Haemophilia

WILEY

Haemophilia WFH

ORIGINAL ARTICLE

The WFH Guidelines for the Management of Haemophilia: AAV Gene Therapy, 2025

Glenn F. Pierce[1] | Margareth C. Ozelo[2] | Johnny Mahlangu[3] | Amy L. Dunn[4] | Marlene Beijlevelt[5] | Rose Bender[6] | Manuel Carcao[7] | Donna Coffin[1] | Enrico Ferri Grazzi[8] | Graham R. Foster[9] | Julie Frantsve-Hawley[10] | Alfonso Iorio[11] | Shannon Jackson[12] | Radoslaw Kaczmarek[13] | Gwendolyn E. Kaeser[14] | Barbara A. Konkle[15] | Magdalena Lewandowska[16] | Wolfgang Miesbach[17] | Brian O'Mahony[18] | Steven Pipe[19] | Ulrike M. Reiss[20] | Amy K. Wilson[21] | Emna Gouider[22] | On behalf of the WFH AAV Gene Therapy Guidelines Expert Panel

[1]World Federation of Hemophilia, Montréal, Québec, Canada | [2]Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil | [3]Department of Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa and Clinical Haematology Unit, Charlotte Maxeke Johannesburg Academic Hospital, Parktown, South Africa | [4]Division of Hematology/Oncology and Bone Marrow Transplant, Nationwide Children's Hospital, Columbus, Ohio, USA and The Ohio State University College of Medicine, Columbus, Ohio, USA | [5]Amsterdam University Medical Center, Amsterdam, Netherlands | [6]Yale University School of Medicine, New Haven, Connecticut, USA | [7]Division of Haematology/Oncology, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada | [8]Federation of Haemophilia Associations (FedEmo), Milan, Italy | [9]Queen Mary University London, London, UK and Barts Health NHS Trust, London, UK | [10]EBQ Consulting, Santa Monica, California, USA | [11]Department of Health Research Methods, Evidence, and Impact and Department of Medicine, McMaster University, Ontario, Canada | [12]Division of Hematology, St. Paul's Hospital and University of British Columbia, Vancouver, British Columbia, Canada | [13]Indiana University School of Medicine, Indianapolis, Indiana, USA | [14]GK Medical Writing, LLC, Bend, Oregon, USA | [15]Washington Center for Bleeding Disorders, University of Washington, Seattle, Washington, USA | [16]Innovative Hematology/Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, USA | [17]Medical Clinic 2, University Hospital Frankfurt, Frankfurt, Germany | [18]Irish Haemophilia Society, Dublin, Ireland | [19]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, Michigan, USA | [20]St. Jude Children's Research Hospital, Memphis, Tennessee, USA | [21]M Health Fairview Center for Bleeding and Clotting Disorders, Minneapolis, Minnesota, USA | [22]Service D'hématologie Biologique Hemophilia Center Aziza Othmana, University Tunis El Manar, Tunis, Tunisia

Correspondence: (TreatmentGuidelines@WFH.org)

Received: 5 February 2025 | **Revised:** 31 July 2025 | **Accepted:** 8 August 2025

Keywords: AAV gene therapy | bleeding disorders | haemophilia | management guidelines | monitoring | outcomes | shared decision-making

The complete WFH AAV Gene Therapy Guidelines Expert Panel can be found in Appendix 1:

Summary

As AAV gene therapy becomes more widely used in clinical practice, evidence-based guidelines with careful interpretation of the evidence by experts are essential to ensure patient safety, standardize clinical practices, address long-term uncertainties, support informed and shared decision-making and build stakeholder trust. This is the first iteration of the WFH Guidelines for the Management of Haemophilia: AAV Gene Therapy. These guidelines were developed to provide comprehensive, evidence-based recommendations to support standardized, safe and effective implementation of gene therapy for haemophilia. They were developed by the WFH AAV Gene Therapy Panel, which is composed of gene therapy experts who were involved in clinical trials and healthcare teams currently treating patients who have received gene therapy, as well as people with haemophilia and their caregivers. Because evidence is rapidly evolving in the treatment landscape for haemophilia, particularly AAV gene therapy, these guidelines have been developed under the WFH LGM, and will be updated as new evidence becomes available.

As treatment with AAV gene therapy for haemophilia becomes more common, multiple stakeholders must work together to ensure a seamless and standardized implementation that prioritizes patient safety. Therefore, these guidelines have recommendations for haemophilia treatment centres, the comprehensive care medical team and people with haemophilia. Other stakeholders who may find these guidelines relevant are payors, policymakers, local governments, patient advocacy organizations and drug manufacturers.

These guidelines were reviewed by external parties of interest and have been endorsed by the European Haemophilia Consortium (EHC), the Coalition of the Americas, the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA), and the Medical and Scientific Advisory Council (MASAC) of the National Bleeding Disorders Foundation.

WFH Guidelines Disclaimer

The World Federation of Hemophilia (WFH) does not endorse any treatment product or manufacturer; any reference to a product name is not an endorsement. The WFH does not engage in the practice of medicine and under no circumstances recommends specific products or treatment types for individuals. Guidelines are intended for general information only and are based on population-level research. Guidelines do not replace professional medical care, physician advice or product insert information, but should be used to educate and inform shared decision-making between patients, caregivers and healthcare providers.

Furthermore, guidelines may not be complete or accurate because new research studies may have been published or treatments, devices or indications approved after the cut-off date for inclusion in this guideline. Through a comprehensive and systematic literature review, the WFH evidence-informed clinical practice guidelines incorporate data from the existing peer-reviewed literature. Although this literature met the pre-specified inclusion criteria for the guideline, and the WFH considered this scientific content to be the best evidence available for general clinical information purposes at the time the guidelines were developed, this evidence is of varying quality and varying methodological rigour.

The WFH and its officers, committees, members, employees, volunteers, guideline authors and reviewers ('WFH Parties') disclaim all liability for the accuracy or completeness and disclaim all warranties, express or implied. The WFH Parties further disclaim all liability for any damages whatsoever (including without limitation, direct, indirect, incidental, punitive or consequential damages) arising out of the use, inability to use, or the results of the use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice on the possibility of such damages.

AAV Gene Therapy for the Management of Haemophilia

1 | Background

- Haemophilia is a rare X-linked congenital bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B.
- The standard of care for severe haemophilia A and B is regular prophylactic treatment that is aimed at preventing bleeding (See Chapter 6: Prophylaxis in Hemophilia from the third Edition [1]).
- Despite the development of therapies beyond standard-half-life clotting factor concentrates, several challenges remain for those on prophylaxis. These challenges include high treatment burdens, breakthrough bleeds, progressive joint damage and impaired quality of life [2]. Gene therapy offers the haemophilia community an opportunity to overcome these unmet needs.
- The goal of gene therapy for haemophilia is to stop or prevent bleeding to achieve better clinical outcomes and a better quality of life than is possible with the currently available haemophilia products. For gene therapy to achieve widespread success, there needs to be a global effort towards equitable access to gene therapy for interested and eligible PwH [3, 4].
- The transition of adeno-associated virus (AAV) gene therapy from clinical trials to regular clinical practice poses challenges at all phases of the process, including country or regional access, patient selection, dosing, organizational infrastructure and ongoing post-treatment follow-up logistics [5]. These challenges are further exacerbated by the significant unknowns related to treatment with AAV gene therapy, including, but not limited to, the durability and variability of the effect, and short and long-term safety issues, as well as evolving patient selection criteria.

The World Federation of Hemophilia (WFH) is adopting a Living Guidelines Model (LGM) to ensure the clinical practice recommendations in the WFH Guidelines for the Management of Haemophilia are based on the most up-to-date evidence. This new approach will focus on selected topic areas with rapidly evolving evidence, allowing for frequent updates to recommended clinical practice. The full methodology of the WFH Living Guidelines Model (LGM) will be published soon. As the first step in the WFH LGM approach, this publication introduces a new chapter on adeno-associated virus (AAV) gene therapy to the WFH Guidelines for the Management of Hemophilia, third Edition. The expert panel will update this chapter as new evidence becomes available. Updates will be published and linked to the original article on the journal website. For a complete and up-to-date list of all WFH Guidelines for the Management of Haemophilia, please refer to https://guidelines.wfh.org.

1.1 | Approved AAV Gene Therapy Products

- At the time of this publication, one AAV gene therapy product is licensed and commercially available for the treatment of haemophilia A, and one AAV gene therapy product is licensed and commercially available for the treatment of haemophilia B (Table 1). These guidelines make use of relevant prescribing information from the European Medicines Agency (EMA) [6–8] and the United States (US) Food & Drug Administration (FDA) [9–11]. Treatment centres and healthcare providers should also refer to the most up-to-date prescribing information from their local regulatory authority.
- Fidanacogene eleparvovec [12, 13], another AAV gene therapy product for the treatment of haemophilia B, was licensed by Health Canada, the FDA and the EMA before it was announced in February 2025 that it would not be marketed [14]. This treatment was considered during the initial drafting phase of these guidelines and then removed during the

TABLE 1 | Licensed and available AAV gene therapy products at the time of publication.

Haemophilia type & severity	Gene therapy product Brand name, Manufacturer (Alternative names)	AAV Vector	Gene product	Year of first license	Phase 1/2 clinical trial references	Phase 3 clinical trial references
Haemophilia A Severe	Valoctocogene roxaparvovec Roctavian, Biomarin (BMN 270, AAV5-hFVIII-SQ)	AAV5	SQ variant of B-domain–deleted human factor VIII	2022	Phase 1-2: NCT02576795 [15] 2,3-year follow-up [16] 4,5-year follow-up [17] 5,6-year follow-up [18] 6,7-year follow-up [19]	Phase 3: GENE-r8-1 NCT02576795 [20] 2-year follow-up [21] 3-year follow-up [22] 4-year follow-up [23]
Haemophilia B Severe and moderately severe	Etranacogene dezaparvovec Hemgenix, CSL-Behring (AMT-061)	AAV5	Factor IX Padua (R338L)	2022	Phase 2b: NCT03489291 [24] 3-year follow-up [25]	Phase 3: HOPE-B NCT03569891 [26] 2-year follow-up [27]

TABLE 2 | FVIII (IU/dL) activity levels reported from clinical trials for valoctocogene roxaparvovec.

	Phase 1/2 ($N = 7$) [17–19] Dose: 6×10^{13} vg/kg		Phase 3 GENE-r8-1 ($N = 132$) [20–23] Dose: 6×10^{13} vg/kg	
	FVIII Mean, IU/Dl	FVIII Median (IQR) IU/dL	FVIII Mean ± SD, IU/dL	FVIII Median (IQR), IU/dL
Year 1	64.3	60.3 (46.6–88.4)	42.8 ± 45.6	23.9 (11.9–62.3)
Year 2	36.4	26.2 (24.1–51.7)	22.9 ± 33.0	11.7 (4.9–25.4)
Year 3	32.7	19.9 (100.8–45.9)	18.4 ± 30.8	8.3 (3.0–17.2)
Year 4	24.2	16.4 (9.2–29.5)	16.1 ± 2.5 (SE)	6.7 (2.8–17.8)
Year 5	11.6	8.2 (1.6–18.6)	18.0 ± 4.9[b] (SE)	8.4 (5.3–36.7)[b]
Year 6	9.8	5.6	––	––
Year 7	16.2[a]	10.3[a]	––	––

Note: Data were extracted from the publication with the longest follow-up. Not all publications present identical values for the same year. Data were obtained using the chromogenic substrate assay to measure FVIII activity.

[a] $N = 5$; excludes those who returned to prophylaxis.

[b] $N = 17$.

TABLE 3 | FIX (IU/dL) activity levels reported from clinical trials for etranacogene dezaparvovec.

Phase 2b ($N = 3$) [24, 25] Mean (Range), IU/dL		Phase 3 HOPE-B ($N = 54$) [26, 27] Mean ± SD, (IU/dL)	
Month 6	47 (33.2–57.0)	Month 6	39.0 ± 18.7
Year 3	36.9 (32.3–41.5)		

Note: Data were extracted from the publication with the longest follow-up. Not all publications present identical values for the same year. Data were obtained using the one-stage assay to measure FIX activity.

revision stage since it would not be entering the commercial market. All background and recommendations were reviewed to ensure that no details were specific to fidanacogene eleparvovec.

1.2 | Efficacy of Gene Therapy for Haemophilia

- Clinical studies for AAV gene therapy in haemophilia have demonstrated that gene therapy may lead to sustained FVIII or FIX production, thereby reducing or eliminating the need for regular prophylactic infusions [12, 13, 15–18, 20–27].
- Efficacy varies between individuals, and there is no way to predict if or how well someone will respond to gene therapy. Data on the long-term durability of protection from bleeding are limited to clinical trial participants.
- Efficacy outcomes include factor activity levels (Tables 2–4); annualized bleeding rates (ABRs) (Table 5) including those for all bleeds, treated bleeds and joint bleeds; annualized factor consumption; annualized infusion rate; return to regular prophylaxis; and quality-of-life measures.
- The reported mean and median factor activity level and ABRs, including data from long-term follow-up studies, are presented in Table 2.
- Head-to-head analyses comparing AAV gene therapies to other prophylactic treatments have not been conducted. All available data come from pre-post analyses of clinical trial participants before and after receiving gene therapy.
- In the phase 3 GENE-r8-1 study for haemophilia A, valoctocogene roxaparvovec resulted in an average of 4.1 fewer bleeds (83.8% reduction) per patient per year compared to the pre-treatment prophylaxis regimen [20]. No participants were using emicizumab for pre-treatment prophylaxis.

TABLE 4 | FIX (IU/dL) activity levels at 24 months post-infusion reported from clinical trials for etranacogene dezaparvovec.

Factor activity level	Number of participants Phase 3 HOPE-B ($N = 54$) [26, 27]
0% to <5%	2%
5% to <12%	7%
12% to <20%	4%
20% to <30%	24%
30% to <40%	22%
40%	33%

Note: Data were obtained using the one-stage assay to measure FIX activity. Four percent had missing or uninterpretable data.

TABLE 5 | Treated ABR reported from clinical trials for valoctocogene roxaparvovec.

	Phase 1/2 (*N* = 7) [19] Dose: 6 × 1013 vg/kg Mean ABR (Median ABR)	Phase 3 GENE-r8-1 (*N* = 132) [20–23] Dose: 6 × 1013 vg/kg Mean ABR (Median ABR)
Baseline	17.6 (24.0)	4.8 (2.8)
Year 1	1.2 (0)	0.9 (0)
Year 2	0.1 (0)	0.7 (0)
Year 3	0.6 (0)	1.0 (0)
Year 4	1.3 (0)	0.9 (0)
Year 5	0.6 (0)	––
Year 6	0.7 (0)	––
Year 7	0.9 (0)	––

Note: Data were extracted from the publication with the longest follow-up. Not all publications present identical values for the same year.

- Of note, an indirect, cross-trial comparison of valoctocogene roxaparvovec AAV gene therapy and emicizumab prophylaxis showed that ABR for all bleeds was significantly lower with valoctocogene roxaparvovec (after 52 weeks) than with emicizumab (after 24 weeks) and that significantly more participants had no treated joint bleeds and no treated bleeds with valoctocogene roxaparvovec [28].
- In the phase 3 HOPE-B study for haemophilia B, etranacogene dezaparvovec resulted in an average of 2.68 (63% reduction) fewer bleeds per patient per year compared to the pre-treatment prophylaxis regimen [26].
- Ongoing clinical trials, post-marketing surveillance and patient registries aim to address these long-term efficacy and durability unknowns.

1.3 | Safety of AAV Gene Therapy

- Clinical evidence to date indicates that gene therapy has an acceptable safety profile. However, several safety concerns exist regarding the administration and long-term effects of gene therapy. Short-term safety issues related to the infusion are many and include the possibility of anaphylaxis and hypersensitivity reactions. Safety issues that may arise after the infusion include transaminitis [elevated alanine aminotransferase (ALT)] and long-term theoretical safety risks such as thromboembolic events and hepatocellular carcinogenicity.
- Safety will be discussed throughout this chapter. See Section 4 Eligibility, Screening and Suitability Assessments for Gene Therapy, Section 5.4 Peri-Infusion Monitoring and Safety and Section 6.3 Post-Infusion Safety.

1.4 | Quality of Life and AAV Gene Therapy

- Gene therapy has the potential to improve the quality of life for people with haemophilia.
- The existing evidence, which uses multiple quality-of-life assessment tools, suggests that gene therapy improves the overall quality of life for people with haemophilia [29–34] and those effects are long-lasting [17, 22, 30].
- Multiple surveys of people with haemophilia who received gene therapy have reported a positive impact on daily life [29–32], specifically that they no longer require frequent injections [31] and have observed improvement in their physical activity levels, travel ease and social life. PwH A or B who have received gene therapy largely describe it as life changing [32]. However, despite overall improvements, some PwH report negative experiences with gene therapy, especially related to corticosteroid use [32].
- Data from clinical trials for licensed products have demonstrated clinically meaningful improvements in overall quality-of-life scores compared to pre-infusion prophylaxis time periods [33, 34].
- Larger studies of more people treated with gene therapy for both haemophilia A and B are needed to fully understand the quality-of-life improvements associated with gene therapy compared with on-demand and prophylactic use of other haemophilia medications.
- Treatment with AAV gene therapy also requires several lifestyle changes that may impact the quality of life for some PwH, such as abstaining from alcohol for at least 1 year, using barrier contraception for at least 1 year and prioritizing liver health. (See Section 6.6 Recommended Lifestyle Choices for People With Haemophilia Who Have Received AAV Gene Therapy).

2 | Site Preparedness for Haemophilia Treatment Centres

2.1 | Introduction

- The introduction of gene therapy presents a new challenge for haemophilia care that will require extensive preparation, education, organization, coordination and infrastructure.
- All haemophilia treatment centres (HTCs), regardless of whether they administer gene therapy, may be involved in some aspects of the gene therapy process.

- The defined centre types are Referring centres (spoke), Dosing centres (hub) and Follow-up centres (spoke). In some geographic locations, this is referred to as the hub-and-spoke model [3, 35, 36].
- A Referring centre is any healthcare facility that identifies people with haemophilia who may benefit from AAV gene therapy. Referring centres may conduct the initial evaluation, provide information about gene therapy options and refer eligible people with haemophilia to Dosing centres for treatment. Referring centres play a key role in the AAV gene therapy process by providing an accurate history to the Dosing centre medical team.
- A Dosing centre is an HTC that has the necessary training and infrastructure to coordinate and/or complete the entire gene therapy infusion process safely and effectively.
- A Follow-up centre is an HTC that is responsible for the post-treatment monitoring and ongoing care of people with haemophilia who have received AAV gene therapy.
- Not all HTCs in a country will be able to serve as gene therapy centres [37]. The availability of resources sufficient to satisfy related policies and quality control will inform which centres provide infusions (i.e., Dosing centres or 'Hubs') and which provide support (i.e., Referring and Follow-up centres or 'Spokes'). If one centre is unable to perform a task, it may collaborate and partner with others to ensure the standard of patient care remains high. For some HTCs, this may represent a new collaborative model of comprehensive care. Communication between the Referring, Dosing and Follow-up centres is critical for successful treatment and long-term management of people with haemophilia who are considering, receiving or have received gene therapy [4, 38].
- The same facility may serve as the Referring, Dosing and/or Follow-up centre. For these guidelines, the WFH has provided recommendations of essential steps for HTC preparedness to provide integrated, comprehensive care to people with haemophilia who are considering, about to receive or have received AAV gene therapy. While developing these recommendations, it was important to avoid unnecessary restrictions on the definition or requirements of a centre so that the recommendations could remain widely applicable to a global audience. It is likely that the roles and responsibilities, training, and infrastructure requirements of Dosing and Follow-up centres will need to be adjusted as more experience is gained outside of clinical trial settings.
- At the time of publication, regional guidelines and models on site preparedness for gene therapy have been published for multiple regions, including the United States [39], European Haemophilia Treatment centres [35], the United Kingdom [40], Germany, Austria, and Switzerland [41], the Gulf region (Kuwait, Oman, Saudi Arabia and the UAE) [42], the Nordic Region (Denmark, Finland, Norway and Sweden) [43], and Italy [44]. Regional guidelines should also be considered when creating standard operating procedures (SOPs) as they will address region-specific factors and limitations.

2.2 | Comprehensive Care

- An integral part of comprehensive care is having a diverse and collaborative clinical team available to support the person with haemophilia in managing life with haemophilia. With the additional challenges posed by gene therapy, collaboration and communication between centres becomes an essential component of comprehensive care.
- For more detail on the integrated comprehensive care approach, see 'Chapter 1: The Principles of Care' and Recommendations 2.2.1–2.2.3 [1].
- All involved centres should be prepared to assist with coordinating patient care, including screening for eligibility [43, 45], scheduling, coordinating travel to and from appointments, and developing a streamlined process for sharing the necessary health information between the Referral/Follow-up centre and the Dosing centre [36, 38, 42].
- Efficient coordination between centres may require new divisions of responsibility for the clinical care staff and possibly new personnel (e.g., a dedicated care coordinator) to assist in navigating the PwH across the entire multidisciplinary gene therapy process. Centres should devise communication plans that define each centre's responsibilities to the person undergoing treatment. The communication plan may also outline the roles and responsibilities of people with haemophilia. Areas that require special attention may include
  - A process for exchanging the necessary health information [38]
  - Psychological evaluation and psychosocial assessment [43]
  - Evaluating seroprevalence of antibodies to AAV serotypes [45]
  - Scheduling patients and coordinating travel to and from appointments [38]
  - Scheduling companions and caregivers
  - Follow-up responsibilities that ensure a rapid response to changes in ALT or factor activity
  - Participation in a Gene Therapy Registry [46, 47]

Recommendation 1: The WFH recommends using an integrated comprehensive care approach that is coordinated between the Referring, Dosing and Follow-up centres during all steps of the AAV gene therapy process.

REMARK: Centres should collaborate to develop a communication plan that delineates their respective roles and responsibilities. CB

2.3 | Clinical Education and Training

- Members of the clinical care team at Referring, Dosing and Follow-up centres should receive tailored education based on their defined role in the AAV gene therapy process [3, 38, 39].
- Personnel at Referring centres should be trained in AAV gene therapy eligibility and suitability requirements and educational topics important to shared decision-making (SDM).
- Key topics for clinical education and training at Dosing and Follow-up centres may include

- Patient education and SDM (see Section 3 Shared and Informed Decision-Making)
  - The basics of haemophilia gene therapy
  - Up-to-date safety, efficacy and durability information for current treatment products
  - The irreversible nature of AAV gene therapy
  - Risks, benefits and limitations of current treatment products
- Patient eligibility and screening assessments (see Section 4 Eligibility, Screening and Suitability Assessments for Gene Therapy)
- Psychosocial evaluation, monitoring and support (see Section 4.4.7 Psychosocial Support and Evaluation)
- Product handling regulations, including biosafety and infection control protocols
- Dosing and infusion procedures (see Section 5.3 Administration)
- Management of adverse reactions associated with gene therapy (see Section 5.4 Peri-Infusion Monitoring and Safety)
- Follow-up requirements post-infusion (see Section 6.1 Post-Treatment Monitoring)
- Haemophilia management post-infusion (see Section 6.4 Haemophilia Management After Gene Therapy)
- Registry data collection (see Recommendation 10 and Recommendation 64)

- Guidelines for the education of clinical pharmacists have been published elsewhere [39, 43].

Recommendation 2: The WFH recommends that Referring centres have personnel trained in AAV gene therapy eligibility requirements and shared decision-making (SDM). CB

Recommendation 3: As an integral part of providing integrated, comprehensive care, the WFH recommends that Dosing and Follow-Up centres ensure that all medical personnel and staff receive education and training that is targeted to the centre's functions and their individual responsibilities related to the AAV gene therapy process.

Remark: **Each team member's responsibilities may vary by country and centre; therefore, it is important to establish clear and defined roles prior to training**.

Remark: **Centres should have a SOP for documenting training, onboarding new staff and for at least annual re-education**.

Remark: **Training may be completed through product-specific training from the manufacturer, more general training from institutional based programmes, and online modules from nationally or internationally recognized expert groups**. CB

2.4 | Dosing Centres

- A Dosing centre is an HTC that has the necessary training and infrastructure to coordinate and/or complete the entire gene therapy infusion process safely and effectively. The Dosing centre (or Hub) should have experience in both comprehensive care and AAV gene therapy [3].
- Several operational changes may be required for a site to be prepared to offer gene therapy, including obtaining approvals for biosafety, hiring and training personnel, and developing SOPs. Dosing centres must have the necessary equipment, materials, supplies, medical team and approvals to demonstrate their ability to perform all stages of the gene therapy process. Only centres at or affiliated with HTCs that meet all the criteria should be Dosing centres.
- Dosing centres must
  - Identify, confirm and/or acquire the appropriate national, local and institutional approvals. These approvals may be required for each individual gene therapy product.
  - Have the proper infrastructure within their clinical pharmacies to support product receipt, storage and handling of the gene therapy product.
  - Conduct a biosafety risk assessment of all work involving recombinant or synthetic nucleic acids, including evaluating risks and the environmental safety of employees.
- Dosing centres may use SOPs and checklists to ensure the highest level of patient care and cover the entire gene therapy process from drug preparation to peri-infusion follow-up. Example SOP topics include
  - Site preparedness, including the identification and acquisition of all necessary facilities, equipment, medical instruments and other supplies.
  - Procurement, handling, storage, preparation, transportation and waste management of the gene therapy product.
  - The responsibilities and support roles of each member of the medical team.
  - Procedures for all peri-infusion stages, including pre-infusion, infusion, monitoring, response to adverse events and discharge procedures.
  - Communication between coordinating centres is necessary to ensure the proper management of follow-up care.
- SOPs and checklists may be developed de novo by a centre, or existing SOPs and checklists from other centres or institutions may be adapted to the centre's specific needs. Sample SOPs and checklists have been published by multiple groups [38, 39, 43].
- Dosing centres should be prepared to handle life-threatening anaphylaxis when administering gene therapy. The appropriate level of higher care at a Dosing centre may be adjusted accordingly. For example, Dosing centres may have access to an intensive care unit or team on site, or Dosing centres may develop an SOP for addressing possibly life-threatening anaphylaxis by defining what triggers stopping the infusion, moving the patient to a hospital, and so forth.
- In the HOPE-B clinical trial for entranacogene dezaparvovec, one patient discontinued treatment after receiving approximately 10% of the full dose after a hypersensitivity adverse reaction [26].
- Dosing centres may also be responsible for obtaining insurance approvals and following the payer approval process. These steps should be coordinated with the Referral centre and addressed early in the gene therapy process to ensure payer requirements are met. Dosing centres may also use manufacturer programmes to facilitate insurance coverage and financial assistance.

Recommendation 4: The WFH recommends that Dosing centres have the necessary approvals and infrastructure to coordinate and/or complete the entire AAV gene therapy infusion process safely and effectively.

Remark: Dosing centres must secure institutional approvals (in keeping with national and regional guidance) and ensure that the necessary infrastructure, facilities, equipment, medical expertise and hospital services, including biosafety and infection control protocols, are in place for proper handling and administration of AAV-based gene therapies.

Remark: Dosing centres must identify and coordinate a designated site for peri-infusion and infusion monitoring. The site(s) must have ready access to a laboratory, pharmacy, appropriate high-level care (i.e., intensive care, advanced life support and/or similar) and psychosocial services.

Remark: Dosing centres must be able to perform and interpret diagnostic tests for eligibility and to quickly perform, interpret and react to liver function tests post-infusion.

Remark: The infusion room must have an emergency medical supply cart that is stocked with all the materials, medications and devices necessary to perform emergent medical intervention and should be a part of, or close to, a hospital with the appropriate high-level care. CB

Recommendation 5: The WFH recommends that Dosing centres have an experienced and well trained medical team to coordinate and/or complete the entire AAV gene therapy infusion process safely and effectively.

Remark: The core medical team should include a haematologist, clinical coordinator, nurse, clinical pharmacist and laboratory personnel, with support from allied medical professionals, including a physiotherapist, a mental health/psychosocial provider, a hepatologist, specialized laboratory services and an emergency/intensive care team.

Remark: The core medical team and the intensive care team should be onsite and readily available throughout the day of infusion, including the post-infusion observation period.

Remark: Back-up staff should be available for each core position or specialty on the day of infusion to help ensure treatment proceeds as scheduled in the event of unforeseen staffing issues.

Remark: Dosing centres should regularly assess staff capacity and the need for additional team members. CB

Recommendation 6: The WFH recommends that Dosing centres have standard operating procedures (SOPs) for the medical team and supporting medical services in accordance with the prescribing information, local, national, and international guidelines, including the WFH guidelines, and institutional policies and procedures.

Remark: SOPs should contain detailed protocols and checklists that address all parts of the gene therapy process. CB

2.4.1 | Clinical Pharmacy

- It is important that sites have well trained pharmacists who follow SOPs in accordance with national regulations and local institution requirements to order, receive, prepare and transport gene therapy to reduce medication error and unnecessary exposure of personnel [38].
- Guidelines specific to clinical pharmacy have been published elsewhere [39, 40, 43].

Recommendation 7: The WFH recommends that Dosing centres ensure that their clinical pharmacy team has the necessary approvals, infrastructure and training to support the procurement, receipt, storage, handling, preparation, transportation and infusion of the AAV gene therapy product. CB

2.5 | Follow-Up Centres

- A Follow-up centre is an HTC that is responsible for the post-treatment monitoring and ongoing care of people with haemophilia who have received AAV gene therapy.
- Follow-up centres must be able to quickly perform, interpret and react to liver function tests post-infusion, including clear and timely communication of the results to patients.
- Follow-up centres may also have SOPs and checklists to ensure the highest level of patient care. SOPs and checklists may be developed de novo by a centre, or existing SOPs and checklists from other centres or institutions may be adapted to the centre's specific needs. Sample SOPs and checklists have been published by multiple groups [38, 39, 43].
- Example SOP topics include
  - The frequency of follow-up calls, follow-up visits, laboratory testing and liver ultrasound.
  - Interventions for when patients are non-adherent to follow-up
  - Management of abnormal results
  - Psychosocial monitoring
  - Management of immunosuppression
  - Management of haemophilia
  - Options for telemedicine, remote laboratory sites and mobile nursing to help decrease patient burden
  - Data collection and reporting to Gene Therapy Registries.

Recommendation 8: The WFH recommends that Follow-up centres manage the short- and long-term care of people with haemophilia who have received AAV gene therapy.

Remark: The core medical team for follow-up care should include a haematologist (or appropriately trained physician), nurse, clinical coordinator, physiotherapist, mental health/psychosocial provider, and laboratory personnel, with support from allied medical professionals, a hepatologist, and the Dosing centre team. Follow-up centres may need to create or define new roles (e.g., a dedicated care coordinator) to provide integrated, comprehensive care and the time-intensive follow-up required after AAV gene therapy.

Remark: **The Referring centre or the Dosing centre may also serve as the Follow-up centre**.

Remark: **Follow-up centres are responsible for managing communications with other haematologists and healthcare practitioners participating in the individual's follow-up care**. CB

Recommendation 9: The WFH recommends that Follow-up centres have standard operating procedures (SOPs) and checklists that address the post-treatment (both short and long-term) follow-up monitoring of people with haemophilia who have received AAV gene therapy. CB

2.6 | Gene Therapy Registries

- Novel and emerging technologies, like AAV gene therapy for haemophilia A and B, have inherent unknowns in their safety and efficacy profiles [48]. Some long-term follow-up data will be available through the extension of clinical studies, but most will come from registries.
- Registries facilitate continuity of care, foster collaboration, maintain confidentiality and conserve resources through a common infrastructure.
- Registry participation is especially important for populations that were not included in clinical trials.
- The collection and dissemination of long-term data is critical for PwH and healthcare professionals engaging in the informed SDM process, as well as regulators, manufacturers and payors.
- Patient registries may be managed on a local, national or global scale. Some countries may also have required gene therapy registries that are not specific to haemophilia.
- The WFH Gene Therapy Registry (GTR) is an international database platform for reporting on the management of care and follow-up of PwH who have received AAV gene therapy [36, 46, 47, 49]. Its goal is to facilitate universal data collection on gene therapy outcomes according to a defined dataset. The WFH GTR has been linked to national registries to streamline data collection [47].
- Centres should coordinate who is responsible for obtaining consent for participation in, collecting data for, and sharing/submitting data to the WFH GTR or other linked registries. Data collection should include screening test results, infusion details, peri-infusion monitoring and reactions, and follow-up on safety, efficacy, adverse events, and quality-of-life outcomes. Data should be gathered in a manner that adheres to local data protection and confidentiality laws and legislation.
- The WFH GTR has been endorsed by the European Medicines Agency (EMA) as a global standard, stating that 'It is expected that utilising the WFH GTR for post-approval safety or efficacy studies of gene therapies will be of particular value and its use as a planned data source for mandated Phase IV studies for new haemophilia treatments is recommended.' [50, 51]
- PwH who have received gene therapy can also input patient-reported outcomes on the WFH GTR platform (see Recommendation 64).

Recommendation 10: The WFH recommends that Dosing and Follow-up centres coordinate and participate in clinical data collection in the WFH Gene Therapy Registry (GTR) or a local or national gene therapy registry that links with the international WFH GTR. CB

3 | Shared and Informed Decision-Making

3.1 | Introduction

- The steps prior to gene therapy infusion include education and information gathering, SDM with the healthcare team, a comprehensive patient assessment and preparation for the infusion itself [38].
- Information gathering, education and SDM with the healthcare team are essential components of the gene therapy process [52–54].
- SDM is a process where PwH and/or caregiver are actively involved in treatment decisions and work with the healthcare team to make informed decisions about their haemophilia management and care. Discussions focus on treatment risks and benefits of all treatment options and how they relate to the person's lifestyle, goals and preferences [52, 54, 55]. Discussions may take place over multiple sessions, allowing the patient time to consider what they have learned, and can be with any member of the healthcare team. Discussions should include a balanced consideration of the risks, benefits and unknowns of all treatment options.
- Regional differences in healthcare, insurance coverage, sustainability of access to care, cultural differences, access to second opinions and availability of alternative treatments may influence decision-making.
- Multiple SDM models and decision aids for general clinician–patient decision-making exist [52, 56–59] and may be used, or new decision aids may be created as part of the centre's shared and informed decision-making process.
- In collaboration with PwH, patient advocates and healthcare professionals, the WFH created an interactive, online- and print-based, patient-centric educational tool that guides PwH and caregivers through the steps of SDM (sdm.wfh.org) [55].
- The WFH SDM Tool guides a PwH or a caregiver through the steps of informed SDM. First, PwH will go through a series of reflection statements and questions to aid patients in determining their life goals, values and preferences and how they relate to managing their haemophilia. After selecting their haemophilia type, PwH are guided through a series of educational videos, fact sheets and attribute tables for each prophylactic treatment class, followed by an attribute comparison table and a list of suggested questions to discuss with their healthcare team. The online SDM tool concludes with a summary output that can be downloaded, emailed or printed so that it can be shared with their healthcare team. The SDM Tool is currently available in English, French, Spanish,

Japanese, Dutch and German, with additional translated versions in the pipeline.

- Manufacturers may have decision-making aids, which often include counselling and education topics specific to the product. Counselling and education topics can also be found in the prescribing information.

Recommendation 11: The WFH recommends that all healthcare providers offer and engage in shared decision-making (SDM) with people with haemophilia A or B who are considering, are about to receive or have received AAV gene therapy. CB

3.2 | Patient Education

- Patient education is a critical component of SDM. Education should include all relevant aspects of AAV-based gene therapy and applicable treatment alternatives and be based on the most up-to-date information about the specific treatment product(s) available [52, 54, 55, 60–62].
- Notably, greater knowledge and understanding of gene therapy is associated with a greater willingness to receive gene therapy [63].
- Healthcare providers should be trained in the proper tools and language for patient education and familiar with best practice terminology in the patient's spoken language. Informal or 'off-the-cuff' attempts at translating the benefits, mechanism of action and risks of gene therapy may create unintended barriers [61]. Language lexicons may be useful tools for healthcare providers engaging in SDM.
- People with haemophilia may have high expectations regarding the efficacy of gene therapy and its impact on their health and daily quality of life [53]. As part of education and SDM, healthcare professionals should also assess patient expectations to ensure they align with the available data on GT outcomes. It is critical that people with haemophilia understand the known limitations of gene therapy treatment.
- Education should be individualized to each person's needs, preferred language, reading and health literacy level, and preferred learning style [61].
- Education should be offered throughout the treatment process and should include discussions, as well as up-to-date print and online resources [62].
- Referral/Dosing centres should work synergistically with local patient organizations, which are likely a source of patient-focused educational materials.

Recommendation 12: The WFH recommends that healthcare providers use individualized, up-to-date education as part of shared decision-making (SDM) for people with haemophilia A or B who are considering AAV gene therapy.

Remark: Education topics that should be covered include

- **The gene therapy process**
- **The post-treatment monitoring requirements**
- **The expectations, limitations and uncertainties of AAV gene therapy**
- **The risks of AAV gene therapy**
- **The recommended lifestyle modifications after gene therapy, with emphasis on liver health**

Remark: A checklist may be used to ensure all topics are covered (see Appendix 2: SDM Topics for People Considering AAV Gene Therapy: A Checklist for Healthcare Professionals). CB

4 | Eligibility, Screening and Suitability Assessments for Gene Therapy

4.1 | Introduction

- Multiple modifiable and non-modifiable characteristics can determine whether a patient is eligible for gene therapy [64].
- The non-modifiable parameters include age, sex, inhibitor status (current or past history of inhibitors), AAV antibody status, liver disease (including fibrosis) and other severe comorbidities [64].
- Many PwH may not be eligible for gene therapy because of non-modifiable characteristics, especially AAV- seropositivity.
- The possibly modifiable variables that render the individual unsuitable for AAV gene therapy are active hepatitis B or C infection, uncontrolled human immunodeficiency virus (HIV) infection, poorly controlled comorbidities, an unwillingness to commit to the post-treatment follow-up requirements, psychosocial uncertainty or instability, geographic factors and socioeconomic issues [64].
- The number of individuals who desire gene therapy may increase as more clinical experience is gained and there are fewer unknowns associated with treatment. As patients develop more knowledge and a deeper understanding of gene therapy, desire and willingness to receive gene therapy increases [63].
- This section will define the eligibility criteria for clinical treatment with AAV gene therapy, including the screening required to assess eligibility and suitability for AAV gene therapy. These recommendations should not be used when considering participation in clinical trials.
- Each centre should establish a Screening and Suitability Checklist to ensure that each PwH has completed all of the required eligibility assessments.

4.2 | Populations Requiring Special Considerations for Eligibility

4.2.1 | Children and Adolescents

- Gene therapy for haemophilia is not currently available to PwH who are < 18 years of age. To date, completed studies have only included patients 18 years and older. Therefore, the safety and efficacy of gene therapy in adolescents under 18 years have not been established.

- The liver hepatocytes targeted in AAV gene therapy are still dividing and growing in young children, which could dilute the effects of gene therapy over time.

4.2.2 | Adults Over 65

- There are limited data available on adults ≥ 65 years of age. Additional research is needed on the safety and efficacy of gene therapy in this population.
- Valoctocogene roxaparvovec was studied in only one adult ≥ 65 years of age. No dose adjustments were made.
- Etranacogene dezaparvovec was studied in seven adults ≥ 60 years of age. No dose adjustments were made. The mean factor IX activity levels were approximately up to two-fold higher in this subgroup compared to the 18 to < 40 years age subgroup ($N = 31$), but comparable to the 40 to < 60 years age subgroup ($N = 15$) [9].

4.2.3 | Women

- As per the FDA, all currently approved gene therapy products are not intended for administration in women. As per the EMA, all currently approved gene therapy products are not intended for administration in women of childbearing potential. To date, no completed studies on gene therapy in haemophilia have enrolled women.
- Some animal studies have shown that sex may influence the efficacy of AAV vector transduction, where female mice show reduced transduction [65, 66]. The majority of preclinical pharmacology and toxicology studies used male animal models.
- Preclinical and clinical studies are needed to understand the safety and efficacy of gene therapy in women with haemophilia, including the effects on concurrent hormonal therapy, reproductive potential, fertility, pregnancy and lactation; potential drug-associated risk of foetal harm or adverse developmental outcome; and potential transmission of transgene DNA through intercourse, conception or breastfeeding/human milk.

4.2.4 | People With Immunosuppressive Disorders

- There are limited clinical data available for people with immunosuppressive disorders, including HIV. PwH with controlled immunosuppressive disorders have been enrolled in clinical trials (Table 6).
- Additional research is needed to understand safety and efficacy in patients with immunosuppressive disorders.
- Efavirenz is not recommended in patients who are treated with valoctocogene roxaparvovec [67]. The use of non-efavirenz treatments should be considered [6, 11]. See Section 4.4.5 Screening of All Concomitant Medications for more details.

4.2.5 | People With Hepatic Impairment

- All clinical studies have excluded people with advanced hepatic impairment and advanced fibrosis. Additional research is needed on safety and efficacy in haemophilia patients with mild hepatic impairment.
- See Section 6.6.2 Optimize Your Liver Health on maintaining liver health before and after gene therapy.

4.2.6 | People With Renal Impairment

- Additional research is needed to understand safety and efficacy in haemophilia patients with mild renal impairment.
- Only etranacogene dezaparvovec has been studied in people with renal impairment [7, 9]. In the phase 3 study, the majority ($n = 45$) of the patients had normal renal function [creatinine clearance (CLCr) = ≥90 mL/min defined by Cockcroft–Gault equation], seven patients had mild renal impairment (CLCr = 60–89 mL/min) and one patient had moderate renal impairment (CLCr = 30–59 mL/min) [7, 9]. No clinically relevant differences in FIX activity were observed between these patients. No patients with severe renal impairment or end-stage renal disease were included in the study.

4.3 | Eligibility for Gene Therapy

- Therapeutic indications, contraindications, warnings and precautions will vary between gene therapy products and regulatory agencies and may evolve as more clinical experience is gained. The prescribing information that contains the most up-to-date information should be used as the primary guidance for eligibility criteria for treatment with AAV gene therapy.
- If a PwH is interested in gene therapy, their healthcare team should conduct an initial assessment with the understanding that not all PwH will be eligible.
- Importantly, payors may have individualized approval processes, and conversations with them should commence early to ensure payer requirements are met.

Recommendation 13: The WFH recommends that eligibility for AAV gene therapy be based on the therapeutic indications and guidance in the prescribing information from the local regulatory agency.

Remark: **Eligible populations may be updated as new evidence becomes available**.

Remark: **All therapeutic indications are currently for adults; therefore, the WFH recommends against AAV gene therapy in children and adolescents under 18 years of age**. CB

Recommendation 14: The WFH recommends adherence to the contraindications, warnings and precautions in the current prescribing information when determining patient eligibility. Therefore, the WFH recommends against AAV gene therapy for the following populations:

TABLE 6 | Clinical evidence from clinical trials of licensed AAV gene therapy products for the treatment of people with HIV and other immunosuppressive disorders.

Haemophilia type	Gene therapy product	Study	HIV*	Previous Hep B†	Previous Hep C‡	Results
Haemophilia A	Valoctocogene roxaparvovec [20, 67]	GENE-r8-1	1.5% (2/134)§	14.9% (20/134)	30.6% (41/134)	No subpopulation analyses have been reported
Haemophilia B	Etranacogene dezaparvovec [26]	HOPE-B	6% (3/54)	17% (9/54)	52% (28/54)	

*HIV = human immunodeficiency virus.

†Hep B = Hepatitis B; determined by serological tests.

‡Hep C = Hepatitis C; determined by serological tests

§Participants were enrolled prior to a protocol amendment that changed the inclusion/exclusion criteria to exclude people with HIV.

a. **People with haemophilia A and AAV antibodies**

b. **People with haemophilia A with active inhibitors to FVIII**

c. **People with haemophilia B with active or a prior history of inhibitors to FIX**

d. **People with active acute viral infections or chronic viral hepatitis B or C with detectable HBV DNA or HCV RNA**

e. **People with uncontrolled HIV, other systemic immunosuppressive disorders or infections**

f. **People who use concomitant systemic immunosuppressive therapy**

g. **People with significant hepatic fibrosis (stage 3 or 4) or cirrhosis**

h. **People with hypersensitivity to any of the active substances or excipients**

i. **People currently using medications with known drug interactions.** CB

Recommendation 15: For people with haemophilia A or B, the WFH recommends using shared decision-making (SDM) to evaluate the benefits, risks, adverse events, impact on quality of life, limited evidence and current unknowns of gene therapy, along with the individual's treatment goals, expectations and preferences for the following populations.

a. **People over the age of 65**

b. **People with haemophilia B and AAV antibodies**

c. **People with mild hepatic impairment**

d. **People with renal impairment**

e. **People with controlled HIV or other immunosuppressive disorders**

Remark: **A specialist, such as a hepatologist, nephrologist, or immunologist, may be consulted to assist in determining if gene therapy is a suitable treatment option for patients with pre-existing conditions**.

Remark: **A risk factor assessment of concomitant immunosuppressive medications and the patient's ability to receive corticosteroids and/or other immunosuppressive therapy following gene therapy should be completed and carefully considered**. CB

Recommendation 16: There is currently insufficient evidence to make a recommendation for or against AAV gene therapy for the following populations:

a. **People with haemophilia A and a prior history of FVIII inhibitors**

b. **Women** CB

4.4 | Screening and Suitability Assessments for Eligibility

4.4.1 | Screening for AAV Antibodies

- All people with haemophilia A who are considering AAV gene therapy should be tested for antibodies against the specific product's AAV serotype. If the individual is positive, they are not currently eligible to receive gene therapy using that AAV serotype.
- However, in people with haemophilia B, treatment with etranacogene dezaparvovec may achieve therapeutic efficacy in patients with pre-existing AAV5-neutralizing antibodies.
- A post hoc analysis of patients treated with AMT-060 (precursor to etranacogene dezaparvovec) and non-human primates showed that the therapeutic efficacy of gene therapy was achieved in individuals with pre-existing anti-AAV5–neutralizing antibodies [68].
- Based on these results, three PwH with pre-existing AAV5-neutralizing antibodies were included in the phase 2b trial for etranacogene dezaparvovec and achieved therapeutic levels of FIX [24, 68]. In the phase 3 study, 21 out of 54 participants had AAV5-neutralizing antibodies; all but one who had the highest titre achieved therapeutic levels of FIX.
- A clinical trial is underway to examine the efficacy and safety of etranacogene dezaparvovec gene therapy in adults with haemophilia B with pretreatment adeno-associated virus serotype 5 (AAV5)-neutralizing antibodies (Nabs) [69]. This trial is designed to determine the AAV5 titre at which the gene therapy is no longer effective.

- A clinical trial examining the use of valoctocogene roxaparvovec in people with pre-existing AAV5-neutralizing antibodies was terminated in 2024 after enrolling three participants [70]. No results have been released.
- Two studies have reported the seroprevalence of neutralizing antibodies in PwH. Klamroth and colleagues found the global prevalence of pre-existing immunity in people with haemophilia A to be 58.5% for AAV2, 34.8% for AAV5, 48.7% for AAV6, 45.6% for AAV8 and 46.0% for AAVrh10 [71]. Seropositivity for all serotypes varied by region and increased with age [71]. A similar multicentre assessment of people with haemophilia A and B determined the prevalence of pre-existing neutralizing antibodies to be 46.9% for AAV2, 53.1% for AAV5 and 53.4% for AAV8. Values remained stable 1 and 2 years later [72]. The co-prevalence of at least two serotypes was present in 40% of participants, and all three were present in 38.2% of participants. For each serotype, approximately 10% of participants who were negative at baseline were positive 1 year later.
- More research is needed to determine the safety and efficacy of AAV gene therapy in people with positive pre-treatment neutralizing antibodies. However, the ability to dose through an AAV-neutralizing antibody titre may be unique to AAV5 and etranacogene dezaparvovec.

Recommendation 17: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends testing for antibodies against the AAV vector serotype according to the prescribing information.

Remark: **AAV antibody testing should be performed using a companion diagnostic laboratory test approved by the FDA, EMA or relevant regulatory authorities**.

Remark: **If the test is positive, refer to the current prescribing information for the most up-to-date indications and contraindications**.

Remark: **For people with haemophilia A and AAV antibodies, the WFH recommends against AAV gene therapy**.

Remark: **For people with haemophilia B and AAV antibodies, the WFH recommends using SDM to determine eligibility**.

Remark: **AAV antibody testing should be conducted no more than 6 months before the scheduled infusion and should be repeated if necessary**. CB

4.4.2 | Screening for Factor Inhibitors

- Initial clinical studies for gene therapy in people with haemophilia A and B have excluded patients with a current or prior history of factor inhibitors. At the time of publication, the prescribing information for all gene therapies states FVIII or FIX inhibitors as a contraindication.
- Clinical trials are ongoing to assess the safety, efficacy and tolerability of valoctocogene roxaparvovec in people with haemophilia A who have active or prior FVIII inhibitors [73].
- People with haemophilia B and inhibitors are at risk for allergic reactions if they receive FIX protein [74].

Recommendation 18: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends testing for FVIII or FIX inhibitors according to the prescribing information.

Remark: **Follow the WFH Guidelines for the Management of Hemophilia, third Edition [1] Chapter 3: Recommendation 3.2.35–3.2.39 and local standards for testing modality**.

Remark: **If the test is positive, refer to the prescribing information for the most up-to-date indications and contraindications**.

Remark: **For people with haemophilia A and active factor inhibitors, the WFH recommends against AAV gene therapy. For people with haemophilia A and a prior history of inhibitors, there is insufficient evidence to recommend for or against AAV gene therapy**.

Remark: **For people with haemophilia B and an active or a prior history of FIX inhibitors, the WFH recommends against AAV gene therapy**.

Remark: **Factor inhibitor testing should be conducted no more than 6 months before the scheduled infusion and should be repeated if necessary**. CB

4.4.3 | Screening for Liver Health

- Liver health is likely vital to the success of gene therapy. Optimal gene therapy outcomes depend on the proper maintenance of liver health throughout the gene therapy process and after the gene therapy infusion [75, 76].
- PwH should be assessed for liver function abnormalities, hepatic steatosis/metabolic dysfunction–associated steatotic liver disease (MASLD), chronic viral B and C hepatitis, alcoholic liver disease and autoimmune hepatitis [77].
- Additional guidance on the management of liver disease in people with bleeding disorders, including recommendations for screening of liver health before AAV gene therapy and monitoring of liver health post-infusion, was recently published as a collaboration between WFH, the European Association for Haemophilia and Allied Disorders, the European Haemophilia Consortium and the International Society of Thrombosis and Hemostasis [78].
- Liver health should be assessed through a combination of hepatic biochemical, serological, and biomarker tests, and non-invasive imaging techniques. Centres and clinicians should refer to the prescribing information and consult with a hepatologist to develop SOPs for the assessment of liver health [76].
- AAV gene therapy is contraindicated for people with hepatic cirrhosis, significant fibrosis (stage 3 or 4 on the Batts–Ludwig scale or equivalent), current active acute or uncontrolled chronic active hepatitis B or C, or active or history of hepatic malignancy (see Recommendation 14).
- Additional precautions should be considered for individuals who have risk factors for hepatotoxicity, including metabolic liver disease, obesity, excessive alcohol use/dependence, and viral liver disease, and anyone who uses concomitant medications that are liver toxic [77].

- Attempts should be made to ensure the individual is in the best liver health possible before gene therapy.
- See Appendix 2: SDM Topics for People Considering AAV Gene Therapy: A Checklist for Healthcare Professionals and Section 6.6.2 Optimize Your Liver Health.

Recommendation 19: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends assessing baseline liver health according to the prescribing information.

Remark: **Refer to the prescribing information for indications and contraindications for people who have compromised liver function**.

Remark: **A hepatologist may be consulted to assess liver health and suitability for gene therapy**.

Remark: **ALT and aspartate transferase (AST) testing should be performed at least twice prior to gene therapy to establish a baseline for immediate and long-term post-treatment monitoring and comparison. The second test should be conducted within 3 months of the scheduled infusion**. CB

- PwH should be tested for hepatitis B and hepatitis C according to the American Association for the Study of Liver Disease (AASLD) guidelines [79, 80], or similar local guidance.
- People with active hepatitis B or C infection are not eligible for AAV gene therapy, but if the infection is resolved could become eligible depending on other eligibility criteria.

Recommendation 20: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends testing for current or past hepatitis B and hepatitis C infection.

Remark: **For people with active acute or chronic hepatitis B or C infections with detectable HBV DNA or HCV RNA, the WFH recommends against gene therapy. Refer to the prescribing information for the most up-to-date indications and contraindications**.

Remark: **Patients should be immunized against hepatitis A and hepatitis B if not already immune**. CB

4.4.4 | Assessment of Ability to Receive Immunosuppressive Therapy

- The ability of an individual to receive corticosteroids or an alternative immunosuppressive therapy must be considered when determining eligibility for AAV gene therapy.
- In clinical studies, many PwH treated with AAV gene therapy experienced ALT elevations and required corticosteroids until transaminitis was resolved (Table 7; median of 230 days for haemophilia A and 74 days for haemophilia B). In most cases, ALT levels peaked at 1.5–2-fold above the upper limit of normal. Transaminitis occurs most commonly in the first 2–5 months post-infusion and is more common with valoctocogene roxaparvovec for haemophilia A, than in etranacogene dezaparvovec for haemophilia B. These transient ALT elevations have been associated with a reduction, and in extreme cases, a loss, of transgene factor expression.
- The prevailing hypothesis is that AAV capsid proteins initiate an immune response that results in elevated ALT, destruction of the vector containing hepatocytes and decreased factor expression. Immunosuppression with corticosteroids helps to suppress the inflammatory response, thereby reducing ALT levels and stabilizing factor expression [48, 81–85].
- Additional precaution is required for individuals who have risk factors related to receiving corticosteroid immunosuppression (or alternative immunosuppression). Risk factors include obesity, metabolic syndrome, diabetes, osteoporosis, a history of peptic ulcer disease and hypertension. Importantly, the safety and efficacy of alternative immunosuppressants have not been established in this population.
- All current medications should be reviewed in the context of possible immunosuppression for hepatoxicity. See Section 4.4.5 Screening of All Concomitant Medications.

Recommendation 21: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends assessing the ability to receive corticosteroid and/or other immunosuppressive therapy.

Remark: **Risk factors or pre-existing conditions that may be exacerbated by corticosteroids or other immunosuppressive therapies include obesity, metabolic syndrome, diabetes, osteoporosis, a history of peptic ulcer disease, hypertension, congestive heart failure, hyperlipidaemia and psychiatric disorders**.

Remark: **Individuals with risk factors related to receiving immunosuppression will require closer monitoring**.

Remark: **All existing medications should be reviewed in the context of possible immunosuppressive therapy use**. CB

4.4.5 | Screening of All Concomitant Medications

- No in vivo interaction studies have been performed on the three licensed gene therapy products. All noted drug interactions are predicted based on clinical trial experience.
- There are no known drug interactions with etranacogene dezaparvovec.
- Valoctocogene roxaparvovec has two suspected drug interactions:
  - Isotretinoin [6, 11]:
    - Clinical experience: In one patient, decreased factor VIII activity without ALT elevation was detected after starting treatment with systemic isotretinoin following valoctocogene roxaparvovec infusion; factor VIII activity was 75 IU/dL at week 60 and transiently decreased to < 3 IU/dL at week 64, after initiating isotretinoin. After discontinuing isotretinoin at week 72, factor VIII activity recovered to 46 IU/dL at week 122.
    - In vitro: Studies of human primary hepatocytes indicated that isotretinoin suppressed factor VIII expression independent of hepatotoxicity.
    - Isotretinoin is not recommended in patients who are benefiting from valoctocogene roxaparvovec.
  - Efavirenz [6, 11]:
    - Clinical experience: one HIV positive patient treated with an antiretroviral therapy regimen consisting of

TABLE 7 | Clinical evidence for ALT elevations and corticosteroid use in clinical trials from licensed AAV gene therapy products.

Haemophilia type	Gene therapy product	Study phase	% with ALT elevations	% requiring corticosteroids	Length of time on corticosteroids (days)	Adverse events from glucocorticoids
Haemophilia A	Valoctocogene roxaparvovec	Phase 3: NCT02576795 [20]	85.8% (115/134)	79.1% (106/134)	Mean ± SD: 234.5 ± 116.0 Median: 230 Range: 22–251	71.8% (79/110[a])
Haemophilia B	Etranacogene dezaparvovec	Phase 3 : NCT03569891 [38]	20% (11/54)	16.7% (9/54)	Mean ± SD: 79.8 ± 26.6 Median: 74 Range: 51–130	0% (0/9)

[a]Includes participants who received any glucocorticoids.

efavirenz, lamivudine and tenofovir experienced asymptomatic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 elevations of ALT, AST and GGT (> 5.0 × ULN) and a Grade 1 elevation of serum bilirubin (> ULN and up to 1.5 × ULN) at week 4, suggestive of an interaction with efavirenz. The reaction did not respond to corticosteroid treatment, but responded to withdrawal of efavirenz and resolved after the antiretroviral therapy regimen was changed to a regimen without efavirenz. The patient later reverted to prophylactic use of factor VIII concentrates/haemostatic agents.
    - In vitro: Studies of human primary hepatocytes indicated that efavirenz suppressed factor VIII expression independent of hepatotoxicity [67].
    - Efavirenz is not recommended in patients who are treated with valoctocogene roxaparvovec. The use of non-efavirenz treatments should be considered.
- Best practice is to minimize exposure to known hepatotoxins, including efavirenz and isotretinoin, at least 4–6 weeks before the infusion and ongoing after the AAV gene therapy infusion [75].

Recommendation 22: For people with haemophilia A or B who are considering AAV gene therapy, the WFH recommends reviewing all current medications prior to gene therapy.

Remark: **No interaction studies have been performed for any of the currently available gene therapy treatments**.

Remark: **Agents that may alter plasma concentrations of corticosteroids (e.g., agents that induce or inhibit cytochrome P450 3A4) and hepatotoxic medicinal products or substances should be evaluated**.

Remark: **For people with haemophilia A, there are known interactions between valoctocogene roxaparvovec and isotretinoin and efavirenz**. CB

4.4.6 | Assessment of Musculoskeletal Health and Expectations

- Physiotherapists (or other musculoskeletal experts, including orthopaedic surgeons and physiatrists) are a crucial part of the gene therapy process for guidance on what might occur after gene therapy based on each person's musculoskeletal status. The role of the physiotherapist will depend on the individual's musculoskeletal status prior to receiving gene therapy, and how they respond to gene therapy.
- Ideally, the musculoskeletal assessment will be completed by a musculoskeletal expert familiar with both AAV gene therapy and the patient.
- Important topics to discuss with the patient include physical activity and lifestyle changes, progressive adaption of the musculoskeletal system to a new range of physical activities, maintenance of joint health, management of bleeds, return to optimal function after bleeds and injuries, and management of residual pain and functional impairment from pre-existing arthropathy.

Recommendation 23: The WFH recommends that people with haemophilia A or B who are considering AAV gene therapy undergo a musculoskeletal assessment by a physiotherapist familiar with AAV gene therapy outcomes to establish a baseline for post-gene therapy observations. CB

4.4.7 | Psychosocial Support and Evaluation

- PwH who are considering AAV gene therapy should also undergo psychosocial screening to determine the person's mental and emotional well-being, strengths and resources, and whether they might be suitable for gene therapy. Evaluation should take place after the patient has initiated informed treatment discussions with their healthcare provider. Evaluation may be completed by the person's primary haematologist, who is familiar with the person and their history of behaviours, in consultation with a psychologist or social worker who is familiar with the risks, benefits, unknowns and demands of AAV gene therapy. Psychologists and social workers are trained to recognize how past trauma, mental health conditions, developmental stage and cultural beliefs shape the ability to process medical information and make decisions.
- Evaluations should include emotional support, and be inclusive of cultural humility, recognizing the importance of

diversity, equity and inclusion. Specific psychosocial constraints, including ability to travel, availability for follow-up, financial considerations, coping skills, support system and psychological stress should be considered. Patient expectations should also be reviewed and revisited throughout the treatment process [62].

- Assessments could include validated tools such as the core-HEM mental health assessment, PHQ-9, GAD-7, and CAGE or AUDIT.

Recommendation 24: The WFH recommends that people with haemophilia A or B who are considering AAV gene therapy undergo psychological/psychosocial screening through discussion with the healthcare team or by a psychologist or social worker who is knowledgeable about the risks, benefits and demands of gene therapy. CB

- PwH who received gene therapy have reported a perceived lack of psychological support [32] and suggested that there should be greater emphasis on psychological needs during the gene therapy process. Proactively attending to these needs could reduce complications and support long-term success.
- It is important for the healthcare provider to emphasize that PwH may wish to seek psychosocial counselling and to ensure that these services are available should they need them.
- Patient organizations and peer support may also provide psychological support throughout the gene therapy process.

Recommendation 25: The WFH recommends that people with haemophilia A or B who are considering and who have received gene therapy have access to a mental health professional for the entire gene therapy process and post-treatment follow-up. CB

4.5 | Obtain Consent for Treatment

- As the final step in the pre-infusion process, the treating healthcare team should obtain consent for treatment.

Recommendation 26: The WFH recommends obtaining consent for treatment after the patient has participated in an informed decision process that ensures the person with haemophilia has the capacity, necessary personalized information, and understanding of the risks and benefits of gene therapy compared to alternative treatments to make an informed choice.

Remark: The process should have a record of all aspects addressed during patient education and include documented commitment to the peri-infusion requirements, post-infusion monitoring requirements and the recommended lifestyle choices after gene therapy.

Remark: The patient must have sufficient time to understand and review materials to ensure they understand and consent to the treatment plan. CB

5 | Peri-Infusion and Infusion Day

5.1 | Confirmation of Eligibility and Informed Consent: The 24 h Prior to the Infusion

- The patient should have contact with the Dosing centre at least 24 h before the start of the infusion for final blood tests, physical assessments and informed consent.
- The Dosing centre's SOPs should define the required assessments to confirm eligibility and informed consent just prior to receiving gene therapy.

Recommendation 27: The WFH recommends that people with haemophilia A or B who are about to receive AAV gene therapy have medical contact at the Dosing centre at least 24 h prior to the infusion and at least 24 h after discharge as part of the infusion process.

Remark: It is medically necessary to evaluate the patient the day prior to the procedure for final evaluation, testing and counselling.

Remark: Travel and lodging accommodations are a required and essential part of the gene therapy process. Public and private healthcare should support travel and lodging-related expenses for patients who do not live near the Dosing centre. CB

Recommendation 28: The WFH recommends that a physical exam, including vital signs (e.g., heart rate, respiratory rate, blood pressure, temperature and oxygen saturation), and standard blood tests be performed prior to the infusion to evaluate for (1) complete blood count, (2) liver function, (3) recent inhibitor development and (4) any potentially concerning symptoms.

Remark: If there are symptoms of concern, appropriate interventions should be applied to resolve them before proceeding with gene therapy infusion. If the symptoms do not resolve, follow the guidance and eligibility criteria in the prescribing information on whether to proceed, postpone or cancel the gene therapy procedure. CB

Recommendation 29: The WFH recommends that the medical team re-confirm that the patient has met all eligibility criteria and passed all screening assessments prior to initiating the preparatory steps in the pharmacy. CB

Recommendation 30: The WFH recommends that the medical team re-confirm and record the patient's agreement to proceed with the haemophilia A or B AAV gene therapy prior to initiating preparatory steps in the pharmacy for the infusion. CB

5.2 | Peri-Infusion Management of Medications and Medical Conditions

- Prior to infusion, PwH should continue to use their usual haemophilia treatment regimen.

- Follow the prescribing information for the use of prophylactic medications to avoid hypersensitivity reactions based on the person's medical characteristics and the clinician's expert opinion.
- Notably, a clinical trial is ongoing to evaluate the efficacy and safety of valoctocogene roxaparvovec, with prophylactic steroids in haemophilia A (GENEr8-3) [86]. Preliminary results indicate that there is no effect on ALT elevations, but prophylactic steroids may diminish the resultant FVIII levels [87].

Recommendation 31: The WFH recommends that people with haemophilia A or B continue their usual haemophilia treatment regimen up to and during the infusion. CB

Recommendation 32: The WFH recommends against the routine use of prophylactic corticosteroids and other medications prior to the AAV gene therapy infusion.

Remark: **Medications to prevent infusion reactions, including hypersensitivity reactions and anaphylaxis, can be used based on the individual's medical characteristics and the clinician's expert opinion**. CB

Recommendation 33: The WFH recommends that people with haemophilia A or B continue using non-contraindicated medications as prescribed to manage other medical conditions up to and during the infusion. CB

5.3 | Administration

- The gene therapy infusion is usually an outpatient procedure that takes 2–3 h or sometimes longer, depending on the gene therapy product and the individual's response to the infusion.
- The infusion usually starts with a lower infusion rate during the first 30 min, and then can be increased if the patient has no adverse symptoms.
- A nurse or other member of the core medical team should stay with the patient throughout the procedure to ensure that the infusion is proceeding as expected and observe the patient for any symptoms of adverse effects.
- SOPs should be developed by the Dosing centre according to the prescribing information and institutional policies and should be followed.

Recommendation 34: The WFH recommends that the core medical team be physically available at the Dosing centre throughout the day of infusion, including the pre-infusion steps and post-infusion observation period.

Remark: **Back-up staff should be available on standby for each core position or specialty to help ensure treatment proceeds as scheduled**.

Remark: **An intensivist or medical professional trained in advanced life support should be on standby for rapid response during the infusion day**. CB

Recommendation 35: The WFH recommends that at least two medical team members be involved in administering the gene therapy product.

Remark: **One provider will administer the infusion, and one will record any data**.

Remark: **The Dosing centre physician will oversee the infusion, provide immediate follow-up post-infusion and collaborate with the referring/follow-up physician as needed**. CB

Recommendation 36: The WFH recommends following the dosage, administration and infusion rate in the prescribing information. CB

5.4 | Peri-Infusion Monitoring and Safety

- Dosing centres should develop SOPs for peri-infusion monitoring and safety according to the prescribing information for the specific gene therapy product. It should include interventions for symptoms of adverse events.
- The patient should be closely observed throughout the infusion, with the regular assessment of vital signs and symptoms every 15 min.
- Common adverse reactions during the infusion include nausea, fatigue, headache, infusion-related reactions such as burning, flu-like symptoms, joint pain and abdominal pain (Table 8). Patients may be treated with systemic antihistamines or corticosteroids or antiemetics to treat infusion reactions.
- If the infusion is paused, the resumed recommended rate of infusion may be lower than the starting rate.

Recommendation 37: The WFH recommends monitoring the patient's vital signs (e.g., heart rate, respiratory rate, blood pressure, temperature and oxygen saturation) and symptoms at least every 15 min throughout the infusion, and as instructed in the prescribing information.

Remark: **A nurse or other member of the core medical team should stay with the patient throughout the infusion and observe for any adverse reactions**. CB

Recommendation 38: In the event of an adverse reaction, the WFH recommends decreasing or temporarily halting the infusion to treat the reaction or until symptoms subside; then, infusions may be resumed at the recommended rate.

Remark: **Reactions should be managed with the intention of continuing the gene therapy infusion. Stopping or significantly postponing the infusion may compromise the individual's response to gene therapy and their ability to receive future gene therapy**.

Remark: **The infusion should be discontinued in the event of an anaphylactic reaction**. CB

5.5 | Observation and Discharge

Recommendation 39: The WFH recommends closely monitoring and observing people who have received AAV gene therapy for at least 3 h after the infusion or according to the product-specific recommendations.

TABLE 8 | Clinical evidence for infusion reactions in clinical trials from licensed AAV gene therapy products.

Haemophilia type	Gene therapy product (Alternative names)	Infusion reactions in > 5% of participants	Hypersensitivity	Anaphylaxis
Haemophilia A	Valoctocogene roxaparvovec [21]	Nausea, headache, tiredness, flu-like symptoms, rash, heartburn, muscle pain, dizziness and itching	5.2% (7/134)	2.2% (3/134)
Haemophilia B	Etranacogene dezaparvovec [26]	Headache, flu-like symptoms, infusion-related reactions (e.g., infusion site reaction, dizziness, pruritus, flushing, abdominal pain, urticaria, chest discomfort and fever), dizziness, nausea, fatigue and malaise [7, 9]	3.7% (2/54)	0% (0/54)

Remark: **If the patient experiences adverse reactions, the observation period should be extended. The patient should be admitted and observed overnight, if necessary**. CB

Recommendation 40: The WFH recommends that people who have received AAV gene therapy have ready access to corticosteroids upon discharge to be taken upon instruction by the physician. CB

Recommendation 41: If the patient will receive follow-up at a Follow-up centre that is different from the Dosing centre, the WFH recommends that the Dosing centre provide the Follow-up centre with a summary of the gene therapy treatment and a plan for the transition between centres.

Remark: **Dosing centres must ensure that people who have received gene therapy know how to contact their healthcare team during the 24 h post-discharge should any adverse events arise**. CB

6 | Post-Infusion

- The AAV gene therapy process continues even after the infusion. People with haemophilia should be prepared to have frequent laboratory tests and clinic visits for several years after the infusion. Some monitoring procedures, such as monitoring for hepatocellular carcinoma, may continue throughout their lifetime. There are also behaviours and lifestyle modifications that should be considered in the immediate short-term after gene therapy, and for long-term health.

6.1 | Post-Treatment Monitoring

- After the infusion, frequent post-treatment monitoring is medically necessary to establish FVIII or FIX gene expression, and the therapeutic effectiveness of gene therapy.
- Short-term monitoring generally refers to the first 6–12 months after the infusion. Long-term monitoring refers to anything after year 1. Both short and long-term post-treatment monitoring focus on factor expression and ALT testing (Table 9). It is also important to monitor for inhibitors and bleeding events following the standard of care according to the WFH Guidelines for the Management of Hemophilia, third Edition [1].
- Drug manufacturers and Regulatory Agencies have established minimum follow-up requirements for each approved AAV gene therapy; however, treatment centres may establish their own follow-up requirements.
- It is important to maintain open communication during this phase of treatment, which can be overwhelming for patients. Some PwH who have received AAV gene therapy have reported feelings of losing control, rather than gaining it, because of a focus on factor levels and perceived pressure to continue immunosuppressive treatments [32].

Recommendation 42: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends post-treatment monitoring of FVIII/FIX, liver health, inhibitor development and bleeding for at least 15 years.

Remark: **Monitoring schedules should, at a minimum, follow the prescribing information**.

Remark: **The frequency of testing should be guided by SDM, clinical assessment and patient-related factors such as lifestyle, physical activity and bleeding patterns**.

Remark: **In people who did not respond to gene therapy, use standard monitoring procedures with a minimum of yearly testing**.

Remark: **In people who have returned to prophylaxis and continue to have measurable factor expression, continue with the follow-up schedules for post-treatment monitoring after gene therapy**.

Remark: **In people who have returned to prophylaxis and do not have measurable factor expression, use standard monitoring procedures with a minimum of yearly testing**.

Remark: **After 15 years, use standard monitoring procedures with a minimum of yearly testing (See the WFH Guidelines for the Management of Hemophilia, third Edition [1])**. CB

TABLE 9 | Post-treatment monitoring schedule of factor levels and alanine amino transferase for licensed AAV gene therapy products.

Valoctocogene roxaparvovec		Etranacogene dezaparvovec	
Time period	**Frequency**	**Time period**	**Frequency**
Weeks 1–26	Weekly	Weeks 1–12	Weekly
		Weeks 13–52	Quarterly
Weeks 26–52	Every 1–2 weeks		
Year 2	Every 3 months	Year 2	Every 6 months
Year 3+	Every 6 months	Year 3+	Annually

Note: Monitoring schedules from prescribing information from the EMA [6–8] and the FDA [9–11, 88].

6.1.1 | Factor Level Monitoring

- Accurate measurement of coagulation factor activity is essential for monitoring the safety, efficacy and durability of gene therapy.
- FVIII and FIX are measured with two types of assays: One-stage clotting assays based on APTT or the chromogenic-substrate assay [89]. One-stage assays are the most commonly used in most regions [90].
- Discrepancies have been reported between the one-stage and chromogenic assays for both FVIII and FIX following gene therapy [12, 15, 91, 92]. Therefore, it is important that centres communicate about and, if possible, coordinate which factor assays are being used in their laboratories. Multiple laboratories have found the chromogenic assay produces a FVIII or FIX level approximately 60% of the one-stage assay [15, 91, 92].
- When measuring FIX, the one-stage assay is considered a more accurate reflection of the haemostatic potential of the FIX Pauda variant. However, this has been shown to be reagent dependent [92]. Therefore, when the one-stage assay is used, the same reagents should be used for serial monitoring of FIX levels.
- This recommendation represents an update to recommendations 3.2.40–3.2.41 in the 'WFH Guidelines for the Management of Hemophilia, third Edition' [1].

Recommendation 43: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends FVIII/FIX levels be assessed regularly and, at a minimum, should follow the schedule set by the prescribing information.

Remark: When possible, testing should be completed at the same facility using the same one-stage assay or the same chromogenic assay for all assessments over time. If it is necessary to compare the two assays, the one-stage assay value is approximately 1.6-fold higher than the chromogenic assay value [15, 91, 92].

Remark: When measuring FVIII levels, it is not clear whether the one-stage assay or the chromogenic assay reflects the true FVIII level [91].

Remark: When measuring FIX, the one-stage assay is considered a more accurate reflection of the haemostatic potential of the FIX Padua variant. This is reagent dependent and can be up to two-fold higher than the chromogenic value [92].

Remark: More frequent monitoring of factor levels is recommended if FVIII/FIX activity levels are < 5 IU/dL within 1 year after infusion.

Remark: If there is a sudden drop in FVIII/FIX activity levels, ALT levels should be assessed. CB

6.1.2 | Alanine Aminotransferase Level Monitoring

- Elevated ALT levels, or transaminitis, is commonly observed, usually asymptomatic, and can occur at any time after gene therapy.
- Elevated ALT has been reported with all clinically investigated AAV gene therapy products (see Table 10 for evidence from licensed and available products).
- The underlying pathophysiology of why some individuals experience elevated ALT, and others do not, is not well understood, but it has been established that even moderate levels of ALT elevation may be associated with decreases in factor level expression [12, 48, 81].
- Most patients receiving AAV gene therapy for haemophilia A are expected to have some degree of ALT elevation.
- Late ALT elevations may occur in people with haemophilia A treated with valoctocogene roxaparvovec [20].
- Some patients receiving AAV gene therapy for haemophilia B are expected to have some degree of ALT elevation [13, 26].
- Elevated ALT levels within the first year will likely require immunosuppressive treatment. These elevations can be severe and may require intravenous steroids. Immunosuppression with corticosteroids or other medications poses significant safety concerns because of the side effects associated with long-term corticosteroid use. General side effects of corticosteroid use are insomnia, hypertension, hyperglycaemia, muscle spasms and altered mood.
- Some PwH report that immunosuppression and its side effects are the worst part of the gene therapy experience [32]. Therefore, it is important to emphasize the potential need for immunosuppressive therapy and the possibility that multiple courses or prolonged exposure for multiple months may be required during the SDM process (see Section 3 Shared and

TABLE 10 | Clinical evidence for ALT elevations in clinical trials from licensed AAV gene therapy products.

Haemophilia type	Gene therapy product	Study phase	% with ALT elevations	Time from infusion to first ALT elevation (weeks)		Length of ALT elevations (days)		% requiring corticosteroids
				Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
Haemophilia A	Valoctocogene roxaparvovec	Phase 3: NCT02576795 [20]	85.8% (115/134)	11.3 ± 12.3	8.0 (1–104)	48.2 ± 81.1	15 (1–488)	79.1% (106/134)
Haemophilia B	Etranacogene dezaparvovec	Phase 3: NCT03569891 [26]	20% (11/54)	6.6 ± 4.1	5.1 (3.1–17.1)	37.9 ± 43.4	17.0 (5–127)	16.7% (9/54)

Informed Decision-Making). Providers should continue to offer access to a trained psychologist or social worker to assist with coping with difficult side effects.

- Individuals who have risk factors for adverse effects related to receiving corticosteroid immunosuppression should have added consideration for alternative immunosuppressants. These risk factors include obesity, metabolic syndrome, diabetes, osteoporosis, a history of peptic ulcer disease and hypertension. The safety and efficacy of alternative immunosuppressants has not been established in this population.
- Other immunosuppressants were used by 29% of participants from the GENE-r8-1 study because of contraindications, side effects, or a low or lack of response to glucocorticoid treatment [20]. There is no evidence from this study that alternative immunosuppressive agents were of benefit.
- Follow-up ALT testing should be ordered rapidly so that it can be repeated quickly, if necessary, and wherever possible should minimize inconvenience to the patient.

Recommendation 44: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends that alanine aminotransferase (ALT) levels be assessed regularly and, at a minimum, should follow the schedule set by the prescribing information.

Remark: When interpreting ALT levels, it is important to consider whether the person has recently undergone strenuous exercise or used alcohol, protein supplementation, or other potential hepatotoxic medications or agents.

Remark: ALT levels indicating Grade 3 or 4 hepatotoxicity require additional laboratory testing [e.g., aspartate aminotransferase (AST), bilirubin (BR), alkaline phosphatase (ALP), creatine phosphokinase (CPK), gamma-glutamyl transferase (GGT) or other clinically indicated tests] and consultation with a hepatologist. CB

6.1.3 | Inhibitor Monitoring

- There is a theoretical risk of FVIII or FIX inhibitor development in people with haemophilia who have received AAV gene therapy. If bleeding is not controlled, or if factor activity levels suddenly decrease, perform inhibitor screening.
- No inhibitors have been reported in clinical trials for valoctocogene roxaparvovec, or etranacogene dezaparvovec [12, 18, 27, 93].
- See The WFH Guidelines for the Management of Hemophilia, third Edition, section 8.2: Inhibitor Screening.

Recommendation 45: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends at least annual monitoring through appropriate clinical observations and laboratory tests for the development of inhibitors for a minimum of 15 years. CB

6.1.4 | Bleed Monitoring

- People with haemophilia should continue to monitor their bleeding episodes. The healthcare team should continue to review the recent bleeding history at every follow-up visit.

Recommendation 46: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends following the WFH Guidelines for the Management of Hemophilia, third Edition, Recommendation 6.8.1 for bleed monitoring [1].

Remark: Bleeding should be tracked in a paper or electronic diary and discussed with healthcare providers. CB

6.2 | Discontinuation of Prophylaxis

- Immediately following the infusion, people who have received gene therapy should continue to use prophylaxis as directed and according to the gene therapy prescribing information.
- The decision of when to discontinue prophylaxis should be made through SDM and with careful consideration of the individual's clinical response to gene therapy, history and preferences. Regular and frequent monitoring is critical when deciding to discontinue prophylaxis.

- When to discontinue prophylaxis will differ from person to person and cannot be defined by absolute times or factor level values. The factor level thresholds provided in this recommendation are the minimum factor levels required to consider discontinuation of prophylaxis.
- The use of different factor assays and reagents may impact factor activity results. Therefore, it is important to minimize possible variability of results by using the same laboratory test and reagent types for monitoring factor levels over time. See Section 6.1.1 Factor Level Monitoring.
- In clinical studies, most patients who respond to gene therapy can discontinue prophylaxis within 2–4 weeks after the infusion. Some individuals will experience elevated factor levels sooner than others and will need to stop prophylaxis sooner to avoid factor levels above the upper limit of normal.
- For people with haemophilia A who use emicizumab prophylaxis, the last dose may be given at the time of the gene therapy infusion, which will provide FVIII equivalent levels of protection for a few months. Care must be used in assessing FVIII levels resulting from the infusion, and only the chromogenic assay using bovine reagents will yield an accurate FVIII level. A model using pharmacokinetic simulations [94] and a single case study [95] have been published that outline multiple strategies for the transition between emicizumab and AAV gene therapy.

Recommendation 47: For people with haemophilia A or B who have received AAV gene therapy, the WFH recommends using shared decision-making (SDM) that is individualized to the person's response to AAV gene therapy, history, current replacement therapy and its half-life, and preferences to determine the appropriate time to discontinue prophylaxis.

Remark: **Deciding when to discontinue prophylaxis is a dynamic process that incorporates many patient-specific parameters, including factor level, current and past bleeding phenotype, lifestyle, physical activity, joint health, bleeding history and goals.** CB

6.3 | Post-Infusion Safety

- There are several warnings and safety precautions to consider in the weeks, months and years following AAV gene therapy. These include transaminitis, or elevated ALT levels, requiring treatment with immunosuppression, factor levels above normal resulting in an increased risk for a thrombotic event, and hepatocellular carcinogenicity.
- All adverse events should be reported to the appropriate governing bodies and gene therapy registries.

6.3.1 | Liver Health and Immunosuppression

- The importance of liver monitoring after gene therapy cannot be overstated [76, 77, 85, 96].
- Additional guidance on the management of liver disease in people with bleeding disorders, including recommendations for screening of liver health before AAV gene therapy and monitoring of liver health post-infusion, were recently published as a collaboration between WFH, the European Association for Haemophilia and Allied Disorders, the European Haemophilia Consortium, and the International Society on Thrombosis and Hemostasis [78].
- Transaminitis, or elevated ALT levels, has been observed in all gene therapy clinical trials (Table 10). In most cases, ALT levels peaked at 1.5–2-fold above the upper limit of normal. Transaminitis occurs most commonly at 7–14 weeks post-infusion and is more common with valoctocogene roxaparvovec for haemophilia A, than in AAV gene therapies for haemophilia B. These transient ALT elevations have been associated with a reduction, and in extreme cases, a loss, of transgene factor expression.
- Many people treated with AAV gene therapy will require immunosuppression to treat transient ALT elevations.
- See Section 4.4.3 Screening for Liver Health and Section 4.4.4 Assessment of Ability to Receive Immunosuppressive Therapy for more information.
- There is a clinical rationale for both reduced and enhanced immunosuppression [85]. More research, including controlled clinical trials, is needed to understand the multiple mechanisms underlying the immune response to AAV gene therapy, which may warrant multiple treatment approaches [84].
- More research is needed to understand and confirm the effects of corticosteroids on FVIII, FIX and ALT levels [48, 77, 84, 85].
- More research is needed to provide evidence of the effectiveness of alternative immunosuppression approaches such as budesonide, tacrolimus, mycophenolate mofetil and others.
- After gene therapy, especially during the first year and during the use of immunosuppressive medications, all concomitant medications should be evaluated. Prescribing information cautions against the use of hepatotoxic medications or substances, as well as those that may alter the plasma concentration and effectiveness of corticosteroids.

Recommendation 48: For people with haemophilia A or B who have received AAV gene therapy and have elevated alanine aminotransferase (ALT) levels, the WFH recommends following the prescribing information for instituting corticosteroid treatment.

Remark: **When interpreting ALT levels, it is important to consider whether the person has recently undergone strenuous exercise or used alcohol, protein supplementation, or other potential hepatoxic medications or agents.**

Remark: **ALT levels should be monitored until enzymes return to baseline.**

Remark: **Alternative immunosuppressive may be used if corticosteroids are contraindicated, ineffective, or if the patient experiences adverse reactions. The efficacy of alternative immunosuppressive treatments has not yet been established in this setting.**

Remark: **Patients should be monitored for adverse reactions to corticosteroids and managed accordingly.** CB

6.3.2 | Monitoring and Prevention of Thrombotic Events

- Some PwH who have received AAV gene therapy have experienced factor level elevations above the normal range. This may result in an increased risk for thromboembolic events [97].
- Rare thromboembolic events have occurred in both FVIII [98] and FIX [99] gene therapy clinical trials.
- Factor activity levels above 150 IU/dL (150%) have been observed in clinical trials for haemophilia A [20].
- At 1 year after infusion with valoctocogene roxaparvovec, 7 of 134 (5.2%) of participants had a factor activity level greater than 150 IU/dL [20].
- High clotting factor levels have been associated with rare thromboses in gene therapy clinical trials for both FVIII [98] and FIX [99]. These products are no longer under clinical investigation.
- No thrombotic events have been reported and deemed related to gene therapy or elevated factor levels in people treated with valoctocogene roxaparvovec [15, 18, 20] or etranacogene dezaparvovec [26].

Recommendation 49: For people with haemophilia A or B who have received AAV gene therapy and have factor levels elevated above normal, the WFH recommends assessing the need for anticoagulation treatment through shared decision-making (SDM) with special consideration for the degree of elevation and any other risk factors for thromboembolic disease. CB

6.3.3 | Carcinogenicity

- AAV vectors can randomly integrate into the cellular genome of hepatocytes; therefore, there is a theoretical risk that integration may result in hepatocellular carcinoma. There may also be unknown compounding effects in people with comorbid hepatic conditions, such as hepatitis C, hepatitis B, MASLD or chronic alcohol consumption, which are also known risk factors for hepatocellular carcinoma.
- Tumorigenesis remains a theoretical long-term safety concern because there have been dose-dependent AAV integration events observed in neonatal murine models [100, 101]. However, recent evidence has called these results into question [102].
- No cases of hepatocellular carcinoma have been reported in people treated with valoctocogene roxaparvovec [26, 103]. One case has been reported in a person treated with etranacogene dezaparvovec [104]. An independent review determined that the individual had pre-existing risk factors and that the carcinoma was unrelated to AAV integration.
- Importantly, the following recommendation is based on the risk factors for hepatocellular carcinoma, regardless of whether a patient has received AAV gene therapy or its clinical outcome [77, 105]. This recommendation also follows the recommendations for screening of high-risk individuals in the AASLD Practice Guidance on prevention, diagnosis and treatment of hepatocellular carcinoma [106].
- At this time, there is a critical need for careful long-term monitoring for hepatocellular carcinoma in people who have received AAV gene therapy. Future research may adjust these monitoring guidelines.

Recommendation 50: For people with haemophilia A or B who have received AAV gene therapy and have risk factors for hepatocellular carcinoma, the WFH recommends liver ultrasounds every 6 months, with or without laboratory testing for alpha-fetoprotein (AFP).

Remark: Risk factors include prior hepatitis B or C infection, liver fibrosis, liver cirrhosis, metabolic liver disease, chronic alcohol consumption, MASLD, advanced age or a family history of liver conditions.

Remark: The need for monitoring is indefinite, as the risk of hepatocellular carcinoma increases with advancing age. CB

6.3.4 | Reporting Adverse Events

- Dosing centres and Follow-up centres should have SOPs in place to report adverse events to gene therapy registries and applicable governing bodies.
- Preferred gene therapy registries include the WFH Gene Therapy Registry and local/national gene therapy registries that link with the WFH Gene Therapy Registry.
- Governing bodies include agencies that regulate drugs and treatments, such as the Food and Drug Administration (USA) and the European Medicines Agency (EU) or your local regulatory agency.

Recommendation 51: The WFH recommends healthcare providers and treatment centres report adverse events to gene therapy registries and applicable governing bodies.

Remark: All adverse events should be reported with particular emphasis on serious adverse events, unexpected adverse events, and adverse events of special interest, including FVIII/FIX inhibitors, thromboembolic events, autoimmune disorders, benign tumours, malignancies, liver disease, sensory paresthesias, infusion/hypersensitivity reactions, hepatitis B (new or reactivated), hepatitis C and serious reactions to immunosuppression. CB

6.4 | Haemophilia Management After Gene Therapy

- It is important to educate PwH that bleed risk still exists even if their factor level is increased. Therefore, episodic therapy with additional factor may be needed to normalize factor levels, and activity levels should be commensurate with factor level. Some activities or procedures may still require normalization with supplemental episodic clotting factor concentrates. Limited clinical evidence is available [107].
- All bleeds should be reported to the WFH GTR (or linked GTR) and the local HTC.

Recommendation 52: For people with haemophilia A and B who have received AAV gene therapy and who may undertake high-risk physical activity, the WFH recommends

that factor levels be normalized with the episodic use of supplemental clotting factor concentrates, if necessary. CB

Recommendation 53: For people with haemophilia A and B who have received AAV gene therapy and who may undergo surgical procedures, the WFH recommends that factor levels be increased to the level appropriate for the procedure, according to the WFH Guidelines for the Management of Hemophilia, third Edition, with supplemental episodic clotting factor concentrates (CFC) therapy, if necessary. CB

Recommendation 54: For people with haemophilia A and B who have received AAV gene therapy, the WFH recommends they continue to manage bleeds according to the WFH Guidelines for the Management of Hemophilia, third Edition [1]. CB

6.4.1 | Musculoskeletal Assessments

- PwH should continue to see a physiotherapist (or other musculoskeletal expert) to provide individual guidance.

Recommendation 55: For people with haemophilia A and B who have received AAV gene therapy, the WFH recommends regular musculoskeletal assessments by a physiotherapist.

Remark: **The physiotherapist should provide individualized guidance on the expected lifestyle changes related to physical activity, including suggested levels of physical activity, the progressive adaption of the musculoskeletal system to a new range of physical activities, maintenance of joint health, return to optimal function after bleeds and injuries, and management of residual pain and functional impairment from pre-existing arthropathy**. CB

6.4.2 | Psychosocial Assessment and Mental Health Support

- PwH should have continued access to a mental health or psychosocial professional if wanted and/or necessary.
- See Section 4.4.7 Psychosocial Support and Evaluation

6.5 | Return to Prophylaxis

- The decision to return to prophylaxis can occur at any point in the months and years following treatment with AAV gene therapy.
- The return to prophylaxis will differ from person to person and is based on multiple factors, including the person's historical and current bleeding pattern, severity and location, physical activity levels, lifestyle, and joint health. The decision should also be guided by measurable parameters such as factor activity level or number of bleeds.

Recommendation 56: For people with haemophilia A or B who have received gene therapy and discontinued their pre-gene therapy haemophilia treatment(s), the WFH recommends that prophylaxis be resumed if the factor level is not sufficient to prevent bleeding in the context of the individual's lifestyle and/or if the factor level drops below an acceptable threshold.

Remark: **The decision to resume prophylaxis and which treatment to use should be a shared decision between the clinician and the person with haemophilia based on multiple factors, including the person's bleeding pattern, severity, and location, physical activity levels, lifestyle, and joint health**.

Remark: **The acceptable factor level threshold may vary based on patient-specific factors**.

Remark: **People with haemophilia A or B should be able to use any of the prophylaxis treatments available, as indicated in the WFH Guidelines for the Management of Hemophilia, third Edition [1]**. CB

6.6 | Recommended Lifestyle Choices for People With Haemophilia Who Have Received AAV Gene Therapy

- AAV gene therapy is a one-time treatment with the potential for long-term benefits and substantial changes in quality of life (see Section 1.4 Quality of Life and AAV Gene Therapy).
- PwH should be informed there are several suggested behavioural modifications to improve overall health and minimize safety risks [38].

6.6.1 | Maintain Connections With Your Local Haemophilia Treatment Centre

Recommendation 57: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy remain connected to their Haemophilia Treatment centre.

Remark: **People with haemophilia who have received AAV gene therapy should maintain a regular follow-up schedule after gene therapy**.

Remark: **Treatment of haemophilia-related bleeding and sequelae from prior bleeding should be managed at the Haemophilia Treatment centre**.

Remark: **Minor and major surgical procedures may require haemostatic agents and should be guided by the Haemophilia Treatment centre**. CB

6.6.2 | Optimize Your Liver Health

- The importance of maintaining good liver health after gene therapy cannot be overstated. AAV gene therapy targets liver hepatocytes to express the new FVIII and FIX proteins. To maintain gene expression, liver cells must remain healthy.
- PwH who have received gene therapy should maintain liver health through healthy lifestyle and diet choices, and by limiting the use of agents that can impact liver health, such as non-prescription medications, herbal and dietary supplements, recreational drugs and alcohol, and protein supplements.
- The healthcare team should provide education and resources to learn more about optimizing liver health.

Recommendation 58: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy are educated about behaviours to achieve and maintain optimal liver health.

Remark: Education should include healthy lifestyle and diet choices, and limiting the use of non-prescription medications, herbal and dietary supplements, recreational drugs and alcohol, and protein supplements.

Remark: All new medications and supplements should be evaluated for liver toxicity. Multiple tools are available to identify drugs and supplements associated with liver toxicity. Examples include the LiverTox website [108] or the AASLD practice guidelines [109]. CB

Recommendation 59: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy abstain from alcohol consumption for at least 1 year following infusion and limit alcohol use thereafter. CB

6.6.3 | Contraception

- Following AAV gene therapy, the vector DNA that does not go to the liver is not needed and will be released or shed from the body.
- Vector DNA can be detected in blood, semen, saliva, urine and faeces within 72 h after the infusion [15, 110].
- The vector DNA can still be detected in semen up to 1 year later [15, 26].
- Notably, vector DNA was absent in purified sperm cells, ruling out the risk of inadvertent germline modifications.
- Therefore, contraception for the first year is recommended out of an abundance of caution. There is no evidence that prior AAV gene therapy should have an effect on fertility or a foetus.
- Products vary in the recommended time for contraception use. The Panelists decided to recommend at least 1 year of contraception following AAV gene therapy based upon the evidence that showed vector DNA in the semen up to 1 year later [15, 26]. This recommendation may be updated as more evidence becomes available.

Recommendation 60: The WFH recommends that males with haemophilia A or B who have received AAV gene therapy use barrier contraception and their female partners of childbearing potential use contraception for at least 1 year following infusion.

Remark: Females who may have received AAV gene therapy and are of childbearing potential should also use contraception for at least 1 year. CB

6.6.4 | Blood, Plasma or Tissue Donation

- Vector DNA can continue to be detected in the blood up to 3 years post-infusion [110].
- The AAV vector is known to have a low level of integration throughout the body, with unknown significance [48].
- Therefore, people who have received gene therapy should not donate any fluid, tissue, organ or cell for allogeneic transplantation. This recommendation does not have a time limit and is lifelong.

Recommendation 61: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy do not donate blood, plasma, organs, tissues or cells for transplant. CB

6.6.5 | Physical Activities

Recommendation 62: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy have physical activity levels that are commensurate with factor levels, muscle strength and range of motion.

Remark: People with haemophilia should be evaluated by a physiotherapist for individualized guidance (see Recommendation 55).

Remark: People with haemophilia should be educated about the relationship between factor levels and the bleeding risk associated with exercise.

Remark: People with haemophilia should be informed that strenuous physical activity can elevate alanine transaminase (ALT) levels. Therefore, exercise schedules may need to be modified according to follow-up laboratory testing schedules during the first 6–12 months post-treatment. CB

6.6.6 | Connection to Patient Organizations

- Maintaining a connection to patient organizations is an important part of comprehensive care for people with haemophilia. Patient organizations are primarily a resource for patients that may provide or facilitate education, support, advocacy and access to specialized services tailored to the needs of the bleeding disorders community. For PwH who have received AAV gene therapy, these connections remain particularly important because of the unique challenges and uncertainties, particularly over the long term, associated with treatment with AAV gene therapy.
- Patient organizations may also be a source of peer-to-peer support for those who are considering or have received gene therapy.

Recommendation 63: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy maintain connections with the bleeding disorders community. CB

6.6.7 | Gene Therapy Registry

- See Section 2.6 Gene Therapy Registries.

Recommendation 64: The WFH recommends that people with haemophilia A or B who have received AAV gene therapy participate in the WFH gene therapy registry or

another local/national gene therapy registry that links with the WFH registry to provide patient-reported data. CB

Remark: **It is important to collect patient-reported outcomes in addition to clinically reported outcomes**.

7 | Discussion

- The addition of this chapter on the management of haemophilia A and B with AAV gene therapy marks an important advancement in the standardization and safety of gene therapy in clinical practice. The novelty of AAV gene therapy and limited long-term data in haemophilia created the need for a robust, evidence-based framework to support its safe and effective implementation. These guidelines provide a comprehensive framework to address the unique challenges and complexities of AAV gene therapy, emphasizing patient-centred care and its safe implementation.
- The adoption of the Living Guidelines Model reflects the WFH's commitment to keep recommendations current with the rapidly evolving evidence, ensuring that clinical practice remains aligned with advancements in AAV gene therapy technology.
- These guidelines are intended to also serve as a resource for people with haemophilia by fostering informed decision-making and improved quality of care.

7.1 | Limitations of These Guidelines

- The limitations of these guidelines include a lack of head-to-head randomized clinical trials comparing gene therapy with other treatment options, preventing recommendations of one treatment option over another. Therefore, these guidelines provide a clinical framework to support its implementation from decision to treatment to follow-up care. Although the scope of these guidelines is intentionally broad, it is possible that they may not address all potential issues related to AAV gene therapy. Although efforts were made to include diverse perspectives, the methodology may not fully capture the global variations in healthcare systems, access to gene therapy, and patient needs, potentially limiting the generalizability of the recommendations. Some recommendations may not be feasible in low-resource settings, where access to and capacity to deliver gene therapy is limited. Finally, the pace of advancements in gene therapy means that the evidence base is likely to change quickly, potentially rendering some recommendations outdated despite adopting a Living Guidelines Model.
- Treatment cost is often relevant to both practitioners and patients, and cost-effectiveness studies often contribute an important perspective for clinical practice guidelines [111, 112]. Several systematic reviews and cost-effectiveness studies have been completed using predictive modelling, but no real-world cost-effectiveness studies have been completed. Cost may be considered during treatment conversations between PwH and their healthcare teams; however, based on the existing cost-effectiveness literature, the WFH cannot consider cost in its current recommendations.
- These guidelines are also limited to AAV-based gene therapy. Future guidelines may need to be modified or developed to incorporate novel vector types or genetic technologies such as gene editing.

7.2 | Implementation

- Addressing facilitators and barriers towards use of the WFH Guidelines for the Management of Haemophilia A and B with AAV Gene Therapy is crucial for the effective implementation of these guidelines.
- The WFH gathered insights into barriers and facilitators through consultation with the expert panel throughout the guideline development process, and through evidence from the included studies.
- The identification of facilitators and barriers helped to shape the guideline development process by enabling the prioritization of rapidly evolving topics, adopting a flexible living model for frequent updates, and creating targeted recommendations that address potential barriers, such as site preparedness, clinical teams, and clinical education and training.
- Potential barriers to implementing these guidelines include rapidly evolving evidence; variability in healthcare resources; knowledge gaps among providers and patients; logistical challenges in adapting workflows; equity issues in ensuring fair access across diverse populations; heterogeneity of healthcare systems with differing policies and funding mechanisms; financial and logistical resource constraints in some regions; and ongoing challenges in disseminating knowledge to all stakeholders.
- Potential facilitators include active stakeholder engagement from clinicians, researchers, patients, caregivers and policy-makers; the availability of high-quality, up-to-date evidence on gene therapy; established networks of HTCs and comprehensive care teams; ongoing education for healthcare providers and PwH; employing a living guideline model to keep recommendations current; a patient-centred approach that enhances relevance and trust; and global accessibility through the WFH website to support worldwide dissemination.
- Users can assess the implementation of the WFH guidelines by evaluating adoption rates among HTCs and clinicians, stakeholder knowledge and awareness through surveys, improvements in patient safety, efficacy, and reported outcomes, and the equity of recommendation implementation across diverse populations and regions.
- The impact of guideline implementation can be assessed by evaluating changes in clinical outcomes such as efficacy and safety of AAV gene therapy, consistency in clinical practices across centres, patient and caregiver satisfaction with care delivery, incorporation of guidelines into health policies, and the cost-effectiveness of resource utilization.
- The suggested frequency for measuring these factors, which can be adjusted based on local factors and resources, includes annual assessments for comprehensive evaluations of adoption, impact and barriers; regular monitoring to track progress

TABLE 11 | Research priorities identified according to major topic areas.

Eligibility, Screening and Suitability
Studies in expanded patient population, including women, adolescents, people over 65, people with immunosuppressive disorders, mild hepatic impairment
Studies designed to confirm and understand the effects of corticosteroids on FVIII, FIX and ALT levels.
Studies that use alternative immunosuppressants
Studies on the efficacy of biomarkers that can help predict an individual's response to AAV gene therapy
Real-world evidence from a population that is more representative of the haemophilia community, including race, ethnicity, age and comorbidity status
Studies on efficacy and safety in patients with AAV antibodies at infusion
Post-Infusion
Real-world studies on long-term liver health and hepatocellular carcinoma
Real-world studies on FVIII and FIX inhibitor development following gene therapy
Efficacy Outcomes
Research studies that examine the cause(s) of the loss of factor activity over time, particularly for FVIII
Research studies that examine possible risk factors for overexpression of FVIII
Real-world studies that measure quality-of-life improvements in larger populations in comparison to treatment with on-demand and prophylaxis regimens. These studies should use instruments that measure outcomes that are important to patients and have known minimally important differences in total score or subscales
Real-world studies on the long-term cost-effectiveness of gene therapy in different countries

and identify challenges; and real-time feedback mechanisms for immediate stakeholder input on guideline implementation and impact.

- To facilitate implementation for an international and diverse audience of healthcare providers, PwH, caregivers, payors and advocates, implementation tools will be developed and posted on the WFH guidelines hub (https://guidelines.wfh.org). Synchronous and asynchronous educational materials and in-person and virtual educational opportunities will be made available for all parties of interest. Language translations of written materials will also be provided.

7.3 | Areas Requiring More Research

- The panelists identified several areas requiring more research, which are summarized in Table 11.

8 | Methodology

8.1 | Trustworthy Consensus-Based Statement Process

Developing treatment guidelines for emerging therapies, like gene therapy in haemophilia, is limited by a small and evolving evidence base, as well as a lack of real-world and long-term data. Despite these limitations, it is still essential to provide healthcare providers and patients with evidence-based and trusted guidance to help them make well informed decisions [113]. This requires a rigorous systematic review of the literature, along with careful evaluation of the relevant evidence and consensus among the panel on its interpretation [113–115]. Therefore, these guidelines for the management of haemophilia A and B with AAV gene therapy were developed using a dual approach that combined a rigorous assessment of the evidence with Trustworthy Consensus-Based Statement (TCBS) methodology, resulting in unbiased, scientifically valid and trustworthy guidance that meets international standards of guideline development [1].

In 2020, the World Federation of Hemophilia (WFH) published the third edition of the WFH Guidelines for the Management of Hemophilia, which also utilized a dual evidence-based and TCBS approach. This dual approach ensures the development of scientifically robust and trustworthy recommendations through a transparent process that integrates systematically identified evidence and expert clinical insights from a diverse panel of experts [116]. The TCBS process complies with the standards set by the Institute of Medicine/National Academy of Medicine (IOM/NAM) [115, 117]. The WFH collaborated with EBQ Consulting to develop these guidelines, ensuring they meet current standards.

Further details on the methodology can be found in the original manuscript [1]. The methodology for these guidelines, including the systematic literature review, was established a priori. This study protocol was not pre-registered. The development of this manuscript adhered to the reporting standards outlined in the AGREE Checklist (Appendix 4) for guidelines and the ACCORD Checklist (Appendix 5) for consensus methods.

As new AAV gene therapy research emerges, clinical practice standards around AAV gene therapies are established, and clinical knowledge advances, the data will become more amenable to quantitative analysis, facilitating more quantitatively driven evidence-based updates.

8.2 | Composition and Function of the Panels

The World Federation of Hemophilia (WFH) established a Steering Committee (SC) and a Guidelines Oversight Committee (GOC) to oversee the guideline development process, establish policies, select panelists and chairs, and address conflict-of-interest management. WFH called for applications and nominations to participate in the guideline panel. The panel members were carefully selected by the GOC to minimize relevant conflicts of interest and represent all appropriate stakeholder perspectives, including haematologists and other members of the healthcare team, PwH, and caregivers. The GOC appointed co-chairs (G.P., E.G.) to oversee the expert panel composed of professionals from various healthcare disciplines alongside a broad representation of patients with haemophilia (PwH) and caregivers. The final panel included 38 individuals, reflecting a diverse range of demographics, geographic locations, clinical specialties and socioeconomic contexts. Meetings were conducted via videoconferences. All panel members participated as volunteers and were not remunerated for their time.

8.2.1 | Conflicts of Interest

Forms were completed by all panel members prior to the start of the guidelines process. All COIs were assessed by WFH staff, guideline consultants and the GOC in accordance with the WFH Policy on Conflicts of Interest for Guideline Panels (Appendix 6). The GOC approved all panelists, and those with primary conflicts in accordance with management terms specified in the WFH COI policy.

Strategies for managing COIs included rules on panel composition and individual member restrictions. The composition of the working panel required at least one chair to have no COIs, and for most members to be free from primary COIs. These criteria were met, with 14/38 (37%) of the panel having primary COIs, 20/38 (53%) having secondary COIs and 4/38 (11%) with no COIs. Panelists with primary COI were excluded from drafting and voting on recommendations in the sections of the guidelines that were relevant to their conflicts. As a result, panelists with primary COIs did not draft or vote on recommendations in Sections 3–5 of the guidelines. Additionally, one member divested a conflicting financial COI prior to starting work on the guidelines.

8.2.2 | Process for Panel Workflow

The expert panel was divided into two workgroups: Workgroup 1 (chaired by E.G.) addressed all steps prior to and including gene therapy treatments, and Workgroup 2 (chaired by G.P.) addressed follow-up care and management. Each workgroup was further divided into smaller subgroups, each led by a designated panel member who facilitated the discussion and ensured that all perspectives were considered. The subgroups and their designated leads are available in Appendix 1.

Each subgroup drafted initial recommendations, which underwent multiple rounds of review and revision by the subgroup until deemed accurate and comprehensive. These recommendations were formulated based on the evidence summaries from the included studies, considering the benefits and harms, alongside the collective experience and expertise of the panelists. Additional remarks were added to each recommendation to provide clarity and/or supplementary details. These remarks are integral components of the recommendations and are therefore included as part of the recommendation.

These recommendations were intentionally not graded because of the limited availability of robust evidence in the field, which is a result of the challenges in conducting clinical research and data collection in rare diseases. Instead, they were clearly identified as "CB" (consensus-based) to denote their derivation from expert consensus. This approach was chosen to maintain transparency in the guideline development process.

8.3 | Evidence Generation and Development of Evidence Summaries

The co-chairs and panelists formulated clinical questions, which were structured using the populations/interventions/comparators/outcomes (PICO) framework. This framework served as the foundation for the search strategies employed in our guideline development. The specific PICO questions used in this process are detailed in Appendix 7.

A comprehensive and systematic literature search was designed, peer-reviewed and conducted across PubMed, Embase and the Cochrane Library from 1 January 2005 to 5 June 2023, with an update performed on 1 May 2024 and 25 November 2024. The detailed search strategies and limits are provided in the accompanying supplement publication (Appendix 8). The initial searches yielded a total of 3919 deduplicated studies, with an additional 918 articles identified in the second round and 233 articles in the third round. The inclusion criteria for the literature search were clinical trials (both randomized and non-randomized), review articles, systematic reviews, meta-analyses and guidelines, with no exclusions based on geography or language. Case series and case reports were included solely to assess safety issues. Exclusion criteria included letters to the editor, conference abstracts, conference reviews, editorials and registry data.

Title and abstract screening, followed by full-text screening, were conducted independently and in duplicate, with any discrepancies resolved through discussion. The results of the search and screening process are summarized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (Appendix 9). Our systematic literature search resulted in 71 studies that met our inclusion criteria.

Trained methodologists conducted data extraction independently and in duplicate, with any discrepancies resolved through discussion. No formal quantitative analyses were performed, and individual study quality was critically assessed using the Newcastle–Ottawa scale (NOS), risk of bias in non-randomized studies of interventions (ROBINS-I), or a measurement tool to assess systematic reviews 2 (AMSTAR 2) for studies that reported efficacy or safety results. Data extraction results are available in Appendix 10. Qualitative evidence summaries were developed and used by the expert panels when developing the recommendations (Appendix 11).

During the initial review stage of this manuscript, Pfizer announced they would cease further development and commercialization activities for fidanacogene eleparvovec. Upon recommendation of the reviewers, and agreement by the expert panel, all background specific to fidanacogene eleparvovec was removed prior to publication and all recommendations were reviewed.

8.4 | Formal Consensus Through mDelphi

A modified Delphi (mDelphi) approach was employed as a robust and transparent method to achieve consensus [118, 119]. A schedule of the mDelphi process is provided in Appendix 12. Prior to the mDelphi process, the entire panel convened via teleconferences to collectively review the evidence and receive instructions on the Delphi process. To mitigate group interaction bias, panelists refrained from discussing drafted recommendations during these sessions.

Up to three rounds of Delphi surveys were permitted to reach consensus, with all panelists encouraged to express their opinions and reminded of the voting instructions during each round. A minimum response rate of 85% for each survey round was required, with an 80% threshold of voters indicating agreement or strong agreement necessary to achieve consensus. The modified Delphi surveys were conducted via SurveyMonkey, with all responses remaining anonymous except to the independent administrator responsible for overseeing the process. Additionally, PwH who did not feel comfortable voting on recommendations outside their expertise were allowed to abstain by voting neutral and indicating 'No experience in this area' in the comments section, ensuring their neutral vote was not included in the denominator during vote tabulation.

Recommendations that did not reach consensus or required significant changes based on the respondent comments were modified based on the feedback to enhance clarity. Recommendations achieving consensus and not requiring changes in the first round were not revoted in the subsequent rounds.

Consensus was achieved after two rounds of voting, and no recommendations failed to achieve consensus. After internal manuscript review, the expert panel identified two recommendations that required modification; these were sent back for a third round of mDelphi voting. After the formal peer-review process, 16 recommendations required an additional round of Delphi. The GOC did not influence recommendations made by the panel and did not engage in the mDelphi voting. Participation rates are provided in Appendix 12. Survey tallies of the consensus of each recommendation are available upon request.

8.5 | Manuscript Development and Review

The final manuscript underwent a comprehensive review process involving panelists, chairs, WFH staff, consultants and external reviewers. Additionally, the guideline was submitted to multiple organizations for their review and potential endorsement. To maintain the integrity of the TCBS process, any suggested changes to recommendations were sent back to the guidelines panel for discussion, and if necessary and in the case of two recommendations, for a third round of mDelphi voting.

8.6 | Future Methods: The Living Guidelines Model

The traditional approach to guideline development can be time-consuming and sporadic. The WFH first created its clinical practice guidelines in 2005 [120], updated them in 2013 [121], and again in 2020 [1]. The guidelines often take several years to complete, and coupled with the sporadic publication, can result in recommendations that are out of date before they are published and remain out of date for years. Living guidelines begin with a living systematic review that is continually updated to incorporate the relevant new evidence. The Living Guidelines Model (LGM) uses standard methods for systematic literature review, but with an increased frequency for the search and synthesis [122, 123]. Guidelines panels then meet to discuss the new evidence and whether it merits a change to any of the existing recommendations. Living guidelines have been adopted across a range of therapeutic areas, including common diseases like stroke [124] and rare diseases like rheumatoid arthritis [125] and stage IV non–small cell lung cancer [126].

This guideline will be updated following the Living Guidelines Model because it fits the following criteria: (1) the recommendations are a priority for decision-making; (2) the recommendations are likely to change as new evidence, practices or interventions emerge; and (3) the research evidence base is evolving [122, 123, 127]. Criteria that trigger a systematic literature review and updated recommendations will be defined in a future methodology publication on the WFH LGM. Briefly, in the event of new evidence identified through informal literature review or regularly scheduled systematic literature reviews, the applicable panel will meet to discuss the evidence and whether recommendations should be updated. In the event of a safety issue, the systematic literature review and update timeline will be moved up and expedited. Updates will be announced in *Haemophilia* if existing evidence warrants a new recommendation or change in an existing recommendation based on specific criteria. Oversight of the living guidelines will be managed by the WFH Guidelines Steering Committee, GOC, panel co-chairs, WFH staff and guideline methodology consultants tasked with continuous literature monitoring, existing recommendation review, new topic consideration, prioritization and coordination with the guideline panel.

PUBLIC COMMENT: Public comments on all WFH guidelines will be solicited on the WFH Guidelines Resource Hub, allowing stakeholders to provide feedback. To ensure transparency, the WFH will publish all comments on the WFH Guidelines Resource Hub and will respond to comments publicly.

9 | Author Contributions, Acknowledgements, Disclosure, and Funding

9.1 | Author Contributions

- All authors provided final approval of the submitted version.

9.1.1 | Panelists Main Authors

- Emna Gouider and Glenn F. Pierce served as co-chairs for the overall guidelines project. They made substantial contributions to the conception, organization of the panel and subgroups, and methodology.
- Other expert panelists who are included as authors contributed to writing and reviewing the manuscript and voted in the mDelphi process:
  - Marlene Beijlevelt, Rose Bender, Manuel Carcao, Amy L. Dunn, Enrico Ferri Grazzi, Graham R. Foster, Julie Frantsve-Hawley, Alfonso Iorio, Shannon Jackson, Radoslaw Kaczmarek, Barbara A. Konkle, Magdalena Lewandowska, Johnny Mahlangu, Wolfgang Miesbach, Brian O'Mahony, Margareth C. Ozelo, Steven Pipe, Ulrike M. Reiss and Amy K. Wilson.
  - All other panelists are included as authors and listed as a part of the Guidelines Expert Panel (Appendix 1).

9.1.2 | Other Main Authors

- The following authors served as consultants or staff and did not vote in the Delphi Process:
  - Donna Coffin provided overall management of the guideline development.
  - Julie Frantsve-Hawley served as the methodology consultant, facilitated discussions and contributed the first draft of the methods section.
  - Gwendolyn E. Kaeser served as the primary medical writer and contributed the first draft of the background information, facilitated discussions, and managed all author comments.

9.2 | Acknowledgements

- The WFH would like to thank the following for their participation in this guideline development process:
  - The WFH AAV Gene Therapy Expert Panelists for their commitment to the lengthy development process and to the bleeding disorders community.
  - The WFH Staff and team of professionals led by Donna Coffin, WFH Director of Data and Research, towards the development and completion of these guidelines.
    - WFH Staff: Mona Mayla, Sarah Clairmont, Debbie Hum and Mélanie Bédard
    - Literature Search: Maura Sostack
    - Literature Screeners and Data Extractors: Sonya Egodage, Zuleika Aponte, Rodin El Hachache, Erin Murray, Sheena Patel, Amy Shim, Aeneas Schofield and Ryan Staples
    - mDelphi Administrator: Melanie Golob
    - Methodologists: Tom Schofield & Sandra Zelman Lewis
  - WFH Guidelines Steering Committee: Alain Baumann, Donna Coffin, Amy Dunn, Emna Gouider, Cedric Hermans, Magdalena Lewandowska, Johnny Mahlangu, Margareth C. Ozelo and Glenn F. Pierce
  - Guidelines Oversight Committee: Enrique David Preza Hernandez, Kate Khair, Mark Skinner, Clive Smith and Sandra Zelman Lewis
  - WFH Executive reviewers: Alain Baumann, Emna Gouider and Glenn F. Pierce
  - External Reviewers: David Page, Maria Elisa Mancuso and William McKeown

9.3 | Author Disclosures

Author	Declaration of Interest
Marlene Beijlevelt	None
Rose Bender	None
Manuel Carcao	M.C. has received research support from Novartis, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda; honoraria for speaking/participating in advisory boards from Bayer, LFB, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda.
Donna Coffin	None
Amy Dunn	A.D. has acted as a paid consultant for Hema Biologics, BioMarin and CSL Behring. Her institution receives research funding from BioMarin, Regeneron, Takeda, Sanofi, Spark, Novo Nordisk and ATHN. She is on the board of Cascade, the National Bleeding Disorders Foundation (NBDF) and the World Federation of Hemophilia (WFH)-USA. She has received travel support from the NBDF, WFH, BioMarin and Hema Biologics.
Enrico Ferri Grazzi	E.F.G. Serves on Advisory Boards for Pfizer, BioMarin, and SOBI, Patient Councils for BioMarin, SOBI, Novo Nordisk, Roche and Bayer; and has been a speaker for BioMarin, SOBI, Novo Nordisk, Bayer, Takeda, CSL Behring and Roche.
Graham R. Foster	G.R.F. has acted as a paid consultant and received speaker fees from AbbVie, GSK, Gilead, BioMarin, CSL Behring and Pfizer.
Julie Frantsve-Hawley	J.F.H. is a paid consultant with EBQ Consulting, an organization that WFH contracted to provide guidance and oversight of the development of this guideline.
Emna Gouider	E.G. has received speaker fees from Octapharma, Amanys, Roche, CSL Behring and Kedrion-BPL as well as fees for a clinical trial from Octapharma and Roche.
Alfonso Iorio	A.I.'s Institution, McMaster University, has received funds for research or consultancy services from Bayer, CSL, Pfizer, Sanofi, Sobi, Takeda and Roche
Shannon Jackson	S.J. has received speaker fees from Sanofi and Bayer, and is on the advisory board for Pfizer Global, Pfizer Canada, Roche Canada, Bayer Canada and Takeda Canada
Radoslaw Kaczmarek	R.K. has received research funding from Bayer and consulting or lecture fees from Bayer, BioMarin, Spark, Novo Nordisk and Pfizer.
Gwendolyn E. Kaeser	G.E.K. is a paid consultant for WFH.
Barbara A. Konkle	B.A.K. has acted as a paid consultant for Be Biopharma, BioMarin, HC Bioscience, Novo Nordisk, Octapharma, Pfizer, Regeneron, Sanofi, Spark and Veralox and has received research funding from CSL Behring, Pfizer, Spark, Takeda and Sanofi.
Magdalena Lewandowska	M.L. has served on the advisory boards for HEMA Biologics and Agios and has received compensation (granted to her institution) for consulting or speaking from Alnylam, BPL, Pfizer and Roche.

(Continues)

Author	Declaration of Interest
Johnny Mahlangu	J.M. has received research grant/research support from BioMarin, Catalyst Biosciences, CSL, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, uniQure; has been a consultant/scientific board for BioMarin, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche, Takeda, Sanofi and Spark; and has received speaker bureau from ISTH, Novo Nordisk, Pfizer, Roche, Sanofi, Takeda and WFH.
Wolfgang Miesbach	W.M. is a paid consultant for Bayer, BioMarin, Biotest, Chugai, CSL Behring, Freeline, LFB, Novo Nordisk, Octapharma Pfizer, Regeneron, Sanofi, Sobi, Takeda and uniQure. He has received funding for research from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Takeda and Shire.
Brian O'Mahony	B.O. has served on advisory boards for BioMarin, CSL Behring and Roche. All compensation went directly to his organization.
Margareth C. Ozelo	M.C.O. has received investigator-initiated grant funding from BioMarin, Pfizer, Roche and Takeda; research support from Bayer, BioMarin, Novo Nordisk, Pfizer, Roche, Sanofi and Takeda; and has participated in advisory boards for Bayer, BioMarin, Pfizer, Roche, Sanofi and Takeda.
Glenn F. Pierce	G.F.P. has served as a paid consultant for BioMarin, Novo Nordisk, Regeneron, Genetech-Roche, Sanofi, Spark Therapeutics, St. Jude Children's Hospital and Third Rock Ventures; advisory boards for Be Bio, Frontera, HC Bio, Metagenomi, US National Bleeding Disorders Foundation Medical and Scientific Advisory Council (NBDF MASAC), and the ISTH Gene Therapy Working Group; and director of WFH and Voyager Therapeutics.
Steven W. Pipe	S.W.P. has served as a consultant to Centessa, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, LFB, Metagenomi, Novo Nordisk, Pfizer, Poseida Therapeutics, Precision Bioscience, Regeneron, Roche/Genetech, Sanofi and Takeda; has received Research funding from Siemens and YewSawin; and serves on Scientific Advisory Boards for Equilibra Bioscience and GeneVentiv.
Ulrike M. Reiss	None
Amy K. Wilson	None

9.4 | Funding

Funding for these guidelines was provided by the Indiana Hemophilia & Thrombosis Center and the National Bleeding Disorders Foundation.

9.5 | Ethics Statement

This guideline was developed using the Trustworthy Consensus-Based Statement (TCBS) process for guideline development.

9.6 | Data Availability Statement

The data that were generated during the systematic literature review are available in the supplementary material of this article.

10 | References

1. A. Srivastava, E. Santagostino, A. Dougall, et al., "WFH Guidelines for the Management of Hemophilia," *Haemophilia* 26, no. S6 (2020): 1–158.

2. J. Windyga, S. Apte, M. Frei-Jones, et al., "Disease and Treatment Burden of Patients With Haemophilia Entering the explorer6 Non-Interventional Study," *European Journal of Haematology* 113, no. 5 (2024): 631–640.

3. W. Miesbach, P. Chowdary, M. Coppens, et al., "Delivery of AAV-Based Gene Therapy Through Haemophilia Centres-A Need for Re-Evaluation of Infrastructure and Comprehensive Care: A Joint Publication of EAHAD and EHC," *Haemophilia* 27, no. 6 (2021): 967–973.

4. W. Miesbach, K. J. Pasi, S. W. Pipe, et al., "Evolution of Haemophilia Integrated Care in the Era of Gene Therapy: Treatment Centre's Readiness in United States and EU," *Haemophilia* 27, no. 4 (2021): 511–514.

5. W. Miesbach, P. Batty, P. Chowdary, et al., "Adeno-Associated Virus-Based Gene Therapy for Hemophilia-Addressing the Gaps," *Research and Practice in Thrombosis and Haemostasis* 9, no. 1 (2025): 102673.

6. BioMarin Pharmaceutical Inc. ROCTAVIAN (valoctocogene roxaparvovec-rvox) [product information]. European Medicines Agency, https://www.ema.europa.eu/en/medicines/human/EPAR/roctavian. Revised June 2022.

7. CSL Behring. HEMGENIX (etranacogene dezaparvovec-drlb) [product information]. European Medicines Agency, https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix. Revised February 2023.

8. Pfizer Inc. BEQVEZ (fidanacogene elaparvovec-dzkt) [package insert]. European Medicines Agency, https://www.ema.europa.eu/en/medicines/human/EPAR/beqvez. Revised October 2024.

9. CSL Behring. HEMGENIX (etranacogene dezaparvovec-drlb) [package insert]. U.S. Food and Drug Administration, https://www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix. Revised November 2022.

10. Pfizer Inc. BEQVEZ (fidanacogene elaparvovec-dzkt) [package insert]. U.S. Food and Drug Administration, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/beqvez. Revised April 2024.

11. BioMarin Pharmaceutical Inc. ROCTAVIAN (valoctocogene roxaparvovec-rvox) [package insert]. U.S. Food and Drug Administration, https://www.fda.gov/vaccines-blood-biologics/roctavian. Revised June 2023.

12. L. A. George, S. K. Sullivan, A. Giermasz, et al., "Hemophilia B Gene Therapy With a High-Specific-Activity Factor IX Variant," *New England Journal of Medicine* 377, no. 23 (2017): 2215–2227.

13. A. Cuker, K. Kavakli, L. Frenzel, et al., "Gene Therapy With Fidanacogene Elaparvovec in Adults With Hemophilia B," *New England Journal of Medicine* 391, no. 12 (2024): 1108–1118.

14. Pfizer Discontinues Hemophilia Treatment Beqvez, Emptying Its Gene Therapy Portfolio [press release]. Fierce Pharma, February 21, 2025.

15. S. Rangarajan, L. Walsh, W. Lester, et al., "AAV5-Factor VIII Gene Transfer in Severe Hemophilia A," *New England Journal of Medicine* 377, no. 26 (2017): 2519–2530.

16. K. J. Pasi, S. Rangarajan, N. Mitchell, et al., "Multiyear Follow-Up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A," *New England Journal of Medicine* 382, no. 1 (2020): 29–40.

17. K. J. Pasi, M. Laffan, S. Rangarajan, et al., "Persistence of Haemostatic Response Following Gene Therapy With Valoctocogene Roxaparvovec in Severe Haemophilia A," *Haemophilia* 27, no. 6 (2021): 947–956.

18. E. Symington, S. Rangarajan, W. Lester, et al., "Long-Term Safety and Efficacy Outcomes of Valoctocogene Roxaparvovec Gene Transfer Up to 6 Years Post-Treatment," *Haemophilia* 30, no. 2 (2024): 320–330.

19. E. Symington, S. Rangarajan, W. Lester, et al., "Valoctocogene Roxaparvovec Gene Therapy Provides Durable Haemostatic Control for Up to 7 Years for Haemophilia A," *Haemophilia* 30, no. 5 (2024): 1138–1147.

20. M. C. Ozelo, J. Mahlangu, K. J. Pasi, et al., "Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A," *New England Journal of Medicine* 386, no. 11 (2022): 1013–1025.

21. J. Mahlangu, R. Kaczmarek, A. von Drygalski, et al., "Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A," *New England Journal of Medicine* 388, no. 8 (2023): 694–705.

22. B. Madan, M. C. Ozelo, P. Raheja, et al., "Three-Year Outcomes of Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A," *Journal of Thrombosis and Haemostasis* 22, no. 7 (2024): 1880–1893.

23. A. D. Leavitt, J. Mahlangu, P. Raheja, et al., "Efficacy, Safety, and Quality of Life 4 Years After Valoctocogene Roxaparvovec Gene Transfer for Severe Hemophilia A in the Phase 3 GENEr8-1 Trial," *Research and Practice in Thrombosis and Haemostasis* 8, no. 8 (2024): 102615.

24. A. Von Drygalski, A. Giermasz, G. Castaman, et al., "Etranacogene Dezaparvovec (AMT-061 phase 2b): Normal/Near Normal FIX Activity and Bleed Cessation in Hemophilia B," *Blood Advances* 3, no. 21 (2019): 3241–3247.

25. A. von Drygalski, E. Gomez, A. Giermasz, et al., "Stable and Durable Factor IX Levels in Patients With Hemophilia B Over 3 Years After Etranacogene Dezaparvovec Gene Therapy," *Blood Advances* 7, no. 19 (2023): 5671–5679.

26. S. W. Pipe, F. W. G. Leebeek, M. Recht, et al., "Gene Therapy With Etranacogene Dezaparvovec for Hemophilia B," *New England Journal of Medicine* 388, no. 8 (2023): 706–718.

27. M. Coppens, S. W. Pipe, W. Miesbach, et al., "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," *Lancet Haematology* 11, no. 4 (2024): e265–e275.

28. J. Astermark, T. W. Buckner, L. Frenzel, et al., "Matching-Adjusted Indirect Comparison of Bleeding Outcomes in Severe Haemophilia A: Comparing Valoctocogene Roxaparvovec Gene Therapy, Emicizumab Prophylaxis, and FVIII Replacement Prophylaxis," *Haemophilia* 29, no. 4 (2023): 1087–1094.

29. E. Aradom and K. Gomez, "The Patient Gene Therapy Journey: Findings From Qualitative Interviews With Trial Participants at One UK Haemophilia Centre," *Journal of Haemophilia Practice* 8, no. 1 (2021): 32–44.

30. J. Quinn, K. A. Delaney, W. Y. Wong, W. Miesbach, and M. Bullinger, "Psychometric Validation of the Haemo-QOL-A in Participants With Hemophilia A Treated With Gene Therapy," *Patient Related Outcome Measures* 13 (2022): 169–180.

31. W. Miesbach and R. Klamroth, "The Patient Experience of Gene Therapy for Hemophilia: Qualitative Interviews With Trial Patients," *Patient Preference and Adherence* 14 (2020): 767–770.

32. S. Fletcher, K. Jenner, L. Pembroke, M. Holland, and K. Khair, "The Experiences of People With Haemophilia and Their Families of Gene Therapy in a Clinical Trial Setting: Regaining Control, the Exigency Study," *Orphanet Journal of Rare Diseases* 17, no. 1 (2022): 155.

33. R. Itzler, T. W. Buckner, F. W. G. Leebeek, et al., "Effect of Etranacogene Dezaparvovec on Quality of Life for Severe and Moderately Severe Haemophilia B Participants: Results From the Phase III HOPE-B Trial 2 Years After Gene Therapy," *Haemophilia* 30, no. 3 (2024): 709–719.

34. B. O'Mahony, A. L. Dunn, A. D. Leavitt, et al., "Health-Related Quality of Life Following Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A in the Phase 3 Trial GENEr8-1," *Journal of Thrombosis and Haemostasis* 21, no. 12 (2023): 3450–3462.

35. A. Boban, F. Baghaei, F. Karin, et al., "Accreditation Model of European Haemophilia Centres in the Era of Novel Treatments and Gene Therapy," *Haemophilia* 29, no. 6 (2023): 1442–1449.

36. W. Miesbach, B. Konkle, P. Chowdary, et al., "Recommendations for a Minimum Data Set for Monitoring Gene Therapy in Hemophilia: Communication From the ISTH SSC Working Group on Gene Therapy," *Journal of Thrombosis and Haemostasis* 22, no. 5 (2024): 1510–1515.

37. W. Miesbach, A. Boban, P. Chowdary, et al., "Administration of Gene Therapy for Haemophilia—The Hub and Spoke Model and Its Regional Differences and Challenges," *Haemophilia* 30, no. 3 (2024): 855–857.

38. S. Pipe, K. Douglas, N. Hwang, G. Young, P. Patel, and P. Fogarty, "Delivery of Gene Therapy in Haemophilia Treatment Centres in the United States: Practical Aspects of Preparedness and Implementation," *Haemophilia* 29, no. 6 (2023): 1430–1441.

39. National Bleeding Disorders Foundation. MASAC Recommendations on Hemophilia Treatment Center Preparedness for Delivering Gene Therapy for Hemophilia. 2023 (MASAC Document #282).

40. P. Chowdary, B. Duran, P. Batty, et al., "UKHCDO Gene Therapy Taskforce: Guidance for Implementation of Haemophilia Gene Therapy Into Routine Clinical Practice for Adults," *Haemophilia* 31, no. 1 (2025): 26–38.

41. W. Miesbach, J. Oldenburg, R. Klamroth, et al., "Gene Therapy of Hemophilia: Recommendations From the German, Austrian, and Swiss Society for Thrombosis and Haemostasis Research (GTH) [in German]," *Hamostaseologie* 43, no. 3 (2023): 196–207.

42. H. Abdulla Alzahrani, A. Warsi, A. Mullah-Ali, et al., "Consensus-Based Expert Recommendations on the Management of Hemophilia A in the Gulf Region," *Acta Haematologica* 148, no. 1 (2025): 91–104.

43. J. Astermark, F. Baghaei, K. Strandberg, et al., "Infrastructural Considerations of Implementing Gene Therapy for Hemophilia in the Nordic Context," *Therapeutic Advances in Hematology* 14 (2023): 20406207231202306.

44. G. Castaman, C. Carulli, R. De Cristofaro, et al., "Laying the Foundations for Gene Therapy in Italy for Patients With Haemophilia A: A Delphi Consensus Study," *Haemophilia* 29, no. 2 (2023): 435–444.

45. S. Stanford, R. Pink, D. Creagh, et al., "Adenovirus-Associated Antibodies in UK Cohort of Hemophilia Patients: A Seroprevalence Study of the Presence of Adenovirus-Associated Virus Vector-Serotypes AAV5 and AAV8 Neutralizing Activity and Antibodies in Patients With Hemophilia A," *Research and Practice in Thrombosis and Haemostasis* 3, no. 2 (2019): 261–267.

46. B. A. Konkle, D. Coffin, G. F. Pierce, et al., "World Federation of Hemophilia Gene Therapy Registry," *Haemophilia* 26, no. 4 (2020): 563–564.

47. B. A. Konkle, M. Recht, A. Hilger, and P. Marks, "The Critical Need for Postmarketing Surveillance in Gene Therapy for Haemophilia," *Haemophilia* 27, no. S3 (2021): 126–131.

48. G. F. Pierce, S. Fong, B. R. Long, and R. Kaczmarek, "Deciphering Conundrums of Adeno-Associated Virus Liver-Directed Gene Therapy: Focus on Hemophilia," *Journal of Thrombosis and Haemostasis* 22, no. 5 (2024): 1263–1289.

49. B. Konkle, G. Pierce, D. Coffin, et al., "Core Data Set on Safety, Efficacy, and Durability of Hemophilia Gene Therapy for a Global Registry: Communication From the SSC of the ISTH," *Journal of Thrombosis and Haemostasis* 18, no. 11 (2020): 3074–3077.

50. European Medicines Agency. Letter of Support for World Federation of Hemophilia (WFH) Gene Therapy Registry (GTR). 2023; Accessed October 23, 2023, https://www.ema.europa.eu/en/documents/leaflet/letter-support-world-federation-hemophilia-wfh-gene-therapy-registry-gtr_en.pdf.

51. B. A. Konkle, F. Peyvandi, D. Coffin, et al., "Landmark Endorsement of a Global Registry: The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Publicly Endorses World Federation of Hemophilia Gene Therapy Registry as Global Standard," *Haemophilia* 30, no. 1 (2024): 232–235.

52. M. Wang, C. Negrier, F. Driessler, C. Goodman, and M. W. Skinner, "The Hemophilia Gene Therapy Patient Journey: Questions and Answers for Shared Decision-Making," *Patient Preference and Adherence* 16 (2022): 1439–1447.

53. J. Limjoco and C. D. Thornburg, "Gene Therapy for Hemophilia A: A Mixed Methods Study of Patient Preferences and Shared Decision-Making," *Patient Preference and Adherence* 17 (2023): 1093–1105.

54. C. Hermans, D. Noone, G. Benson, et al., "Hemophilia Treatment in 2021: Choosing the "Optimal" Treatment Using an Integrative, Patient-Oriented Approach to Shared Decision-Making Between Patients and Clinicians," *Blood Reviews* 52 (2022): 100890.

55. D. Coffin, M. W. Skinner, C. D. Thornburg, et al., "Development of the World Federation of Hemophilia Shared Decision-Making Tool," *Haemophilia* 30, no. 6 (2024): 1298–1308.

56. J. Limjoco and C. D. Thornburg, "Development of a Haemophilia A Gene Therapy Shared Decision-Making Tool for Clinicians," *Haemophilia* 29, no. 5 (2023): 1184–1190.

57. The SHARE Approach. 2014, https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html.

58. Shared decision making. Accessed September 23, 2024, https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/shared-decision-making.

59. Ottawa Personal Decision Guides. 2015, https://decisionaid.ohri.ca/decguide.html.

60. G. Pietu, N. Giraud, V. Chamouard, G. Duport, A. Lienhart, and Y. Dargaud, "Perspectives and Perception of Haemophilia Gene Therapy by French Patients," *Haemophilia* 30, no. 1 (2024): 68–74.

61. D. P. Hart, B. R. Branchford, S. Hendry, et al., "Optimizing Language for Effective Communication of Gene Therapy Concepts With Hemophilia Patients: A Qualitative Study," *Orphanet Journal of Rare Diseases* 16, no. 1 (2021): 189.

62. W. Miesbach, G. Mulders, D. Breederveld, K. Pinachyan, S. Le Quellec, and I. Pabinger, "A 360-Degree Perspective on Adeno-Associated Virus (AAV)-Based Gene Therapy for Haemophilia: Insights From the Physician, the Nurse and the Patient," *Orphanet Journal of Rare Diseases* 19, no. 1 (2024): 193.

63. I. Cutica, M. Mortarino, I. Garagiola, G. Pravettoni, and F. Peyvandi, "Knowledge and Attitudes Toward Gene Therapy of a Cohort of Italian Patients With Hemophilia," *Journal of Thrombosis and Haemostasis* 22, no. 4 (2024): 1001–1008.

64. E. Krumb, C. Lambert, and C. Hermans, "Patient Selection for Hemophilia Gene Therapy: Real-Life Data From a Single Center," *Research and Practice in Thrombosis and Haemostasis* 5, no. 3 (2021): 390–394.

65. A. Paneda, L. Vanrell, I. Mauleon, et al., "Effect of Adeno-Associated Virus Serotype and Genomic Structure on Liver Transduction and Biodistribution in Mice of Both Genders," *Human Gene Therapy* 20, no. 8 (2009): 908–917.

66. A. M. Davidoff, C. Y. Ng, J. Zhou, Y. Spence, and A. C. Nathwani, "Sex Significantly Influences Transduction of Murine Liver by Recombinant Adeno-Associated Viral Vectors Through an Androgen-Dependent Pathway," *Blood* 102, no. 2 (2003): 480–488.

67. M. V. Ragni, E. Majerus, S. Fong, et al., "Valoctocogene Roxaparvovec Gene Transfer in Participants With HIV," *Blood Advances* 7, no. 8 (2023): 1525–1530.

68. A. Majowicz, B. Nijmeijer, M. H. Lampen, et al., "Therapeutic hFIX Activity Achieved After Single AAV5-hFIX Treatment in Hemophilia B Patients and NHPs With Pre-Existing Anti-AAV5 NABs," *Molecular Therapy Methods and Clinical Development* 14 (2019): 27–36.

69. NCT06003387. Efficacy and Safety of CSL222 (Etranacogene Dezaparvovec) Gene Therapy in Adults With Hemophilia B With Pretreatment Adeno-Associated Virus Serotype 5 (AAV5) Neutralizing Antibodies (Nabs).

70. NCT03520712. Gene Therapy Study in Severe Hemophilia A Patients With Antibodies Against AAV5 (GENEr8-AAV5+).

71. R. Klamroth, G. Hayes, T. Andreeva, et al., "Global Seroprevalence of Pre-Existing Immunity Against AAV5 and Other AAV Serotypes in People With Hemophilia A," *Human Gene Therapy* 33, no. 7-8 (2022): 432–441.

72. I. Pabinger, M. Ayash-Rashkovsky, M. Escobar, et al., "Multicenter Assessment and Longitudinal Study of the Prevalence of Antibodies and Related Adaptive Immune Responses to AAV in Adult Males With Hemophilia," *Gene Therapy* 31, no. 5-6 (2024): 273–284.

73. NCT04684940. Safety, Tolerability, and Efficacy Study of Valoctocogene Roxaparvovec in Hemophilia A With Active or Prior Inhibitors (GENEr8-INH).

74. C. Santoro, G. Quintavalle, G. Castaman, et al., "Inhibitors in Hemophilia B," *Seminars in Thrombosis and Hemostasis* 44, no. 6 (2018): 578–589.

75. M. V. Ragni, H. Mead, Y. P. de Jong, et al., "Optimizing Liver Health Before and After Gene Therapy for Hemophilia A," *Blood Advances* 8, no. 19 (2024): 5203–5212.

76. W. Miesbach, G. R. Foster, and F. Peyvandi, "Liver-Related Aspects of Gene Therapy for Hemophilia: Need for Collaborations With Hepatologists," *Journal of Thrombosis and Haemostasis* 21, no. 2 (2023): 200–203.

77. A. Maina and G. R. Foster, "Hepatitis After Gene Therapy, What Are the Possible Causes?," *Journal of Viral Hepatitis* 31, no. S1 (2024): 14–20.

78. V. La Mura, M. Colombo, and G. R. Foster, "The Management of Liver Disease in People With Congenital Bleeding Disorders: Guidance From European Association for Haemophilia and Allied Disorders, European Haemophilia Consortium, ISTH, and World Federation of Hemophilia," *Journal of Thrombosis and Haemostasis* 22, no. 12 (2024): 3629–3639.

79. N. A. Terrault, A. S. F. Lok, B. J. McMahon, et al., "Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance," *Hepatology* 67, no. 4 (2018): 1560–1599.

80. D. Bhattacharya, A. Aronsohn, J. Price, V. Lo Re, and A.-I. Panel, "Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection," *Clinical Infectious Diseases* (2023), https://pubmed.ncbi.nlm.nih.gov/37229695/.

81. C. S. Manno, G. F. Pierce, V. R. Arruda, et al., "Successful Transduction of Liver in Hemophilia by AAV-Factor IX and Limitations Imposed by the Host Immune Response," *Nature Medicine* 12, no. 3 (2006): 342–347.

82. A. C. Nathwani, U. M. Reiss, E. G. Tuddenham, et al., "Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B," *New England Journal of Medicine* 371, no. 21 (2014): 1994–2004.

83. A. C. Nathwani, E. G. Tuddenham, S. Rangarajan, et al., "Adenovirus-Associated Virus Vector-Mediated Gene Transfer in Hemophilia B," *New England Journal of Medicine* 365, no. 25 (2011): 2357–2365.

84. B. R. Long, T. M. Robinson, J. R. S. Day, et al., "Clinical Immunogenicity Outcomes From GENEr8-1, a Phase 3 Study of Valoctocogene Roxaparvovec, an AAV5-Vectored Gene Therapy for Hemophilia A," *Molecular Therapy* 32, no. 7 (2024): 2052–2063.

85. E. G. D. Tuddenham and G. R. Foster, "The Complex, Confusing and Poorly Understood Immune Responses to AAV-Mediated Gene Transfer in Haemophilia-Is More or Less Immunosuppression Required?," *Journal of Viral Hepatitis* 31, no. S1 (2024): 21–25.

86. NCT04323098. Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Hemophilia A (GENEr8-3).

87. M. C. Ozelo, J. Mason, A. L. Dunn, et al., Safety and Efficacy of Valoctocogene Roxaparvovec With Prophylactic Corticosteroids: 1-Year GENEr8-3 Results. paper presented at 17th Annual Congress of the European Association for Haemophilia and Allied Disorders 2024.

88. Pfizer Inc. Beqvez (Fidanacogene elaparvovec) [product monograph]. Health Canada, https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=103268. Revised December 2023.

89. R. A. Marlar, K. Strandberg, M. Shima, and D. M. Adcock, "Clinical Utility and Impact of the Use of the Chromogenic vs One-Stage Factor Activity Assays in Haemophilia A and B," *European Journal of Haematology* 104, no. 1 (2020): 3–14.

90. K. Gomez, M. Chitlur, and G. panel, "Survey of Laboratory Tests Used in the Diagnosis and Evaluation of Haemophilia A," *Thrombosis and Haemostasis* 109, no. 4 (2013): 738–743.

91. S. Rosen, S. Tiefenbacher, M. Robinson, et al., "Activity of Transgene-Produced B-Domain-Deleted Factor VIII in Human Plasma Following AAV5 Gene Therapy," *Blood* 136, no. 22 (2020): 2524–2534.

92. M. M. Robinson, L. A. George, M. E. Carr, et al., "Factor IX Assay Discrepancies in the Setting of Liver Gene Therapy Using a Hyperfunctional Variant Factor IX-Padua," *Journal of Thrombosis and Haemostasis* 19, no. 5 (2021): 1212–1218.

93. B. R. Long, P. Veron, K. Kuranda, et al., "Early Phase Clinical Immunogenicity of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A," *Molecular Therapy* 29, no. 2 (2021): 597–610.

94. S. Agarwal, C. Hermans, W. Miesbach, et al., "Transitioning From Emicizumab Prophylaxis to Valoctocogene Roxaparvovec Gene Therapy: A Simulation Study for Individuals With Severe Haemophilia A," *Haemophilia* 30, no. 4 (2024): 905–913.

95. R. Klamroth and S. Gottstein, "Transitioning Patients With Severe Haemophilia A From Emicizumab Prophylaxis to Valoctocogene Roxaparvovec Gene Therapy: Real-World Clinical Experience," *Haemophilia* 30, no. 5 (2024): 1247–1249.

96. Y. Dargaud, M. Levrero, F. Bailly, A. Lienhart, and F. Zoulim, "Liver Health in Hemophilia in the Era of Gene Therapy," *Thrombosis Research* 240 (2024): 109064.

97. P. A. Kyrle, E. Minar, M. Hirschl, et al., "High Plasma Levels of Factor VIII and the Risk of Recurrent Venous Thromboembolism," *New England Journal of Medicine* 343, no. 7 (2000): 457–462.

98. A. D. Leavitt, B. A. Konkle, K. C. Stine, et al., "Giroctocogene Fitelparvovec Gene Therapy for Severe Hemophilia A: 104-Week Analysis of the Phase 1/2 Alta Study," *Blood* 143, no. 9 (2024): 796–806.

99. P. Chowdary, S. Shapiro, M. Makris, et al., "Phase 1–2 Trial of AAVS3 Gene Therapy in Patients With Hemophilia B," *New England Journal of Medicine* 387, no. 3 (2022): 237–247.

100. A. Donsante, D. G. Miller, Y. Li, et al., "AAV Vector Integration Sites in Mouse Hepatocellular Carcinoma," *Science* 317, no. 5837 (2007): 477.

101. A. Donsante, C. Vogler, N. Muzyczka, et al., "Observed Incidence of Tumorigenesis in Long-Term Rodent Studies of rAAV Vectors," *Gene Therapy* 8, no. 17 (2001): 1343–1346.

102. R. Ferla, M. Alliegro, M. Dell'Anno, et al., "Low Incidence of Hepatocellular Carcinoma in Mice and Cats Treated With Systemic Adeno-Associated Viral Vectors," *Molecular Therapy Methods and Clinical Development* 20 (2021): 247–257.

103. M. Schmidt GRF, M. Coppens, H. Thomsen, et al., *Liver Safety Case Report From the Phase 3 HOPE-B Gene Therapy Trial in Adults With Hemophilia B. paper presented at Proceedings and Abstracts of the ISTH 2021 Congress* (Philadelphia: International Society on Thrombosis and Haemostasis, 2021).

104. M. Schmidt, G. R. Foster, and M. Coppens, *Liver Safety Case Report From the Phase 3 HOPE-B Gene Therapy Trial in Adults With Hemophilia B. paper presented at Proceedings and Abstracts of the ISTH 2021 Congress* (Philadelphia, 2021).

105. National Bleeding Disorders Foundation. MASAC Recommendations on Screening for Development of Hepatocellular Cancer in Persons With Hepatitis B and C. 2023 (MASAC Document #281).

106. A. G. Singal, J. M. Llovet, M. Yarchoan, et al., "AASLD Practice Guidance on Prevention, Diagnosis, and Treatment of Hepatocellular Carcinoma," *Hepatology* 78, no. 6 (2023): 1922–1965.

107. N. O'Connell, P. van der Valk, and S. Le Quellec, "Invasive Procedures and Surgery Following Etranacogene Dezaparvovec Gene Therapy in People With Hemophilia B," *Journal of Thrombosis and Haemostasis* 23, no. 1 (2025): 73–84.

108. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]* (National Institute of Diabetes and Digestive and Kidney Diseases, 2012), https://www.ncbi.nlm.nih.gov/books/NBK547852/.

109. R. J. Fontana, I. Liou, A. Reuben, et al., "AASLD Practice Guidance on Drug, Herbal, and Dietary Supplement-Induced Liver Injury," *Hepatology* 77, no. 3 (2023): 1036–1065.

110. S. Agarwal, K. Sandza, K. Obrochta Moss, et al., "Blood Biodistribution and Vector Shedding of Valoctocogene Roxaparvovec in People With Severe Hemophilia A," *Blood Advances* 8, no. 17 (2024): 4606–4615.

111. E. K. Hummel and P. A. Ubel, "Cost and Clinical Practice Guidelines: Can Two Wrongs Make It Right?," *Virtual Mentor* 6, no. 12 (2004): 558–560, https://pubmed.ncbi.nlm.nih.gov/23260287/.

112. S. Knies, J. L. Severens, and W. B. F. Brouwer, "Integrating Clinical and Economic Evidence in Clinical Guidelines: More Needed Than Ever," *Journal of Evaluation in Clinical Practice* 25, no. 4 (2019): 561–564.

113. I. Neumann and H. J. Schunemann, "Guideline Groups Should Make Recommendations Even If the Evidence Is Considered Insufficient," *CMAJ* 192, no. 2 (2020): E23–E24.

114. B. Djulbegovic and G. Guyatt, "Evidence vs Consensus in Clinical Practice Guidelines," *JAMA* 322, no. 8 (2019): 725–726.

115. A. Qaseem, F. Forland, F. Macbeth, et al., "Guidelines International Network: Toward International Standards for Clinical Practice Guidelines," *Annals of Internal Medicine* 156, no. 7 (2012): 525–531.

116. S. Z. Lewis, R. Diekemper, J. Ornelas, and K. R. Casey, "Methodologies for the Development of CHEST Guidelines and Expert Panel Reports," *Chest* 146, no. 1 (2014): 182–192.

117. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Board on Health Care Services, Institute of Medicine of the National Academies. Clinical Practice Guidelines We Can Trust. 2011; Accessed May 23, 2024, https://www.ncbi.nlm.nih.gov/books/NBK209539/pdf/Bookshelf_NBK209539.pdf.

118. N. I. Whitman, "The Delphi Technique as an Alternative for Committee Meetings," *Journal of Nursing Education* 29, no. 8 (1990): 377–379.

119. J. S. Kwong, H. Chen, and X. Sun, "Development of Evidence-Based Recommendations: Implications for Preparing Expert Consensus Statements," *Chinese Medical Journal* 129, no. 24 (2016): 2998–3000.

120. Guidelines for the Management of Hemophilia. *World Federation of Hemophilia* (2005).

121. A. Srivastava, A. K. Brewer, E. P. Mauser-Bunschoten, et al., "Guidelines for the Management of Hemophilia," *Haemophilia* 19, no. 1 (2013): e1–e47.

122. E. A. Akl, J. J. Meerpohl, J. Elliott, L. A. Kahale, and H. J. Schunemann, and Living Systematic Review Network, "Living Systematic Reviews: 4. Living Guideline Recommendations," *Journal of Clinical Epidemiology* 91 (2017): 47–53.

123. J. H. Elliott, T. Turner, O. Clavisi, et al., "Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap," *PLoS Medicine* 11, no. 2 (2014): e1001603.

124. L. Wiles, P. D. Hibbert, Y. Zurynski, et al., "Is It Possible to Make 'Living' Guidelines? An Evaluation of the Australian Living Stroke Guidelines," *BMC Health Services Research [Electronic Resource]* 24, no. 1 (2024): 419.

125. G. S. Hazlewood, J. P. Pardo, C. Barnabe, et al., "Canadian Rheumatology Association Living Guidelines for the Pharmacological Management of Rheumatoid Arthritis With Disease-Modifying Antirheumatic Drugs," *Journal of Rheumatology* 49, no. 10 (2022): 1092–1099.

126. N. Singh, S. Temin, and S. Baker Jr., "Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline," *Journal of Clinical Oncology* 40, no. 28 (2022): 3310–3322.

127. J. H. Elliott, A. Synnot, T. Turner, et al., "Living Systematic Review: 1. Introduction-the Why, What, When, and How," *Journal of Clinical Epidemiology* 91 (2017): 23–30.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix 1: WFH AAV Gene Therapy Guidelines Panel and Assigned Working Groups. **Appendix 2:** SDM Topics for People Considering AAV Gene Therapy: A Checklist for Healthcare Professionals. **Appendix 3:** Sample Screening and Suitability Checklist for Referral and Dosing Centres. **Appendix 4:** AGREE Checklist. **Appendix 5:** ACCORD Checklist. **Appendix 6:** WFH Conflicts of Interest Policy for Guideline Panelists. **Appendix 7:** PICO questions. **Appendix 8:** Systematic Literature Search Strategies. **Appendix 9:** Prisma Overview. **Appendix 10:** Evidence Summary Table. **Appendix 11:** Evidence Summaries. **Appendix 12:** mDelphi Survey Dates and Results. **Appendix 13:** Glossary of Terms. **Appendix 14:** COI Form Responses Evaluated by the GOC and Designations from May 2024 for the WFH AAV Gene Therapy Guidelines Expert Panel.