MSAC Application 1728.1

Etranacogene dezaparvovec for the treatment of congenital haemophilia B

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Test (AAV5 NAb): Adult patients (≥18 years) with severe or moderately severe (≤2%) congenital haemophilia B (cHMB), currently receiving stable FIX prophylactic therapy.

Intervention (Hemgenix®): Adult patients (≥18 years) with severe or moderately severe (≤2%) congenital haemophilia B (cHMB), currently receiving stable FIX prophylactic therapy, who also meet the following criteria:

- anti-AAV5 NAb titre < 1:900 using 9-point assay as determined by the AAV5 NAb assay
- No active infections, either acute or uncontrolled chronic
- No known advanced hepatic fibrosis, or cirrhosis

Congenital haemophilia is a rare bleeding disorder caused by deficiencies in coagulation factors arising from mutations in clotting factor genes (Srivastava et al. 2020). There are 2 main types of congenital haemophilia, with type A (HMA) accounting for 80–85% of the total prevalent population and type B (HMB) around 15% (Srivastava et al. 2020). A much rarer form known as type C is estimated to occur in less than 5% of cases. Congential HMB (cHMB) is characterised by partial or complete deficiency in the activity of essential coagulation factor IX (FIX) due to X-linked heritable variants of the HMB gene. It occurs primarily in males, with females typically being carriers with a mild or absent phenotype.

Acquired HMB, due to the formation of anti-FIX antibodies occurring in an individual without cHMB, is out of scope of this application.

Severity

Most bleeding occurs internally, with intra-articular, intramuscular, intracerebral and mucocutaneous bleeds considered severe (AHCDO and NBA 2016). Repeated bleeding, especially joint bleeds (haemarthrosis), is a major cause of significant morbidity and decreased quality of life (QoL) in people living with HMB (AHCDO and NBA 2016). Although infrequent, intracranial and gastrointestinal bleeding, and bleeding into the neck and throat, can be life-threatening (AHCDO and NBA 2016). For patients with cHMB, bleeding tendency correlates with FIX concentrations, so cHMB-associated severity and risk of bleeding is classified according to endogenous plasma FIX concentrations. FIX concentrations <1% is classified as severe disease, 1–5% is moderate disease and >5–40% is mild disease (Srivastava et al. 2020).

Individuals may exhibit severe bleeding irrespective of FIX concentrations and require use of FIX for ongoing prophylaxis. It should also be noted that a subgroup of patients in the moderate severity categories has been specifically defined for the purpose of this PICO. Patients who have FIX concentrations between 1–2% (<0.02 IU/mL) are considered as "moderately severe", and this is a definition which is used in clinical trials (ClinicalTrials.gov 2022). Besides the FIX concentrations, patients with moderately severe cHMB experience frequent spontaneous bleeding, and their bleeding management may require more aggressive and intensive treatments. Table 1 shows the classification of cHMB according to clinical severity, based on FIX clotting activity, symptoms and usual age of diagnosis.

Table 1 Classification of congenital haemophilia B

Clinical severity	FIX clotting activity	Symptoms	Usual age of diagnosis
Severe	<1% (<0.01 IU/mL)	Frequent spontaneous bleeding	Age ≤2 years
Moderately severe	1–≤2% (<0.02 IU/mL)	Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions, *used in the HOPE-B trial**	
Moderate	1–5% (0.01–0.05 IU/mL)	Rare spontaneous bleeding Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions	Age <5-6 years
Mild	>5–<40% (>0.05–0.4 IU/mL)	No spontaneous bleeding Excessive and/or prolonged bleeding after major injuries, surgery or tooth extractions	Often later in life, depending on haemostasis challenges

Abbreviations: FIX = factor IX; **IU** = international units
Notes: * = Not part of historical haemophilia categorisation but was used as an inclusion criterion in the HOPE-B trial (ClinicalTrials.gov 2022).
Sources: (Konkle and Fletcher 1993; Srivastava et al. 2020; ClinicalTrials.gov 2022)

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Australian haemophilia B patients are managed via haemophilia treatment centres (HTC), located in select tertiary hospitals in the major cities (19 in total across the country, with 7 specialising in paediatric patients). The HTCs are staffed by haematologists, nurses, allied health, and medical scientists who specialise in treating haemophilia. All existing adult HTCs nationally will be designated as Hub or Spoke sites with individual and shared responsibilities.

As per to the (Australian Haemophilia Centre Director's Organisation (AHCDO) Clinical Implementation Plan, assessment of suitability for Hemgenix, including AAV5 antibody testing, administration of the therapy and subsequent follow-up, is expected to be conducted exclusively within an established HTC setting.

Provide a rationale for the specifics of the eligible population:

In adult patients with cHMB, the objective of Hemgenix® is to enable FIX production at a level high enough to reduce bleeding rates, to allow for discontinuation of routine prophylactic FIX replacement therapy and to greatly reduce the need for on-demand FIX therapy (Thornburg 2021).

The eligible population is aligned to the TGA indication and population investigated in clinical trial for Hemgenix® (etranacogene dezaparvovec). Prior to the treatment with Hemgenix patients should be assessed for the titre of preexisting neutralising anti-AAV5 antibodies. Preexisting neutralising anti-AAV antibodies above a titre of 1:678 (1:898 with the 9-point assay) may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of Hemgenix therapy. There is limited data in patients with neutralising anti-AAV5 antibodies above 1:678 using the clinical utility standard or 7-point assay (1:898 with the 9-point assay). In 1 patient with

a preexisting neutralising anti-AAV5 antibody titre of 1:3212 in the clinical study, no Factor IX expression was observed and restarting of exogenous Factor IX prophylaxis was needed.

In the clinical studies with Hemgenix® (etranacogene dezaparvovec), for the patient sub-group with detectable preexisting neutralising anti-AAV5 antibodies up to a titre of 1:678 (1:898 with the 9-point assay), mean Factor IX activity levels were within the same range but numerically lower compared to those of the patient sub-group without detectable preexisting neutralising anti-AAV5 antibodies. However, both patient groups, with and without detectable preexisting neutralising anti-AAV5 antibodies, demonstrated an improved haemostatic protection compared to the standard of care Factor IX prophylaxis after Hemgenix® administration.

The anti-AAV5 assay is to inform patient eligibility for Hemgenix® (etranacogene dezaparvovec). Patients with a pre-existing antibody titre <1:900 (9-point assay [≈ <1:700 7-point assay]) are eligible for Hemgenix® (etranacogene dezaparvovec).

Intervention

Name of the proposed health technology:
AAV5 Neutralising Antibody (NAb) assay to determine eligibility for etranacogene dezaparvovec for the treatment of Haemophilia B.

Describe the key components and clinical steps involved in delivering the proposed health technology:

HEMGENIX® (etranacogene dezaparvovec) is an adeno-associated virus serotype 5 (AAV5)–based gene therapy that is registered for use in adults with haemophilia B in Australia. Further detail on the key components and clinical steps for the delivery of HEMGENIX® is available in the Ratified PICO for Application 1728.

Pre-existing neutralizing antibodies (NAbs) to AAV5 can be present in the population due to exposure to naturally occurring AAV infection. Neutralising antibodies (NAbs) to Hemgenix® (etranacogene dezaparvovec) are measured with a custom-developed, in vitro cell-based assay to detect NAbs by measuring inhibition of transduction of cells with an AAV5 virus carrying a reporter transgene that encodes the luciferase protein, which can emit light when successfully transduced into cells.

Before a treatment decision is made, the healthcare professional should discuss the risks, benefits, and uncertainties of HEMGENIX® (etranacogene dezaparvovec) with the patient when presenting Hemgenix as a treatment option, including that high preexisting neutralising anti-AAV5 antibodies may reduce the efficacy of Hemgenix® therapy; patients should be assessed for the titre of preexisting neutralising antiAAV5 antibodies to determine eligibility.

Identify how the proposed technology achieves the intended patient outcomes:

The AAV5 NAb assay measures neutralising antibodies to identify patients that have NAb titres <1:900 (9-point assay) and are eligible for HEMGENIX®. HEMGENIX® is a gene therapy infusion treatment designed to introduce a copy of the human FIX gene to address the lack of functional FIX protein expression in a patient with cHMB (CSL Behring LLC 2022; Thornburg 2021). After infusion, Hemgenix preferentially targets liver cells, where vector DNA is released into the

nucleus, instructing the cell to produce FIX (CSL Behring LLC 2022; Thornburg 2021). Following transduction, functional FIX is produced at near-normal to normal levels that circulate in the body, reducing the risk of bleeding (CSL Behring LLC 2022; Thornburg 2021). As Hemgenix® delivers a functional gene that acts as a blueprint for FIX, the treatment is offered as a one-off infusion with effects anticipated to last a lifetime.

In the absence of the AAV5 NAb assay and Hemgenix, eligible patients would be managed with standard of care, including FIX replacement therapies for prophylaxis treatment as routine management plus on-demand and procedural prophylaxis to control for elevated risk of bleeding event. The proposed therapy has the potential to reduce the need for FIX replacement therapy or even make FIX replacement therapy obsolete.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
Yes, Hemgenix® is the brand name of the gene therapy.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:
Hemgenix® will be administered once only to eligible patients as a single intravenous administration by a haematology at a hub HTC trained in the delivery of gene therapy (AHCDO 2022). The AHCDO roadmap proposes a hub and spoke model of care for the administration of gene therapy in Australia. While it is the spoke centre's responsibility to identify and screen patients for selection, the decision of which patients to treat is shared by the hub and spoke centres, and the hub is responsible for the administration of gene therapy. Provided as a sterile solution in 10 mL glass vials Hemgenix would be administered by IV infusion at a dose of $2x10^{13}$ gc/kg and as a single-dose IV infusion into a peripheral vein over 1–2 hours in an outpatient setting (CSL Behring LLC 2022).

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Haematologist required for NAb assay ordering. Haematologists and infusion specialists will be responsible for administering Hemgenix®. Nurse or phlebotomist required for blood draw. Testing will be run-off shore by trained pathology experts at Precision for Medicine (supplier of AAV5 NAb assay).

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

The AAV5 NAb assay will solely be conducted at a single site located at Precision for Medicine (PfM), the third-party supplier of the assay. This single site will support testing requirements for

all Hemgenix markets globally. The delivery of Hemgenix® is the responsibility of treating haematologist and their support team with support from spoke HTC's in the broader management of the patient.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Haematologists at Hub/Spoke Haemophilia Treatment Centres (HTCs) will order the proposed test for patients considered for treatment with Hemgenix®. It is not intended for patients to be referred for the AAV5 NAb test outside of these centres. As discussed above, haematologists at hub HTCs will be solely responsible for administering Hemgenix® with support provided by haematologists at spoke HTCs in the broader management of these patients.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Test: No.

Intervention: Yes

Provide details and explain:

Test: There are no specific training or qualifications required to provide or deliver the NAb assay from a local perspective. The proposed assay will be performed by PfM Laboratory Scientists who have been trained to conduct the test.

Intervention: Hemgenix® infusion will be provided at five hub HTCs by highly specialised experts. AHCDO has provided a roadmap for the implementation of gene therapy for haemophilia in Australia (AHCDO 2022). The roadmap recommends training and accreditation of clinicians and other healthcare professionals at hub centres for the implementation of gene therapy in Australia. Some HTCs already have existing capabilities in the delivery of gene therapy from clinical trial experiences, including necessary accreditations and processes such as those relating to the handling of genetically modified organisms (GMO).

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☐ Inpatient private hospital
☐ Inpatient public hospital
☐ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Test: No

Intervention: Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

The AAV5 NAb assay will solely be conducted at a single site located at Precision for Medicine (PfM), the third-party supplier of the assay. This single site will support testing requirements for all Hemgenix® markets globally.

During the screening period, an AAV5 assay will be requested if the patient is deemed suitable. The sampling kit, shipping, and analysis is supported by CSL at no cost. Sampling kits can be ordered and stocked at HTCs. After blood sample collection, the sample is sent to the dedicated central laboratory for analysis. This single offshore site will support testing requirements for all Hemgenix markets globally to ensure test rigour and accuracy.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Provide a name for your comparator:

Test: The comparator to the AAV5 NAb assay is no testing. Without testing, patients will continue to receive standard of care cHMB therapy with no gene therapy.

Intervention: Standard of care for cHMB with no gene therapy

Provide an identifying number for your comparator (if applicable):
N/A

Provide a rationale for why this is a comparator:

Test: There are no available alternative tests for detection of anti-AAV5 antibodies in human plasma for informing eligibility of haemophilia B patients for treatment with Hemgenix® (etranacogene dezaparvovec), as such, a comparator to the proposed test does not exist.

Intervention: Refer to the Ratified PICO for Application 1728.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☒ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

For some patients, the proposed therapy may completely reduce the need for standard of care FIX replacement therapy, and for others, may greatly reduce the use of FIX therapy.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources

Test outcomes:

Safety:

- Direct harms of the test

Test performance:

- Test reliability (intra-observer and intra-instrument variability/agreement)
- Concordance to the clinical utility standard
- Predictive effect, change in clinical management, value in decision making
- Rate of failed tests, test turn-around time

Intervention outcomes:

Refer to the Ratified PICO for Application 1728

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

The AAV5 NAb test will inform eligibility for treatment with Hemgenix® (etranacogene dezaparvovec), and as such, patient management will change to include Hemgenix® as a treatment option.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

Test

Relative to the comparator: Compared with not testing, the AAV5 NAb test is superior in detecting patients eligible for Hemgenix®.

Relative to the clinical utility standard: The analytical performance studies show that the AAV5 NAb test (9-point assay) is concordant with the clinical utility standard (7-point assay) and is a reliable and reproducible test.

Intervention

The applicant claims that compared to standard of care with no gene therapy, the proposed intervention (Hemgenix®) has:

- superior efficacy outcomes: annualised bleed rates (overall, categorised bleed severity, and site/type specific) over time, Reduction in FIX utilisation.
- endogenous FIX activity concentration and trough FIX activity over time, occurrence and resolution of target joint bleeding, central venous access no longer required, events of central venous access related sepsis or thrombosis.
- non-inferior and acceptable safety outcomes: acute peri-infusion adverse effects, long-term adverse events (e.g. thrombosis, hepatitis, hepatocellular carcinoma), laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology), formation of post-infusion FIX inhibitors and formation of anti-AAV5 NAbs in relation to suboptimal therapeutic effect or intervention failure.
- superior health-related quality of life (HRQoL) outcomes: EQ-5D-5L (EuroQol 5-dimension health related quality of life questionnaire–5 levels), SF-36 (36-item short form health survey), HWBI (haemophilia wellbeing index), HAEMO-QoL-A (haemophilia-specific QoL questionnaire for adults), PROBE (patient reported outcomes, burdens and experiences) questionnaire, HAL (haemophilia activities list), FISH (functional independence score in haemophilia).

Rationale: HOPE-B (pivotal phase 3 trial) demonstrates a significantly reduce annualised bleeding rate (ABR), sustained increases to FIX % activity level, significant reduction in FIX consumption and frequency and improvements in QoL metrics. The pivotal Phase III trial also shows that Hemgenix® is reasonably safe and well tolerated in the target population of patients with severe or moderately severe HMB receiving routine FIX prophylaxis, being associated with similar or even lower rates of adverse events than the pre-treatment standard of care (Pipe 2023).

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
N/A

Identify how the proposed technology achieves the intended patient outcomes:
The intended patient outcome is to determine if a patient is eligible for HEMGENIX® (etranacogene dezaparvovec). The AAV5 NAb assay measures neutralising antibodies to identify patients that have NAb titres <1:900 (9-point assay) and are eligible for HEMGENIX®. Compared to standard of care with no gene therapy, HEMGENIX® has superior efficacy outcomes including annualised bleeding rates (ABR), significantly reduced FIX utilisation, endogenous FIX activity, improved quality of life (QoL) and a sustained change in patient disease categorisations (to mild or non-haemophilic categories).

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes, the test detects patients eligible for treatment with Hemgenix® that, without the test, would not have been detected.

A change in health outcome? Yes, superior outcomes are achieved with Hemgenix® relative to standard of care cHMB therapy, which patients would remain on if no testing occurred.

Other benefits? No, there are no other reasons to use this test other than to determine whether or not the patient is eligible for treatment with Hemgenix®.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

Test: The sampling kit, shipping, and analysis is supported by CSL at no cost to Governments.

Intervention: HEMGENIX® may be associated with a higher costs compared to standard of care therapies for cHMB, however as a one-time infusion with expected long-term durability, significant cost savings are expected due to the reduced requirement of FIX prophylaxis and on-demand therapy. A cost-effectiveness model will be provided in the ADAR along with justification on the unit price and payment structure of HEMGENIX®.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Refer to the Ratified PICO for Application 1728 for additional detail on clinical management algorithms.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

Under the proposed clinical management algorithm, patients with severe or moderately severe HMB receiving stable prophylaxis (± on-demand FIX) will be tested for FIX inhibitors, active infections, and severe liver disease (patients testing positive to inhibitors will follow the appropriate management guidelines).

Patients with active infections or severe liver disease are ineligible for Hemgenix®, so will continue to be treated with standard of care cHMB therapy. Active hepatitis or severe liver disease do not need to be ruled out for the current management strategies.

Patients without active infections or severe liver disease are eligible to undergo testing for anti-AAV5 antibodies using the AAV5 NAb assay. This is not a requirement for current treatment strategies. Patients who test positive for an anti-AAV5 antibody titre >1:900 (9-point assay) are ineligible for Hemgenix®, so are treated with standard of care cHMB. Patients testing negative for anti-AAV5 antibodies or have an anti-AAV5 antibody titre < 1:900 are eligible for treatment with Hemgenix®.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
Yes

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Diagnosis and assessment of inhibitors will take place regardless of the use of the proposed health technology. However, patients with active hepatitis or severe liver disease need to be ruled out prior to being eligible for the AAV5 NAb assay. This is not a requirement for the current management of patients with haemophilia B.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Minor additional healthcare resources may be required in conjunction with delivering the proposed health technology, such as additional infusion specialist resource (however these will be covered within the usual operation of the HTC).

Explain what other healthcare resources are used in conjunction with the comparator health technology:
N/A

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

As described above, additional healthcare resources will be required during the patient assessment (suitability and eligibility), infusion and post-dose monitoring periods. These however are not expected to be significant and will be part of usual HTC operations.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

Continued prophylaxis or on-demand therapy may be required in the first few weeks after administration. Continued haemostatic support with exogenous FIX may be required during the first weeks after HEMGENIX® administration to provide sufficient factor IX coverage for the initial days post-treatment. Monitoring of the factor IX activity is recommended post-dose to follow the patient`s response to HEMGENIX®. Exogenous FIX or other haemostatic products may be required in the case of surgery, invasive procedures, trauma or bleeds in the event that FIX activity is deemed insufficient for adequate haemostasis.

Overall monitoring after the use of the proposed intervention will differ compared to current clinical management. Following administration of Hemgenix®, weekly liver function tests would be required for at least 3 months and then every 3 months in the first year, every 6 months in the second-year post-treatment, with subsequent yearly testing for at least 5 years to routinely assess liver function.

Factor IX activity should also be monitored (e.g. weekly for at least 3 months, then every 3 months in the first year and every 6 months in the second year, with subsequent yearly testing for at least 5 years.

For patients with pre-existing risk factors for hepatocellular carcinoma perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g. annually) for 5 years following administration.

Patients should be monitored for human factor IX inhibitors. Post-dose testing should be performed if plasma factor IX activity levels are not achieved, decrease or if bleeding is not controlled or returns.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

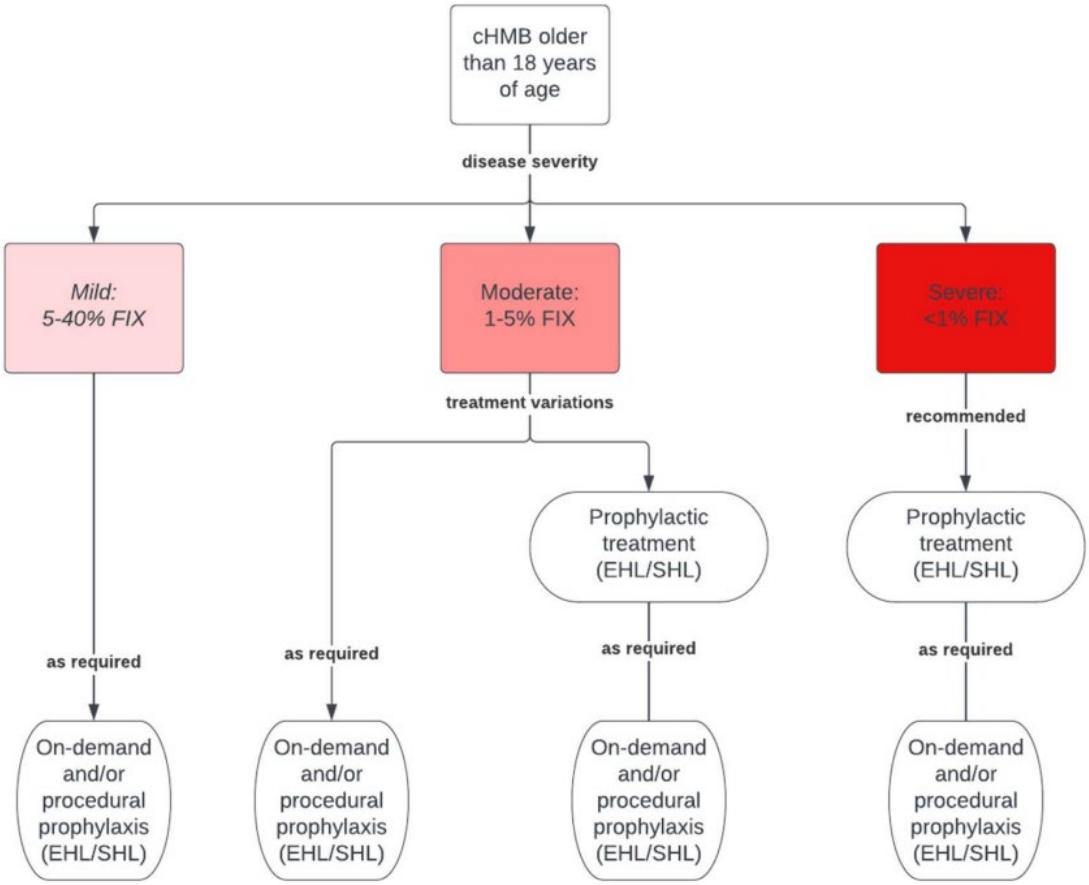
Patients should be monitored for human factor IX inhibitors if receiving standard of care cHMB therapy comprising of FIX prophylaxis.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

Overall, monitoring after the use of AAV5 NAb assay leading to dosing with Hemgenix®, will differ for the first 12-24 months compared to no testing and standard of care cHMB therapy.

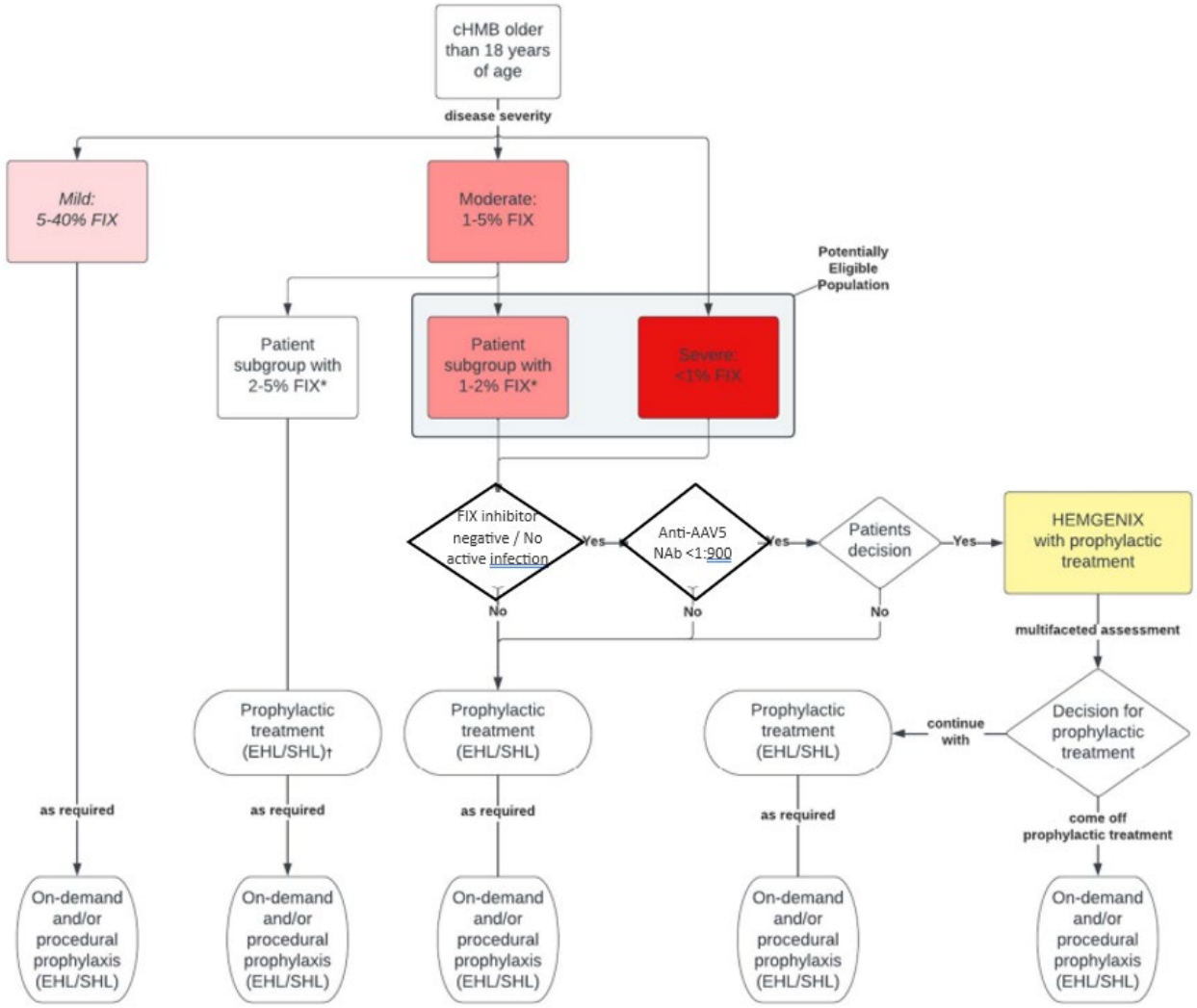
Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Without the proposed health technologies



Abbreviations: cHMB = congenital haemophilia B; FIX = factor IX; EHL = extended half-life recombinant FIX replacement therapy; SHL = standard half-life recombinant FIX replacement therapy
Source: Figure 1 in Application 1728 Ratified PICO

With the proposed health technologies



Abbreviations: Anti-AAV5 NAbs = anti-adeno-associated virus 5 neutralising antibodies; cHMB = congenital haemophilia B; FIX = factor IX; EHL = extended half-life recombinant FIX replacement therapy; SHL = standard half-life recombinant FIX replacement therapy

Source: Adapted from Figure 2 in Application 1728 Ratified PICO.

Notes: The anti-AAV5 NAb threshold has been updated to 1:900 to reflect the 9-point assay, and order of FIX inhibitor testing and testing for active infections has been moved to before AAV5 NAb testing to better reflect expected sequencing of testing.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design*	**Title of journal article or research project** *(including any trial identifier or study lead if relevant)*	**Short description of research** *(max 50 words)***	**Website link to journal article or research** *(if available)*	**Date of publication*****
1.	Phase III, open-label, single-dose, multi-centre multinational trial NCT03569891	1. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B HOPE-B 2. Etranacogene dezaparvovec gene therapy for haemophilia B (HOPE-B): 24-month post-hoc efficacy and safety data from a single-arm, multicentre, phase 3 trial	Phase III, open-label, single-dose, multi-centre multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon optimized human Factor IX gene (AMT-061) administered to adult subjects with severe or moderately severe haemophilia B	1. https://www.nejm.org/doi/full/10.1056/NEJMoa2211644 2. https://pubmed.ncbi.nlm.nih.gov/38437857/	1. February 22, 2023 2. Apr 11, 2024
2.	Phase IIb, open-label, single-dose, single-arm, multi-centre trial NCT03489291	1. Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B 2. Stable and durable factor IX levels in patients with hemophilia B over 3 years after etranacogene dezaparvovec gene therapy	Phase IIb, open-label, single-dose, single-arm, multi-centre trial to confirm the factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AMT-061) administered to adult subjects with severe or moderately severe haemophilia B.	1. https://doi.org/10.1182/bloodadvances.2019000811 2. https://doi.org/10.1182/bloodadvances.2022008886	1. Oct 30, 2019 2. Sep 27, 2023
3.	Phase I/II, non-randomised, open-label, two-cohort, dose-ascending, multi-centre trial NCT02396342	1. Gene therapy with adeno-associated virus vector 5–human factor IX in adults with hemophilia B 2. Therapeutic hFIX Activity Achieved after Single AAV5-hFIX Treatment in Hemophilia B Patients and NHPs with Pre-existing Anti-AAV5 NABs	Phase I/II, non-randomised, open-label, two-cohort, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a precursor codon-optimized human Factor IX gene therapy construct (AMT-060) administered to adult patients with severe or moderately severe haemophilia B.	1. https://doi.org/10.1182/blood-2017-09-804419 2. https://doi.org/10.1016/j.omtm.2019.05.009	1. Mar 1, 2018 2. Sep 13, 2019

References: (Pipe et al. 2023), (Shah et al. 2023), (Drygalski et al. 2019), (Drygalski et al. 2023), (Miesbach et al. 2018), (Majowicz et al. 2019), (Coppens et al. 2024)

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