South African National Department of Health
Brief Report of Rapid Review
Component: Subcommittee for Haemophilia

TITLE: Prophylactic Factor VIII compared to on-demand treatment for patients (adults and children) with haemophilia A without inhibitors

Date: June 2023

UPDATE: This document serves as an update to the medicine review conducted previously, on individuals under the age of 18 years only, which was presented to the NEMLC in October 2022 by the Paediatric Hospital Level Expert Review Committee. The update extends the population group to include both children and adults.

Key findings

- Current South African standard of care for severe haemophilia A patients is treatment of bleeding on-demand with blood factor VIII. A potential alternative is blood factor VIII prophylaxis.
- We conducted a rapid review of systematic reviews, meta-analyses and clinical trials reporting on the efficacy and safety of factor VIII prophylaxis for patients with severe haemophilia A.
- In August 2022, a literature search was conducted using PubMed, Cochrane Database and Epistemonikos. Three systematic reviews were found. One study which most closely matched our PICO and country context was selected for data extraction. **An updated search in February 2023 extending inclusion to patients of all ages found no other studies which matched the PICO question.**
- Most studies included in the systematic review had small samples sizes and overall, the evidence was reported as very low certainty.
- Low dose blood factor VIII prophylaxis (10IU/kg twice weekly) versus on-demand treatment:
  - Total annualised bleeds; 2 RCTs found a significantly smaller number of mean bleeds per annum in the low dose prophylaxis groups (Ratio of means: 0.27, 95% CI 0.17 to 0.43; P < 0.00001; 2 RCTS; n=71; 2 RCTs, n=71, very low quality).
  - Annualised joint bleeds; 2 RCTs found a significantly smaller number of mean joint bleeds per annum in the low dose prophylaxis groups (Ratio of means: 0.17, 95% CI 0.06 to 0.43; P=0.0002; 2 RCTs, n=71, very low quality).
- Intermediate dose blood factor VIII prophylaxis (20-30 IU/Kg twice or thrice weekly) versus on-demand treatment
  - Total annualised bleeds; 4 RCTs found a significantly smaller number of mean bleeds per annum in the intermediate dose prophylaxis groups (Ratio of means: 0.15, 95% CI 0.07 to 0.36; P < 0.00001; 4 RCTs, n=237, very low quality).
  - Annualised joint bleeds; 2 RCTs found a significantly smaller number of mean joint bleeds per annum in the intermediate dose prophylaxis groups (Ratio of means: 0.14 – reduction of 86% in bleeds per annum, 95% CI 0.07 to 0.27; 4 RCTs, n=237, very low quality).
- Adverse events were reported in two studies; one RCT reported no difference in development of inhibitors. Two RCTS reported on central venous access device related infections; one RCT reported more infections in the prophylaxis group however no devices were inserted in the on-demand group and another RCT reported no difference between groups (p values not reported for both RCTs).
- Low and intermediate dose factor VIII prophylaxis are potentially more cost saving than treating bleeds on-demand when considering drug acquisition costs of factor VIII only (base case – intermediate prophylaxis). Scenarios including treatment of minor bleeds only found that low and intermediate dose prophylaxis may be more effective but incrementally more costly than treatment on demand. Intermediate dose factor VIII prophylaxis was estimated to be more cost saving than low dose prophylaxis.
- *See Summary of Findings Table*

SUBCOMMITTEE FOR HAEMAPHILIA RECOMMENDATION:

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

Rationale: The Committee suggests using intermediate factor VIII prophylaxis for severe haemophilia A patients without inhibitors. There is very low certainty evidence to suggest that low dose and intermediate dose factor VIII prophylaxis therapies are more effective than treatment on-demand for patients with haemophilia A. Basic cost-effectiveness analysis shows low and intermediate dose prophylaxis are potentially more cost-saving than treatment on demand if only considering acquisition costs of factor VIII. Sensitivity scenarios which accounted only for treatment of minor bleeds (and not major or life-threatening bleeds) showed that low and intermediate dose prophylaxis were more effective but more costly than treatment on demand. The analysis did not account for quality of life, mortality, cost of surgeries or long-term complications. Intermediate dose prophylaxis is potentially more effective and may have higher cost savings than low dose prophylaxis.

Level of Evidence: Level 1 – systematic review, very low certainty of evidence for low dose prophylaxis, low certainty of evidence for intermediate.
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price.

(Refer to appendix 1 for the evidence to decision framework)

Monitoring and evaluation considerations	Monitoring is compulsory, details regarding implementation to be determined for each relevant Standard Treatment Guidelines

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NEMLC RECOMMENDATION (20 JULY 2023):

The NEMLC accepted the haemophilia subcommittee recommendation for factor VIII prophylaxis for patients with severe haemophilia A and the relevant updates to the Adult and Paediatric Hospital Level Standard Treatment Guidelines.

Summary of findings Table – From Delgado-Flores et al. (2022)[1]

Low Dose Prophylaxis vs On-Demand Treatment

Table 2. Summary of findings for episodic treatment vs prophylaxis (either low, intermediate, or high dose).

Outcomes (follow-up in months)	of participants (studies)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk with Control	Risk with Intervention		
Episodic treatment (control) vs Low-dose prophylaxis (intervention)					
Annualized bleeding rate (12 m)	71 (2 RCTs)	Range of means: 9.4–25.3	Range of means: 2.2–7.7	RM 0.27 (0.17 to 0.43)	⊕◯◯◯ VERY LOW [a,d]
Annualized joint bleeding rate (12 m)	71 (2 RCTs)	Range of means: 5.8–10.3	Range of means: 1.0–1.8	RM 0.17 (0.06 to 0.43)	⊕◯◯◯ VERY LOW [a,d]
Change in the Hemophilia joint health score-2.1 (HJHS-2.1). Range: 0 to 124. Higher score = worst (12 m)	66 (2 RCTs)	• **Verma 2016** Low-dose prophylaxis: median change of 0 points. Episodic treatment: median change of 4.5 points ($p<0.05$). • **Chozie 2019** Low-dose prophylaxis: median change of -1 points. Episodic treatment: median change of 2 points ($p<0.001$).			⊕◯◯◯ VERY LOW [a,d]

Intermediate Dose Prophylaxis vs On-Demand Treatment

Outcomes (follow-up in months)	of participants (studies)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk with Control	Risk with Intervention		
Episodic treatment (control) vs Intermediate-dose prophylaxis (intervention)					
Annualized bleeding rate (12.0 to 82.5 m)	237 (4 RCTs)	Range of means: 13.0–57.7	Range of means: 2.5–6.2	RM 0.15 (0.07 to 0.36)	⊕◯◯◯ VERY LOW [a,b,c]
Annualized joint bleeding rate (12.0 to 82.5 m)	237 (4 RCTs)	Range of means: 4.9–43.8	Range of means: 0.6–5.2	RM 0.14 (0.07 to 0.27)	⊕◯◯◯ VERY LOW [a,b,c]
Radiographic findings (49.0 to 82.5 m)	95 (2 RCTs)	413 per 1000	149 per 1000	RR 0.36 (0.18 to 0.71)	⊕◯◯◯ VERY LOW [a,d]

Quality of life (36.0 to 82.5 m)	123 (2 RCTs)	• **Gringeri 2011 (82.5 months):** Score in the "family" dimension of the Haemo-QoL scale was lower (better) in patients with intermediate-dose prophylaxis (mean: 11.3) than in those with episodic treatment (mean 44.0), $p<0.05$.
		• **Manco-Johnson 2017 (36 months):**
		  • Mean change in the score of the Haemo-QoL-A: Intermediate-dose prophylaxis group: 3.98 points. Episodic treatment: 6.00 points ($p = 0.27$).
		  • Mean change in the score of the EQ VAS (higher = better): Intermediate-dose prophylaxis: 10.49 points. Episodic treatment: −1.80 points. No p-value provided.
		  • Mean change in the EQ-5D utility index score (higher = better): Intermediate-dose prophylaxis: 0.06 points. Episodic treatment: −0.01 points. No p-value provided.
					⊕◯◯◯ VERY LOW [a,d]

Adverse events (12.0 to 82.5 m)	154 (3 RCTs)	• **Gringeri 2011:**
		  • Inhibitors developing: 3/21 patients in the prophylaxis group and 2/19 in the episodic group.
		  • CVAD-related infection: 6/20 patient in the prophylaxis group, and 0/19 in the episodic group (no indwelling catheters required).
		• **Manco-Johnson 2007** reported that 6/32 patients had CVAD-related infection in the prophylaxis group and 6/33 in the episodic group.
					⊕◯◯◯ VERY LOW [a,d]

CI: Confidence interval; **yr**: years **RM**: ratio of means; **RR**: Risk ratio; **Haemo-QoL**: Hemophilia quality of life questionnaire for children; **Haemo-QoL-A**: Hemophilia-specific quality of life questionnaire for adults; **EQ VAS**: EuroQol visual analogue scale; **SD**: Standard deviation; **CVAD**: Central venous access device-related infections.

Explanations

[a]. We rated down one level for risk of bias.

[b]. We rated down one level for imprecision due to the small number of participants that presented the outcome (200–400).

[c]. We rated down one level for inconsistency ($I^2 > 70\%$).

[d]. We rated down two levels for imprecision due to the small number of participants that presented the outcome (less than 200)

[e]. We rated down one level for publication bias.

clotting factor VIII resulting in abnormal bleeding. Severe haemophilia A is categorised by a factor VIII

level of less than 1% of normal. Patients with severe haemophilia A can experience spontaneous and/or life-threatening bleeds.[1,2] The current standard of care in the South African public health sector for patients with haemophilia A is treatment with blood factor VIII on demand (for bleeds or pre-surgery)[i]. An alternative is preventive treatment with blood factor prophylaxis which is recommended by in the World Federation of Hemophilia guidelines.[3] Uncontrolled bleeds may lead to mortality and disability leading to lower quality of life and absenteeism[4]. Despite prophylactic factor VIII recommendations in international guidelines, a barrier to implementation in LMICs is affordability. However recent trials conducted in LMICs have been conducted exploring lower doses of Factor VIII prophylaxis[5,6]. The delays in obtaining 'on demand' treatment due to lack of immediate transport capacity to reach health care facilities results in poorer outcomes, increased requirement for factor VIII replacement and the development of inhibitors[7]. The latter is associated with marked increase in cost to treat future bleeds.

This document serves as an update to the medicine review, conducted previously on individuals under the age of 18 years only, which was presented to the NEMLC in October 2022 by the Paediatric Hospital Level Expert Review Committee. The NEMLC recommended that a group be formed to address haemophilia across ages and the levels of care. As such the Haemophilia Subcommittee was established. This medicine review has been updated to include evidence and costing across all ages.

RESEARCH QUESTION

For patients, **of all ages**, with haemophilia A without inhibitors, how effective is Factor VIII prophylaxis compared to treatment of bleeds on demand with Factor VIII? Table 1 outlines the scope of the review.

Table 1. Scope of the technical review

Population 1	Haemophilia A patients **of all ages** without inhibitors (Includes patients who have been previously treated or untreated, patients with mild, moderate or severe haemophilia, patient with or without joint damage, and patients who have or haven't experienced their first bleed)
Intervention/s and comparisons	Intervention: Factor VIII prophylaxis weekly, twice weekly or three times weekly Comparator: Treatment of bleeds on demand with factor VIII
Outcomes	**Efficacy** - Frequency of any bleeds per year - Frequency of minor bleeding episodes per year - Frequency of major bleeding episodes per year - Clotting factor concentrate levels in plasma (mean difference) - Joint assessment (Orthopaedic joint score or clinical joint function or radiological assessment) **Safety** - Mortality - Serious adverse events / effects - Adverse events / effects **Quality of Life** - Quality of life on validated scales (disease-specific where possible)
Study designs	Systematic reviews, Randomised controlled trials

METHODS

A search was conducted in Cochrane Library, PubMed and Epistemonikos databases focusing on systematic reviews of RCTs in 2022. The search strategies for the systematic literature searches are detailed in Appendix 2. Disagreements regarding exclusion and inclusion of studies were handled through discussion (KM, AH, JR). Data from included studies were extracted and analysed (KM & AH). An AMSTAR 2 was conducted independently and in duplicate on the selected systematic review (AH and KM). In addition, both AH and KM reviewed the GRADE of included systematic reviews. Where

[i] Paediatric Hospital Level Standard Treatment Guidelines, Blood and Blood Forming Organs Chapter

multiple eligible SRs were included, we reported evidence from the most relevant, recent and high-quality review or reviews in order to provide evidence across all a priori outcomes. Relevant study data were extracted into a narrative table of results. **The original search strategy was not limited by population thus the search was rerun in February 2023. Search results were reassessed considering the expanded population (KM & JR).**

RESULTS

The search for systematic reviews resulted in 50 articles. After screening, 40 articles were excluded (including five duplicates). Full text review of articles resulted in the exclusion of 7 studies (Appendix 3 shows the excluded studies). **No new studies emerged from the search update**. The three remaining systematic reviews had slightly different PICOs (see Appendix 4). Included and excluded studies in each systematic review were explored for overlaps and gaps. After discussion between the reviewers and members of the Paediatric Hospital Level ERC, it was agreed that the Delgado-Flores *et al*. (2022)[1] systematic review most closely met the medicine review PICO and included trials from LMICs which utilised low dose prophylaxis regimens. In addition, the Delgado-Flores et al study (2022)[1] also included all the relevant studies included in the Iorio *et al*. (2011)[8] and Olasupo *et al*. (2021)[2] reviews. **The studies were re-evaluated during the update and after discussion with the Haemophilia subcommittee it as agreed that Delgado-Flores *et al*. systematic review (2022) still best matched the PICO question.** Data was extracted from the Delgado-Flores et al. (2022)[1] systematic review (see appendix for included studies in Delgado-Flores 2022) and an AMSTAR 2 assessment conducted to assess overall quality.

Internal validity of the systematic reviews

AMSTAR II was used to determine the internal validity of included SRs (Appendix 6). In an effort to reduce duplication of effort in synthesis, we used the most relevant (to the PICO), up-to-date and highest quality SRs, among those, we prioritized reviews using GRADE. Where needed, outcomes were re-GRADED accounting for differencing in contextual/clinical interpretation such as indirectness and imprecision. However, this was deemed not necessary. Delgado-Flores *et al*. 2022 had a low AMSTAR II score (low quality review). However, the review was the most up to date, relevant, and internally valid. As such, meeting the PICO question set out a priori.

Effectiveness of the intervention

The review pooled data from 6 RCTs trials (n=359) comparing factor VIII prophylaxis with treatment on demand. The data were pooled for low (2 RCTs, n=71) and intermediate (4 RCTs, n=237) comparisons. **Comparison of high dose prophylaxis (three times a week) was not included in this medicine review due to feasibility concerns in the South African context.**

Comparison 1: Low dose Factor VIII prophylaxis versus on-demand treatment

The two RCTS included in the meta-analyses for low dose prophylaxis were conducted in LMICs and in children younger than 18 years (mean ages 6.11 and 11.95 years for Verma *et al*. 2016[5] and Chozie et al. 2019[6] respectively).

Outcome 1.1 - Annualised total bleeding rate

The annualised mean bleeding rate in the prophylaxis group of 5.07 (bleeds per annum) was significantly lower compared to the on-demand group at 17.74 (Ratio of means: 0.27 – reduction in 73% in bleeds per annum, 95% CI 0.17 to 0.43; P < 0.00001; 2 RCTS; n=71; low heterogeneity i^2=0%); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

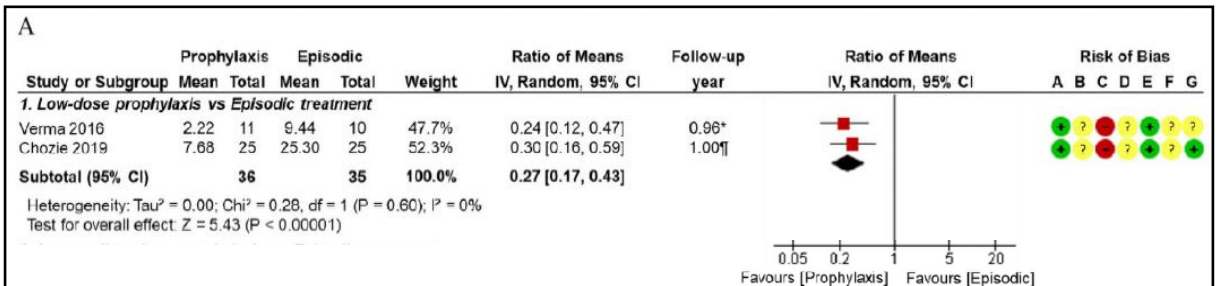


Figure 1: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Bleeding Rate for Low Dose Prophylaxis

Outcome 1. 2 - Annualised joint bleeding rate

The annualised mean joint bleeding rate in the prophylaxis group of 1.11 (bleeds per annum) was significantly lower compared to the on-demand group at 6.66 (Ratio of means: 0.17 – reduction of 83% in bleeds per annum, 95% CI 0.06 to 0.43; P=0.0002; 2 RCTS; n=71; low heterogeneity i^2=0%); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

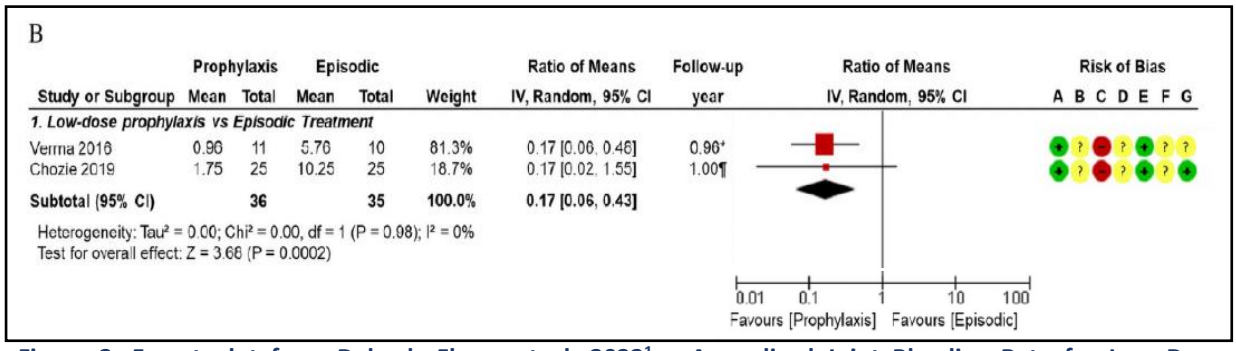


Figure 2: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Joint Bleeding Rate for Low Dose Prophylaxis

Outcome 1.3 - Change in the Haemophilia joint health score-2.1 (HJHS-2.1). Range: 0 to 124. Higher score = worse

Both included RCTs reported a significant difference over a 12-month period. Verma *et al*. 2016[5] showed a median change of 0 points (no worsening) for the low dose prophylactic group compared to a change of 4.5 points (worsening) in the on-demand treatment group (p<0.05). Chozie *et al*. 2019[6] reported a median change of -1 points (improvement of 1 point) in the low-dose prophylaxis group compared to a median change of 2 points (worsening) in the on-demand group (P<0.001); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

Comparison 2: Intermediate dose Factor VIII prophylaxis versus on-demand treatment

The four RCTS included in the meta-analyses for intermediate dose prophylaxis were conducted in a range of settings and across different age groups. The mean ages for the RCTs were 1.6 years (Manco-Johnson *et al*. 2007), 4.10 years (Gringeri *et al*. 2011), 29.6 years (Kavakli *et al*. 2015) and 29 years (Manco-Johnson *et al*. 2017).

Outcome 2.1 - Annualised total bleeding rate

The annualised mean bleeding rate in the prophylaxis group of 4.41 (bleeds per annum) was significantly lower compared to the on-demand group at 31.59 bleeds per annum (Ratio of means: 0.15 – reduction of 85% in bleeds per annum, 95% CI 0.07 to 0.36; P < 0.00001; 4 RCTS; n=237; substantial heterogeneity i^2=88%); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome 200-400, one level for inconsistency).

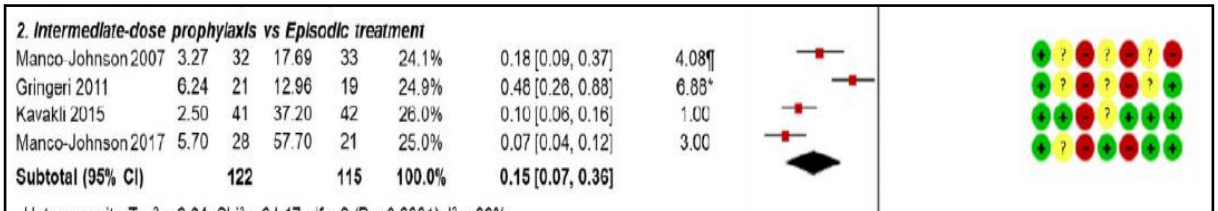


Figure 3: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Bleeding Rate for Intermediate Dose Prophylaxis

Outcome 2.2 – Annualised joint bleeding rate

The annualised mean joint bleeding rate in the prophylaxis group of 2.64 (bleeds per annum) was significantly lower compared to the on-demand group at 22.12 bleeds per annum (Ratio of means: 0.14 – reduction of 86% in bleeds per annum, 95% CI 0.07 to 0.27; 4 RCTS; n=237; substantial heterogeneity i^2=73%); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome 200-400, one level for inconsistency).

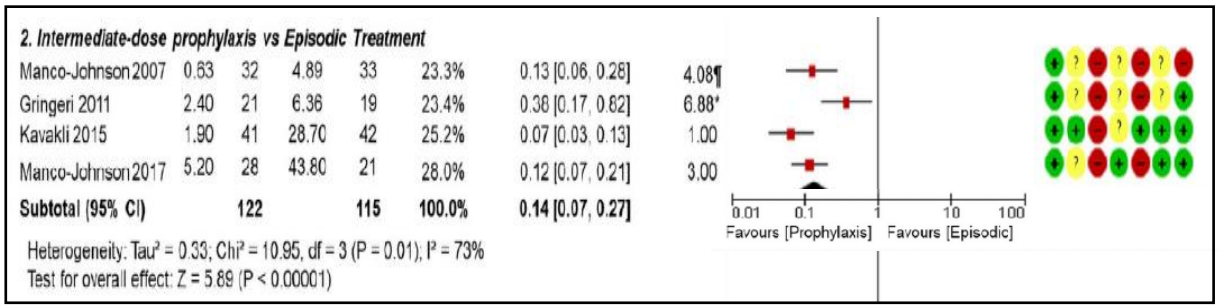


Figure 4: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Joint Bleeding Rate for Intermediate Dose Prophylaxis

Outcome 2.3 – Radiographic findings

There was a significant difference found in radiographic findings between intermediate dose prophylaxis and on-demand treatment. The number of participants with negative radiographic findings was larger in the on-demand treatment groups (19 events) than for intermediate prophylaxis groups (7 events) and was found to be significant (RR 0.36, 95% CI 0.18 to 0.71; 2 RCTS; n=95; low heterogeneity i^2=0%, Chi^2 p=0.52); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome less than 200, one level for publication bias).

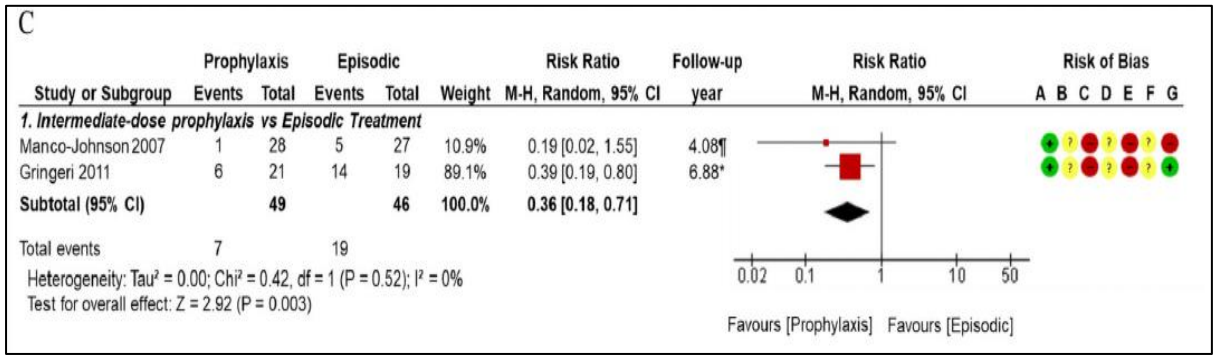


Figure 5: Forest plot from Delgado-Flores et al. 2022[1] – Radiographic Findings for Intermediate Dose Prophylaxis

Adverse events

Two RCTs reported on adverse events but data could not be pooled thus discussed narratively. Gringeri *et al*. (2011)[9] reported three and two patients in the prophylaxis and on-demand treatment groups respectively (no p value reported). A central-venous-access device related infection was reported for 6 out 20 patients. In the Manco-Johnson *et al*. (2007)[10] study an equal number of participants had a central-venous-access device related infection (19% in the prophylaxis group and 18% in the on-demand treatment group). No p values reported for adverse events.

EVIDENCE QUALITY

For the outcomes of interest, the Delgado-Flores 2022 systematic review rated the certainty as very low. Evidence was downgraded for imprecision, inconsistency and risk of bias (open-label trials). See Summary of Findings Table.

COSTING AND BUDGET IMPACT

A costing and budget impact analysis was conducted to investigate the potential budget impact per annum for treating paediatric patients with severe haemophilia A without inhibitors as well as the cost per bleed averted. The analysis was undertaken from the payer perspective and only direct costs to the public health sector are considered. Indirect and societal costs, such as school or work absenteeism, are not included. **Update to costing for adults was inclusion of the total potential population (children and adults), selection of intermediate dose prophylaxis as the base case and accounting for acquisition costs of factor VIII only, and treatment of all bleeds (including severe). Low dose prophylaxis, treatment of minor bleeds only, and inclusion of facility and staff costs are explored in different sensitivity scenarios.**

Population of interest

Population estimates were sourced from the World Federation of Haemophilia, annual global survey[11] and the South Africa Haemophilia Foundation registry data[12]. Uncertainty around population estimates were explored in the sensitivity analysis. A proportion in each age group was assumed to calculate dose estimates for low (10IU twice a week) and intermediate prophylaxis (25IU twice a week). Table 1 shows the number of patients with age group, estimated weights per age group[13] and factor VIII requirements.

Table 3: Average weight, IU requirements and number of patients per age group

Age	Weight (male)	IU required per dose (low)	IU required per week (low)	IU per dose (intermediate)	IU per week (intermediate)	Est. Number of patients
0-1	8	80	160	200	400	23
1-2	11	110	220	275	550	23
2-3	13.5	135	170	337.5	675	23
3-4	15.5	155	310	387.5	775	23
4-5	17.5	175	350	437.5	875	23
5-6	19.5	195	390	487.5	975	23
6-7	22	220	440	550	1100	23
7-8	24	240	480	600	1200	23
8-9	27	270	540	675	1350	23
9-10	30	300	600	750	1500	23
10-11	34	340	680	850	1700	23
11-12	38	380	760	950	1900	23
>12	70	700	1400	1750	3500	640

Costs

Costs for factor VIII products were sourced from the National Department of Health Master Health Product List[14] (contract prices). Proxies for facility and health worker costs for administration of prophylaxis and treatment of bleeds were obtained from the Uniform Patient Fee Schedule (dated April 2023)[15]. Consumables were assumed to be included in the facility costs. Facility and health worker costs were not included in base case but accounted for in sensitivity analysis. It was assumed that administration of prophylaxis would occur at community clinic level. It was assumed that there would no vial sharing but no wastage. Thus in practice patients may receive an intermediate, rather than low dose depending on vial size (sensitivity analysis scenarios). Costs for surgery and complications were not included. Costs for all bleeds (minor, major and life threating bleeds) were included in the base case. Accounting only for minor bleeds was explored in the sensitivity analysis as well as inclusion of facility and staff costs and low dose prophylaxis. Table 1 shows the cost components included in the analyses.

Table 4. Cost point estimates

Item		Value	Reference
Medication			
Haemosolvate® Factor VIII 300 IU 10ml vial		R1 183.67	MHPL 2023 (14)
Haemosolvate® Factor VIII 500 IU		R1 757.73	
Haemosolvate® Factor VIII 1000 IU (2 x 500IU)		R3 515.48	
Health Worker and Facility Costs* (sensitivity analysis)			
Health worker cost for administration of prophylaxis	Nursing Practitioner	R76	UPFS 2023 (15)
Facility cost for administration of prophylaxis	Facility Level 1	R130	
Health worker cost for treatment of minor bleed	Nursing Practitioner	R76	
Facility cost for treatment of minor bleed	Facility Level 1	R130	
Health worker cost for treatment of severe bleeds intensive care	Specialist medical practitioner	R662	
	Nursing Practitioner	R132	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R7 795	
Health worker cost for treatment of severe bleeds general ward	Specialist medical practitioner	R172	
	Nursing Practitioner	R132	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R1 155	

Outcomes

Data sourced from the Delgado-Flores systematic review (see 'Effectiveness and safety of the intervention above') was utilised to input into the analysis for estimated total number of bleeds per annum for a patient on intermediate dose factor VIII prophylaxis versus on-demand treatment (as well as low dose effectiveness estimates in sensitivity analysis). Estimates for number of severe bleeds (major and life-threatening) were sourced from literature. Number of days of treatment and hospitalization for bleeds was based on expert opinion of members of the Paediatric Hospital Level ERC. Table 5 shows the point estimates utilised in the analysis. Outcomes for disability, quality of life, surgeries and mortality were not included in the analysis.

Table 5. Outcome point estimates

Item	Value	Reference
No. of minor bleeds per annum per one patient on low dose prophylaxis *sensitivity analysis	5.7	Delgado-Flores et al. 2022 (1) – values

No. of minor bleeds per annum per one on-demand patient (low dose prophylaxis comparison) *sensitivity analysis	17.1	reduced to offset severe bleeds
No. of minor bleeds per annum per one patient on intermediate dose prophylaxis	4.75	
No. of minor bleeds per annum per one on-demand patient (intermediate dose prophylaxis comparison)	30.4	
% of major bleeds that occur in haemophilia A patients as a % of all bleeds	5%	Srivastava et al. 2021[ii] (3)
% of children experiencing a life-threatening bleed annually on low dose prophylaxis	0.5%	Touré et al. 2022[iii] (16)
% of children experiencing a life-threatening bleed annually on-demand treatment (low dose comparison)	1.2%	
% of children experiencing a life-threatening bleed annually on intermediate dose prophylaxis	0.5%	
% of children experiencing a life-threatening bleed annually on-demand treatment (intermediate dose comparison)	2.7%	
No. of days required for treatment of a minor bleed – outpatient	3	Expert opinion (Paediatric Hospital Level ERC)
No. of days required for treatment of a major bleed – inpatient	7	
No. of days required for treatment of an LTB - inpatient	16	

RESULTS

Base Case analysis

Table 6 shows the results of the base case analysis which accounts for **drugs costs only** (at contract price) for **intermediate dose prophylaxis and treatment of all bleeds** (See sensitivity analysis for scenarios including treatment of minor bleeds only, facility and health worker costs, and low dose prophylaxis). The total cost per patient on intermediate dose factor VIII prophylaxis was estimated to be R R561 126 per annum, compared to R684 908 per annum for treating one patient on demand (incremental savings of R123 782 per patient per annum). Total budget impact was an estimated R311 962 320 for 916 patients on low dose factor VIII prophylaxis per annum versus R242 338 176 for 916 patients on demand (incremental impact of R69 624 144). Low dose prophylaxis could potentially avert 11 426 bleeds a year at an estimated incremental cost of R6 094 per bleed averted.

Table 6: Base case analysis results

	Costs per annum				**Benefits per annum**	
	Cost of Prophylaxis	**Treatment of bleeds**	**Total**	**Incremental Cost**	**No. of bleeds**	**No. bleeds averted**
FVIII intermediate dose prophylaxis	R415 680 564	R98 311 240	R513 991 804	-R113 383 948	4 587	24 751
FVII treatment on demand	NA	R627 375 752	R627 375 752		29 338	

[ii] Value was applied equally across low and intermediate effect sizes to obtain number of major bleeds per comparison

[iii] Value for LTB for intermediate cases proportionally increased in line with minor bleeds from low dose values

Cost of providing prophylaxis for 1 patient p/ annum	R561 126	R684 908	-R123 782	ICER – Savings with each bleed	-R 4 581

Sensitivity analysis - Scenarios

Deterministic sensitivity analysis

Ten different scenarios were run in the analysis to explore impact of changing certain variables and assumptions (See table 7 below). Scenarios were also explored for low dose prophylaxis (25IU/kg twice weekly).

Table 7: Scenarios explored in the deterministic sensitivity analysis

Scenario	Type of analysis	Variable and/or assumption changed
Base case intermediate prophylaxis, drug acquisition costs only and all bleeds		
1	Univariate	Base case but **low instead of intermediate dose prophylaxis**
2	Univariate	Base case AND includes treatment of minor bleeds only
3	Multivariate	Base case but low dose AND includes treatment of minor bleeds only
4	Univariate	Base case AND includes facility and health worker costs
5	Multivariate	Base case but **low dose prophylaxis** AND includes facility and health worker costs
6	Multivariate	Base case AND includes treatment of minor bleeds only AND includes facility and health worker costs
7	Multivariate	Base case but **low dose prophylaxis** AND includes treatment of minor bleeds only AND includes facility and health worker costs
8	Univariate	Base case but reduced patient estimates based on consumption data
9	Univariate	Base case but reduced bleeding rate estimates of intervention and control groups by 15%
10	Univariate	Base case but reduced bleeding rate estimates of intervention and control groups by 25%

Scenario 4 resulted in the largest **cost savings** of R152 704 996 per annum (for 916 patients), **savings** of R6 170 per bleed averted. The largest ICER was observed in Scenario 7 with an incremental cost of R82 187 260 (R7 193 per bleed averted). Table 8 outlines the results for each scenario. Scenarios highlighted in green are cost saving. See Appendix 7 for full details.

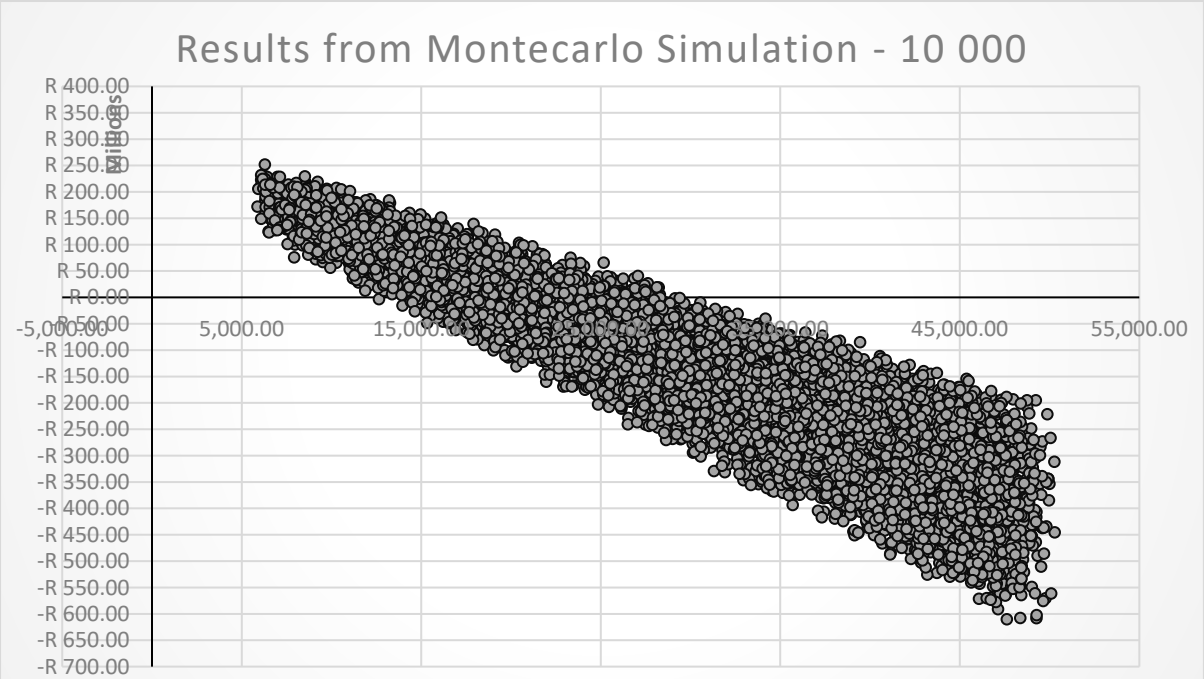
Table 8: Results of the deterministic sensitivity analysis

Scenario	Incremental budget impact	Incremental cost per patient	Number of bleeds averted	Cost per bleed averted
1	-R38 708 300	-R42 258	12 217	-R3 168
2	R57 061 444	R62 294	23 496	R2 429
3	R69 624 144	R76 009	11 426	R6 094
4	-R152 704 996	-R166 709	24 751	-R6 170
5	-R54 143 332	-R59 108	12 217	-R4 432
6	R62 165 300	R67 866	23 496	R2 646
7	R82 187 260	R89 724	11 426	R7 193
8	-R64 836 256	-R70 782	14 456	-R4 485
9	-R35 519 464	-R38 777	21 087	-R1 684
10	R22 849 696	R24 945	18 340	R1 246

Scenarios which included treatment of minor bleeds only (Scenarios 2, 3, 6 and 7) were found to be more costly. Scenarios with intermediate dose prophylaxis were more cost-effective than lose dose prophylaxis scenarios, regardless of whether only minor bleeds were included, or facility and staff costs were included. Reducing annualised bleeding rates of both intervention and control groups by 15% still resulted in an estimated cost savings (Scenario 9). If annualised bleeding rates for both groups reduced by 25% then factor VIII prophylaxis is still estimated to be more beneficial but more costly (Scenario 10).

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted to account for parameter uncertainty, where all model parameters were varied at the same time, using statistical distributions. Distributions were based on confidence intervals in the Delgado-Flores et al. 2022 systematic review for effectiveness estimates and varied by 15% for cost and other estimates, such as number of days treated for major bleeds. A microsimulation was undertaken with 10,000 runs. The results presented in Figure x show that the new intervention (factor VIII prophylaxis) was estimated to be cost saving in 69% of the runs. After 10 000 runs the average cost difference was -R115 605 693 with a benefit difference of 28 113 bleeds resulting in an ICER of means of -R 4 112.



Limitations

Costs for surgeries required for treating major or life threatening bleeds are not included as well as costs for treating long term complications. This costing and budget impact does not look at the impact of mortality, quality of life and disability which a cost utility model would include. Many CEA articles show that prophylaxis is more costly and more effective with the decision on cost-effectiveness based on varied willingness-to-pay thresholds. There is a large variation in CEA results due to lack of standardised approaches (types of costs, perspective, time horizon and model structure).[171819] Lastly the analysis assumes 100% uptake and does not account for current use of factor VIII prophylaxis. Patient number estimates for haemophilia are difficult to source and thus patient numbers may differ in reality to estimates utilised in the model. However, national procurement data shows an average

(last five years) annual spend of R138 130 410 on haemosolvate® products.[iv] Utilising the above base case modelled cost estimate for one patient per annum on demand treatment (R684 908) and the national procurement costs, roughly 200 patients of patients with severe haemophilia are being actively treated for bleeds on demand. Scenarios including facility and staff costs assume that all prophylaxis will be administered at facilities whereas in practice there may be some home-based administration.

DISCUSSION AND CONCLUSION

This medicine review focussed on evidence from the Delgado-Flores 2022[1] systematic review. Two other systematic reviews which were found during the search were Cochrane reviews (Iorio *et al*. 2011[8] and Olasupo *et al.* 2021[2]) concluded in favour of factor VIII prophylaxis over on-demand treatment stating strong evidence (Iorio *et al*. 2011) and low certainty of evidence (Olasupo *et al*. 2021) for some outcomes. However, none of the studies that were included in both reviews, were conducted in LMICs or with lower doses. Affordability is an important consideration thus despite the evidence from Delgado-Flores being of very low certainty (open label trials, small samples and inconsistency), it was agreed that this evidence was the most appropriate and direct. The evidence reported that low dose and intermediate Factor VIII prophylaxis reduced total bleeds by 12 and 27 per annum respectively.

A basic cost effectiveness analysis considered acquisition costs, health worker and facility costs for prophylaxis and treatment of bleeds. For this group of patients, it is estimated that low and intermediate dose factor VIII prophylaxis is incrementally more costly than treating on-demand in the base case (considering acquisition costs and treatment of minor bleeds only). A conservative approach to the base case was selected, however scenarios which included acquisition costs for treatment of major and life-threatening bleeds were cost saving, even after including facility and health worker costs. This was the case for both low and intermediate dose prophylaxis. Intermediate dose prophylaxis was less costly than low dose prophylaxis compared to treatment on demand even after including all bleeding types and facility and staff costs. Costs and effectiveness of surgeries and treatment of long-term complications were not considered and a cost utility analysis incorporating mortality and disability was not undertaken. Due to efficacy and modelled cost estimates in particular, potential cost savings when including treatment of severe bleeds, intermediate dose prophylaxis is suggested over low dose prophylaxis and treatment on demand.

REVIEWERS

Ms Kim MacQuilkan, Mr A Hohlfeld, Dr Jane Riddin, Prof P Jeena, Dr G Reubenson, Mr A Gray
UPDATE: Supported by Haemophilia subcommittee of NEMLC

Author Affiliation and Conflict of Interest Details

- Ms K MacQuilkan (Right to Care, SCTA) has no interests to declare.
- Mr A Hohlfeld (Cochrane South Africa, South African Medical Research Council) has no interests to declare.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare
- Prof P Jeena has no interests to declare
- Dr G Reubenson has no interests to declare
- Mr A Gray – No interests to declare

[iv] RSAPharma data (2020-2022)

APPENDIX 1 - EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Low dose prophylaxis vs on-demand treatment* - Very low certainty - 2 RCTs (n=71) ages 1-18 years *Intermediate dose prophylaxis vs on-demand treatment* - Very low certainty 4 RCTs (n=237) ages 1 to 65 years See Summary of Findings Table
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [X] Moderate: [ ] Small: [ ] None: [ ]	***Low dose prophylaxis vs on-demand*** **Overall annualised bleeding rate** - 2 RCTs, n=71, ratio of means 0.27 (73% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.17 to 0.43, p < 0.00001. **Joint annualised bleeding rate** - 2 RCTs, n=71, ratio of means 0.17 (83% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.06 to 0.43, p < 0.0002 ***Intermediate dose prophylaxis vs on-demand*** **Overall annualised bleeding rate** - 4 RCTs, n=237, ratio of means 0.14 (86% reduction in the mean bleeds per annum in the prophylaxis group) 95% CI 0.07 to 0.27, p < 0.0001. **Joint annualised bleeding rate** - 4 RCTs, n=71, ratio of means 0.17 (83% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.06 to 0.43, p < 0.00001
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Intermediate dose prophylaxis vs on-demand treatment* - Very low certainty 4 RCTs (n=237) ages 1 to 65 years *See Summary of findings table*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	*Adverse events not quantitatively analysed however one RCT reported more* central-venous-access device related infections but CVADs not inserted in on-demand group.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [X] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	In the committee's opinion the intervention is feasible, however, where this is not the case on-demand treatment will still be available.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	BASE CASE: Incremental cost for providing one patient with intermediate-dose prophylaxis per annum = (-)R123 782 (cost-savings) Incremental budget impact per annum for all patients = -R113 383 948 (cost savings) **Cost savings** per bleed = R4 581 **Scenarios including acquisition costs for treatment of minor only are more beneficial but more costly** Intermediate dose prophylaxis provided more cost savings than low dose prophylaxis scenarios. Scenario 1: Low dose prophylaxis Incremental budget impact per annum for all patients = **cost savings** of R38 708 300
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [x] Major: [ ] Uncertain: [ ] **Is the option acceptable to key stakeholders?** Yes: [x] No: [ ] Uncertain: [ ]	

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	Where home-based care is not feasible, children in less well-resourced areas may struggle to access prophylactic factor VIII, however, since this can be administered at clinic level inequity should be minimal.

APPENDIX 2 -SEARCH STRATEGY

PUBMED

#	Query	Search Details	Results
10	#6 AND filter for systematic review and meta-analyses	(("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	42
9	#6 AND #5	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract])	50
8	#6 AND Filter for clinical trials and RCTs	(("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	169
7	#6 AND #4	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR	1 201

		"Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	
6	#1 AND #2 AND #3	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])	2 036
5	Systematic reviews	"systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	388 961
4	RCTs	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	4 843 051
3	Prophylaxis (intervention)	"prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]]	1 812 441
2	Factor VIII (intervention & comparator)	"Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]	26 891
1	Hemophilia A (population)	"haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]	24 162

COCHRANE

search	Query	Results
#1	MeSH descriptor: [Hemophilia A] explode all trees	**467**
#2	MeSH descriptor: [Factor VIII] explode all trees	**396**
#3	#1 AND #2	**243**
#4	#3 in Cochrane Reviews	**6**

Epistemonikos

(title:((title:("hemophilia A" OR "haemophilia A") OR abstract:("hemophilia A" OR "haemophilia A")) AND (title:("factor VIII" OR "factor 8") OR abstract:("factor VIII" OR "factor 8")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia A" OR "haemophilia A") OR abstract:("hemophilia A" OR "haemophilia A")) AND (title:("factor VIII" OR "factor 8") OR abstract:("factor VIII" OR "factor 8")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))

All studies – 445 results
Filtered for RCTs – 17 results
Filtered for systematic reviews & Interventions = 7 results

APPENDIX 3 - Table of excluded studies

No.	Study	Reason for exclusion
1	Sun J, Zhou X, Hu N. Factor VIII replacement prophylaxis in patients with hemophilia A transitioning to adults: a systematic literature review. Orphanet J Rare Dis. 2021 Jun 26;16(1):287. doi: 10.1186/s13023-021-01919-w. PMID: 34174912; PMCID: PMC8236177.	Qualitative synthesis
2	Stobart K, Iorio A, Wu JK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD003429. doi: 10.1002/14651858.CD003429.pub2. Update in: Cochrane Database Syst Rev. 2006;(2):CD003429. PMID: 15846666.	Earlier review of Iorio et al. 2011 Cochrane review
3	O'Hara J, Sima CS, Frimpter J, Paliargues F, Chu P, Presch I. Long-term outcomes from prophylactic or episodic treatment of haemophilia A: A systematic review. Haemophilia. 2018 Sep;24(5):e301-e311. doi: 10.1111/hae.13546. Epub 2018 Jul 13. PMID: 30004613.	Qualitative synthesis
4	Oldenburg J, Brackmann HH. Prophylaxis in adult patients with severe haemophilia A. Thromb Res. 2014 Nov;134 Suppl 1:S33-7. doi: 10.1016/j.thromres.2013.10.019. Epub 2014 Sep 26. PMID: 25263019.	Qualitative synthesis
5	Makris M. Systematic review of the management of patients with haemophilia A and inhibitors. Blood Coagul Fibrinolysis. 2004 May;15 Suppl 1:S25-7. doi: 10.1097/00001721-200405001-00005. PMID: 15166930.	Incorrect intervention/ comparator
6	van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE. Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev. 2019 Apr 19;4(4):CD011385. doi: 10.1002/14651858.CD011385.pub3. PMID: 31002742; PMCID: PMC6474399.	Incorrect intervention/ comparator
7	Castro HE, Briceño MF, Casas CP, Rueda JD. The history and evolution of the clinical effectiveness of haemophilia type a treatment: a systematic review. Indian J Hematol Blood Transfus. 2014 Mar;30(1):1-11. doi: 10.1007/s12288-012-0209-0. Epub 2012 Nov 4. PMID: 24554812; PMCID: PMC3921319.	Qualitative synthesis

APPENDIX 4: Description of eligible systematic reviews

Study	Date	Population	Intervention	Comparators	Outcomes	Any trials in LMICs
Iorio et al. (Cochrane) [8]	2011	Haemophilia A or B without inhibitors of all ages and severity	Primary and secondary Factor VIII prophylaxis	• prophylaxis versus placebo; • prophylaxis versus on-demand treatment; • prophylaxis versus alternative prophylaxis	1. Number of bleeding episodes or bleeding frequency Secondary outcomes 1. Pain scores 2. Radiologic joint score or radiologic measurements or descriptions of joint damage 3. Orthopedic joint score or clinical joint function 4. QoL 5. Clotting factor concentrate plasma levels 6. Time loss to school or employment 7. Integration into society	None

					8. Scales recording feeling of well-being and global functioning 9. Cost effectiveness, cost benefit, cost utilization, cost minimization 10.Any reported adverse effects or toxicity of clotting factor concentrates will be recorded (e.g. inhibitors, reactions, transmission of infection)"	
Olasupo et al. [2]	2021	Haemophilia A or B without inhibitors any severity. Adults only or if under 18 only if had 1. proven haemophilic arthropathy; or 2. presence of one or more target joint; or 3. previous on-demand treatment.	Secondary Factor VIII prophylaxis	• prophylaxis versus prophylaxis with a different regimen; • prophylaxis versus on-demand treatment; • prophylaxis versus no treatment; • prophylaxis versus placebo."	Primary outcomes 1. Number of joint bleeding episodes or joint bleeding frequency during the trial 2. Orthopedic joint score or clinical joint function 3. QoL on validated scales (disease-specific where possible) Secondary outcomes 1. Number of total bleeding episodes or total bleeding frequency during the trial period 2. Pain scores 3. Radiologic joint score or radiologic measurements or descriptions of joint damage 4. Clotting factor concentrate plasma levels 5. Time loss to school or employment 6. Integration into society (i.e. absenteeism) 7. Scores on scales recording feeling of well-being and global functioning 8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation 9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)"	A-Long (Brazil, India, Russia, South Africa); LEOPOLD included SA, PROPEL Malaysia, SPINART (Bulgaria, Romania, Argentina)
Delgado-Flores et al. [1]	2022	Patients with Haemophilia A without inhibitors of all ages and severity (primary and secondary prophylaxis)	Primary and secondary Factor VIII prophylaxis	• Different prophylactic • Episodic • Tailored factor replacement treatments.	1. Annualized bleeding rate (ABR) 2. Annualized joint bleeding rate (AJBR) 3. Radiographic findings 4. Hemophilia joint health score 2.1 (HJHS-2.1) 5. Joint structural changes (using extended magnetic resonance imaging-eMRI) 6. Petterson score 7. Adverse events (AEs) 8. Quality of life	Verma (India); Chozie (Indonesia); LEOPOLD included SA; SPINART (Bulgaria, Romania, Argentina)

Appendix 5: Characteristics of included studies in Delgado-Flores 2022

Table 1. Study and participants' characteristics in the included RCTs.

N	Author (year)	Countries or regions	Population: hemophilia type, age and sex	Factor activity level**	Product: type of clotting factor concentrates and half-life (hours)	Control (n)	Intervention (n)	Follow-up	Fun-ding
Episodic treatment compared with prophylaxis (at low, intermediate, and high doses)									
1	Verma (2016)	India	• Hemophilia A • Age range: 1 to 10 yr (mean: 6.11 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Hemofil M)** • Plasma-derived, mAb-purified • 15 h	**Episodic (n = 10)** 1. 25 IU/kg or more as early as possible after the joint bleed, 2. 25 IU/kg every 12–24 h until resolution	**Low-dose prophylaxis** (n = 11) • **Weekly dose: 20 IU/kg** (10 IU/kg twice a week)	Median: 0.96 yr	Self-funded
2	Chozie (2019)	Indonesia	• Hemophilia A • Age range: 4 to 18 yr (mean: 11.95 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Koate-DVI)** • Plasma-derived, chromatography purified • 16 h	**Episodic (n = 25)** • Not specified	**Low-dose prophylaxis (n = 25)** • **Weekly dose: 20 IU/kg** (10 IU/kg twice a week)	Mean: 1 yr	Grifols
3	Manco-Johnson (2007) and Hacker (2007)	United States	• Hemophilia A • Age range: 1 to 2.5 yr (mean: 1.6 yr) • Sex: 100% males	≤ 2%	**FVIII concentrate (Kogenate or Kogenate FS)** • Recombinant • 11 to 15 h	**Episodic (n = 33)** 1. 40 IU/kg at the time of joint hemorrhage. 2. 20 IU at 24 hours and 72 hours after the first dose 3. 20 IU/kg every second day, until 4 weeks.	**Intermediate-dose prophylaxis (n = 32)** • **Weekly dose: 75 IU/kg** (25 IU/kg every second day)	Mean: 4.08 yr	CDC, NIH, Bayer
4	Gringeri (2011)	Italy	• Hemophilia A • Age range: 1 to 7 yr (mean: 4.10 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Recombinate® until 2003 / Advate® since 2004)** • Both were recombinant • Recombinate: 15 h / Advate: 9 to 12 h • 1° generation / 3° generation	**Episodic (n = 19)** 1. 25 IU/kg or more, possibly within 6 h from the bleeding, 2. Repeated every 12–24 h until complete resolution	**Intermediate-dose prophylaxis (n = 21)** • **Weekly dose: 75 IU/kg** (25 IU/kg three times a week)	Median: 6.88 yr	Baxter
5	Manco-Johnson (2014) and Manco-Johnson (2017)	United States, Bulgaria, Romania and Argentina	• Hemophilia A • Age range: 12 to 50 yr (mean: 29 yr) • Sex: 100% males	< 1%	**FVIII concentrate (Kogenate FS)** • Recombinant • 11 to 15 h	**Episodic (n = 42)** • Not specified	**Intermediate-dose prophylaxis (n = 41)** • **Weekly dose: 75 IU/kg** (25 IU/kg three times a week)	3 yr	Bayer
6	Kavakli (2015)	Europe, South Africa, North America, South America, and Asia	• Hemophilia A • Age range: 12 to 65 yr (mean: 29.6 yr) • Sex: 100% males	< 1%	**FVIII concentrate (BAY 81–8973, Kovaltry)** • Recombinant • 12 to 14 h	**Episodic (n = 21)** • Dependent on the location and severity of the bleed	**Intermediate-dose prophylaxis** (n = 28) • **Weekly dose: 40 to 60 IU/kg** (20–30 IU/kg twice a week) **High-dose prophylaxis (n = 31)** • **Weekly dose: 90 to 120 IU/kg** (30–40 IU/kg three times a week)	1 yr	Bayer

APPENDIX 6 – AMSTAR 2 Results of review of Delgado-Flores 2022

Effects of replacement therapies with clotting factors in patients with hem is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	Yes Yes Yes Yes

10. Did the review authors report on the sources of funding for the studies included in the review?	Yes Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its **likely impact on the results of the review?**	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

APPENDIX 7 – Sensitivity Analysis – Deterministic - Scenarios

		Costs				Benefits		Cost/benefit	Per patient		
BASE CASE	Intermediate prophylaxis, includes severe bleeds, factor costs only	Cost for prophylaxis (factor ONLY)	Treatment of bleeds (factor ONLY)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R98 311 240	R513 991 804	-R113 383 947,93	4587,00	24750,80	-R4 581,02	R561 126,42	5,01	-R4 581,02
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R627 375 751,46	R627 375 751		29337,80			R684 908,03	32,03	
									-R123 781,60		
SCENARIO 1	Base case but low dose prophylaxis (assumes no wastage thus accounts for intermediate effects where larger dose can be given	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R232 501 950,72	R85 759 160	R318 261 110	-R38 708 299,75	5249,00	12217,40	-R3 168,29	R347 446,63	5,73	-R3 168,29
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R356 969 410,20	R356 969 410		17466,40			R389 704,60	19,07	
									-R42 257,97		
SCENARIO 2	Base case but minor bleeds only, factor only	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R66 410 948	R482 091 512	R57 061 443,53	4351,00	23496,00	R2 428,56	R526 300,78	4,75	R2 428,56
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R425 030 068,70	R425 030 069		27847,00			R464 006,63	30,40	
									R62 294,15		
SCENARIO 3	Base case but low dose prophylaxis (assumes no wastage thus accounts for intermediate effects where larger dose can be given due to vial size) minor bleeds only	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R232 501 950,72	R79 460 369	R311 962 320	R69 624 144,37	5156,00	11426,00	R6 093,48	R340 570,22	5,63	R6 093,48
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R242 338 175,52	R242 338 176		16582,00			R264 561,33	18,10	
									R76 008,89		
SCENARIO 4	Base case, but includes facility/staff costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R435 304 948,00	R109 352 602	R544 657 550	-R152 704 995,93	4587,00	24750,80	-R6 169,70	R594 604,31	5,01	-R6 169,70
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R697 362 545,46	R697 362 545		29337,80			R761 312,82	32,03	

SCENARIO 5	Base case but low dose prophylais and includs facility/staff costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R252 126 334,72	R92 282 854	R344 409 188	-R54 143 331,75	5249,00	12217,40	-R4 431,66	R375 992,56	5,73	-R4 431,66
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R398 552 520,20	R398 552 520		17466,40			R435 101,00	19,07	
									-R59 108,44		
SCENARIO 6	Base case but includes administration/facility costs, minor bleeds only	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R435 304 948,00	R69 099 866	R504 404 814	R62 165 299,53	4351,00	23496,00	R2 645,78	R550 660,28	4,75	R2 645,78
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R442 239 514,70	R442 239 515		27847,00			R482 794,23	30,40	
									R67 866,05		
SCENARIO 7	Base case but low dose dose, minor bleeds only and includes administration/facility costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R252 126 334,72	R82 646 777	R334 773 112	R82 187 260,37	5156,00	11426,00	R7 193,00	R365 472,83	5,63	R7 193,00
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R252 585 851,52	R252 585 852		16582,00			R275 748,75	18,10	
									R89 724,08		
SCENARIO 8	Base case with reduced patient estimates (consumption data)	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R240 647 874,48	R56 735 893	R297 383 768	-R64 836 255,98	2679,00	14455,80	-R4 485,14	R324 654,77	2,92	-R4 485,14
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R362 220 023,54	R362 220 024		17134,80			R395 436,71	18,71	
									-R70 781,94		
SCENARIO 9	Base case with reduced estimates for bleeding rates (-25%)	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R98 311 240	R513 991 804	-R35 519 463,98	4587,00	21086,80	-R1 684,44	R561 126,42	5,01	-R1 684,44
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R549 511 267,51	R549 511 268		25673,80			R599 903,13	28,03	
									-R38 776,71		

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