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

TITLE: Prophylactic Factor IX compared to on-demand/episodic treatment for patients with severe haemophilia B without inhibitors

Date: June 2024

Key findings

- Current South African standard of care for haemophilia B patients is on-demand/episodic treatment for bleeding with blood factor IX. A potential alternative is blood factor IX prophylaxis.
- A search was conducted in PubMed, Cochrane Database and Epistemonikos. No systematic reviews or randomised controlled trials (randomising on-demand vs prophylaxis patients) were found meeting the review criteria. Most studies included had small sample sizes and high risk of bias (due to open-label and patient reported outcomes). Overall, the evidence was determined as low quality, level II evidence.
- **Comparison 1: Standard half-life products (plasma or recombinant) versus on-demand treatment**

  Annualised bleeding rate (2 studies – low quality, n=75):

  - 50 IU twice weekly prophylaxis vs 1st on-demand period = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100 IU once weekly prophylaxis vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). No difference between prophylaxis regimens (P=0.2167) – *1 randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand) study – use of historic controls, open-label.*
  - Lower mean ABR in the 100 IU once weekly prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001) – *1 single arm, non-randomised study, use of historic controls, open-label, n=25.*

  Annualised joint bleeding rate (2 studies – low quality, n=75)

  - Joint ABR lower in the 50 IU/kg twice a week prophylaxis (MD 1.9 ± 4.5) and 100 IU/kg once a week prophylaxis (MD 3.6 ± 8.3) compared to the first on-demand period (MD 25.4 ± 19.1) and second on-demand period (MD 24.3 ± 21.5); p values not reported/calculated – *1 randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand) study – use of historic controls, open-label.*
  - Lower mean joint ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 2.1 SD +/- 3.2 vs 27.7 SD +/- 16.9; P value not reported/calculated) – *1 single arm, non-randomised study, use of historic controls, open-label.*

  Safety (2 studies – low quality, n=75): No patient developed a FIX inhibitor during the studies reported. No serious concerns with safety.
- **Comparison 2: Extended half-life products (recombinant) versus on-demand treatment**

  Annualised bleeding rate (3 studies – low quality, n=260):

  - Annualised median bleeding rate higher in the on-demand group (median 15.58, IQR 9.56 to 26.47) compared to the 10 IU/kg prophylaxis (median 2.93, IQR 0.99 to 6.02) and 40 IU/kg prophylaxis (median 1.04, IQR 0.00 to 4.00) groups – 1 *randomised (prophylaxis groups randomised only), single-blind trial, on demand open label, parallel group.*
  - Significant reduction in mean ABR between the weekly dose adjusted (starting 50 IU/kg) prophylaxis (Mean: 3.12, 95% CI [2.46 to 3.95]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (83% reduction; p<0.001). Significant reduction in mean ABR between the interval adjusted 100 IU prophylaxis (Mean: 1.4, 95% CI [0.0 to 3.4]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (87% reduction; p<0.001) – 1 non-randomised, open-label study, parallel on demand group.

- Significant reduction in total ABR when patients switched from the on-demand treatment (ABR 20.09, 95% CI [16.808 to 24.003]) period to the prophylaxis (ABR 2.22, 95% CI [0.942 to 5.243) period (Median % reduction: 90.94, IQR (81.19 to 100.00); p<0.0001) – non-randomised, open-label, 2 periods, 2 groups.

Annualised joint bleeding rate (1 study – low quality, n=123):

- Lower median joint ABRs in the weekly dose adjusted (starting 50IU/kg) prophylaxis (Median: 1.1, IQR (0.0 to 4.0]) and interval adjusted 100IU/kg prophylaxis (Median: 0.4, IQR (0.0 to 3.2) groups compared to the on-demand (Median: 13.6 IQR (6.1 to 21.6) group; p value not reported/calculated).

Safety (3 studies – low quality, n=260): No patient developed a FIX inhibitor during the studies reported. No serious concerns with safety in two trials. One trial reported one serious adverse event considered related to the product (obstructive clot in urinary collecting system).

➡ The two moderate quality guidelines included recommended factor IX prophylaxis for severe haemophilia B patients.

➡ Low, intermediate and high dose factor IX prophylaxis are potentially more cost saving than treating bleeds on-demand when considering drug acquisition costs of factor IX only (base case – intermediate prophylaxis). Intermediate dose factor IX prophylaxis was estimated to be more cost saving than low dose prophylaxis and high dose prophylaxis. Low dose prophylaxis was more cost saving than high dose prophylaxis. Several limitations are noted related uncertainties in patient estimates, treatment of bleeds in practice, and extrapolation of efficacy estimates from haemophilia A studies.

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

SUBCOMMITTEE FOR HAEMOPHILIA 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	

The Haemophilia subcommittee suggests the use of factor IX prophylaxis for patients with severe haemophilia B.

Rationale: There is very limited, low quality evidence available for prophylaxis in the management of haemophilia B. However, the benefit of factor IX prophylaxis compared to on-demand/episodic treatment for haemophilia B patients has been shown in non-randomised controlled trials and recommended in guidelines. The majority of guidelines follow the recommendations for haemophilia A. A cost analysis revealed potential cost-savings for all prophylaxis regimens, with intermediate dose prophylaxis found to be the most cost-saving. Low dose prophylaxis was shown to be less cost saving, but more cost-saving than high dose prophylaxis. The costing model relied on many assumptions including uncertain estimates of the number of patients requiring prophylaxis. Despite these limitations, the potential benefit of prophylaxis is acknowledged and alignment with haemophilia A is considered to be beneficial.

Level of Evidence: Level 2 – nonrandomised trials, low quality
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price
Monitoring and evaluation considerations: Monitoring is compulsory, details regarding implementation to be determined for each relevant Standard Treatment Guidelines

NEMLC RECOMMENDATION 27th June 2024:

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

BACKGROUND

A medicine review on factor VIII prophylaxis versus treatment on demand for paediatric patients with severe haemophilia A without inhibitors was completed by the Paediatric Expert Review Committee and presented to the NEMLC in October 2022. The NEMLC recommended that a technical working group be established to review the management of haemophilia across levels of care and for all age groups. Additionally NEMLC recommended that costing analysis be conducted. The haemophilia subcommittee was established comprising NEMLC and ERC members (PHC/Adult Hospital, Paediatric Hospital and Tertiary & Quaternary Hospital Levels). The updated medicine review for factor VIII prophylaxis for patients of all ages with severe Haemophilia A without inhibitors was presented to the NEMLC in July 2023 (See Rapid Medicine Review of Factor VIII Prophylaxis for Haemophilia A[14]. Intermediate dose prophylaxis was approved, subject to the proposed amendments to the Standard Treatment Guidelines (Adult and Paediatric Hospital Level) being presented to the NEMLC. This review explores the evidence for IX prophylaxis for patients with severe haemophilia B without inhibitors.

RESEARCH QUESTION

For patients with haemophilia B without inhibitors, how effective is Factor IX prophylaxis compared to treatment of bleeds on demand with Factor IX? Table 1 outlines the scope of the review.

METHODS

Table 1. PICO for medicine review

Population:	Haemophilia B patients without inhibitors
Intervention:	Intervention: Factor IX prophylaxis (facility-based or home-based) – any dose or frequency*
Comparators:	Comparator: On-demand/Episodic Factor IX for minor or major bleeds (facility-based or home-based)
Outcomes:	**Efficacy** • Frequency of any bleeds per year • Frequency of joint bleeding episodes per year **Safety** • Mortality • Development of inhibitors • 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, observational studies, guidelines

*including human plasma, recombinant, standard and extended half-life products

A search was conducted in Cochrane Library, PubMed and Epistemonikos databases in May 2024. The search strategies are detailed in Appendix 2. A general search for guidelines and HTAs was also conducted in Google Scholar, Google and targeted websites, for example Guidelines International Network (G-I-N), utilising a combination of the search terms such as 'haemophilia', 'Factor IX', and 'prophylaxis'.

Screening and full text review was conducted independently by two reviewers (KM, JR) with disagreements regarding exclusion and inclusion of studies handled through discussion. Data from included studies were extracted and analysed by two reviewers (KM & JR). Guidelines were assessed with the AGREE II[1] tool independently by two reviewers (KM, JR or DF) and included if overall assessment was >5 out of 7.

RESULTS

The search resulted in 874 publications and 96 duplicates were removed. After screening, a further 703 articles were excluded. Full text review of 39 remaining articles resulted in the exclusion of 31 studies (Appendix 3 shows the excluded studies). Data was extracted from the 5 studies (See Table 2 below for Characteristics of the included studies). Two guidelines were included (See Guidelines Section for details). Figure 1 below shows the PRISMA diagram.

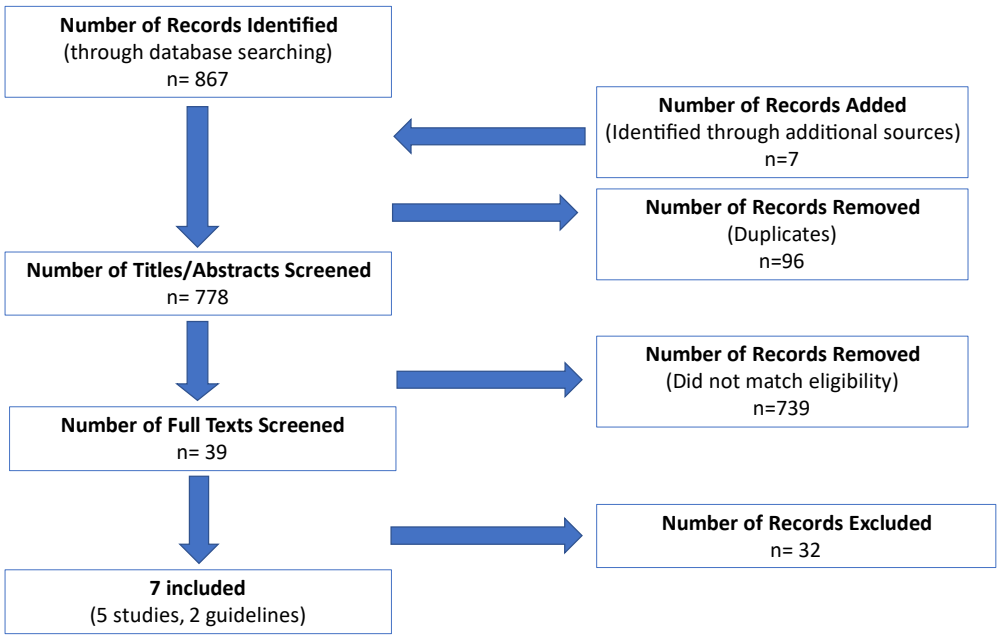

Figure 1: PRISMA diagram for medicine review

Table 2: Characteristics of included studies

Trials						
Study	Date	Study Design	Population	Comparisons	Results	Limitations
Valentino[2]	2014	Phase 4 multicentre randomised, open-label, four-period crossover study (randomization only of prophylaxis groups post on-demand period)	Males with severe or moderately severe Haemophilia B (FIX:C ≤2% and ≥12 bleeding episodes (including ≥6 haemarthrosis episodes) within 12 months of participation Ages 6-65 years, n=50	**Product:** Standard Life Recombinant coagulation factor IX (nonacog alfa) for all groups and periods • Prophylaxis 50IU/kg twice a week (2nd & 4th period) **Vs** On demand treatment (historic control – 1st period) • Prophylaxis 100IU/kg weekly (2nd & 4th period) **Vs** On demand treatment (historic control – 1st period)	Mean ABR • 50 IU twice weekly prophylaxis vs on-demand (Mean difference = -32.5; 95% CI [-38.5 to -26.6]; P<0.0001, n=43 • 100IU once weekly prophylaxis versus on-demand (MD = -30.5; CI [-36.5 to-24.5); P<0.0001, n=44 Safety Most treatment emergent adverse events were mild to moderate *Any adverse event* • On-demand 1st period: 42%; • 50 IU twice weekly prophylaxis: 31.8%; • 100 IU once weekly prophylaxis: 31.8% *Inhibitors:* No patient developed inhibitors during the study	Historic controls; Capturing of bleeds with patient diaries Randomisation for prophylaxis regimens and not on-demand Small number, open label, non-randomised
Kavalki[3]	2016	Open label, non-randomised, 2 period, multicentre trial *Period 1: 26 weeks (on-demand)* *Period 2: 52 weeks (prophylaxis)*	Males with moderately severe to severe haemophilia B (FIX:C ≤2% and ≥12 bleeding episodes (including ≥6 haemarthrosis episodes) within 12 months of participation and >100 exposure days to FIX products. Ages 12-65, n=25	**Product:** Standard Life Recombinant coagulation factor IX (nonacog alfa) for both periods • Prophylaxis 100IU/kg once a week (period 2) **Vs** On demand treatment (period 1)	Mean ABR (+/- SD) On-demand period: 32.9 (17.4) Prophylaxis period: 3.6 (4.6) p < 0.0001 Number of bleeding events On-demand period: 417 Prophylaxis period: 90 Mean joint bleeds (SD) On-demand period: 27.7 (16.9) Prophylaxis period: 2.1 (3.2) Number of patients experiencing joint bleeding events On-demand period: 25 (100%) Prophylaxis period: 12 (48%) Safety Adverse events Most treatment emergent AEs were mild Number of patients with treatment emergent AE	Historic controls; Non-randomised Unclear how data obtained – patient reported? Or at visit? Small number, open label, non-randomised

					On-demand: 16 (64%) Prophylaxis: 24 (96%) Inhibitors and SAE No patient developed a FIX inhibitor or experienced a thrombotic event during the study.	
Collins[4]	2014	Multinational randomised (**prophylaxis groups randomized only**) single-blind trial – prophylaxis groups, on demand parallel group	Moderate or Severe Haemophilia B (FIX activity ≤2 IU/dL) with at least 150 exposure days to any FIX product. Ages 13-70, n=74	**Product:** Recombinant factor IX (nonacog beta pegol) with extended half-life • Prophylaxis 10IU/kg weekly (52 weeks) **Vs** Prophylaxis 40IU/kg weekly (52 weeks) • On-demand group (26 weeks)	Estimated median ABR (IQR) 10 IU/kg prophylaxis: 2.93 (0.99 to 6.02) 40 IU/kg prophylaxis: 1.04 (0.00 to 4.00) On-demand: 15.58 (9.56 to 26.47) Number of patients with bleeds 10 IU/kg prophylaxis: 25/30 40 IU/kg prophylaxis:16/29 On-demand: 14/15 Safety No inhibitor development or thrombotic or hypersensitivity event reported	Allocation into on-demand or prophylaxis not randomised – based on decision of patient and clinician. Open label, non-randomised
Powell[5]	2013	Phase 3, non-randomised, open-label study, parallel group *(allocated based on standard of care at clinical sites by clinician)*	Males with severe haemophilia B (FIX activity ≤2 IU/dL) receiving prophylaxis or had a history of at least 8 bleeding episodes in year before enrolment with at least 100 exposure days to FIX. Ages >12 years, n=123	**Product:** Recombinant factor IX Fc fusion protein (rFIXFc, eftrenonacog alfa) – extended half life • Group 1: rFIXFc weekly dose adjusted prophylaxis (50IU/kg initially) • Group 2: rFIXFc 100IU/kg interval-adjusted prophylaxis (10 days to start) • Group 3: rFIXFc On-demand • Group 4: rFIXFc Treatment in perioperative period	ABR Prophylaxis reduced ABR compared to on demand group 3 for group 1 (83%) and group 2 (87%); p<0.001. Group 1: 3.12, 95% CI [2.46 to 3.95] Group 2: 1.4, 95% CI [0.0 to 3.4] Group 3 (On-demand): 18.67, 95% CI [14.01 to 24.89] Consistent for prespecified subgroup analyses Median ABR for 12 month pre and study result Group 1: 23.0 vs 2.5 Group 2: 25 vs 1.9 Group 3 (on-demand): 18 vs 17.7 Joint ABR Median, IQR Group 1: 1.1, IQR (0.0 to 4.0) Group 2: 0.4, IQR (0.0 to 3.2) Group 3 (On-demand): 13.6, IQR (6.1 to 21.6) Safety Inhibitors	*(groups alloacted based on clinical sites standard of care)* Open label, non-randomised

					One participant had a borderline positive study for inhibitors at the end of the study however were deemed to be transient and low with no clinical effect. <u>Adverse events</u> Across groups, a total of 73.9% had at least 1 adverse event during treatment period - most judged as unrelated to FIX <u>Serious Adverse events</u> 10.9% had at least one serious adverse event, one considered to be related to factor (obstructive clot in urinary collecting system).	
Santagostino[6]	2016	Phase 3, nonrandomised, open-label, multinational trial 2 periods, 2 groups	Severe haemophilia B (FIX activity <2 IU/dL) with at least 150 exposure days to FIX. Males, ages 12-61 years, n=63	Product: Recombinant factor IX Fc fusion protein (rFIXFc) – extended half life <u>Group 1: Period 1 - Prophylaxis / Period 2 - Prophylaxis</u> • Prophylaxis 35-50IU/kg once a week for 26 weeks • Followed by 75IU for 10 or 14 days <u>Group 2: Period 1 - On demand / Period 2 - Prophylaxis</u> • On demand for >/- 26 weeks • Followed by 35-50IU once a week (median 45.1 weeks and *median dose 40.3IU/kg*) *Primary efficacy analysis conducted on group 2	<u>Annualised spontaneous bleeding rate (AsBR)</u> Group 2 (on-demand/prophylaxis) – estimated rate On-demand period: 13.62 95% CI [11.001 to 16.868] Prophylaxis period: 0.55 95% CI [0.233 to 1.322) Median IQR % reduction = 100.00 (90.53 to 100.00); p<0.0001. <u>Total ABR</u> Group 2 (on-demand/prophylaxis) – estimated rate On-demand period: 20.09 95% CI [16.808 to 24.003] Prophylaxis period: 2.22 95% CI [0.942 to 5.243) Median IQR % reduction = 90.94 (81.19 to 100.00); p<0.0001. <u>Safety</u> Inhibitors against FIX were not detected in any patient <u>Adverse events</u> Treatment emergent adverse events were reported in 85.7% of participants. Most were deemed to be of mild of moderate severity and events in 7.9% were considered to be potentially associated with the product (mild to moderate severity). Two patients withdrew after an adverse event (mild to moderate and resolved within the same day without treatment) <u>Serious adverse events.</u> Two patients had an SAE which were deemed unrelated to the product (synovitis and acquired epileptic aphasia)	Unclear on how participants were allocation to groups, only patients who received on demand treatment previously were eligible for on-demand period. Open label, non-randomised

Effectiveness of the intervention

Comparison 1: Prophylaxis versus on-demand/episodic treatment with human plasma or recombinant standard half-life Factor IX (Two trials, n=75).

- *Valentino 2014[2] – randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand – use of historic controls, open-label, n=50).*
- *Kavalki 2016[3] single arm, non-randomised, historic control, open-label, n=25)*

Outcome 1.1 – Annualised bleeding rate

Valentino 2014 (n=50) reported an annualised mean bleeding rate (ABR) in the 50IU/kg twice a week prophylaxis, and 100IU once weekly prophylaxis regimens of 2.6 and 4.6 respectively, and was significantly lower compared to the first on-demand period of 35.1 ABR (50IU prophylaxis vs on-demand = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100IU vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). Difference between prophylaxis regimens was not significantly different (P=0.2167).

It was found in the trial reported upon by Kavalki 2016 (n=25), that there was lower mean ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001).

Outcome 1.2 – Annualised joint bleeding rate

Valentino 2014 (n=50) reported that the annualised joint bleeding rates were lower in the 50IU/kg twice a week prophylaxis (MD 1.9 ± 4.5) and 100IU/kg once a week prophylaxis (MD 3.6 ± 8.3) compared to the first on-demand period (MD 25.4 ± 19.1) and second on-demand period (MD 24.3 ± 21.5); p values not reported/calculated.

It was found in the trial reported upon by Kavalki 2016 (n=25), that there was lower mean joint ABR in the 100IU once weekly prophylaxis period compared to the preceding on-demand period (Mean ABR 2.1 SD +/- 3.2 vs 27.7 SD +/- 16.9; P value not reported/calculated).

Outcome 1.3 – Safety (Mortality)

This outcome was not reported in the included studies for this comparison

Outcome 1.4 – Safety (Development of inhibitors)

No patient developed a FIX inhibitor during the studies reported by Valentino 2014 and Kavalki 2016.

Outcome 1.5 – Safety (Adverse events)

Majority of the adverse events reported by Valentino 2014 and Kavalki 2016 were considered mild. Valentino 2014 reported that more adverse events occurred during the first on-demand period (42%) compared to the prophylaxis period (31.8% for both the 50IU/kg twice weekly and 100IU/kg once weekly regimens). Kavalki 2016 reported more adverse events in the prophylaxis period (96%) compared to the on-demand period (64%).

Outcome 1.6 – Safety (Serious Adverse events)

Seven serious adverse events deemed to be unrelated to the intervention were reported in by Valentino 2014, occurring five patients (kidney pain, urolithiasis, pneumothorax, accidental injury, severe lower back pain, severe testicular pain, and worsening arthropathy). Kavalki 2016 reported that five patients experienced a serious adverse event with one event (low blood pressure) occurring in the on-demand period deemed to be potentially related to the study drug.

Comparison 2: Prophylaxis versus on-demand/episodic treatment with recombinant extended half-life Factor IX (Three trials, n=260).

- *Collins 2014[4] – randomised (prophylaxis groups randomised only), single-blind trial, on demand open label, parallel group, n=74).*
- *Powell 2013[5] – non-randomised, open-label study, parallel on demand group, n=123)*
- *Santagostino 2016[6] – nonrandomised, open-label, 2 periods, 2 groups, n=63*

Outcome 2.1 - Annualised total bleeding rate

All three trials observed differences in on-demand and prophylaxis treatment. Collins 2014 (n=74) reported that the annualised median bleeding rate was higher in the on-demand group (median 15.58, IQR 9.56 to 26.47) compared to the 10IU/kg prophylaxis (median 2.93, IQR 0.99 to 6.02) and 40IU/kg prophylaxis (median 1.04, IQR 0.00 to 4.00) groups.

Powell 2013 (n=123) found a significant reduction in mean ABR between the weekly dose adjusted (starting 50IU/kg) prophylaxis (Mean: 3.12, 95% CI [2.46 to 3.95]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (83% reduction; p<0.001). A significant reduction was also reported in mean ABR between the interval adjusted 100IU prophylaxis (Mean: 1.4, 95% CI [0.0 to 3.4]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (87% reduction; p<0.001). Findings were consistent across prespecified subgroup analyses including bleeding trough level of FIX. On comparing the median ABRs 12 months pre study with the study result, larger reductions were observed in the both the weekly dose adjusted (23.0 vs 2.5) group and interval adjusted 100IU/kg prophylaxis (25 vs 1.9) group than in the on-demand group (18 vs 17.7).

Santagostino 2016 (n=63) reported a significant reduction in total ABR when patients switched from the on-demand treatment (est. ABR 20.09, 95% CI [16.808 to 24.003]) period to the prophylaxis (est. ABR 2.22, 95% CI [0.942 to 5.243) period (Median % reduction: 90.94, IQR (81.19 to 100.00); p<0.0001).

Outcome 2.2 – Annualised joint bleeding rate

Powell 2013 (n=123) reported lower median joint ABRs in the weekly dose adjusted (starting 50IU/kg) prophylaxis (Median: 1.1, IQR (0.0 to 4.0]) and interval adjusted 100IU/kg prophylaxis (Median: 0.4, IQR (0.0 to 3.2) groups compared to the on-demand (Median: 13.6 IQR (6.1 to 21.6) group; p value not reported/calculated).

Outcome 2.3 – Safety (Mortality)

This outcome was not reported in the included studies for this comparison

Outcome 2.4 – Safety (Development of inhibitors)

No inhibitor development event was recorded in the trials reported by Collins 2014 and Santagostino 2016. One participant had a borderline positive study for inhibitors at the end of the study reported upon by Powell 2013, however it was deemed to be transient and low with no clinical effect.

Outcome 2.5 – Safety (Adverse events)

Powell 2014 reported that a total of 73.9% of participants had at least one adverse event during treatment period however majority were deemed to be unrelated to FIX. Treatment emergent adverse events were reported in 85.7% of participants as reported by Santagostino 2016. Most were deemed to be of mild of moderate severity. Events in 7.9% of patients were considered to be

potentially associated with the product (mild to moderate severity). Two patients withdrew after an adverse event (mild to moderate and resolved within the same day without treatment)

Outcome 2.6 – Safety (Serious Adverse events)

No thrombotic or hypersensitivity event was recorded in the trial reported by Collins 2014. Powell 2014 reported that 10.9% of participants had at least one serious adverse event, one considered to be related to factor (obstructive clot in urinary collecting system). Two patients had a serious adverse event in the trial reported on by Santagostino 2016, which were both deemed to be unrelated to the product (synovitis and acquired epileptic aphasia)

EVIDENCE QUALITY AND LIMITATIONS

Trials for haemophilia often include both haemophilia A and B patients and with higher proportions of haemophilia A patients. The number of haemophilia B patients included in trials are proportionally low and very few trials focus predominantly on haemophilia B. The search found no RCTs where the on-demand/episodic group and prophylaxis groups were randomised. All trials were open-label and only one trial had a sample size over 100. This condition is however rare, and the feasibility of a patient blinded study is a consideration. Estimates were derived from either parallel comparison to unrandomized groups or results from same individuals either pre-study or at different phases within the same study. Allocation to groups comprising on-demand or prophylaxis components were sometimes unclear or described to be based on clinical practice at the local sites in the trial. Recording of bleeding rates were either not described or recorded by patients in electronic diaries. Overall quality of evidence was considered to be low, level II (non-randomised prospective trials).

GUIDELINES

Five guidelines were assessed with the AGREE II tool (see Appendix x for summary of the assessments). Two guidelines met the eligibility criteria (scoring at least 5 out of 7); conducted by the Malaysian Health Technology Assessment Section (MaHTAS)[7], and the World Federation of Hemophilia (WFH)[15] (See Table 4 below). The paucity of evidence, rare nature of the condition, and design of the studies were cited as limitations for meta-analysis and conducting quality assessments. Recommendations are for haemophilia A and B. Prophylaxis regimens included in the guidelines are summarised in Table 3.

Table 3: Summary of prophylaxis dosing from included guidelines

Prophylaxis Intensity	**WFH 202015**	**MaHTAS[7]**
High-dose prophylaxis	40-60 IU FIX/kg twice per week (>4000 IU/kg per year)	30 - 50 IU/kg twice/week for haemophilia B (preferred)
Intermediate-dose prophylaxis	20-40 IU FIX/kg twice per week (2000-4000 IU/kg per year)	30 - 50 IU/kg once or twice/week
Low-dose prophylaxis (with escalation of dose-intensity; as needed)	10-15 IU FIX/kg twice per week (1000-1500 IU/kg per year)	20 IU/kg once/week

Table 4. Clinical guideline recommendations

Guideline	Recommendations	Strength of evidence	AGREE II
MaHTAS 2018[7]	Prophylaxis should be given to ALL persons with severe haemophilia*. • Primary prophylaxis should start following intracranial haemorrhage, first joint bleed, severe intramuscular bleed or by three years old, whichever comes first. • Malmo protocol** is the preferred prophylactic therapy regimen in haemophilia. *Recommendation for haemophilia A and B; severe classified as <1 IU/dL (<0.01 IU/ml) or <1% of normal *High dose prophylaxis 30 - 50 IU/kg twice/week for haemophilia B	Strength of evidence not provided for overall recommendations, but levels were provided for contributing components were level I and level II-2. Recommendations and evidence were for haemophilia A and B combined.	**Overall assessment score:** 73%, 6 out of 7 **Score for rigour and methodology domain:** 77%
WFH 2020[15]	**Recommendation 6.1.1:** • For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference. • REMARK : Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding. • REMARK : In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. **Recommendation 6.2.1:** • For patients with severe phenotype hemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, episodic therapy is essential treatment for acute hemorrhages, but it will not prevent long-term joint damage. • REMARK : In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes, reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future. **Recommendation 5.1.1:** • For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates. • REMARK : The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences.	Consensus based recommendations. Guideline developers selected to not assign a strength of evidence through GRADE or other assessment due inability to conduct meta-analysis and nature of the condition. For transparency all recommendations are designated as 'consensus based'. Evidence was acknowledged to be likely low or very low if evaluated.	**Overall assessment score:** 75%, 6 out of 7 **Score for rigour and methodology domain:** 74%

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 B 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.

Dosing for prophylaxis regimens and treatment of bleeding events

Several prophylaxis regimens were considered in the analysis, See Table 5. In line with the haemophilia A costing analysis, an intermediate option will be selected for the base case with the twice a week frequency. The high dose and low dose regimens will be explored in the sensitivity analysis. Treatment of bleeds in adults was assumed to be 40IU/kg for minor bleeds and 60IU/kg for major and life threatening bleeds and in paediatrics, 50IU/kg and 65IU/kg for minor and major bleeds respectively.

Table 5: Summary of prophylaxis dosing from included guidelines

Prophylaxis Intensity	Regimen	Sources	Notes
High-dose prophylaxis	50IU/kg **twice a week**	Valentino 2014[2]; WHF 2020[15], MaHTAS 2018[7]	Exact match for trial efficacy estimates; matches high dose for WHF and MaHTAS guidelines
Intermediate-dose prophylaxis	25IU/kg **twice a week**	WHF 2020[15], MaHTAS 2018[7]; Delgado-Flores 2022[13]	WFH and MaHTAS Guideline recommendations for intermediate, efficacy estimates assumed for Haemophilia A intermediate prophylaxis
Low-dose prophylaxis	10IU/kg **twice a week**	WHF 2020[15]; Delgado-Flores 2022[13]	WFH guideline recommendation for low dose, efficacy data from haemophilia A low dose prophylaxis

Population of interest

Population estimates were sourced from the World Federation of Haemophilia, annual global survey[8] and the South Africa Haemophilia Foundation registry data[9]. This provided an estimate of 160 severe haemophilia B patients. An equal proportion in each age group for paediatrics and remainder in adult group was assumed to calculate dose estimates. Table 6 shows the number of patients with age group, estimated weights per age group and factor IX requirements for the base case regimen. There is uncertainty around patients estimates for haemophilia in South Africa and numbers currently treated in the public sector, this be explored in the sensitivity analysis.

Table 6: Average weight, IU requirements and number of patients per age group

Age	Weight (male)	IU per dose (intermediate 25IU/kg)	IU per week (twice a week)	Est. Number of patients
0-1	8	200	400	4
1-2	11	275	550	4
2-3	13.5	337,5	675	4
3-4	15.5	387,5	775	4
4-5	17.5	437,5	875	4
5-6	19.5	487,5	975	4
6-7	22	550	1100	4
7-8	24	600	1200	4
8-9	27	675	1350	4
9-10	30	750	1500	4
10-11	34	850	1700	4

11-12	38	950	1900	4
>12	70	1750	3500	112
			TOTAL	160

Costs

Costs for factor IX products were sourced from the National Department of Health Master Health Product List (contract prices[10]) and the Single Exit Price[11]. Products on contract (haemosolvex ©) will be utilised in the base case and products not on contract (octanine© will be explored in sensitivity analysis). 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 2024)[12]. 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. Costs for surgery and complications were not included. Costs for all bleeds (minor, major and life threating bleeds) were included. Table 7 shows the cost components included in the analyses.

Table 7. Cost point estimates

Item		Value	Reference
Medication Costs			
Haemosolvex® Factor IX complex 500 IU 10ml vial		R2 189.86	MHPL May 2024[10]
Octanine Factor IX 500IU 5ml vial (sensitivity analysis)		R2002.28	SEP May 2024[11]
Health Worker and Facility Costs* (sensitivity analysis only)			
Health worker cost for administration of prophylaxis	Nursing Practitioner	R80	UPFS 2024
Facility cost for administration of prophylaxis	Facility Level 1	R136	
Health worker cost for treatment of minor bleed	Nursing Practitioner	R80	
Facility cost for treatment of minor bleed	Facility Level 1	R136	
Health worker cost for treatment of severe bleeds intensive care	Specialist medical practitioner	R694	
	Nursing Practitioner	R138	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R9 091	
Health worker cost for treatment of severe bleeds general ward	Specialist medical practitioner	R210	
	Nursing Practitioner	R138	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R3 341	

Outcomes

Data estimates sourced for Haemophilia B standard half-life products all pertained to high-dose prophylaxis. Thus for the base case (intermediate-dose prophylaxis), estimates for total number of bleeds per annum for each arm were assumed to be same as those utilised for intermediate factor VIII prophylaxis for Haemophilia A intermediate which were sourced from Delgado-Flores 2022[13] (See Rapid Review for Factor VIII Prophylaxis for Haemophilia A)[14]. This was also assumed for low-dose Factor IX prophylaxis; estimates for low-dose factor VIII prophylaxis utilised.

Data sourced from the Valentino 2014[2] (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 for the high dose factor IX prophylaxis versus on-demand treatment. Estimates for calculating number of severe bleeds (major and life-threatening) as well as number of days of treatment and hospitalization for bleeds were assumed to be the same as those utilised in the haemophilia A costing. Table 8 shows

the point estimates utilised in the analysis. Outcomes for disability, quality of life, surgeries and mortality were not included in the analysis.

Table 8. Outcome point estimates

Item	Value	Reference
No. of minor bleeds per annum per one patient on intermediate dose prophylaxis (25IU/kg twice a week)	4.75	Delgado-Flores 2022 (Haemophilia A[13] - Intermediate-dose) – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	29.45	
% of major bleeds that occur in haemophilia B patients as a % of all bleeds	5%	Srivastava et al. 2021[i 15]
% of children experiencing a life-threatening bleed annually on intermediate-dose prophylaxis	0.5%	Touré et al. 2022[ii 16]
% 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) – assumed to be same for Haemophilia B
No. of days required for treatment of a major bleed – inpatient	7	
No. of days required for treatment of an LTB - inpatient	16	
Efficacy for other prophylaxis regimens* (sensitivity analysis only)	Value	Reference
No. of minor bleeds per annum per one patient on high dose prophylaxis (50IU/kg twice a week)	2.85	Valentino 2014[2] – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	33.250	
No. of minor bleeds per annum per one patient on low dose prophylaxis (10IU twice a week)	5.75	Delgado-Flores 2022 (Haemophilia A[13] - low-dose) – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	17.1	

RESULTS

Base Case analysis

Table 9 shows the results of the base case analysis which accounts for **drugs costs only** (at contract price) for **intermediate dose prophylaxis (25IU/kg twice weekly) and treatment of all bleeds** (See sensitivity analysis for scenarios including facility and health worker costs, different prophylaxis regimens and reduction in patient estimates). The total cost per patient on intermediate dose factor IX prophylaxis (25IU/kg twice weekly) was estimated to be R948 998 annum (cost of prophylaxis and treatment of breakthrough bleeds), compared to R1 291 128 per annum for treating one patient on demand (**incremental savings** of R342 130 per patient per annum). Total budget impact was an estimated R151 839 637 for 160 patients on intermediate prophylaxis per annum versus R206 580 443 for 160 patients on demand (incremental cost savings of R54 740 806). Intermediate prophylaxis (25IU/kg twice a week) could potentially avert 4212 bleeds a year; estimated incremental cost of **-R13 265** per bleed averted (**cost saving**).

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

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

Table 9: Base case analysis results

	Costs per annum for all patients				Benefits per annum	
	Cost of Prophylaxis	**Treatment of bleeds**	**Total**	**Incremental Cost**	**No. of bleeds**	**No. bleeds averted**
FIX intermediate dose prophylaxis	R117 516 647	R34 322 990	R151 839 637	-R54 740 806 (cost saving)	842	4212
FIX treatment on demand	NA	R206 580 443	R206 580 443		5054	
Cost per patient per annum					ICER	
Prophylaxis Arm	Prophylaxis	Treatment of bleeds	Total	**Incremental Cost**	ICER – Savings with each bleed averted	
	R734 479	R214 519	R948 998	-R342 130 (cost saving)		
On-demand/ episodic Arm	NA	R1 291 128	R1 291 128		-R12 996 (cost saving)	

Sensitivity analysis - Scenarios

Deterministic sensitivity analysis

Seven different scenarios were run in the analysis to explore impact of changing certain variables and assumptions (See table 10 below).

Table 10: Scenarios explored in the deterministic sensitivity analysis

Scenario	Type of analysis	Variable and/or assumption changed
Base case intermediate prophylaxis (25IU/kg twice a week), drug acquisition costs only and all bleeds		
1	Univariate	Base case but **low dose (10IU/kg twice a week)** instead of intermediate dose prophylaxis, use of estimates from Haemophilia A low dose (Delgado-Flores 2022)
2	Univariate	Base case but **high dose (50IU/kg twice a week)** instead of intermediate dose prophylaxis, uses estimates from Valentino 2014.
3	Univariate	Base case but **assumes 25% less bleeds in the on-demand/episodic arm**
4	Univariate	Base case **AND includes facility and health worker costs**
5	Univariate	Base case but **utilisation of octanine (SEP)**
6	Multivariate	Base case **low dose (10IU/kg twice a week) AND includes facility and health worker costs**
7	Univariate	Base case **but matching consumption (reducing duration of treatment and number of patients)**

Scenario 4 which was intermediate dose prophylaxis but also included facility and health worker costs was the most cost-effective. Using conservative estimates for efficacy (25% less bleeds in the on-demand/episodic arm was the least cost-effective option but still resulted in cost-savings (Scenario 3). Low dose prophylaxis (scenario 1) was less cost-effective than intermediate dose however still results in an estimated savings of R24 575 923 per annum and was more cost-effective than high dose prophylaxis (scenario 2). The scenario with Octanine© using SEP (scenario 5) shows a slightly lower cost savings than the base case with haemosolvex©, however that is assuming the same product is utilised for prophylaxis and bleeds. Table 11 outlines the results for each scenario and Appendix 4 shows full results for base case and scenarios.

Table 11: Results of the deterministic sensitivity analysis

Scenario	Short name	Incremental budget impact	Incremental cost / patient	No. of bleeds averted	Cost per bleed averted
1	Low Dose	-R24 575 923	-R153 600	2 370	-R10 370 (cost saving)

2	High Dose	-R13 126 459	-R82 040	5380	-R2 440 (cost saving)
3	Lower bleeds in on-demand arm	R5 636 700	-R35 229	3 029	-R1 861 (cost-saving)
4	+ facility and health worker costs	-R61 989 062	-R387 432	4 221	-R14 717 (cost-saving)
5	Octanine SEP	-R50 027 109	-R312 699	4 212	-R11 877 (cost-saving)
6	Low dose + facility and health worker costs	-R26 913 438	-R168 209	2 370	-R11 356 (cost-saving)
7	25% of patients, shorter treatment duration for bleeds	-R5 341 945	-R166 936	1043	-R5 124 (cost-saving)

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. As noted with the haemophilia A rapid review, 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).[17,18,19]

Lastly the base case analysis assumes 100% uptake and does not account for current use of factor IX prophylaxis. Patient number estimates for haemophilia are difficult to source and thus patient numbers may differ in reality to estimates utilised in the model. There may be patients that are not treated for bleeds and/or treated with lower doses or shorter durations. National procurement data shows an average (last five years) annual spend of around R30 million on haemosolvex® products. Utilising the above base case modelled cost estimate for one patient per annum on demand treatment (R1 291 128) and the national procurement costs, roughly 15% of estimated 160 patients with severe haemophilia are being actively treated for bleeds on demand. Sensitivity analysis was conducted which modelled 25% of the patient estimate (32 patients) and decreased duration of treatment for bleeds to attempt to match consumption data (see Scenario 7). 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 review was conducted to explore the efficacy, safety and costs for factor IX prophylaxis for haemophilia B patients compared to episodic/on-demand treatment of bleeds. No RCTs were found which randomised prophylaxis and on-demand patients thus five non-randomised trials were included. Quality of studies were considered low due to high risk of bias from open-label design and patient reported or unclear mechanism for reporting/recording outcomes as well as small sample sizes. The rarity and the nature of the condition is a consideration when assessing feasibility of conducting RCTs and ability to recruit larger samples. The studies showed benefit of factor IX prophylaxis over treatment on-demand in annualised bleeding rate and no concerns were found for safety. Two moderate to high quality guidelines were included which recommended prophylaxis for haemophilia B. Costing was conducted on intermediate-dose prophylaxis 25IU/kg twice weekly and resulting in estimated cost-savings. However patient estimates are very uncertain and as with all the other population groups, there are challenges with matching current expenditure to modelled estimates. Despite the limitations outlined, the potential benefit of the intervention (factor IX prophylaxis) is acknowledged. Furthermore, alignment with recommendations for haemophilia A would be beneficial for implementation.

REVIEWERS

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- Ms K MacQuilkan (EPiC-SCTA) has no interests to declare.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare

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 [X] Very low [ ]	Non-randomised trials, open-label, mechanisms for reporting outcomes not always clear.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [X] Moderate [ ] Small [ ] None [ ]	Comparison 1: Standard half-life recombinant Factor IX prophylaxis vs on-demand <u>Annualised Bleeding Rate (ABR)</u> Valentino 2014: n=50 • 50IU/kg twice a week prophylaxis = 2.6 • 100IU/kg once weekly prophylaxis = 4.6 • On-demand = 35.1 Both prophylaxis groups significantly lower compared to the first on-demand period of 35.1 ABR (50IU prophylaxis vs on-demand = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100IU vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). Difference between prophylaxis regimens was not significantly different (P=0.2167). Kavalki 2016 (n=25) • Lower mean ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *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	Non-randomised trials, open-label, mechanisms for reporting outcomes not always clear.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Comparison 1: Standard half-life recombinant Factor IX prophylaxis vs on-demand • Majority of the adverse events reported by Valentino 2014 and Kavalki 2016 were considered mild. • Valentino 2014 reported that more adverse events occurred during the first on-demand period (42%) compared to the prophylaxis period (31.8% for both the 50IU/kg twice weekly and 100IU/kg once weekly regimens). • Kavalki 2016 reported more adverse events in the prophylaxis period (96%) compared to the on-demand period (64%).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ 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.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
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 = (-)R342 130 (cost-savings) Incremental budget impact per annum for all patients = -R54 740 806 (cost savings) **Cost savings** per bleed = R12 996 Intermediate dose prophylaxis provided more cost savings than low dose and high dose prophylaxis scenarios however low dose provides more cost-savings than high dose. Scenario 1: Low dose prophylaxis Incremental budget impact per annum for all patients = **cost savings** of R24 575 923 Incremental cost per patient = **cost savings** of R153 600
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: ☐	
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 IX, 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 B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	10
9	#6 AND #5	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[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])	10
8	#6 AND Filter for clinical trials and RCTs	(("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	69
7	#6 AND #4	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[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]))	357
6	#1 AND #2 AND #3	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])	581
5	Systematic reviews	"systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	434 688
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])	5 082 662
3	Prophylaxis (intervention)	"prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]]	1 917279
2	Factor IX (intervention & comparator)	"Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]	8 911
1	Hemophilia B (population)	"haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]	5 792

COCHRANE

search	Query	Results
#1	MeSH descriptor: [Hemophilia B] explode all trees	**196**
#2	MeSH descriptor: [Factor IX] explode all trees	**89**
#3	#1 AND #2	**42**
#4	#3 in Cochrane Reviews	**1**

Epistemonikos

Search String	(title:((title:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))) OR abstract:((title:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))))	
Limits/Filters	All studies	109 results
	Filtered for RCTs	3 results
	Filtered for primary studies	98 results
	Filtered for systematic reviews	6 results

APPENDIX 3 - Table of excluded studies

No.	Study	Reason for exclusion
1	Klukowska A, Laguna P, Svirin P, Shiller E, Vdovin V. Efficacy and safety of OCTANINE F in children with haemophilia B. Haemophilia. 2008 May;14(3):531-8. doi: 10.1111/j.1365-2516.2008.01678.x. Epub 2008 Mar 18. PMID: 18355266.	Incorrect study design
2	Andersson NG, Auerswald G, Barnes C, Carcao M, Dunn AL, Fijnvandraat K, Hoffmann M, Kavakli K, Kenet G, Kobelt R, Kurnik K, Liesner R, Mäkipernaa A, Manco-Johnson MJ, Mancuso ME, Molinari AC, Nolan B, Perez Garrido R, Petrini P, Platokouki HE, Shapiro AD, Wu R, Ljung R. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. Br J Haematol. 2017 Oct;179(2):298-307. doi: 10.1111/bjh.14844. Epub 2017 Jul 12. PMID: 28699675.	Incorrect study design
3	Young G, Collins PW, Colberg T, Chuansumrit A, Hanabusa H, Lentz SR, Mahlangu J, Mauser-Bunschoten EP, Négrier C, Oldenburg J, Patiroglu T, Santagostino E, Tehranchi R, Zak M, Karim FA. Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase III safety and efficacy extension trial (paradigm™4). Thromb Res. 2016 May;141:69-76. doi: 10.1016/j.thromres.2016.02.030. Epub 2016 Mar 2. PMID: 26970716.	Incorrect study design
4	Windyga J, Stasyshyn O, Lissitchkov T, Mamonov V, Serban M, Rusen L, Ploder B, Tangada S. Safety, Immunogenicity, and Hemostatic Efficacy of Nonacog Gamma in Patients With Severe or Moderately Severe Hemophilia B: A Continuation Study. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620950836. doi: 10.1177/1076029620950836. PMID: 32866032; PMCID: PMC7469725.	Incorrect study design
5	Wu R, Luke KH, Poon MC, Wu X, Zhang N, Zhao L, Su Y, Zhang J. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. Haemophilia. 2011 Jan;17(1):70-4. doi: 10.1111/j.1365-2516.2010.02348.x. PMID: 20579111.	Incorrect population
6	Roy S, De AK. Effect of Prophylactic Management of Hemophilia on Bleeding Episodes. Indian J Hematol Blood Transfus. 2019 Jul;35(3):496-501. doi: 10.1007/s12288-018-1054-6. Epub 2018 Dec 3. PMID: 31388263; PMCID: PMC6646620.	Incorrect population
7	Yang R, Wu R, Sun J, Sun F, Rupon J, Huard F, Korth-Bradley JM, Xu L, Luo B, Liu YC, Rendo P. First open-label, single-arm, prospective study of real-world use of FIX replacement therapy in a predominantly pediatric hemophilia B population in China. Medicine (Baltimore). 2021 May 28;100(21):e26077. doi: 10.1097/MD.0000000000026077. PMID: 34032739; PMCID: PMC8154445.	Incorrect study design
8	Fukutake K, Taki M, Matsushita T, Sakai M, Takata A, Yamaguchi H, Karumori T. Postmarketing safety and effectiveness of recombinant factor IX (nonacog alfa) in Japanese patients with haemophilia B. Haemophilia. 2019 Jul;25(4):e247-e256. doi: 10.1111/hae.13783. Epub 2019 Jun 6. PMID: 31168882; PMCID: PMC6852692.	Incorrect study design
9	Shapiro AD, Kulkarni R, Ragni MV, Chambost H, Mahlangu J, Oldenburg J, Nolan B, Ozelo MC, Foster MC, Willemze A, Barnowski C, Jain N, Winding B, Dumont J, Lethagen S, Barnes C, Pasi KJ. Post hoc longitudinal assessment of the efficacy and safety of recombinant factor IX Fc fusion protein in hemophilia B. Blood Adv. 2023 Jul 11;7(13):3049-3057. doi: 10.1182/bloodadvances.2022009230. PMID: 36848635; PMCID: PMC10331408.	Incorrect study design
10	Windyga J, Lin VW, Epstein JD, Ito D, Xiong Y, Abbuehl BE, Ramirez JH. Improvement in health-related quality of life with recombinant factor IX prophylaxis in severe or moderately severe haemophilia B patients: results from the BAX326 Pivotal Study. Haemophilia. 2014 May;20(3):362-8. doi: 10.1111/hae.12315. Epub 2013 Nov 20. PMID: 24251442	Incorrect study design
11	Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Rusen L, Lamas JL, Oh MS, Chapman M, Fritsch S, Pavlova BG, Wong WY, Abbuehl BE. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014 Jan;20(1):15-24. doi: 10.1111/hae.12228. Epub 2013 Jul 9. PMID: 23834666.	Incorrect study design

12	Kavakli K, Nişli G, Aydinok Y, Oztop S, Cetingül N, Aydoğdu S, Yalman O. Prophylactic therapy for hemophilia in a developing country, Turkey. Pediatr Hematol Oncol. 1997 Mar-Apr;14(2):151-9. doi: 10.3109/08880019709030901. PMID: 9089743.	Incorrect population
13	Swedish Council on Health Technology Assessment. Treatment of Hemophilia A and B and von Willebrand Disease: A Systematic Review [Internet]. Stockholm: Swedish Council on Health Technology Assessment (SBU); 2011 May. SBU Assessment No. 208E. PMID: 26153606.	Incorrect study design – narrative summary only
14	Polack B, Calvez T, Chambost H, Rothschild C, Goudemand J, Claeyssens S, Borel-Derlon A, Bardoulat I, Maurel F, Woronoff-Lemsi MC; EQOFIX Study Group. EQOFIX: a combined economic and quality-of-life study of hemophilia B treatments in France. Transfusion. 2015 Jul;55(7):1787-97. doi: 10.1111/trf.13016. Epub 2015 Feb 5. PMID: 25652955.	Incorrect outcome
15	Chowdary P, Kearney S, Regnault A, Hoxer CS, Yee DL. Improvement in health-related quality of life in patients with haemophilia B treated with nonacog beta pegol, a new extended half-life recombinant FIX product. Haemophilia. 2016 Jul;22(4):e267-74. doi: 10.1111/hae.12995. Epub 2016 Jun 28. PMID: 27352908.	Incorrect intervention, comparator
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APPENDIX 4 – Full results of base case and scenarios

		Costs				Benefits		Cost/benefit	Per patient			
BASE CASE	Intermediate prophylaxis 25IU twice weekly, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Intermediate dose factor IX prophylaxis	R117 516 647,04	R34 322 990	R151 839 637	-R54 740 806,36	842,00	4212,00	-R12 996,39	R948 997,73	5,26	-R12 996,39	R734 479,04
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R206 580 443,10	R206 580 443		5054,00			R1 291 127,77	31,59		
									-R342 130,04			
SCENARIO 1	Base case but low dose, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Low dose factor IX prophylaxis	R61 946 759,68	R40 757 674	R102 704 434	-R24 575 922,84	985,00	2370,00	-R10 369,59	R641 902,71	6,16	-R10 369,59	R387 167,25
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R127 280 356,84	R127 280 357		3355,00			R795 502,23	20,97		
									-R153 599,52			
SCENARIO 2	Base case but high dose prophylaxis, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - High dose factor IX prophylaxis	R204 970 896,00	R20 768 632	R225 739 528	-R13 126 458,81	506,00	5380,00	-R2 439,86	R1 410 872,05	3,16	-R2 439,86	R1 281 068,10
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R238 865 987,05	R238 865 987		5886,00			R1 492 912,42	36,79		
									-R82 040,37			
SCENARIO 3	Base case but lower effect size - 25% less demand 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 benef	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Intermedite dose factor IX prophylaxis	R117 516 647,04	R34 322 990	R151 839 637	-R5 636 699,64	842,00	3029,00	-R1 860,91	R948 997,73	5,26	-R1 860,91	R734 479,04
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R157 476 336,38	R157 476 336		3871,00			R984 227,10	24,19		
									-R35 229,37			
SCENARIO 4	Base case, but includes facility/staff costs	Cost for prophylaxis	Treatment of bleeds (factor &	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benef	ICER	
	Intervention - Intermediate dose factor IX prophylaxis	R121 110 887,04	R36 516 014	R157 626 901	-R61 989 062,36	842,00	4212,00	-R14 717,25	R985 168,13	5,26	-R14 717,25	
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R219 615 963,10	R219 615 963		5054,00			R1 372 599,77	31,59		
									-R387 431,64			
SCENARIO 5	Base case but octanine at SEP	Cost for prophylaxis	Treatment of bleeds (factor	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - intermediate IX prophylaxis	R107 450 353,92	R31 407 621	R138 857 975	-R50 027 108,54	842,00	4212,00	-R11 877,28	R867 862,35	5,26	-R11 877,28	R671 564,71
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R188 885 083,80	R188 885 084		5054,00			R1 180 531,77	31,59		
									-R312 669,43			
SCENARIO 6	Base case but low dose includes administration/facility costs	Cost for prophylaxis	Treatment of bleeds (factor &	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	
	Intervention - Low dose factor IX prophylaxis	R65 540 999,68	R43 306 863	R108 847 863	-R26 913 437,84	985,00	2370,00	-R11 355,88	R680 299,14	6,16	-R11 355,88	
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R135 761 300,84	R135 761 301		3355,00			R848 508,13	20,97		
									-R168 208,99			
arios but in narra	HAEM A estimates for intermediate											
SCENARIO 7	Base case but adjusting to match consumption, factor only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - intermediate dose factor IX prophylaxis	R23 503 329,41	R3 103 470	R26 606 799	-R5 341 944,48	103,20	1042,70	-R5 123,18	R831 462,47	3,23	-R5 123,18	R146 895,81
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R31 948 743,48	R31 948 743		1145,90			R998 398,23	35,81		

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