 2018;124(21):4192-201. doi: 10.1002/cncr.31658 [published Online First: 20181011]

34. Jin Y, Li R, Lin S, et al. A real-word experience of eltrombopag plus rabbit antithymocyte immunoglobulin-based IST in Chinese patients with severe aplastic anemia. *Ann Hematol* 2022;101(11):2413-19. doi: 10.1007/s00277-022-04966-w [published Online First: 20220827]

35. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia. *N Engl J Med* 2022;386(1):11-23. doi: 10.1056/NEJMoa2109965

36. Shinn LT, Benitez LL, Perissinotti AJ, et al. Multicenter evaluation of the addition of eltrombopag to immunosuppressive therapy for adults with severe aplastic anemia. *Int J Hematol* 2023;118(6):682-89. doi: 10.1007/s12185-023-03670-3 [published Online First: 20231026]

37. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *Biol Blood Marrow Transplant* 2014;20(11):1711-6. doi: 10.1016/j.bbmt.2014.06.028 [published Online First: 20140710]

38. Gao L, Li Y, Zhang Y, et al. Long-term outcome of HLA-haploidentical hematopoietic SCT without in vitro T-cell depletion for adult severe aplastic anemia after modified conditioning and supportive therapy. *Bone Marrow Transplant* 2014;49(4):519-24. doi: 10.1038/bmt.2013.224 [published Online First: 20140127]

39. Xu LP, Xu ZL, Wang FR, et al. Unmanipulated haploidentical transplantation conditioning with busulfan, cyclophosphamide and anti-thymoglobulin for adult severe aplastic anaemia. *Bone Marrow Transplant* 2018;53(2):188-92. doi: 10.1038/bmt.2017.237 [published Online First: 20180115]

40. Alashkar F, Oelmüller M, Herich-Terhürne D, et al. Immunosuppressive therapy (IST) in adult patients with acquired aplastic anemia (AA): A single-center experience over the past 15 years. *Eur J Haematol* 2019;103(1):18-25. doi: 10.1111/ejh.13235 [published Online First: 20190521]

41. Lommerse IN, Hinnen C, van Vliet LM, et al. Quality of life after immune suppressive therapy in aplastic anemia. *Ann Hematol* 2024;103(6):2113-21. doi: 10.1007/s00277-024-05731-x [published Online First: 20240405]

42. Lengline E, Drenou B, Peterlin P, et al. Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia. *Haematologica* 2018;103(2):212-20. doi: 10.3324/haematol.2017.176339 [published Online First: 20171123]

43. GOSH. Aplastic anaemia 2021 [Available from: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/aplastic-anaemia/ accessed 21st March 2025.

44. Montané E, Ibáñez L, Vidal X, et al. Epidemiology of aplastic anemia: a prospective multicenter study. *Haematologica* 2008;93(4):518-23. doi: 10.3324/haematol.12020 [published Online First: 20080305]

45. Vaht K, Göransson M, Carlson K, et al. Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000-2011. *Haematologica* 2017;102(10):1683-90. doi: 10.3324/haematol.2017.169862 [published Online First: 20170727]

46. Vallejo C, Rosell A, Xicoy B, et al. A multicentre ambispective observational study into the incidence and clinical management of aplastic anaemia in Spain (IMAS study). *Ann Hematol* 2024;103(3):705-13. doi: 10.1007/s00277-023-05602-x [published Online First: 20240104]

47. Stojkov I, Conrads-Frank A, Rochau U, et al. Core set of patient-reported outcomes for myelodysplastic syndromes: an EUMDS Delphi study involving patients and hematologists. *Blood Adv* 2022;6(1):1-12. doi: 10.1182/bloodadvances.2021004568

Appendix A – Search strategies

Embase (Ovid)

Embase Classic+Embase <1947 to 2024 October 25> Searched 28th October 2024

#	Terms	# Records
1	exp aplastic anemia/	64007
2	(aplastic adj3 (anemi* or anaemi*)).ab,ti.	18353
3	aplastic an?emia.ab,ti.	17979
4	(aplast$ anem$ or aplast$ anaem$).ab,ti.	18203
5	or/1-4	66060
6	practice guideline/	594673
7	guideline*.ab,ti.	823785
8	or/6-7	1078329
9	systematic review/	493429
10	meta analysis/	334827
11	("meta-analys*" or "meta analys*" or "systematic review*" or "systematic overview*").ab,ti.	606736
12	or/9-11	775344
13	biomedical technology assessment/	18353
14	("health technology assessment*" or HTA or NICE).ab,ti.	41596
15	or/13-14	53803
16	8 or 12 or 15	1786419
17	5 and 16	2566
18	limit 17 to yr="2014-Current"	1650

MEDLINE (Ovid)

Ovid MEDLINE(R) ALL <1946 to October 25, 2024> Searched 28th October 2024

#	Terms	# Records
1	exp Anemia, Aplastic/	18164
2	(aplastic adj3 (anemi* or anaemi*)).ab,ti.	11482
3	aplastic an?emia.ab,ti.	11283
4	(aplast$ anem$ or aplast$ anaem$).ab,ti.	11387
5	or/1-4	21431
6	practice guideline/	32512
7	guideline*.ab,ti.	528486
8	or/6-7	542943
9	systematic review/	277019
10	meta-analysis/	210678
11	("meta-analys*" or "meta analys*" or "systematic review*" or "systematic overview*").ab,ti.	489833
12	or/9-11	531350
13	Technology Assessment, Biomedical/	11384

#	Terms	# Records
14	("health technology assessment*" or HTA or NICE).ab,ti.	19450
15	or/13-14	27436
16	8 or 12 or 15	1028411
17	5 and 16	254
18	limit 17 to yr="2014-Current"	176

CDSR (Cochrane Library)

Searched 28th October 2024

#	Terms	# Records
#1	MeSH descriptor: [Anemia, Aplastic] explode all trees	270
#2	(aplastic anemia):ti,ab,kw	697
#3	(aplastic anaemia):ti,ab,kw	697
#4	#1 OR #2 OR #3	704*

* n=704 = 699 trials (not screened) and 5 systematic reviews (screened)

DARE (CRD)

Searched 28th October 2024

Field	Terms	
any field	aplastic anemia	OR
any field	aplastic anaemia	
	Total # records	**14**

Epistemonikos

Searched 28th October 2024

Terms	# Records
(title:((title:(paroxysmal nocturnal hemoglobinuria) OR abstract:(paroxysmal nocturnal hemoglobinuria)) OR (title:(paroxysmal nocturnal haemoglobinuria) OR abstract:(paroxysmal nocturnal haemoglobinuria)) OR (title:(PNH) OR abstract:(PNH)) OR (title:(Marchiafava Micheli Syndrome) OR abstract:(Marchiafava Micheli Syndrome)) OR (title:(paroxysmal hemoglobinuria) OR abstract:(paroxysmal hemoglobinuria)) OR (title:(paroxysmal haemoglobinuria) OR abstract:(paroxysmal haemoglobinuria))) OR abstract:((title:(paroxysmal nocturnal hemoglobinuria) OR abstract:(paroxysmal nocturnal hemoglobinuria)) OR (title:(paroxysmal nocturnal haemoglobinuria) OR abstract:(paroxysmal nocturnal haemoglobinuria)) OR (title:(PNH) OR abstract:(PNH)) OR (title:(Marchiafava Micheli Syndrome) OR abstract:(Marchiafava Micheli Syndrome)) OR (title:(paroxysmal hemoglobinuria) OR abstract:(paroxysmal hemoglobinuria)) OR (title:(paroxysmal haemoglobinuria) OR abstract:(paroxysmal haemoglobinuria))))	-
Broad synthesis filter	3
Structured summary filter	10
Systematic review filter	98
Total # records	**111**

G-I-N

Searched 28th October 2024

Terms	# Records
aplastic anemia	0
aplastic anaemia	0
Total # records	**0**

ECRI

Searched 28th October 2024

Terms	# Records
aplastic anemia	0
aplastic anaemia	1
Total # records	**1**

HTA

Searched 28th October 2024

	Terms	
any field	aplastic anemia	OR
any field	aplastic anaemia	
	Selected HTA box plus HTA in progress and HTA published	**9**

INAHTA

Searched 28th October 2024

#	Terms	# records
#1	(aplastic anemia) OR (aplastic anaemia)	13

NICE

Searched 28th October 2024

#	Terms	# records
#1	aplastic anaemia	**4**

G-BA

Searched 8th March 2025

#	Terms	# records
#1	aplastic anaemia	**33**

IQWiG

Searched 8th March 2025

#	Terms	# records
#1	aplastic anaemia	**23**

Appendix B – Excluded studies at full paper screening

[Double click the image above to open the embedded file]

Appendix C – Risk of bias assessments

Full details of the risk of bias assessments in the included primary studies and the source studies are provided in the embedded file below.

[Double click the image above to open the embedded file]