A report on the treatment options for patients with severe congenital hemophilia A without current factor VIII inhibitors:

factor VIII prophylaxis, antibody prophylaxis or gene therapy

SHARE TO CARE
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LIST OF ABBREVIATIONS

AAV5	Adeno-associated virus 5
ABR	Annual bleeding rate
AE	Adverse events
AMNOG	Arzneimittelmarktneuordnungsgesetz
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
ECHO-group	Expanding Communications on Hemophilia-A-Outcomes-group
EHL	Extended half-life
FAQ	Frequently asked question
FVIII	Factor VIII
HL	Half-life
HR	Hazard ratio
HrQoL	Health-related quality of life
IQWiG	Institute for Quality and Efficiency in Health Care
IPD	Individual patient data analysis
IRR	Incidence rate ratio
IV	Intravenous
MA	Meta-analysis
MD	Mean difference
n.a.	Not applicable
NMA	Network meta-analysis
n.r.	Not reported
n.s.	Not specified
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Preferred Reporting of Systematic Reviews and Meta-Analyses
QOL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
SC	Subcutaneous
SDM	Shared decision making
SD	Standard deviation
SEAE	Serious adverse events
SHL	Standard half-life
SMD	Standardized mean difference
SR	Systematic review
TRAE	Treatment-related adverse events
ULHL	Ultra-long half-life
UKSH	Universitätsklinikum Schleswig-Holstein
vWF	von Willebrand factor

WFH	World Federation of Hemophilia
1W	Once weekly
2W	Every two weeks

1. PROJECT OBJECTIVES

A key aim of the present project is to inform patients with severe congenital hemophilia A on different prophylactic therapy options as part of shared decision making (SDM). In a teamwork with clinical Experts from the ECHO-group and patients we developed an evidence based online decision aid.

For each of SHARE TO CARE's Decision Aids we prepare and regularly update evidence reports, that cover the relative effects of interventions defined in the inclusion criteria (PICOS). The update of the report 2025 aimed to conduct a focused literature search on the novel treatment using ULHL factor VIII concentrate and to systematically update the evidence on the gene therapy, which was still emerging at the time of the original HTA.

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with clinicians of the ECHO-group. These questions pertain to the relevant characteristics of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1. Randomized controlled trials (RCTs) evaluated herein will aim to inform patients, clinicians, researchers, and health policy makers on relevant evidence relating to the treatment options for hemophilia A. If a comparison is not covered by RCTs we will choose lower evidence levels (e.g., non-randomized comparative intervention studies, registries, or cohort studies).

Table 1: Inclusion and exclusion criteria The PICO criteria remained consistent throughout the update but to improve clarity regarding the factor VIII therapy categorization we added explicit definitions.

	Included	Excluded
Population	Previously factor VIII treated patients 12 years of age or older with severe congenital hemophilia A (endogenous factor VIII activity, <1%), without current factor VIII inhibitors (<0.6 Bethesda units per milliliter), who were receiving episodic or prophylactic factor VIII infusions)	patients <12 years; mild and moderate forms, very old patients with comorbidities, current factor VIII inhibitors
Intervention	Clotting factor VIII replacement therapy; intravenous • Standard half-life (SHL) • extended half-life (EHL) • Ultra long half-life (ULHL) (efanesoctocog alfa)	n.a.
Comparator I	• Humanized, bispecific monoclonal antibody (Emicizumab); subcutaneous	n.a.
Comparator II	• Gene therapy (valoctocogene roxaparvovec); intravenous	previous AAV antibodies
Outcomes	• Annual Bleeding Rates (ABR) • All bleeding events (treated or not treated) • Spontaneous and joint bleeding events • protection for minor/major surgeries/interventions • Quality of life • Pain-reduction • Life expectancy • Adverse effects / side effects - thrombotic events, embolism, viral infections, occurrence of factor VIII inhibitors - long-term negative effects of treatment	n.a.
Study design	Randomized controlled trials comparing the 3 interventions to no prophylaxis (episodic treatment) or against each other. Systematic reviews, clinical practice guidelines (based on systematic searches)	Narrative reviews*; expert opinions; letters' overviews of reviews**

n.a.= not applicable
* narrative reviews are only used for additional information
** = The list is not exhaustive

2.2 FREQUENTLY ASKED QUESTIONS

The following FAQs were identified:

1. What does the treatment involve?
2. Will the therapy be capable to prevent bleeds?
3. How long will treatment effect last?
4. Can the treatment prevent joint damage?
5. How will treatment impact my quality of life?
6. What are the risks or side effects?
7. Are there long-term negative effects of treatment to be expected?

FAQs remained unchanged throughout the update of the report.

2.3 LITERATURE SEARCHES

Preliminary literature searches were conducted to identify systematic reviews, evidence-based guidelines or IQWiG-AMNOG-dossiers about any of the treatment alternatives.

2.3.1 Search sources

Systematic reviews and guidelines

The following systematic review and health technology assessment specific databases were searched:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 3 of 12, March 2023
- Epistemonikos (Internet) (https://www.epistemonikos.org/): 2019-2023
- International HTA Database (INAHTA) (https://database.inahta.org/): 2019-2023
- The following guidelines resources were searched:
  - Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): up to 12.03.2023
  - NICE Evidence (Internet) (www.evidence.nhs.uk/): 2019-2023
  - NICE Guidance (Internet) (https://www.nice.org.uk/guidance): 2019-2023
  - ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): 2019-2023
  - Trip Database (https://www.tripdatabase.com/): 2019-2023
  - Canadian Agency for Drugs and Technologies in Health (CADTH) (www.cadth.ca): 2019-2023

Randomized controlled trials (RCT)

The following databases were searched:

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid): 1946 to May 08, 2025

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 2 of 12, February 2025.

During the 2025 update the following systematic review and health technology assessment specific databases were searched, with particular focus on identifying evidence for ULHL FVIII replacement therapy and recent data on gene therapy:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 5 of 12, 01.2023-May 2025
- Epistemonikos (Internet) (https://www.epistemonikos.org/): 2023-2025
- International HTA Database (INAHTA) (https://database.inahta.org/): 2023-2025
- PubMed (Internet) 01.03.2023-08.05.2025
- The following guidelines resources were searched:
  - NICE Evidence (Internet) (www.evidence.nhs.uk/): 2023-2025

3. RESULTS

3.1 OVERVIEW OF INCLUDED STUDIES

Table 2 and 3 summarizes the sources of evidence used to answer the seven FAQs. We identified a network meta-analysis (1), three individual patient data indirect comparison (2–4), an IQWiG-AMNOG report (5), an EHC review (6), a Cochrane review (7) and the WFH Guidelines for the Management of Hemophilia (8). None of the above-mentioned sources reported a direct comparison between two of the three included interventions. The comparator for two of the interventions (factor VIII infusions and antibody prophylaxis) was treatment on demand or episodic treatment (9,10). The novel gene therapy was evaluated in a single armed study (11,12) . For these reasons the comparative effectiveness of the interventions could only be estimated by indirect comparisons. For these we considered the network meta-analysis (1) and the individual patient data indirect comparison (2–4) to be sufficient.

Table 2: Evidence sources (primary studies)

Study/year reference	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will the therapy be capable to prevent bleeds?	FAQ3: How long will treatment effect last?	FAQ4: Can the treatment prevent joint damage?	FAQ5: How will treatment impact my quality of life?	FAQ6: What are the risks or side effects?	FAQ7: Long- term negative effects of treatment?
A-Long(10)	RCT	FVIII prophylaxis (EHL)	✓	✓	✓	✓	✓	✓	
HAVEN 3 (9,13)	RCT	Antibody Prophylaxis	✓	✓	✓	✓	✓	✓	✓
		No prophylaxis							
		No prophylaxis							
GENEr8-1 (11,12)	before-after study	Gene therapy*	✓	✓			✓	✓	
XTEND-1 (14)	Open-label multicenter study	FVIII prophylaxis (UL)	✓	✓	✓	✓	✓	✓	

RCT = Randomized Controlled Trial
*adeno-associated virus 5 (AAV5)–based gene-therapy

Table 3: Evidence sources (systematic reviews, indirect comparisons)

Study/year reference	Evidence source	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will the therapy be capable to prevent bleeds?	FAQ3: How long will treatment effect last?	FAQ4: Can the treatment prevent joint damage?	FAQ5: How will treatment impact my quality of life?	FAQ6: What are the risks or side effects?	FAQ7: Long- term negative effects of treatment?
Reyes 2019 (1)	MA	Antibody Prophylaxis FVIII prophylaxis	✓	✓					
Klamroth 2021 (2)	Indirect comparison (IPD)	Antibody Prophylaxis FVIII prophylaxis	✓	✓				✓	
EHC-Review 2022 (6)	Narrative Review	Antibody prophylaxis FVIII prophylaxis Gene therapy*						✓	
IQWiG-AMNOG 2019 (5)	AMNOG-report	Antibody prophylaxis FVIII prophylaxis	✓	✓				✓	
Olasupo 2024(7)	Cochrane Review	Antibody prophylaxis On demand treatment	✓	✓			✓	✓	
Klamroth 2025 (3)	Indirect comparison (MAIC)	FVIII prophylaxis (ULHL) FVIII prophylaxis	✓	✓					
Alvarez Roman 2024 (4)	Indirect comparison (MAIC)	FVIII prophylaxis (ULHL) Antibody prophylaxis	✓	✓		✓			

AMNOG = Arzneimittelneuordnungsgesetz; IPD = Individual Patient Data Analysis; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MA = Meta-analysis MAIC= matching adjusted indirect comparison ULHL= Ultra long half-life
*adeno-associated virus 5 (AAV5) - based gene-therapy

3.2 FAQ 1: What does the treatment involve?

This section covers the main prophylactic treatment groups for severe hemophilia A i.e., FVIII prophylaxis, antibody prophylaxis, and gene therapy (for adults only). All treatment options alongside the mechanisms of action are described in Table 4 (below). This is partly a new and fast developing field of research and only covers options which were approved as a treatment for hemophilia in Germany May 2025, but does not cover hemostatic rebalancing therapy.

Table 4: Description of treatments

Rationale for treatment
Severe Hemophilia A is a deficiency of coagulation factor VIII, resulting in impaired blood clotting. To reduce the frequency of bleeding episodes, particularly recurrent joint bleeds that can lead to joint damage, prophylactic treatment can be beneficial, to prevent bleeds and the development of hemophilic arthropathy. To prevent bleeding and the subsequent damage that develops, prophylaxis with factor replacement concentrates is the standard of care for severe hemophilia A. In recent years, alternative treatment options have been developed. These include treatment with antibodies as well as gene therapy. Numerous studies have shown that early prophylaxis (primary prophylaxis) can largely prevent joint damage. If prophylaxis can only be started when joint damage is already manifested, the aim is to reduce the frequency of bleeding and improve the patient's quality of life.
Factor VIII replacement
The standard care of severe hemophilia A has been substitution of the deficient factor VIII (FVIII). In the last decades, both plasmatic and recombinant factor concentrates have developed further, i.e., they have become safer regarding a possible transmission of pathogens and are also more user-friendly (smaller volume, larger factor quantity per vial). Nevertheless, the regular venous puncture several times a week is a great burden for many patients. Despite intensive prophylaxis some patients still experience bleeding episodes and need higher factor levels to successfully prevent bleeding episodes. Recent studies show that factor VIII trough level of 1% does not seem to be sufficient. This is also true for the prevention of so-called micro hemorrhages (smallest hemorrhages in the joint mucosa), so that nowadays rather higher trough levels (>3%) are aimed for in many patients. Based on their half-life (HL), factor replacement therapies can be subdivided into three subclasses: ○ Standard half-life (SHL): prophylaxis is conventionally the regular infusion with the missing coagulation factor to maintain adequate factor levels. As SHLs have the shortest HL, injection intervals tend to be shorter and prophylaxis leads to peaks and troughs in factor levels. ○ Extended half-life (EHL): In recent years, factor concentrates have been developed for which the half-life could be extended by means of various technologies, so-called EHL factor concentrates. An extension of the half-life is a prerequisite to enable the patient to have longer application intervals and/or higher factor levels in the context of prophylaxis for hemophilia. There are currently 5 approved FVIII-EHL concentrates for which an extension of the half-life to 1.2–1.9-fold could be achieved through various technologies. Further concentrates are still in development (12,15). ○ Ultra-long half-life (ULHL): Efanesoctocog alfa is a novel factor replacement option for the treatment of hemophilia A and has been approved by the European commission in June 2024. It is a recombinant factor which is decoupled from endogenous von Willebrand factor (vWF) and therefore overcomes the vWF imposed half-life ceiling (4,16) Due to its prolonged half-life, it has been proposed that this factor should be classified as an 'ultra-

long factor' to distinguish it from EHL factors. As this is a newly emerging category and currently includes only one substance, the nomenclature may still evolve (17).
Antibody treatment (Emicizumab)
With antibody prophylaxis, a completely new class of drugs has been developed compared to the FVIII concentrates, which not only differs from the classic coagulation factors through a different type of injection ("under the skin" instead of "into the vein") but also changes the complete therapy. Emicizumab is a recombinant humanized bispecific monoclonal antibody. It binds activated factor IX and factor X to replace the function of the missing activated factor VIII, thereby restoring hemostasis (13). This normally happens in healthy people through the sufficiently present natural factor VIII.
Gene therapy (for adults only)
In general, the aim of gene therapy is to treat genetic diseases by correcting/replacing the defective gene. Gene therapy is preferably used for monogenetic diseases, i.e., diseases that are based on the defect of a single gene. Gene therapy for hemophilia involves gene transfer. Hemophilia offers very good conditions, as it is a monogenetic disease and the treatment response can be examined and monitored by laboratory determination of the clotting factor at regular intervals. The gene therapy product is injected intravenously and consists of the gene for the coagulation factor carried by a vector. In this case it is based on adeno-associated viruses (AAV). At the same time, the vectors contain the control elements necessary for the expression of the gene in the target cell, such as promoters and enhancers. The promotor enables target gene expression in the liver and ensures translation of the coagulation factor. To date there is only one available gene therapy, valoctocogene roxaparvovec. After a single, intravenous infusion of the treatment, continuous production of the clotting factor in the liver cells begins, which can be monitored in regular checks of the factor activity in the laboratory (15). Preexisting antibodies against AAV5 are a contraindication for this gene therapy. Approximately 70% of patients are estimated to be eligible for treatment; however, this proportion tends to decrease with age (18)

3.3 FAQ 2: Will the therapy be capable to prevent bleeds?

As mentioned above no primary studies with direct comparisons between the treatment options with FVIII prophylaxis (SHL, EHL or ULHL), antibody prophylaxis or gene therapy are available today. Available studies compare FVIII prophylaxis to no prophylaxis (= on-demand treatment) or antibody prophylaxis to no prophylaxis. Similarly, the novel ULHL FVIII was not directly compared to the other treatment options. Gene therapy was assessed only in a single arm study. Table 5 summarizes results of these studies for bleeding events. As a direct comparison is not available, indirect comparisons of treatments were considered (table 6). The evidence on the comparative effectiveness of different prophylactic treatment options was examined by reviewing six additional studies. Four of these studies compared FVIII-based prophylaxis with AB-based prophylaxis, one study compared AB-based prophylaxis with ULHL FVIII. One study assessed the comparative efficacy of SHL and EHL FVIII prophylaxis versus the ULHL FVIII agent.

To date, no studies have directly or indirectly compared gene therapy with other prophylactic treatment modalities. The absence of such comparative data limits conclusions on the relative effectiveness of gene therapy and other prophylactic strategies.

Annualized bleeding rate (ABR) all bleeds

Prophylactic treatment consistently demonstrated lower annualized bleeding rates (ABRs) compared to on-demand treatment, irrespective of the specific prophylactic agent.

Gene therapy (GENEr8-1 study) and FVIII prophylaxis (A-Long; XTEND-1) have similar bleeding rates to those of antibody (HAVEN3) prophylaxis. However, follow up differed and a comparison is not possible due to different study protocols and characteristics of included patients. A network meta-analysis and systematic review found a difference in favor of antibody prophylaxis. Certainty of these results is low, due to small sample sizes, open label studies, and imprecision. An individual patient data analysis that controlled for several confounders found no difference between EHL FVIII prophylaxis and antibody prophylaxis for once a week and once every two weeks application of the latter. Indirect comparisons show that ULHL FVIII prophylaxis exceeds ABR reduction compared to antibody, SHL or EHL FVIII prophylaxis. Indirect conclusion from the mean differences of ABR reported by Klamroth et al. can be drawn with caution, implying that EHL prophylaxis is able to reduce ABR more than SHL. Certainty of these results are low, due to open label studies, indirectness, and imprecision.

Zero bleeds

The percentage of patients with zero bleeds ranges from 20% to 65% for FVIII prophylaxis (ULHL FVIII agent at the upper range). Antibody prophylaxis increases this percentage to 30–70% of patients with zero bleeds while gene therapy provides 25% of patients with zero bleeds. Comparability of these results are not given due to vastly different length of the studies (24 weeks to four years).

Comparison of prophylaxis with antibody treatment compared to (EHL) FVIII prophylaxis does not result in statistically significant results if antibody treatment was given every week or bi-weekly. When antibody treatment was applied every fourth weeks, EHL FVIII treatment resulted in significantly higher percentages of patients experiencing zero bleeds. Certainty is likewise low here for the same reasons as mentioned above. The IQWiG-AMNOG dossier concluded that due to heterogeneity between the studies and the absence of an adequate bridging comparator, an indirect comparison is not possible. Therefore, a net benefit of FVIII or antibody prophylaxis was not deductible.

Joint bleeds

Prophylaxis can lower joint bleeds from 20–30 to 0–2 per year. The type of treatment appears to be less decisive in determining the effectiveness of bleed reduction. There are no available primary studies comparing joint bleeds between treatments. Indirect comparison indicates that ULHL FVIII can reduce joint bleeds when compared to antibody, SHL or EHL prophylaxis. Antibody treatment is more effective in preventing joint bleeds than on-demand treatment. Gene therapy has not been compared to the other treatment options. Indirect conclusion

from the mean differences of joint bleeds reported by Klamroth et al. can be drawn with caution, implying that EHL prophylaxis is able to reduce joint bleeds more than SHL.

Certainty of these results is low, due to open label studies, indirectness, imprecision, and different length of the studies

Conclusion for decision aid: Evidence indicates that prophylaxis considerably reduces bleeding compared to no prophylaxis, irrespective of the specific agent used. Annual bleeding rates range between 1 and 9 bleeding events per year with FVIII prophylaxis, depending on which specific subclass is used. Newly developed FVIII agents generally provide better security against bleeding events leading to the amount of bleeding events at the lower end. Non-factor antibody prophylaxis provides ABR of 1–2 while gene therapy provides similar ABRs if the treatment is successful. As a comparison, ABRs without prophylaxis are around 35–50.

Percentage of patients with zero bleeds range from 20% to 65% for FVIII prophylaxis (again, newer FVIII agents will be at the upper range). Antibody prophylaxis results in percentages of patients with zero bleeds of 30–70%. Gene therapy provides 26% of patients with zero bleeds over a time period of four years.

Prophylaxis can lower joint bleeds from 20–30 to 0–2 joint bleeds.

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Table 5: FAQ 2 – Evidence synthesis (primary studies)

Author	Type of study (n)	Follow-up time	Intervention (prophylaxis)	Comparator (no prophylaxis)	% Reduction (P)*	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Rate /control group event rate (95% CI)				
ABR (Annualized rate of bleeding events); all; model-based							
A-Long (EHL) (10)	RCT (46)	28 weeks	1W: 8.9 (5.5–14.5))	37.3 (24.0–57.7)	76 (< .001)	Moderate (small sample size, open label; upgrade due to effect size)	Difference in favor of prophylaxis with EHL ⇗
HAVEN 3 (9,13)	RCT (89)	24 Weeks	1W: 1.5 (0.9–2.5) 2W: 1.3 (0.8–2.3)	38.2 (22.9–63.8)	–96 –97	Moderate (small sample size, open label; upgrade due to effect size)	Difference in favor of prophylaxis ⇗
GENEr8-1(11,12)	before-after study (112)	4 years	1.3 (2.2)**without patients resuming prophylaxis: 1.4(2.6)**	(5.4****).	–76.5	Moderate (single armed, open label; upgrade due to effect size)	Difference in favor of prophylaxis ⇗
XTEND-1 (14)	Open-label multicenter study (133)	52 weeks	0.71 (0.52–0.97)[#]	(3.2±5.4****)	n.s	Moderate (open label, non-randomized; upgrade due to effect size)	n.a.
ABR: Subjects with no bleeding episodes; model-based							
A-Long (10)	RCT (46)	28 weeks	1W: 4 (17.4%)	0 (0)		Low (small sample size, open label)	Difference in favor of prophylaxis ⇗
HAVEN 3 (9,13)	RCT (89)	24 weeks	1W: 50 (33–67) 2W: 40 (24–58)	0 (0–18)		Low (small sample size, open label)	Difference in favor of prophylaxis ⇗

Author	Type of study (n)	Follow-up time	Intervention (prophylaxis)	Comparator (no prophylaxis)	% Reduction (P)*	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Rate /control group event rate (95% CI)				
GENEr8-1 (12)	before-after study (112)	4 years	25.9	(30.4****)	n.a.	Low (single armed, open label)	n.a.
XTEND-1 (14)	Open-label multicenter study (133)	52 weeks	65	n.s	n.s	Low (open label, non-randomized)	n.a
ABR: Subjects with spontaneous joint bleeding episodes; model-based							
A-Long (10)	RCT (46)	28 weeks	1W: 0.0 (0.0–3.8)	18.6 (7.6–29.6)		Low (small sample size, open label)	Difference in favor of prophylaxis ⇗
HAVEN 3 (9,13)	RCT (89)	24 weeks	1W: 1.1 (0.6–1.9)$^{+}$ 2W: 0.9 (0.4–1.7)$^{+}$	26.5 (14.7–47.8)$^{+}$	−96 −97	Low (small sample size, open label)	Difference in favor of prophylaxis ⇗
GENEr8-1 (11,12)	before-after study (112)	49–52 weeks	0.4***±1.5**	n.a.	n.a	Low (single armed, open label)	n.a.
XTEND-1 (14)	Open-label multicenter study (133)	52 weeks	0.52±1.09	(2.3±4.5****)	n.a	Low (open label, non-randomized)	n.a
(10) Table 2; (13) Table 1; (12) Figure 1B;1D; (11) Supplementary Table S4; (14) Table 2. 1W = Once Weekly; 2W= every two weeks SHL= Standard half-life EHL= Extended half-life ULHL= Ultra long half-life *Reduction in ABR, calculated using negative binomial model; **standard deviation; *** all							

Author	Type of study (n)	Follow-up time	Intervention (prophylaxis)	Comparator (no prophylaxis)	% Reduction (P)*	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Rate /control group event rate (95% CI)				
spontaneous bleeds ****prior gene therapy/UL and with prophylaxis with FVIII or Antibodies [+] treated joint bleeds; [#] model based							

Table 6: FAQ 2 – Evidence synthesis (NMA, IPD indirect comparison)

Author	Type of study (n)	Follow-up time	Intervention (prophylaxis)	FVIII prophylaxis	Rate ratio (95% CI)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Mean ABR (95% CI)				
ABR (Annualized rate of bleeding events); all bleeds							
Reyes 2019 (1)	NMA	Converted to bleed-rates per day and multiplied to ABRs	n.s.	n.s.	1W: 2.80 (1.06, 7.64) 2W: 3.19 (1.19, 9.21)	Low (small sample size, open label, indirectness)	Difference in favor of Antibody prophylaxis ⇗
Klamroth 2021 (2)	Indirect comparison (IPD)	Antibody prophylaxis 25.6 to 33.7 weeks FVIII prophylaxis (EHL) 32.1 weeks	1W: 2.93 (n.s.) 2W: 2.60 (n.s.)	2.73 (n.s.) 1.49 (n.s.)	IRR 0.93 (0.63–1.39) IRR 0.57 (0.28–1.17)	Low (small sample size, open label, indirectness)	No difference shown ⇔

Author	Type of study (n)	Follow-up time	Intervention (prophylaxis)	FVIII prophylaxis	Rate ratio (95% CI)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Mean ABR (95% CI)				
IQWiG-AMNOG 2019 (5)	AMNOG-dossier	Antibody prophylaxis	n.a.	n.a.	n.a.	Low (indirectness)	Indirect comparison not possible as studies are too different. No difference shown ⇔
		FVIII prophylaxis					

Author	Type of study (n)	Follow-up time	Intervention	comparator	Mean difference (MD) (95% CI)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Mean ABR (95% CI)				
ABR (Annualized rate of bleeding events); all bleeds							
Klamroth 2025 (3)	Indirect comparison (MAIC)	FVIII prophylaxis (UL) 52 weeks	n.s		SHL:-3.61 (-4.43;-2.79) EHL-2.24 (-3.24;-1.25) IRR: 0.23 (0.18; 0.31) 77% reduction	Low (indirectness, open label)	Difference in favor of FVIII prophylaxis (UL) ⇗
		FVIII prophylaxis (SHL) 52 weeks	n.s				
		FVIII prophylaxis (EHL) 10-52 weeks	n.s				
Alvarez Roman 2025 (4)	Indirect comparison (MAIC)	FVIII prophylaxis (ULHL) 52 weeks	n.s		IRR: 0.32 (0.19;0.56)	Low (Indirectness, open label)	Difference in favor of FVIII prophylaxis (UL) ⇗
		Antibody prophylaxis 1W 24 weeks	n.s				
Olasupo 2024 (7)	Cochrane review	Antibody prophylaxis 1W 24 weeks	1W: 2.5 2W: 2.6	on demand 47.6	1W: MD: -45.1 (-63.44; -26.76)	Moderate	Difference in favor of Antibody prophylaxis ⇗
		Antibody					

		prophylaxis 2W 24 weeks On-demand			2W: MD: -45 (-63.19; -26.81)		
(1)Supplementary table 10; (2) Figure 1; (3) Figure 1; (4) Figure 2 (7) Analysis 4.1.5; 5.1.6; SHL= Standard half-life EHL= Extended half-life ULHL= Ultra long half-life							
Proportion of Patients with zero bleeds							
Klamroth 2021 (2)	Indirect comparison (IPD)	Antibody prophylaxis 25.6 to 33.7 weeks FVIII prophylaxis 32.1 weeks	1W: 46.5% 2W: 40.0% 4W: 29.3%	47.6% 54.2% 51.2%	OR 1.05 (0.60–1.82) OR 1.78; 95% CI 0.62–5.11 OR 2.53; 1.09–5.89	Low (small sample size, open label, indirectness)	1W and 2W: No difference shown ⇔ 4W: Difference in favor of Antibody FVIII prophylaxis ⇗
Olasupo 2024 (7)	Cochrane review	Antibody prophylaxis 1W 24 weeks Antibody prophylaxis 2W 24 weeks On-demand	1W : 50% 2W: 40%	on demand 0%	RR: 1W: 19(1.21; 298.40) RR: 2W:15.31 (0.96; 242.76)	Low (open label, indirectness)	Difference in favor of Antibody ⇗
(2)Figure 2A; (7) Analysis 4.2.1; 5.2.1. RR: Risk ratio							
AjBR: Annualized joint bleeding Rate							
Klamroth 2025 (3)	Indirect comparison (MAIC))	FVIII prophylaxis (ULHL) 52 weeks FVIII prophylaxis (SHL) 52 weeks	n.s	n.s	SHL: -3.42 (-4.77;-2.08) EHL: -1.60 (-2.32;-0.88	Low (open label, indirectness)	Difference in favor of FVIII prophylaxis (ULHL) ⇗

		FVIII prophylaxis (EHL) 52 weeks					
Alvarez Roman 2025 (4)	Indirect comparison (MAIC)	FVIII prophylaxis (ULHL) 52 weeks	n.s	n.s	IRR: 0.48 (0.24; 0.95**	Low (open label, indirectness)	Difference in favor of FVIII prophylaxis (ULHL) ⇗
		Antibody prophylaxis 1W 24 weeks					
Olasupo 2024 (7)	Cochrane review	Antibody prophylaxis 1W 24 weeks	1W: 1.1 2W: 0.9	On-demand: 26.5	1W: -25.4 (-45.23; -5.57) 2W: -25.6 (-45.4; -5.8	Moderate	Difference in favor of Antibody ⇗
		Antibody prophylaxis 2W 24 weeks					
		On-demand					

(2)(4) Figure 2; (3) Figure 1 (7)Analysis 4.1.2; 5.1.3
1W = Once Weekly 1.5mg/kg/week; 2W= bi-weekly 3mg/kg/biweekly; 4W after 4 weeks 6.0mg/kg for 24 weeks; IRR = Incidence Rate Ratio; NMA = network meta-analysis; IPD = individual patient data analysis MAIC= matching adjusted indirect comparison SHL= Standard half-life EHL= Extended n.s.= not specified; n.a. = not applicable half-life ULHL= Ultra long half-life **AjBR (treated)

3.4 FAQ 3: How long will treatment effect last?

This question should be divided in 2 sub questions:

3.4.1 How long will one application of a treatment last?

The SHL factor concentrates have to be injected every second or third day depending on the intensity of prophylaxis (8). Some EHL FVIII preparations with extended half-life can be injected once or twice a week (8). While ULHL FVIII is typically injected only once a week.

For prophylaxis with antibodies, the medication is usually injected at fixed intervals after a saturation phase with weekly doses. The drug can be administered once a week, but, if necessary, also only every 2 weeks or every 4 weeks (8).

Gene therapy for hemophilia A involves a single intravenous infusion. The goal is to achieve a sustained increase of factor VIII to reach levels in the mild hemophilic to normal range. Approximately four weeks after administration, gene expression leads to endogenous production of factor VIII, compensating for the underlying deficiency. As a result, prophylactic factor VIII replacement therapy can be discontinued. Patients must be aware that close medical monitoring is necessary following gene transfer. This includes regular follow-up visits as follows: weekly during the first 26 weeks; every 2 to 4 weeks from week 26 to 52; every 3 months during years 1 to 2; and from year 2 on every 6 months (19).

3.4.2 How long will the effect of one treatment alternative last?

Factor VIII Prophylaxis:

The main cause of insufficient efficacy of FVIII treatment with SHL or EHL concentrates are neutralizing anti-FVIII antibodies inhibitors. Hemophilia A patients who develop an inhibitor against factor VIII can no longer be treated with a classic factor VIII preparation, as factor VIII is neutralized by the inhibitor. Inhibitory antibodies develop in approximately 30 of 100 previously untreated patients with severe hemophilia A. Among these 30 patients, inhibitors occur within the first 20 dosages of FVIII in 24 patients and within the first 75 dosages of FVIII in the remainders (8).

Hay et al. found inhibitor formation also in previously treated patients. Starting at 2–6 cases per 1.000 patients after 5 years of treatment, the incidence of inhibitors declined with increasing age before reaching a second peak of 10.5 new inhibitors per 1.000 patient-years in patients >60 years or age (20). Patients treated with ULHL FVIII did not develop inhibitors to factor VIII (incidence 0%; 95% Cl, 0.0–2.3). Preexisting antidrug antibodies were detected in 7% of patients and 3% developed antidrug antibodies, but these have been reported to not disrupt factor VIII activity (14).

Antibody prophylaxis:

Antibody prophylaxis like prophylaxis with emicizumab is also an approved treatment option for patients with inhibitors. However, antibodies against emicizumab can be formed: 5,1% of

668 patients in a synthesis of 7 phase-3 studies (21) developed these antidrug antibodies (ADAs). About half of them were non-neutralizing antibodies (2,4%), 1% were transient and 1,6% were persistent. In clinical studies of emicizumab, a loss of efficacy due to ADAs is an infrequent (≥1/1000 to <1/100) event (21).

Gene therapy:

Once gene therapy begins to take effect, no further daily or weekly injections are needed. Gene therapy has shown a sustained increase in factor VIII activity levels, with published data indicating a mean factor level of 18.0 IU/dl in a five-year follow-up in a small cohort and 16.1 IU/dL over 4 years in a larger cohort (12). Factor activity has been demonstrated for up to 7 years. Here, however, a gradual decrease in factor VIII activity is shown. Although factor VIII activity decreases, it appears to be highest in the first years after treatment. The trial with the only gene therapy approved so far has been running for 5 years. At the end of year 4 factor VIII activity was as follows: 7.7% (≥40 IU/dL; non hemophilia), 52.3% (<40 and ≥5 IU/dL; mild hemophilia), 13.8% (<5 and ≥3 IU/dL; moderate hemophilia), 26.2% (<3 IU/dL moderate to severe hemophilia). Around 17.9% of patients had to resume prophylaxis treatment over the course of four years (12). In addition, preliminary, non-peer-reviewed modeling data suggests a predicted median durability of 11.0–17.0 years. However, the validity of these estimates cannot be confirmed, and should be interpreted with caution.

Gene therapy has not been associated with the development of Inhibitors (12). Due to gene therapy, all participants developed anti-AAV5 antibodies (22). Due to this AAV antibody development, this treatment option cannot be repeated.

Conclusion for the decision aid: Frequency of applications differs between treatment categories and subclasses. Factor replacement prophylaxis (SHL, EHL, ULHL) has to be applied every day up to once a week. Prophylaxis with antibodies has to be applied weekly, every 2 or every 4 weeks, while gene therapy is a once in a lifetime treatment, and enables 82 of 100 patients to stay off additional prophylaxis. How long the treatment remains effective is still uncertain and needs to be evaluated further, as current data only demonstrate effectiveness for up to five years. FVIII replacement prophylaxis can be used, until an inhibitor is developed. This occurs in < 1% of cases per year in previously treated patients. For antibody prophylaxis so called antidrug antibodies (ADAs) are recognized in < 1% of cases per year, while antibodies against the carrier of the gene therapy are detected in all patients after treatment.

3.5 FAQ 4: Can the treatment prevent joint damage?

The only study investigating joint health to date compares ULHL FVIII and antibody prophylaxis (table 7), indicating that ULHL FVIII prophylaxis is associated with an improvement from baseline in comparison to antibody prophylaxis.

The primary cause of joint destruction in patients with hemophilia A are hemorrhages. Therefore, it can be assumed that the reduction of joint hemorrhages also slows down the destruction of the joints. However, none of the other studies provided results concerning joint health and cannot be assessed.

Table 7: FAQ 4 – Joint health Change from baseline of HJHS

Author	Type of study (n)	Follow-up time	Mean difference (MD) (95% CI)	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Alvarez Roman 2024(4)	Indirect comparison (MAIC)	FVIII prophylaxis (ULHL) 1W Antibody prophylaxis	Joint score: -2.06 (-3.97; -0.14) Total: -2.37 (-4.36; -0.39)	Low (Indirectness, open label)	Difference in favor of FVIII prophylaxis (ULHL) ⇗
(4) Figure 5. MAIC: matching adjusted indirect comparison ULHL= Ultra long half-life					

Conclusion for the decision aid: ULHL FVIII seems to improve joint health more than antibody prophylaxis. Due to the limited number of studies encompassing joint health as an outcome the current evidence base is insufficient to draw a conclusion. There might be a connection between frequency of joint bleeds and joint dam. age

3.6. FAQ 5: Will it impact my quality of life?

Health related quality of life (HrQoL) was assessed by the Hemophilia quality of life questionnaire (Haem-A-QoL), or by Haemo-QOL-A. No studies could be identified that assessed HrQoL in patients with prophylactic treatment compared to episodic treatment. EHL FVIII and antibody prophylaxis reported HrQoL data in the intervention arms alone, gene therapy was an uncontrolled cohort study. Unfortunately, different measurement tools, items or subscales were used. Moreover, HrQoL was not reported for the EHL FVIII cohort alone. Therefore, no comparison of the three options is possible.

EHL FVIII showed a reduction in painful swellings or pain in the joints and in the number of days absent from work compared to the beginning of the study. In antibody prophylaxis this was only the case for participants with >9 bleeds at start of the study. ULHL FVIII mean physical Haem-A-QoL score at baseline was 37.02±23.83, and after 52 weeks reduced to 29.66±23.40 which reflects a change from baseline of −6.79±18.59 least square means: −6.74 (−10.13 to −3.36) (14).

HrQoL was assessed for antibody prophylaxis by Haem-A-QoL included in the Cochrane Review, which concluded, that emicizumab 3.0 mg/kg biweekly may improve the HrQoL

physical health score (baseline adjusted mean: 28.35) when compared to on-demand therapy (MD –15.97, 95% CI −29.14 to –2.80). 1.5 mg/kg/week did not change the HrQolL score(7).

For gene therapy the four years follow-up showed an increase in the total score of HrQoL measured with the Haemo-QOL-A. Gene therapy improved the Haemo-QOL-A score by a mean of 6.5 (95% CI, 4.0–9.1; n = 103; P < .0001) in comparison to previous prophylaxis (FVIII or antibody prophylaxis) (12).

Conclusion for the decision aid: Studies show improvement in pain, HrQoL and working ability with FVIII or antibody prophylaxis as well as gene therapy when compared to baseline for patients with severe hemophilia A. Whether one of these prophylactic methods improves HrQoL more than the others is still unknown.

3.7. FAQ 6: What are the risks or side effects?

Comparability of results between SHL, EHL and ULHL FVIII, antibody and gene therapy as prophylactic treatments is limited due to differences in study design, follow-up duration and adverse event reporting. There are no available studies comparing adverse events across treatments.

Prophylaxis with antibodies led to an increase in the risk ratio (RR) of adverse events of 2.83 (1.47; 5.47) when weekly applied, and an increase of 1.71 (1.06; 2.77) when biweekly injected when compared to on-demand therapy. No change was detected in serious adverse events, and no cancer or mortality was reported (7). The most common adverse event in the gene therapy group was elevated alanine aminotransferase levels (90.3%) which led to treatment with glucocorticoids in 79% during the first three years. Again, it must be considered that there is no direct comparison between the treatment alternatives. Therefore, the numbers presented may be biased by several causes (selection bias, patient characteristics, duration of follow-up, methods of assessing AEs, etc.). To our knowledge no adjusted indirect comparison exists similar to those for bleeding events.

Conclusion for the decision aid:

Adverse events occurred across all groups, including the on-demand group. Therefore, no clear conclusion can be drawn about whether one treatment option is safer than another. Arthralgia and headache have been reported for all treatment options as two of the most common adverse effects but with varying prevalence depending on the treatment. For example, headaches were reported for FVIII prophylaxis in 25 of 100 patients; for ULHL FVIII in 19 of 100; with antibody prophylaxis the incidence was 8–11 of 100 (10) and gene therapy reported the highest incidence with reported headaches in 45 of 100 patients in four years.

Serious AEs seem to occur more frequently in the gene therapy group (low certainty evidence). In the gene therapy group, 28 of 100 patients experienced a serious adverse event (e.g., ALT increased, diarrhea, gastroenteritis or rectal hemorrhage (12)) compared with 9 of 100 in the FVIII group (2).

Table 8: FAQ 6 – Risks and side effects

Variable	**EHL FVIII prophylaxis 1W** (10)	**Episodic treatment**(10)	**FVIII prophylaxis (ULHL) (Arm-a)** (23)	**Antibody prophylaxis 1W** (13)	**Antibody prophylaxis 2W** (13)	**No prophylaxis** (13)	**Gene therapy** (12)		
Median duration of exposure period (range) — wk	30 (1–54)	30 (1–54)	52	29.3 (17.3–49.1)	30.1 (6.1–50.1)	7.1 (0.1–26.1)	year 1	Year3	All 4 years
Subjects with ≥1 AE %	75.0	43.5	77	n.s.	n.s.	n.s	100	80.2	100
Number of AE; n	46.	23	n.s.	143	145	19			
serious AE; %	8.3	0.0	9.77	2.7	8.6	0	15.7	6.9	27.6
Adverse event leading to discontinuation	n.s.	n.s.	2	0	3	0			
Fatal AE; %	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0	0	1.5
Most common AEs, ≥3%							**Most common AEs, ≥30%**		
Nasopharyngitis	4.2	13.0	n.s.	6	17	0			
Arthralgia	8.3	4.3	18.80	19	17	6	27.6	12.2	46.3
Upper respiratory tract infection	0	13.0	n.s.	11	11	0	18.7	3.8	32.1
Headache	25.0	8.7	19.55	8	11	6	34.3	9.9	44.8
Influenza	0	0	n.s.	3	9	0			
COVID-19	n.s	n.s	n.s.	n.s	n.s	n.s	0	17.6	32.1
Pyrexia	4.2	4.3	n.s.	n.s	n.s.	n.s.			
Injection-site reaction / Infusion-related reaction/ Infusion-associated	n.s.	n.s.	n.s.	25	20	12	9/37.3	0/0	9/ 37.3

Alanine aminotransferase increase (ALT)	n.a.	n.a.	n.s.	n.a.	n.a.	n.a.	85.1	23.7	90.3
Nausea	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	37.3	1.5	39.6
Aspartate aminotransferase increase (AST)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	32.8	3.8	38.1
Fatigue	n.s.	n.s.	5.26	n.s.	n.s.	n.s.	26.9	3.1	31.3
Fall	n.s	n.s	7.52	n.s	n.s	n.s	n.s	n.s	n.s
Back pain	n.s	n.s	6.02	n.s	n.s	n.s	n.s	n.s	n.s
Anaphylactic or anaphylactoid reaction	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	2.2	0	2.2
Thromboembolic event	0	0	0	0	0	0	0	0	0
1W = once weekly; 2W = every two weeks; n.s.= not specified; n.a. = not applicable									

3.8. FAQ 7: ARE THERE LONG-TERM NEGATIVE EFFECTS OF TREATMENT TO BE EXPECTED?

For FVIII prophylaxis data from 3 decades and several randomized controlled trials give a precise guess about benefits and risks. The main risk in FVIII prophylaxis is the development of inhibitors, that occurs in 34–54 of 100 patients (24).

For antibody prophylaxis an analysis of a 24-week follow-up showed no significant change in the ABR. During 970 patient-years of exposure, antibody prophylaxis had a favorable long-term safety profile with no new or unexpected signals (25). Finally, since the licensing of emicizumab (antibody prophylaxis), 2 treated patients with hemophilia A without inhibitors have died. Circumstances of these fatalities have not been fully elucidated (26).

Long-term data collection is used, among other things, to investigate the theoretical risk of tumor development after gene therapy. During a 5-year period one case of B-cell acute lymphoblastic leukemia (B-ALL) was diagnosed but was very likely not related to the gene therapy (27). The two deaths during the study duration of gene therapy were likely not related to the gene therapy (12,28).

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

This evidence review aimed at comparing benefits and risks of different prophylactic therapies for patients with severe hemophilia A. The standard prophylactic regimen is FVIII infusions. In the last years, also humanized, bispecific monoclonal antibody (emicizumab) in a subcutaneous application has been established. The gene therapy was recently approved for adult patients.

In general, low certainty (imprecise) evidence suggests inconsistent findings for all FAQs/outcomes. As there is no study with a direct comparison, confounding effects are likely (bias by indication, selection bias, etc.). Indirect comparisons often have the problem that patient collectives, inclusion criteria or methods for measuring outcomes are too different to allow for a fair comparison. In the case of gene therapy, no comparison exists yet.

Overall, prophylaxis seems to be more effective for preventing bleeds and joint damage than on-demand therapy. However, more data is needed on-long term effectiveness and probable harms of antibody and gene therapy. Also, data on joint preservation and quality of life is missing and should be collected in larger comparative studies. An ongoing routine practice data collection (AbD number: 2020-AbD-002) for gene therapy, initiated on 30 August 2024 and expected to result in a benefit assessment by 2 November 2029, represents a potential opportunity to systematically compare the gene therapy to standard of care under real-world conditions.

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report has several strengths that ought to be noted. These include comprehensive searches of the most recent evidence summarized in the approval trials, clinical practice guidelines, meta-analyses and HTA-reports (AMNOG), as well as coverage of a wide range of FAQs and outcomes of interest. Nevertheless, some limitations should also be mentioned. Firstly, there was an unequal distribution of data under FAQs, with FAQ 2 and 6 having the highest data coverage; and FAQs 3, 4 and 5 with the least. Secondly, operationalizations of outcomes were different and mostly only one study was found for a single comparison, so pooling was not possible. The studies included heterogeneous populations, .(e.g., different disease severities), interventions and co-interventions as well as varying outcome measures. Thirdly, in the indirect comparisons all outcomes were based on low certainty evidence with the most relevant reason for downgrading being imprecision (small sample size, typically <50 per treatment arm and associated wide confidence intervals). Fourthly, a high potential for bias in the primary studies resulted solely from the fact that the underlying primary studies could not be blinded.

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APPENDIX

PubMed:

("Hemophilia"[Mesh] OR "Hemophilia A"[tiab] OR "Haemophilia A"[tiab] OR "Hämophilie A"[tiab]) AND ("Factor VIII"[Mesh] OR "Factor VIII"[tiab] OR FVIII[tiab] OR "Recombinant Factor VIII"[tiab] OR Emicizumab[tiab] OR "Monoclonal antibody"[tiab] OR antibody[tiab] OR "Gene Therapy"[Mesh] OR "Gene Therapy"[tiab] OR Efanesoctocog[tiab] OR "Efanesoctocog Alfa"[tiab] OR Valoctocogene[tiab] OR "Valoctocogene roxaparvovec"[tiab])

Cochrane Library:

("hemophilia A" OR "haemophilia A" OR "hämophilie A"):ti,ab,kw AND ("factor VIII" OR FVIII OR "recombinant factor VIII" OR emicizumab OR efanesoctocog OR "efanesoctocog alfa" OR valoxtocogene OR "valoctocogene roxaparvovec" OR antibody OR "monoclonal antibody" OR "gene therapy"):ti,ab,kw

HTA:

("hemophilia A" OR "haemophilia A" OR "hämophilie A")

Epistemonikos:

("hemophilia A" OR "haemophilia A" OR "hämophilie A") AND ("emicizumab" OR "efanesoctocog" OR "efanesoctocog alfa" OR "valoxtocogene" OR "valoctocogene roxaparvovec" OR "monoclonal antibody" OR "gene therapy")

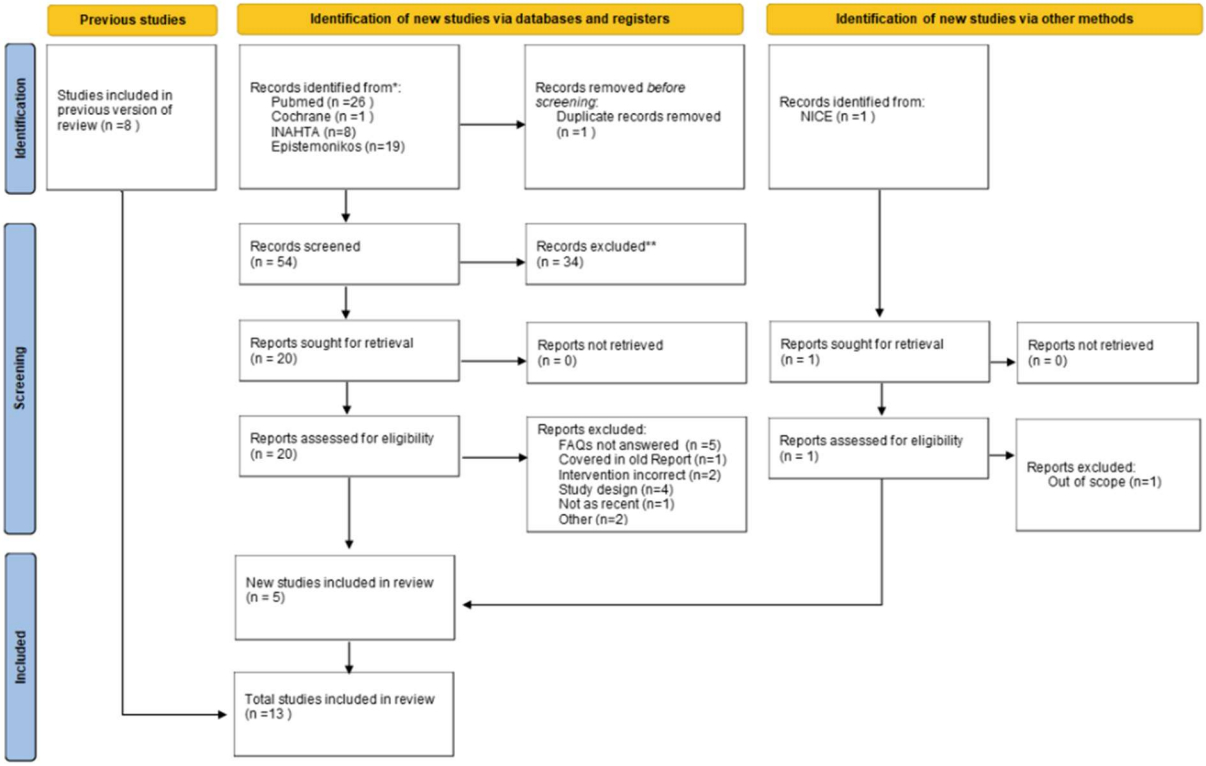

Figure 1: PRISMA flow chart of the updated Report. Source: Page MJ, et al. BMJ 2021:372:n71 doi:10.1136/bmj.n71.