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ISTH SSC COMMUNICATIONS

A comprehensive care pathway of gene therapy for hemophilia based on current guideline documents and summary of product characteristics: communication from the ISTH SSC working group on gene therapy

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Abstract

Background: Gene therapy for hemophilia has recently been implemented as standard clinical care, requiring organizational and multistakeholder preparedness and clear guidelines. In addition to pharmaceutical summaries of product characteristics

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(SMPCs), various (inter)national guidance documents have been published. However, no guidance document or SMPC covers the entire gene therapy care pathway.

Objectives: This study provides a complete and comprehensive overview of current guidance documents and SMPCs to develop a comprehensive care pathway for hemophilia gene therapy delivery.

Methods: Published gene therapy guidance documents and collected SMPCs were complemented by a selective search in online databases, including PubMed and scientific societies' websites. Reference lists were checked for additional relevant articles.

Results: Four SMPCs and 11 (inter)national guidance documents and recommendations were collected. The documents were focused on either the intervention or the care pathway, and none were comprehensive covering all aspects of hemophilia gene therapy delivery. Considerable differences were found between the 2 approved gene therapy products and between the SMPCs issued by the 2 regulatory authorities, the Food and Drug Administration and the European Medicines Agency. (Inter)national guidance documents provided additional information and recommendations not covered in SMPCs.

Conclusion: Based on SMPCs and (inter)national guidance documents and recommendations a care pathway has been developed and visualized in a Metro Map. This provides a clear and comprehensive overview of all activities, contact moments, and responsibilities within the longitudinal gene therapy treatment process. This comprehensive care pathway may help navigate gene therapy implementation, providing guidance to clinicians, patients, and caregivers.

KEYWORDS
care pathway, gene therapy, guideline, hemophilia, SMPC

1 | INTRODUCTION

Over the past years, the therapeutic landscape for hemophilia has expanded as new nonfactor replacement therapies have entered the market [1–3] and more are expected to become available in the near future [4–6]. Although these new treatment modalities have lowered the treatment burden, and improved treatment outcomes and quality of life (QoL) [1,2,7,8], challenges remain regarding the clinical management of breakthrough bleeds and medical procedures, treatment monitoring, and long-term musculoskeletal health, as there is still a risk of arthropathy and other complications related to breakthrough bleeding including microbleeds [9,10]. Gene therapy with adenoassociated viral (AAV) vectors can be a beneficial treatment for patients with hemophilia A or hemophilia B [11]. With a single infusion, gene therapy has the potential to provide long-term increased factor activity levels, reaching normal factor (F)IX activity of 40 to 100 IU/dL in 33% of the patients [12]. This reduces and may eliminate bleeding episodes and the necessity of prophylaxis, thereby improving QoL [13,14]. However, this new therapeutic approach still has limitations and remaining uncertainties, including risks of low factor levels as an outcome.

A commonly observed gene therapy–related complication, seen to a greater extent in patients with hemophilia A, is an increased alanine aminotransferase (ALT) level, which is most probably caused by an adaptive or innate immune response to the vector capsid, cellular stress, and/or preexisting liver disease [15–17]. This response can be associated with a decrease in factor activity level and, therefore, may require immune and cellular stress suppressive regimens. Furthermore, treated patients demonstrate (large) variability in the expressed factor activity levels, and in hemophilia A, over the time, declining levels are observed [18]. Moreover, supratherapeutic levels have been seen, and in trials, patients have also been unsuccessfully treated due to limited durability of the treatment effect, especially in those with hemophilia A [15,19]. Therefore, a longitudinal follow-up is obligatory to monitor long-term safety and efficacy for which the World Federation of Hemophilia (WFH), European Association for Haemophilia and Allied Disorders (EAHAD), and the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) together have proposed a (core) dataset to be collected within a global gene therapy registry [20–22].

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have granted conditional marketing authorizations for valoctocogene roxaparvovec (VR; Roctavian; hemophilia A) and etranacogene dezaparvovec (ED; Hemgenix; hemophilia B) [23–26]. Thereby, gene therapy for hemophilia has been implemented as standard clinical care. The arrival of these advanced, complex therapies will change hemophilia care and necessitate altered infrastructure requirements for delivery of gene therapy. The EAHAD and European Haemophilia Consortium (EHC) proposed a "hub and spoke" model to ensure smooth coordination of multidisciplinary care for patient screening, dosing, and long-term surveillance, ensuring patient access [27]. Moreover, gene therapy implementation requires organizational and multistakeholder preparedness, including clear guidelines and local protocols. Besides pharmaceutical summaries of product characteristics (SMPCs), various national and international guidance documents as well as those from scientific societies have been published, but none of these cover the entire gene therapy care pathway [28–38]. This review aimed to fill these gaps and provide a complete and comprehensive overview of current guidance documents and SMPCs to develop a comprehensive care pathway for hemophilia gene therapy delivery and address remaining challenges and needs. This care pathway guides physicians and patients with hemophilia, before and after receiving gene therapy.

2 | METHODS

For this review, collected gene therapy guidance documents by the ISTH SSC Gene Therapy Working Group were complemented by a selective search in online databases, including PubMed, as well as on websites of scientific societies between May 1, 2024, and January 31, 2025. Relevant search terms included hemophilia, gene therapy and guideline in various configurations. Moreover, SMPCs and United States prescribing information (USPI) of approved gene therapies from the EMA and FDA, respectively, were collected, hereafter referred to as SMPCs.

Besides gene therapy SMPCs, eligible articles included publications discussing perspectives on or providing recommendations for the delivery of gene therapy for hemophilia, including care delivery models, implementation of gene therapy into clinical care, and site preparation and readiness. Reference lists of included articles were checked for additional relevant articles.

3 | RESULTS

Four SMPCs from the EMA and FDA on the currently approved gene therapies were collected, which include VR and ED [23–26]. In addition, 11 published national and international guidance documents and recommendations, including publications from scientific societies, were gathered, and 2 articles on (core) datasets for longitudinal data collection [20,22,28–38]. An overview of the included articles is presented in Table 1.

Included guidance documents differ regarding their structure and content. Some publications provide detailed information on the different phases of gene therapy delivery (eg, site preparation, screening, administration, and/or follow-up) [31–33,35,37], while others focused on care delivery models and required preparatory steps toward gene therapy implementation into standard clinical care [28,29,34,38]. In general, current guidance documents do not provide a complete overview of all care pathway aspects. Guidance documents mainly focus on site preparedness, the screening process—eg, eligibility screening parameters, patient information, and follow-up of longitudinal data for collection in registries. Information on gene therapy product handling and preparation and day of infusion is often not available in these documents but is extensively outlined in SMPCs, as well as inclusion and exclusion criteria, diagnostic assessment during screening and follow-up, and specification of follow-up regimen including immunosuppressive management. Whereas most guidance documents focus on both hemophilia A and B, the proposed care delivery model from Italy specifically focuses on ED [31].

3.1 | Care pathway of gene therapy delivery

Based on SMPCs and (inter)national guidance documents that are systematically outlined further, we developed a care pathway for AAV-based hemophilia gene therapy delivery, visualized in a Metro Map (Figure) [39]. Metro Mapping is a service design tool for codesigning care pathways, which has originally been developed to improve shared decision making and patient experiences in oncology [39]. The developed care pathway provides a clear overview of all care activities, contact moments, and responsibilities within the different phases of the care trajectory. A link to the original care pathway in Microsoft Visio is provided as a Supplementary Material S2, allowing for modification of the care pathway according to local practice.

Within the care pathway, 5 different phases can be identified as follows:

1. Site preparation and readiness
2. Eligibility screening and assessments
3. Gene therapy product handling and preparation
4. Day of infusion
5. Follow-up

Site preparation and readiness includes institutional preparation such as biological risk assessment by a biosafety officer, education and training of personnel, the development of protocols, standardized operating procedures (SOPs), and reimbursement models. In addition, some countries require accreditation [29]. The screening phase comprises determination of patient eligibility including diagnostic assessment, information provision, and consent. Handling and preparation involves procurement, receipt and storage of the gene

TABLE 1 Overview of current summaries of product characteristics and (inter)national guidance documents regarding gene therapy for hemophilia.

Title	First author	Year of publication	Country	Hemophilia A or B
Summaries of product characteristics				
Valoctocogene roxaparvovec (Roctavian)	EMA [23]	2022	Europe	Hemophilia A
Valoctocogene roxaparvovec (Roctavian)	FDA [26]	2023	United States	Hemophilia A
Etranacogene dezaparvovec (Hemgenix)	EMA [24]	2023	Europe	Hemophilia B
Etranacogene dezaparvovec (Hemgenix)	FDA [25]	2022	United States	Hemophilia B
National guidance documents and recommendations				
Clinical implementation plan: a roadmap for the implementation of gene therapy for hemophilia in Australia	Australian Haemophilia Centre Directors' Organisation [28]	2022	Australia	Both
Delivery of gene therapy in hemophilia treatment centers in the United States: practical aspects of preparedness and implementation	Pipe et al. [37]	2023	United States	Both
Perspectives and perception of hemophilia gene therapy by French patients	Pietu et al. [36]	2023	France	Both
Laying the foundations for gene therapy in Italy for patients with hemophilia: a Delphi consensus study	Castaman et al. [30]	2022	Italy	Hemophilia A
Gene therapy for people with hemophilia B: a proposed care delivery model in Italy	Castaman et al. [31]	2024	Italy	Hemophilia B
UKHCDO gene therapy taskforce: guidance for implementation of hemophilia gene therapy into routine clinical practice for adults	Chowdary et al. [32]	2024	United Kingdom	Both
Suitability and readiness assessment of organizational resources for the implementation of gene therapy in Spain and Portugal: a survey-based study	Villas et al. [38]	2024	Spain and Portugal	Both
International guidance documents and scientific societies				
Evolution of hemophilia integrated care in the era of gene therapy: Treatment center's readiness in United States and EU	Miesbach et al. [34]	2021	United States and EU	Both
Gene therapy for hemophilia: recommendations from the German, Austrian, and Swiss Society for Thrombosis and Haemostasis Research (GTH)	Miesbach et al. [33]	2022	Germany, Austria, and Switzerland	Both
MASAC recommendations on hemophilia treatment center preparedness for delivering gene therapy for hemophilia	MASAC [35]	2023	United States	Both
Accreditation model of European Haemophilia Centres in the era of novel treatments and gene therapy	Boban et al. [29]	2023	Europe	Both
Guidance documents regarding longitudinal data collection				
Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH	Konkle et al. [20]	2020	WFH	Both

(Continues)

TABLE 1 (Continued)

Title	First author	Year of publication	Country	Hemophilia A or B
Recommendations for a minimum data set for monitoring gene therapy in hemophilia: communication from the ISTH SSC Working Group on Gene Therapy	Miesbach et al. [22]	2023	ISTH	Both

EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; ISTH, International Society on Thrombosis and Haemostasis; MASAC, Medical and Scientific Advisory Council; SSC, Scientific and Standardization Committee; UKHCDO, United Kingdom Haemophilia Centre Doctors' Organisation; WFH, World Federation of Hemophilia.

therapy product, and preparation for infusion. Day of infusion consists of gene therapy administration, postinfusion monitoring for infusion reactions and management if necessary, and decontamination and waste disposal after completion. Lastly, follow-up includes short- and long-term monitoring of outcomes and adverse events, possible management of hepatotoxicity, and longitudinal data collection.

3.2 | Site preparation and readiness

Preparational steps for centers to be ready for gene therapy dosing are outlined in (inter)national guidance documents and not necessarily in SMPCs.

3.2.1 | Organizational model

The EAHAD and EHC have proposed the hub and spoke model for organizing hemophilia gene therapy [27,29]. This model is recommended by most guidance documents that discuss gene therapy organization [28–33,35,37,38]. The hub is a comprehensive care and experienced gene therapy dosing center, and the spoke is a follow-up center, usually patients' home center, which supports patients before and after gene therapy infusion. The hub is generally responsible for confirmation of eligibility criteria and informed consent; procurement, storage, handling, preparation, and administration of gene therapy; postinfusion monitoring and management of infusion reactions; follow-up in close cooperation with the spoke; and longitudinal data collection and submission in registries. Spoke tasks include identification of eligible patients; screening including (diagnostic) assessments and information provision; long-term follow-up and management; and longitudinal data collection. Under some circumstances, the hub and spoke may be the same hemophilia treatment center (HTC).

According to guidance documents, the core multidisciplinary treatment team should consist of hematologists, nurse practitioners (advance practice providers), (hemophilia) nurses, physical therapists, psychologists and social workers, pharmacy staff including clinical pharmacists, and the hemophilia laboratory team [29–31,33–35,37]. Additionally, hepatologists, immunologists, orthopedists, and case managers may also be involved. The publication from Italy recommends involvement of anesthesiologists in case of allergic or anaphylactic reactions [31]. The presence of data managers and financial administrators is also mentioned [30,35].

3.2.2 | Institutional preparation

Before centers can treat patients with gene therapies, institutional-specific approvals should be compiled, which include quality assurance procedures and a biological risk assessment [32,33,35,37]. In some countries, accreditation is required. Moreover, necessary facilities and equipment for gene therapy product handling, preparation, and administration should be available [32,35,37,38].

The development of protocols, SOPs, and guidelines is recommended in multiple guidance documents [10,28,29,33–35,37]. SOPs should be developed for gene therapy procurement, receipt, storage, preparation, and administration; clinical guidelines regarding patient eligibility and screening, day of infusion, and follow-up including management of adverse events are needed. Other important topics include patient information and education, insurance authorization and reimbursement, data collection and sharing between registries, and a framework outlining responsibilities of hub and spoke centers, particularly when they are different institutions.

In addition, all involved members of the multidisciplinary care team should receive tailored training and education on gene therapy based on their role and activities [28,30,31,34,35,37,38]. Specific educational modules should be completed, for which different programs and online modules are currently available [35]. Documentation of training and annual reeducation is also recommended [35].

3.3 | Eligibility screening and assessments

3.3.1 | Inclusion and exclusion criteria for gene therapy

SMPCs by the EMA and FDA provide inclusion and exclusion criteria for gene therapy eligibility (Table 2). VR can be given to adult patients with severe hemophilia A (FVIII < 1 IU/dL) without antibodies to AAV5. Patients should have a negative history of FVIII inhibitors according to the EMA [23] or have absent active inhibitors according to the FDA [26].

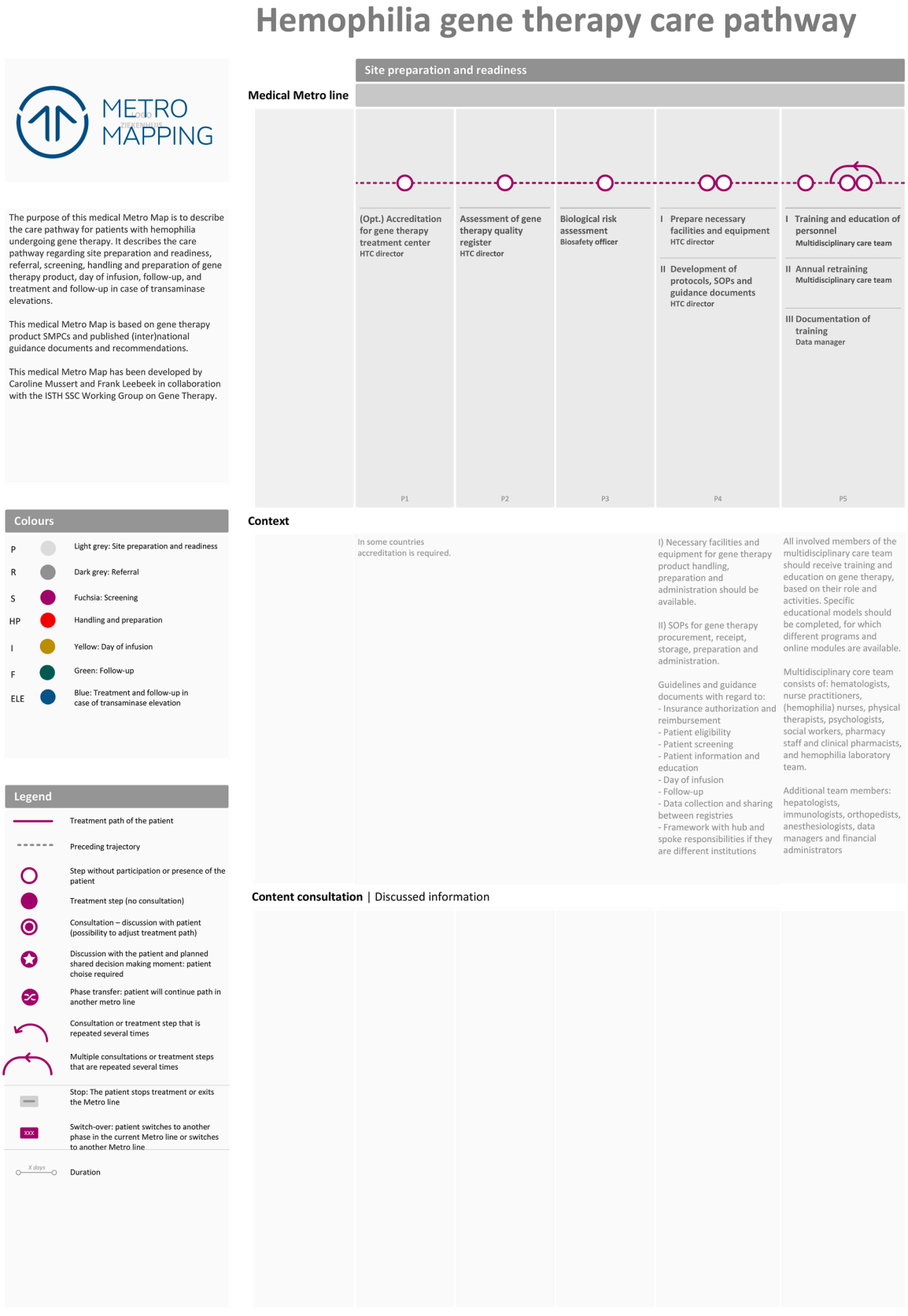


FIGURE Proposed care pathway for gene therapy delivery in hemophilia.

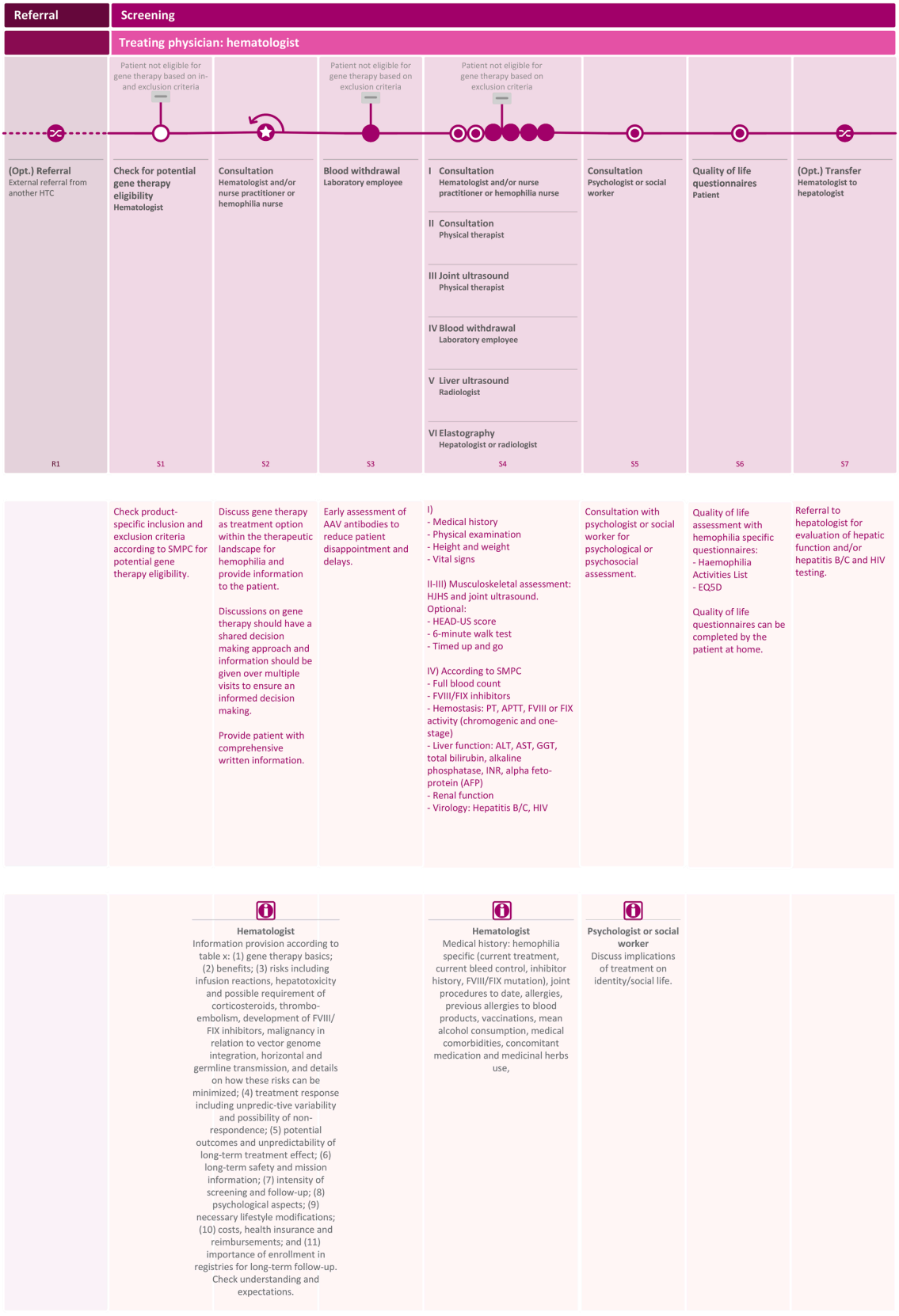


FIGURE (*continued*).

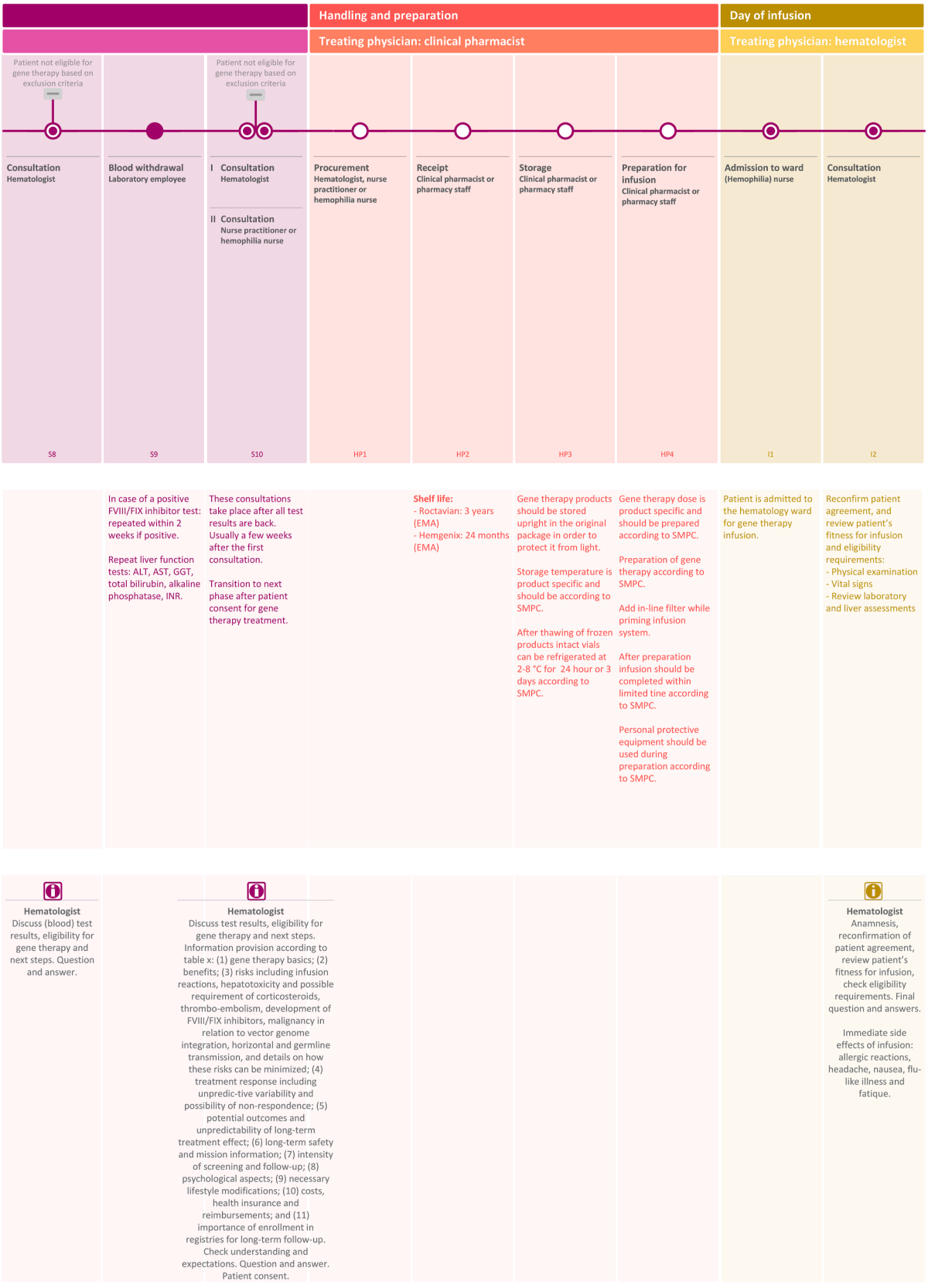
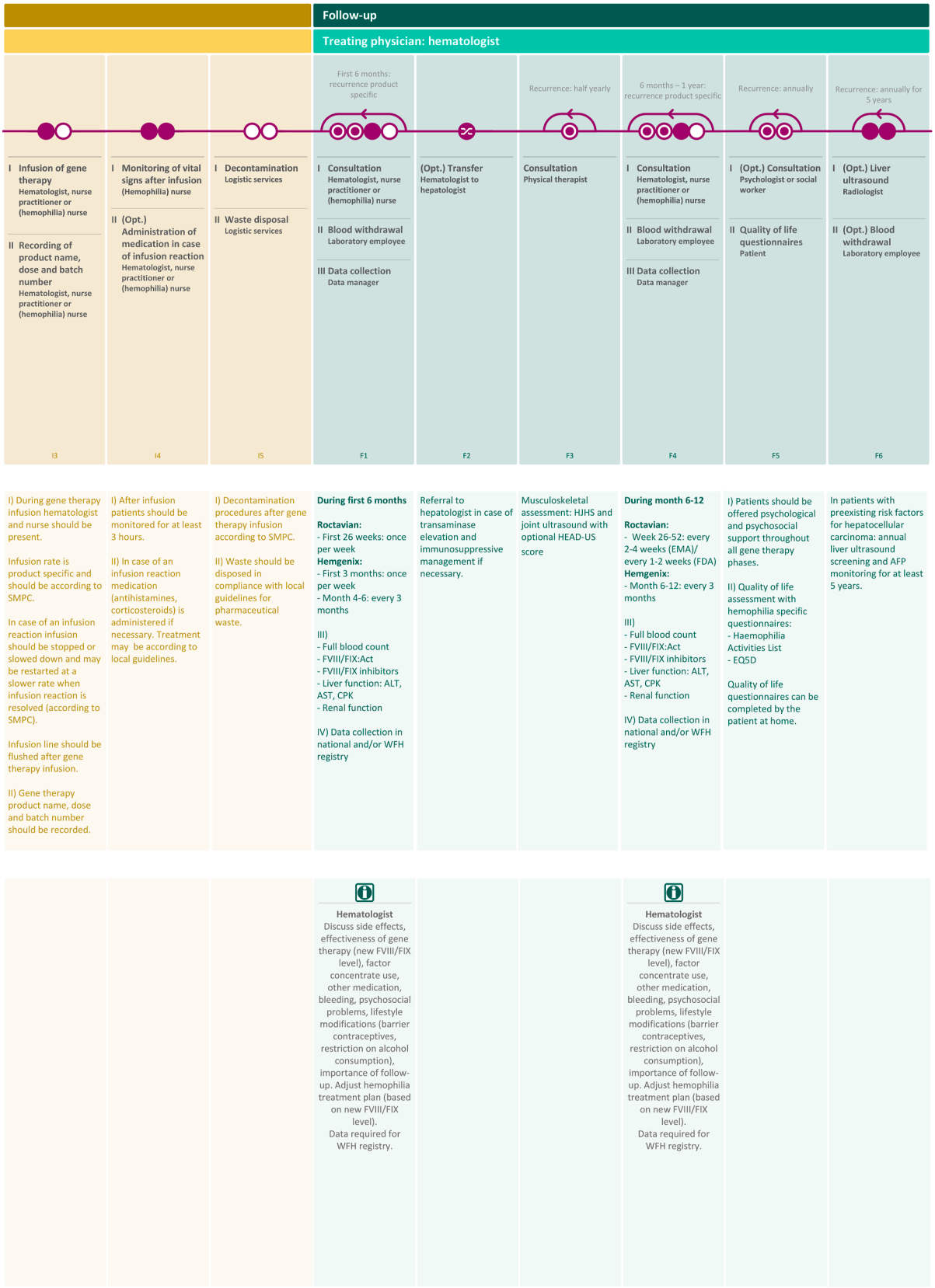


FIGURE (*continued*).



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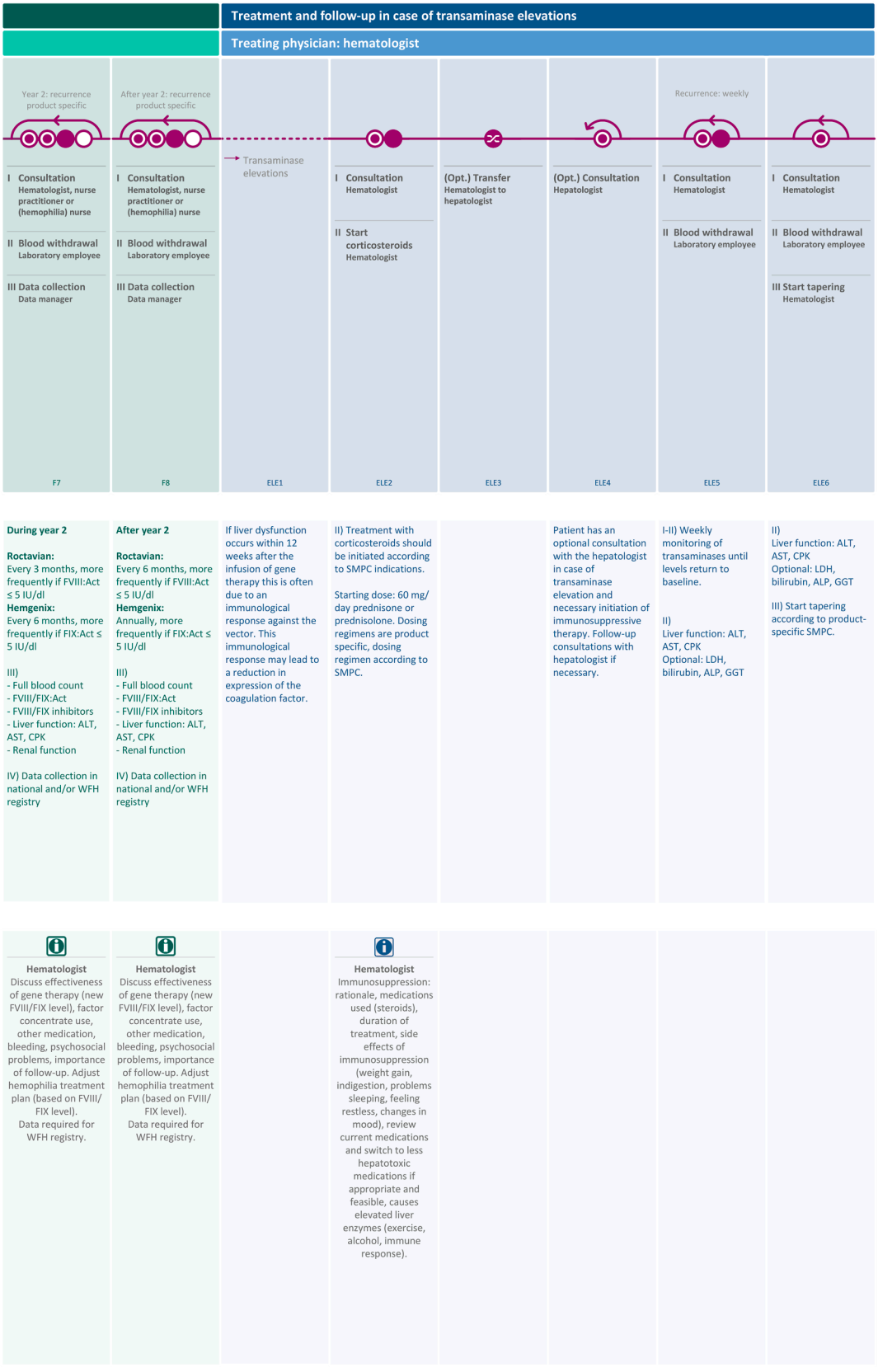

FIGURE (*continued*).

TABLE 2 Inclusion and exclusion criteria for hemophilia gene therapy.

	Valoctocogene roxaparvovec (HemA) [23,26]	Etranacogene dezaparvovec (HemB) [24,25]
Inclusion criteria	- Severe hemophilia A (FVIII < 1 IU/dL) - Adult patients - No history of FVIII inhibitors (EMA) or no presence of active FVIII inhibitors (FDA)[a] - No detectable antibodies to AAV5	- Severe and moderately severe hemophilia B who Currently use factor FIX prophylaxis (FDA)[a] Have current or historical life-threatening hemorrhage (FDA)[a] Have repeated, serious spontaneous bleeding episodes (FDA)[a] - Adult patients - No history of FIX inhibitors (EMA) or no presence of active FIX inhibitors (FDA)[a]
Exclusion criteria	- History of FVIII inhibitors (EMA), presence of active FVIII inhibitors (FDA)[a] - Anti–AAV5 antibodies - Age < 18 y - Hypersensitivity to the product excipients - Active infections (acute or uncontrolled chronic) - Significant hepatic fibrosis or cirrhosis	- Presence of FIX inhibitors - Age < 18 y - Hypersensitivity to the product excipients (EMA)[a] - Active infections (acute or uncontrolled chronic) (EMA)[a] - Advanced hepatic fibrosis or cirrhosis (EMA)[a]

EMA, European Medicines Agency; FDA, Food and Drug Administration.
[a] Differences between summaries of product characteristics of EMA and United States prescribing information of FDA.

ED is available for adults with severe and moderately severe hemophilia B. FIX activity levels are not specified in SMPCs, but according to the FDA, patients should currently use FIX prophylaxis, have current or historical life-threatening hemorrhage, or have repetitive, serious spontaneous bleeding episodes [25]. The EMA does not mention these specific criteria. Patients with a negative history of FIX inhibitors should be treated with ED according to the EMA [24], whereas the FDA only excludes patients with a current positive inhibitor test [25]. Patients with anti-AAV5 antibodies may be treated with ED, although data in patients with titers above 1:678 are limited, and 1 patient with a titer of 1:3200 failed to respond [24,25].

Except for the FDA regarding ED, all SMPCs mention contraindications for gene therapy, including hypersensitivity to product excipients; active infections, either acute or uncontrolled chronic; and significant liver fibrosis or cirrhosis [23,24,26]. Both gene therapies are only available for adults, but none of the SMPCs mention a maximum age or minimal life-expectancy. Within (inter)national guidance documents, only publications from Australia and Italy regarding hemophilia B mention inclusion and exclusion criteria which are in line with SMPCs [28,31].

3.3.2 | Diagnostic assessment for screening

SMPCs provide detailed information on the performance of different diagnostic tests during screening to assess inclusion and exclusion criteria for gene therapy (Table 3). For both products, diagnostic assessment consists of measuring FVIII/FIX inhibitors and anti-AAV antibodies [23–26]. Regarding ED, FIX inhibitor testing should be repeated within 2 weeks in case of a positive-result test [24,25]. Measurement of anti-AAV antibodies is not obligatory for ED according to the FDA. Sites are, however, offered to send samples for antibody screening to a central laboratory [25,40].

Liver function tests include ALT, aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase (ALP; ALP for VR required only by FDA), with possibly required retesting for some tests according to the EMA. Additionally, VR requires assessment of γ-glutamyl transferase and international normalized ratio [23,26]. For both products, fibrosis assessment should be performed with liver ultrasound, elastography, and/or other laboratory assessments (not specified) [23–26]. In case of radiological liver abnormalities or

TABLE 3 Diagnostic assessment for gene therapy eligibility.

Valoctocogene roxaparvovec (HemA) [23,26]	Etranacogene dezaparvovec (HemB) [24,25]
Factor VIII inhibitors	Factor IX inhibitors (1× repeated within 2 weeks if positive)
Liver function[a] - ALT[b] - AST - GGT - Total bilirubin - INR - Alkaline phosphatase (FDA)[c]	Liver function[a] - ALT[b] - AST - Total bilirubin - Alkaline phosphatase
Anti-AAV antibodies	Anti-AAV antibodies (encouraged to be tested in antibody study—FDA)[c]
Fibrosis assessment: liver ultrasound and elastography or laboratory assessment[d]	Fibrosis assessment: liver ultrasound and elastography[d]

AAV, adenoassociated viral; ALT, alanine transaminase; AST, aspartate transaminase; FDA, Food and Drug Administration; GGT, γ-glutamyl transferase; INR, international normalized ratio.
[a] Within 3 mo according to the European Medicines Agency (EMA).
[b] 1× repeated according to the EMA. Regarding valoctocogene roxaparvovec, an average of prior measurements can be used for baseline value according to the EMA.
[c] Differences between summaries of product characteristics of EMA and United States prescribing information of FDA.
[d] Within 6 mo according to the EMA.

sustained liver enzyme elevations, a consultation with a hepatologist is recommended [24–26]. For VR, the EMA recommends the evaluation of hepatic function through a multidisciplinary approach with standard involvement of a hepatologist [23]. Only the EMA incorporated a time frame in which specific tests should be performed prior to gene therapy administration.

For VR (FDA) and ED (EMA and FDA), the use of the same assay and reagents for monitoring of coagulation factor levels over time is recommended since all products show a marked discrepancy in values. For routine clinical monitoring of FVIII, chromogenic substrate assay (CSA) or one-stage assay (OSA) may be used. In general, OSA gives a 1.5- to 1.6-fold higher result than CSA [23,26,41]. Moreover, use of the same laboratory and assays for hepatic testing is recommended [24]. Anti-AAV antibodies should be measured with an approved AAV test [23–26]. According to the FDA for VR, AAV5 DetectCDx is approved for measurement of anti-AAV5 antibodies [42].

Limited information is available on the diagnostic assessment of these parameters in (inter)national guidance documents, but it is in line with SMPCs [28,30–32,37]. The United Kingdom specifically recommends to start eligibility screening with the assessment of AAV antibodies, as early testing can reduce patient disappointment and delays [32]. Moreover, they recommend to repeat baseline liver function tests.

3.3.3 | Additional assessments before gene therapy

International guidance documents propose additional assessments before gene therapy [28,30–33,35,37] including assessment of (hemophilia specific) a medical history [31–33,37]; physical examination with measurement of vital signs, height, and weight [32,37]; and assessment of musculoskeletal status (Table 4) [30–32,37]. Additionally, a psychological/psychosocial assessment by a psychologist or social worker and measurement of QoL are recommended [30–33,37]. Support should be given both preinfusion and postinfusion and should also be extended to individuals who are deemed ineligible or who choose not to proceed. Preinfusion psychological support can identify and align patient's expectations, values, and preferences and enables the understanding of the physical and emotional demands of gene therapy. The diagnostic assessment should also include full blood count and renal function and assessment of hepatitis B/C virus and HIV status [32,33], as well as measurement of α-fetoprotein [31,37].

3.3.4 | Shared decision making: patient information and discussion topics

The screening phase includes consultations with health care professionals in which information on gene therapy is provided to the patient. Gene therapy should be presented as one of the options within the therapeutic landscape for hemophilia, and all available treatment options should be evaluated [32,33,35,37]. Discussions on gene therapy should have a shared decision-making approach and information should be given over multiple visits to ensure informed decision making. To facilitate shared decision-making, different tools have been developed [43,44].

SMPCs and nearly all (inter)national guidance documents provide information on topics that should be discussed if a patient is interested in gene therapy. Based on the detailed publication from the United Kingdom [32], a comprehensive overview of information that should be covered according to SMPCs and available guidance documents is displayed in Supplementary Material S1 [23–26,28,30–37]. Discussions should cover information on (1) gene therapy basics; (2) benefits; (3) risks including infusion reactions, hepatotoxicity and possible requirement of corticosteroids, thromboembolism, development of FVIII/FIX inhibitors, theoretical risk of malignancy in relation to vector genome integration, horizontal and germline transmission, and how these risks can be minimized; (4) treatment response including unpredictive variability and possibility of no response; (5) potential outcomes and unpredictability of long-

TABLE 4 Additional assessments before gene therapy.

Medical history	Assessments	Additional diagnostic assessments

- Hemophilia specific history
  ○ Current treatment
  ○ Current bleed control
  ○ Inhibitor history
  ○ Factor (F)VIII or FIX mutation
- Joint procedures to date
- Allergies
- Previous allergy to blood products
- Vaccinations
- Mean alcohol consumption
- Medical comorbidities
- Concomitant medication and medicinal herbs use
	- Physical examination
	- Height and weight
	- Vital signs
	- Musculoskeletal assessment:
	  ○ Joint score (hemophilia joint health score)
	  ○ Joint ultrasound
	  ○ Optional: hemophilia early arthopathy detection with ultrasound score (HEAD-US)
	  ○ Optional: 6-min walk test
	  ○ Optional: timed up and go
	- Psychological/psychosocial assessment (by a psychologist or social worker)
	- Quality of life measures:
	  ○ Haemophilia Activities List (HAL)
	  ○ EuroQoL 5 Dimension (EQ-5D)
		- Full blood count
		- Renal function
		- α-fetoprotein
		- Virology (hepatitis B/C virus and HIV)

term treatment effect; (6) long-term safety and gene therapy unknowns; (7) intensity of screening and follow-up; (8) psychological aspects; (9) necessary lifestyle modifications; (10) costs, health insurance, and reimbursements; and (11) importance of enrollment in registries for long-term follow-up. Health care providers should ensure that patients have a clear understanding before they consent and discuss expectations regarding gene therapy including worries and doubts. Moreover, it is important to provide patients with comprehensive written information in plain language that patients can take with them and reread at home [32,35].

3.4 | Gene therapy product handling and preparation

Information on gene therapy product handling and preparation is discussed in SMPCs (Table 5). Except for the publication from the German, Austrian, and Swiss Society for Thrombosis and Haemostasis Research (GTH), (inter)national guidance documents do not discuss handling and preparation. GTH provides several overall instructions for preparation and infusion, which are in line with SMPCs [33]. Additionally, the use of a cool box for transportation to the treatment site is specified.

Upon receipt, hemophilia A and B gene therapy products should be stored upright in the original package in order to protect it from light [23–26]. VR is stored frozen at ≤−60 °C and intact vials can be refrigerated at 2 to 8 °C for 3 days after thawing [23,26]. The recommended dose of VR is a single dose of 6×10^{13} vg/kg [23,26]. After preparation, the infusion should be completed within 10 hours at 25 °C. ED is stored at 2 to 8 °C, and the recommended dose is 2×10^{13} gc/kg [24,25]. After preparation, the infusion should be completed within 24 hours. During preparation and administration, personal protective equipment is recommended; only FDA did not specify this for ED [23,24,26].

3.5 | Day of infusion

According to SMPCs, gene therapy should be administered in a qualified treatment center by a physician who is experienced in hemophilia treatment and in a setting where personnel and equipment are immediately available to treat possible infusion-related reactions [23,24,26]. These conditions are not specified in the FDA SMPC for ED.

3.5.1 | Gene therapy infusion

VR and ED are infused intravenously using an in-line filter. VR infusion is started at 1 mL/min and can be increased every 30 minutes by 1 mL/min to a maximum of 4 mL/min and flushed afterward at the same rate [23,26]. ED is infused continuously at 500 mL/h (8 mL/min) and flushed accordingly [24,25]. In case of an infusion reaction, the infusion should be stopped or slowed down and may be restarted at a slower rate once resolved [23–26]. VR may be restarted at 1 mL/min and maintained at a previously tolerated rate [23,26]. Infusion reactions can be treated with antihistamines, corticosteroids, or other measures [23–26]. To monitor infusion reactions, all patients should be monitored after infusion for at least 3 hours with measurement of vital signs [24–26]. Only the EMA does not specify the monitoring time for VR [23]. For both gene therapies, the EMA states that names and batch numbers should be recorded [23,24].

TABLE 5 Preparation and handling of gene therapy.

	Valoctocogene roxaparvovec (HemA) [23,26]	Etranacogene dezaparvovec (HemB) [24,25]
Shelf-life	3 y (EMA)	24 mo (EMA)
Dose	6×10^{13} vg/kg	2×10^{13} gc/kg
Storage	Storage after receipt: - Store upright in original package to protect from light - Store frozen at ≤ −60 °C - After thawing: intact vials can be refrigerated at 2-8 °C for 3 d Storage after preparation: At 25 °C, complete infusion within 10 hours	Storage after receipt: - Store in original package to protect from light - Store in refrigerator at 2-8 °C Storage after preparation: At 15-25 °C protected from light, administer within 24 hours
Preparation	1. Thaw at room temperature 2. Inspect vials: should be clear and colorless to pale yellow 3. Extract into syringes 4. Dilute with sodium chloride 5. Prime infusion system and add in-line filter	1. Inspect vials for particulates, cloudiness or discoloration (FDA)[a] 2. Extract into syringes 3. Dilute with sodium chloride 4. Prime infusion system and add in-line filter
Personal protective equipment	Gloves, safety goggles Gown and mask (EMA)[a]	Gloves, safety goggles, protective clothing, and mask (EMA)[a]

EMA, European Medicines Agency; FDA, Food and Drug Administration.
[a] Differences between summaries of product characteristics of EMA and United States prescribing information of FDA.

3.5.2 | Decontamination and waste disposal

The specificity of proposed decontamination procedures after gene therapy administration differs among SMPCs. For VR, the EMA recommends to wipe spills with gauze pad and disinfect with bleach solution and alcohol wipes [23]. The FDA recommends to treat VR spills with a virucidal agents with proven activity against non-enveloped viruses [26], which is also recommended for ED by both authorities [24,25]. Waste should be disposed of in compliance with local guidance for pharmaceutical waste [23–26].

3.5.3 | (Inter)national guidelines and recommendations

Guidance documents from GTH, Medical and Scientific Advisory Council, the United States, and the United Kingdom provide recommendations regarding the day of infusion which are in line with or should be performed according to SMPCs [32,33,35,37]. Publications from the United States and United Kingdom additionally recommend reconfirmation of patient agreement and review of patient's fitness for infusion and eligibility requirements before gene therapy preparation, including physical examination, measurement of vital signs and review of laboratory and liver assessments [32,37]. Medical and Scientific Advisory Council, the United States, and the United Kingdom highlight the presence of a physician during gene therapy infusion and monitoring to evaluate and respond to treatment reactions. However, Italy's publication on hemophilia B proposes the presence of an anesthesiologist to manage anaphylactic reactions [31]. The United Kingdom also highlights the recording of product name, dose, and batch number for traceability [32].

3.6 | Follow-up after gene therapy

3.6.1 | Follow-up frequency and diagnostic assessment

Gene therapy with AAV vectors may cause immune-mediated hepatotoxicity, leading to transaminase elevations and concomitant decrease of FVIII/FIX expression [15–17]. Other possible causes of transaminase elevations include AAV capsid intracellular toxicity and an unfolded protein response to FVIII [17]. Therefore, ALT and AST and FVIII/FIX activity should be measured regularly following gene therapy administration. SMPCs provide detailed monitoring regimen (Table 6) [23–26]. Follow-up regimens are product specific and slightly differ between EMA and FDA for the first year. Regarding ED, the FDA does not provide information on monitoring after the first 3 months [25]. In addition, measurement of creatine phosphokinase is recommended by the EMA to evaluate for alternative causes of ALT elevation [23,24], which the FDA recommends only for VR [26].

Furthermore, the development of FVIII/FIX inhibitors should be monitored especially if bleeding is not controlled or FVIII/FIX activity decreases, although a clear frequency is not mentioned [23–26]. Regular (annual) liver ultrasound and α-fetoprotein monitoring is recommended in patients with preexisting risk factors for hepatocellular carcinoma for at least 5 years [24–26]. This is not advised by the EMA for VR-treated patients.

Information on follow-up frequency and diagnostic assessment in (inter)national guidance documents is limited [30–33]. Italy and the United Kingdom recommend follow-up schedules according to SMPCs [30–32], although the United Kingdom also recommends standard measurement of full blood counts and renal function [32]. GTH recommends a slightly different follow-up frequency with weekly follow-up during the first 6 months, monthly from month 6 to 24 and every 6 months from year 2 onward [33]. Moreover, GTH recommends the measurement of lactate dehydrogenase, γ-glutamyl transferase, alkaline phosphatase, and bilirubin to assess differential diagnoses and severity of ALT elevation.

Additionally, monitoring of musculoskeletal status is recommended [29–31,33], which should be performed half-yearly according to GTH [33]. Follow-up should also comprise annual monitoring of QoL [28,30,33], preferably with hemophilia-specific QoL questionnaires [30]. Giving psychological support during follow-up is also recommended [29,31,32,34,37], because patients may face emotional challenges as they transition from chronic disease management to a potentially new health status and may experience drug side effects, including those associated with immunosuppression. The United States highlights continuation of follow-up care to monitor potential long-term risks and when gene therapy fails [37].

3.6.2 | Transaminase elevations and immunosuppressive management

In case of transaminase elevations, treatment with corticosteroids should be initiated. SMPCs provide detailed information on indications for treatment initiation and treatment regimens (Table 7). In general, corticosteroids should be started if ALT increases above the upper limit of normal or above baseline values of the individual patient. Reasons for initiation are similar between the EMA and FDA [23–26]. Recommended treatment regimens including tapering are product specific and do not differ between the EMA and FDA [23–26]. Follow-up monitoring of transaminases is recommended to be performed on a regular basis, specifically weekly for VR, until levels return to baseline. Earlier trials have studied prophylactic immunosuppression to mitigate vector-related hepatotoxicity, but based on poor outcomes, this is not recommended in current SMPCs [19].

Information on immunosuppressive management in (inter)national guidance documents is limited [32,33,37]. The United Kingdom and the United States recommend immunosuppressive approach based on the product specific SMPC [32,37], while GTH aligns with

TABLE 6 Monitoring of hepatic function and factor VIII/factor IX activity after gene therapy.

Valoctocogene roxaparvovec (HemA) [23,26]		Etranacogene dezaparvovec (HemB) [24,25]	
ALT, AST, CPK, and FVIII:Act		**ALT, AST, CPK (EMA only)[a] and FIX:Act**	
First 26 wk	Once per week	First 3 mo	Once per week
Weeks 26-52	Every 2-4 wk (EMA)[a]	Months 4-12 (EMA)[a]	Every 3 mo[a]
	Every 1-2 wk (FDA)[a]	Year 2 (EMA)	FIX:Act > 5 IU/dL: every 6 mo[a]
Year 2	FVIII:Act > 5 IU/dL: every 3 mo		FIX:Act ≤ 5 IU/dL: more frequently[a]
	FVIII:Act ≤ 5 IU/dL: more frequently	After year 2 (EMA)[a]	FIX:Act > 5 IU/dL: annually[a]
After year 2	FVIII:Act > 5 IU/dL: every 6 mo		FIX:Act ≤ 5 IU/dL: more frequently[a]
	FVIII:Act ≤ 5 IU/dL: more frequently		
Factor VIII inhibitors[b]		Factor IX inhibitors[b]	
In patients with preexisting risk factors[c] for hepatocellular carcinoma: regular (annually) liver ultrasound screening and AFP monitoring for at least 5 years (FDA)[a]		In patients with preexisting risk factors[c] for hepatocellular carcinoma: Regular (annually) liver ultrasound screening and AFP monitoring for at least 5 years	

AFP, α-fetoprotein; EMA, European Medicines Agency; FDA, Food and Drug Administration.
[a] Differences between summaries of product characteristics of EMA and United States prescribing information of FDA.
[b] Especially if bleeding is not controlled or plasma factor VIII/factor IX activity decreases.
[c] Such as hepatic fibrosis, hepatitis C or B virus, nonalcoholic fatty liver disease.

the VR SMPCs [33]. GTH additionally recommend to start immunosuppression if factor activity levels decrease by >20% of the previous value and to only start tapering when ALT has been reduced by 50% or returned to baseline. If ALT increases >1.5 times during tapering, the dose should be increased to the last effective dose and tapering should be retried after 14 days.

3.6.3 | Lifestyle modifications

Recommended lifestyle modifications by SMPCs and (inter)national guidance documents include the use of barrier contraceptives and restriction on alcohol consumption [23,24,26,28,32,33,35,37]. After treatment with VR, patients should use barrier contraceptives for 6 months [23,26] and, after ED, for 12 months according to the EMA [24]. Moreover, for VR, it is recommended to refrain from alcohol consumption within the first year after gene therapy infusion and limit intake thereafter [23,26]. Information on lifestyle modifications is not available in the FDA SMPC of ED.

3.6.4 | Discontinuation and reinitiation of prophylaxis

For both products, the EMA recommends to continue prophylactic treatment until FVIII/FIX activity levels are considered sufficient

TABLE 7 Initiation of corticosteroids and recommended treatment regimen.

Valoctocogene roxaparvovec (HemA) [23,26]	Etranacogene dezaparvovec (HemB) [24,25]
Start corticosteroid treatment: [a] - ALT > upper limit of normal - ALT > 1.5× baseline - Absence of other cause for ALT increase	Start corticosteroid treatment: - ALT > upper limit of normal - ALT > 2× baseline
Starting dose: 60 mg/d prednisone or equivalent dose of another corticosteroid	Starting dose: 60 mg/d prednisolone or prednisone
Week 1-2: 60 mg/d	Week 1: 60 mg/d
Week 3-5: 40 mg/d	Week 2: 40 mg/d
Week 6: 30 mg/d	Week 3: 30 mg/d
Week 7: 20 mg/d	Week 4: 30 mg/d
Week 8: 10 mg/d	After week 4: 20 mg/d maintenance dose until ALT level returns to baseline level
Dose can be increased up to a max of 1.2 mg/kg if ALT continues to rise or has not improved after 2 weeks	
Tapering: can start after 2 weeks if ALT levels remain stable and/or earlier when ALT levels start to decline. Taper may be individualized.	Tapering: can start after baseline level has been reached. Reduce daily dose by 5 mg/wk.

ALT, alanine transaminase.
[a] ALT test should be repeated within 24 to 48 h to confirm ALT elevation prior to initiation of corticosteroid treatment.

enough to prevent spontaneous bleeding [23,24]. Reinitiation of FVIII/FIX concentrates is recommended if FVIII/FIX activity is consistently <5 IU/dL with recurrent spontaneous bleeding episodes, in concordance with current treatment guidelines [23,24]. Information on restarting prophylaxis is not available in FDA SMPCs. Only Italy's publication on hemophilia B covers this and recommends to reinitiate prophylaxis if endogenous FIX activity is <2% and consider it if levels are between 2% and 5% for at least 2 consecutive measurements [31].

3.6.5 | Longitudinal data collection and gene therapy outcomes

According to SMPCs, all treated patients are expected to be enrolled in a registry for 15 year, to assess long-term efficacy and safety [23,24,26]. This was not specified by the FDA for ED.

Most (inter)national guidance documents recommend enrollment and (life-long) longitudinal data collection in national registries and/or the WFH Gene Therapy Registry [28,29,31,33,35,37], following published frameworks by the ISTH SSC [31,32,34,35]. The ISTH SSC has proposed an extensive core dataset for longitudinal data collection in the WFH Gene Therapy Registry and a minimum dataset to enhance data collection and ensure documentation of most essential data [20,22]. This subset includes data on efficacy and safety among others (eg, factor levels, bleeding rates, factor concentrate use, reinitiation of prophylaxis, transaminase elevation and immunosuppression, and adverse events) and is recommended to be collected mandatory for all patients who receive gene therapy if the more extensive dataset cannot be collected. The EAHAD has also developed a Haemophilia Gene Therapy Clinical Outcome Database [21].

4 | DISCUSSION

This review provides an overview of recently published guidance documents and SMPCs for hemophilia gene therapy delivery. It shows that none of the SMPCs or published (inter)national guidance documents cover all important phases and aspects. In addition, our review showed considerable differences between USPIs and SMPCs from the 2 regulatory authorities, the FDA and EMA, respectively—for example, regarding inclusion and exclusion criteria, diagnostic assessment for gene therapy eligibility, and recommended follow-up regimen. Differences were also found between the 2 approved gene therapy products. Moreover, (inter)national guidance documents provide additional information and recommendations to SMPCs, mainly regarding site preparation and readiness, eligibility screening, and assessments. Based on our findings, we have developed a comprehensive gene therapy care pathway using the Metro Mapping methodology. Activities and responsibilities within the different phases of the gene therapy care trajectory have been combined and visualized in a care pathway that can be used in clinical practice by the multidisciplinary team, also in a hub and spoke model.

Although the EAHAD and EHC have proposed a hub and spoke model, this model will need to be modified per country or even per region based on eg, the geographical distribution of HTCs and HTCs possibility to administer gene therapy, as available facilities may differ [27,45]. Moreover, with 2 involved centers, a clear division of tasks and responsibilities of the involved multidisciplinary team is essential, as well as careful consideration and planning with regard to the location of laboratory measurements during screening and follow-up [45]. This division in tasks can easily be visualized using the Metro Map. To facilitate monitoring and evaluate gene therapy efficacy, it is crucial to accurately measure FVIII and FIX activity. However, discrepancies between OSA and CSA, and analytical variation in OSA and CSA measurements have been demonstrated [46–48]. This highlights the need for standardization strategies to enable short- and long-term intraindividual and interindividual data comparison to improve the understanding of response variability and long-term safety [49]. In addition, standardization is required regarding the evaluation of liver health before and after gene therapy [49]. Our review showed that currently used liver function tests, threshold values for test results based on when immunosuppression is initiated, and the timing of tests are heterogeneous, which complicate interpretation and comparability of long-term collected data in registries to evaluate safety. Data with immunosuppression other than corticosteroids are limited and inconsistent at present. Moreover, during screening, only liver ultrasound is performed to assess liver health and identify preexisting cirrhosis or hepatocellular carcinoma. Patients are not screened for other types of occult cancer.

Another area that necessitates standardization is the assessment of anti-AAV antibodies, including used assays and interpretation of antibody titers [49]. Anti-AAV assays are essential in the screening process. However, different assay types are currently used and international standards to calibrate antibody quantitation to enable comparison are lacking [50]. Several efforts have been initiated to standardize anti-AAV antibody assays [50–52]. This remains an important issue because the presence of anti-AAV antibodies is a strict exclusion criteria for treatment with VR, but for ED, it is not [24,25]. With the limited data that are available, the phase 3 study with ED suggests that titers >1:678 may hamper transgene expression and reduce treatment efficacy [40]. A trial is underway to more precisely determine cutoff points for efficacy of ED (NCT06003387).

Notably, currently published guidance documents are all from developed countries with prior gene therapy experience from trials and appropriate (laboratory) facilities to work with genetically modified organisms, promoting clinical implementation. Developing countries might face challenges in the realization of this treatment modality due to limited experience and knowledge, and absence of qualified treatment centers [53]. Besides, the higher incidence of hepatitis B and C viral infections and preexisting AAV antibodies may reduce the number of eligible patients, and the lack of centralized patient registries can complicate the identification process. Strong international collaboration and sharing of experiences and knowledge is essential to enhance access.

Following this review and current literature limitations in gene therapy remain. Most important limitations comprise the lack of standardization on (1) anti-AAV assay type to screen for preexisting antibodies, (2) type of FVIII/FIX assay to monitor treatment efficacy, and (3) the evaluation of liver health. Moreover, the practical implementation of the hub and spoke model should be determined and consensus is needed on the length and intensity of follow-up especially in case of declining factor activity levels.

This review is, however, limited to SMPCs and (inter)national guidance documents. As only a limited number of patients has been treated outside gene therapy trials, real-world and registry data on the gene therapy care pathway is still hardly available. Therefore, the practical implementation of the developed care pathway is yet unknown. This should be evaluated in future studies after which the care pathway can be adapted with integration of real-world and registry data when they become available.

5 | CONCLUSION

This review provides a complete and comprehensive overview of current guidance documents and SMPCs regarding the entire gene therapy delivery process in hemophilia and highlights existing differences among regulatory authorities, gene therapy products, and countries. In addition, based on these guidance documents and SMPCs, a care pathway has been developed and visualized in a Metro Map, comprising a clear overview of all activities, contact moments, and responsibilities within the longitudinal gene therapy treatment process. Adapted to local practice, this comprehensive care pathway may further navigate gene therapy implementation providing guidance to clinicians from different institutions, patients, and caregivers.

AUTHOR CONTRIBUTIONS

C.M.A.M.: study design, data collection, data analysis, data interpretation, original draft, review process, writing. W.M.: study design, data collection and interpretation, review and editing. P.C., D.L., J.M., F.P., S.W.P., A.S., J.V., G.F.P., R.K., P.B., I.C., A.N.: review and editing. F.W.G.L.: study design, data interpretation, review and editing, and supervision. This manuscript was approved for submission by all authors.

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REFERENCES

[1] Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica*. 2020;105:545–53.

[2] Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397:630–40.

[3] Franchini M, Marano G, Pati I, Candura F, Profili S, Veropalumbo E, Masiello F, Catalano L, Piccinini V, Vaglio S, Pupella S, Liumbruno GM. Emicizumab for the treatment of haemophilia A: a narrative review. *Blood Transfus*. 2019;17:223–8.

[4] Mahlangu J, Luis Lamas J, Cristobal Morales J, Malan DR, Teeter J, Charnigo RJ, Hwang E, Arkin S. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: phase II study results. *Br J Haematol*. 2023;200:240–8.

[5] Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, d'Oiron R, Frei-Jones M, Goh AS, Haaning J, Hald Jacobsen S, Mahlangu J, Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K, Villarreal Martinez L, et al. Phase 3 trial of concizumab in hemophilia with inhibitors. *N Engl J Med*. 2023;389:783–94.

[6] Young G, Srivastava A, Kavakli K, Ross C, Sathar J, You CW, Tran H, Sun J, Wu R, Poloskey S, Qiu Z, Kichou S, Andersson S, Mei B, Rangarajan S. Efficacy and safety of fitusiran prophylaxis in people with haemophilia A or haemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial. *Lancet*. 2023;401:1427–37.

[7] Skinner MW, Négrier C, Paz-Priel I, et al. The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies. *Haemophilia*. 2021;27:854–65.

[8] Tran H, von Mackensen S, Abraham A, Castaman G, Hampton K, Knoebl P, Linari S, Odgaard-Jensen J, Neergaard JS, Stasyshyn O, Thaung Zaw JJ, Zulfikar B, Shapiro A. Concizumab prophylaxis in persons with hemophilia A or B with inhibitors: patient-reported outcome results from the phase 3 explorer7 study. *Res Pract Thromb Haemost*. 2024;8:102476. https://doi.org/10.1016/j.rpth.2024.102476

[9] Gualtierotti R, Solimeno LP, Peyvandi F. Hemophilic arthropathy: current knowledge and future perspectives. *J Thromb Haemost*. 2021;19:2112–21.

[10] Chowdary P. Nonfactor therapies: new approaches to prophylactic treatment of haemophilia. *Hamostaseologie*. 2021;41:247–56.

[11] Samelson-Jones BJ, George LA. Adeno-associated virus gene therapy for hemophilia. *Annu Rev Med*. 2023;74:231–47.

[12] Coppens M, Pipe SW, Miesbach W, Astermark J, Recht M, van der Valk P, Ewenstein B, Pinachyan K, Galante N, Le Quellec S, Monahan PE, Leebeek FWG, HOPE-B Investigators. 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 Haematol*. 2024;11:e265–75.

[13] O'Mahony B, Dunn AL, Leavitt AD, Peyvandi F, Ozelo MC, Mahlangu J, Peerlinck K, Wang JD, Lowe GC, Tan CW, Giermasz A, Tran H, Khoo TL, Cockrell E, Pepperell D, Chambost H, López Fernández MF, Kazmi R, Majerus E, Skinner MW, et al. Health-related quality of life following valoctocogene roxaparvovec gene therapy for severe hemophilia A in the phase 3 trial GENEr8-1. *J Thromb Haemost*. 2023;21:3450–62.

[14] Itzler R, Buckner TW, Leebeek FWG, Miller J, Recht M, Drelich D, Monahan PE, Pipe SW. 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*. 2024;30:709–19.

[15] Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. *Blood*. 2021;138:923–31.

[16] Maina A, Foster GR. Hepatitis after gene therapy, what are the possible causes? *J Viral Hepat*. 2024;31(Suppl 1):14–20.

[17] Pierce GF, Fong S, Long BR, Kaczmarek R. Deciphering conundrums of adeno-associated virus liver-directed gene therapy: focus on hemophilia. *J Thromb Haemost*. 2024;22:1263–89.

[18] Leavitt AD, Mahlangu J, Raheja P, Symington E, Quon DV, Giermasz A, López Fernández MF, Kenet G, Lowe G, Key NS, Millar CM, Pipe SW, Madan B, Chou SC, Klamroth R, Mason J, Chambost H, Peyvandi F, Majerus E, Pepperell D, 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. *Res Pract Thromb Haemost*. 2024;8:102615. https://doi.org/10.1016/j.rpth.2024.102615

[19] Chowdary P, Shapiro S, Makris M, Evans G, Boyce S, Talks K, Dolan G, Reiss U, Phillips M, Riddell A, Peralta MR, Quaye M, Patch DW, Tuddenham E, Dane A, Watissée M, Long A, Nathwani A. Phase 1-2 trial of AAVS3 gene therapy in patients with hemophilia B. *N Engl J Med*. 2022;387:237–47.

[20] Konkle B, Pierce G, Coffin D, Naccache M, Clark RC, George L, Iorio A, O'Mahony B, Pipe S, Skinner M, Watson C, Peyvandi F, Mahlangu J, ISTH subcommittee on Factor VIII, Factor IX, rare bleeding disorders. Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020;18:3074–7.

[21] Miesbach W, Boban A, Chowdary P, Coppens M, Crato M, Jimenez-Yuste V, Klamroth R, Makris M, Mulders G, Peyvandi F. EAHAD haemophilia gene therapy clinical outcome database (EAHAD-GTD). *Haemophilia*. 2024;30:852–4.

[22] Miesbach W, Konkle B, Chowdary P, Kaczmarek R, Leebeek F, Mahlangu J, Makris M, Pipe SW, Srivastava A, Voorberg J, Pierce GF, Peyvandi F. Recommendations for a minimum data set for monitoring gene therapy in hemophilia: communication from the ISTH SSC Working Group on Gene Therapy. *J Thromb Haemost*. 2024;22:1510–5.

[23] European Medicines Agency. Roctavian: EPAR—product information. https://www.ema.europa.eu/en/documents/product-information/roctavian-epar-product-information_en.pdf; 2022 [accessed September 17, 2024].

[24] European Medicines Agency. Hemgenix: EPAR—product information. https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf; 2023 [accessed September 17, 2024].

[25] U.S. Food & Drug Administration. Package Insert—HEMGENIX. https://www.fda.gov/media/163467/download?attachment; 2022 [accessed September 17, 2024].

[26] U.S. Food & Drug Administration. Package Insert—ROCTAVIAN. https://www.fda.gov/media/169937/download?attachment; 2023 [accessed September 17, 2024].

[27] Miesbach W, Chowdary P, Coppens M, Hart DP, Jimenez-Yuste V, Klamroth R, Makris M, Noone D, Peyvandi F. 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*. 2021;27:967–73.

[28] Australian Haemophilia Centre Directors' Organisation. Clinical impementation plan; a roadmap for the implementation of gene therapy for haemophilia in Australia. https://static1.squarespace.com/static/65e57496e7267569196f1baf/t/664c768f6f08a82eef4ce1ef/1716287124047/20221014.AHCDO.ClinicalImplementationPlan+F.pdf; 2022 [accessed September 10, 2024].

[29] Boban A, Baghaei F, Karin F, Klamroth R, Miesbach W, Stephensen D, Kavanagh M, Noone D, Crato M, Peyvandi F, EAHAD Accreditation and Audit of Haemophilia Centres Working Group. Accreditation model of European Haemophilia Centres in the era of novel treatments and gene therapy. *Haemophilia*. 2023;29:1442–9.

[30] Castaman G, Carulli C, De Cristofaro R, Follino M, Lupi A, Mancuso ME, Mansueto MF, Molinari AC, Pasquetti P, Santoro C, Santoro RC, Siragusa S, Solimeno LP, Tripodi A, Zanon E, Minno GD. Laying the foundations for gene therapy in Italy for patients with haemophilia A: a Delphi consensus study. *Haemophilia*. 2023;29:435–44.

[31] Castaman G, Di Minno G, Simioni P, Molinari AC, Siragusa S, Baldacci E, La Mura V, Lupi A, Grazzi EF, Peyvandi F. Gene therapy for people with Haemophilia B: a proposed care delivery model in Italy. *J Thromb Haemost*. 2024;22:3084–94.

[32] Chowdary P, Duran B, Batty P, Lowe G, Jones A, Pollard D, Boyce S, Motwani J, Amirloo B, Musgrave K, Hopper D, Classey S, Whitaker S, Dunn N, Bowyer A, Shapiro S. UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults. *Haemophilia*. 2025;31:26–38.

[33] Miesbach W, Oldenburg J, Klamroth R, Eichler H, Koscielny J, Holzhauer S, Holstein K, Hovinga JAK, Alberio L, Olivieri M, Knöfler R, Male C, Tiede A. *[Gene therapy of Hemophilia: Recommendations from the German, Austrian, and Swiss Society for Thrombosis and Haemostasis Research (GTH)]*. 43. Hamostaseologie; 2023:196–207.

[34] Miesbach W, Pasi KJ, Pipe SW, Hermans C, O'Mahony B, Guelcher C, Steiner B, Skinner MW. Evolution of haemophilia integrated care in the era of gene therapy: treatment centre's readiness in United States and EU. *Haemophilia*. 2021;27:511–4.

[35] National Bleeding Disorders Foundation. MASAC recommendations on hemophilia treatment center preparedness for delivering gene therapy for hemophilia. https://www.bleeding.org/sites/default/files/document/files/MASACGeneTherapyPreparedness.pdf; 2023 [accessed May 22, 2024].

[36] Pietu G, Giraud N, Chamouard V, Duport G, Lienhart A, Dargaud Y. Perspectives and perception of haemophilia gene therapy by French patients. *Haemophilia*. 2024;30:68–74.

[37] Pipe S, Douglas K, Hwang N, Young G, Patel P, Fogarty P. Delivery of gene therapy in haemophilia treatment centres in the United States: practical aspects of preparedness and implementation. *Haemophilia*. 2023;29:1430–41.

[38] Villas JMC, López MR, Tovar JC, Boix SB, Calatayud JCR, Álvarez-Román MT. Suitability and readiness assessment of organizational resources for the implementation of gene therapy in hemophilia in Spain and Portugal: a survey-based study. *Thromb Res*. 2024;244:109180.

[39] Stiggelbout A, Griffioen I, Brands J, Melles M, Rietjens J, Kunneman M, van der Kolk M, van Eijck C, Snelders D. Metro Mapping: development of an innovative methodology to co-design care paths to support shared decision making in oncology. *BMJ Evid Based Med*. 2023;28:291–4.

[40] Pipe SW, Leebeek FWG, Recht M, Key NS, Castaman G, Miesbach W, Lattimore S, Peerlinck K, Van der Valk P, Coppens M, Kampmann P, Meijer K, O'Connell N, Pasi KJ, Hart DP, Kazmi R, Astermark J, Hermans CRJR, Klamroth R, et al. Gene therapy with etranacogene dezaparvovec for hemophilia B. *N Engl J Med*. 2023;388:706–18.

[41] Robinson M, George LA, Samelson-Jones BJ, Arruda VR, High KA, Carr ME, Tiefenbacher S. Activity of a FIX-Padua transgene product in commonly used FIX:C one-stage and chromogenic assay systems following PF-06838435 (SPK-9001) gene delivery. *Blood*. 2018;132:2198.

[42] U.S. Food & Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools; November 11, 2024 [accessed November 26, 2024].

[43] Coffin D, Skinner MW, Thornburg CD, Hayes BK, Sannié T, Kaeser GE, Chadwick J, Naccache M, Pierce GF. Development of the World Federation of Hemophilia shared decision-making tool. *Haemophilia*. 2024;30:1298–308.

[44] Wang M, Negrier C, Driessler F, Goodman C, Skinner MW. The hemophilia gene therapy patient journey: questions and answers for shared decision-making. *Patient Prefer Adherence*. 2022;16:1439–47.

[45] Miesbach W, Boban A, Chowdary P, Coppens M, Crato M, Jimenez-Yuste V, Klamroth R, Makris M, Mulders G, Peyvandi F. Administration of gene therapy for haemophilia—the hub and spoke model and its regional differences and challenges. *Haemophilia*. 2024;30:855–7.

[46] Robinson MM, George LA, Carr ME, Samelson-Jones BJ, Arruda VR, Murphy JE, Rybin D, Rupon J, High KA, Tiefenbacher S. Factor IX assay discrepancies in the setting of liver gene therapy using a hyperfunctional variant factor IX-Padua. *J Thromb Haemost*. 2021;19:1212–8.

[47] Rosen S, Tiefenbacher S, Robinson M, Huang M, Srimani J, Mackenzie D, Christianson T, Pasi KJ, Rangarajan S, Symington E, Giermasz A, Pierce GF, Kim B, Zoog SJ, Vettermann C. Activity of transgene-produced B-domain-deleted factor VIII in human plasma following AAV5 gene therapy. *Blood*. 2020;136:2524–34.

[48] van Moort I, Meijer P, Priem-Visser D, van Gammeren AJ, Péquériaux NCV, Leebeek FWG, Cnossen MH, de Maat MPM. Analytical variation in factor VIII one-stage and chromogenic assays: Experiences from the ECAT external quality assessment programme. *Haemophilia*. 2019;25:162–9.

[49] Miesbach W, Batty P, Chowdary P, Fong S, Kaczmarek R, Leebeek FWG, Long B, Mahlangu J, Makris M, Pierce GF, Pipe SW, Srivastava A, Voorberg J, Peyvandi F. Adeno-associated virus-based gene therapy for haemophilia—addressing the gaps. *Res Pract Thromb Haemost*. 2024;9:102673. https://doi.org/10.1016/j.rpth.2024.102673

[50] Miesbach W, Batty P, Chowdary P, Fong S, Long B, Mahlangu J, Pierce GF, Srivastava A, Peyvandi F. Communication of the ISTH SSC Gene Therapy Working Group: standardization of methods in hemophilia gene therapy. https://cdn.ymaws.com/www.isth.org/resource/resmgr/ssc/ssc_admin/Final_2023_Gene_therapy_ISTH.pdf; 2023 [accessed July 1, 2025].

[51] Falese L, Sandza K, Yates B, Triffault S, Gangar S, Long B, Tsuruda L, Carter B, Vettermann C, Zoog SJ, Fong S. Strategy to detect pre-existing immunity to AAV gene therapy. *Gene Ther*. 2017;24:768–78.

[52] Patton KS, Harrison MT, Long BR, Lau K, Holcomb J, Owen R, Kasprzyk T, Janetzki S, Zoog SJ, Vettermann C. Monitoring cell-mediated immune responses in AAV gene therapy clinical trials using a validated IFN-γ ELISpot method. *Mol Ther Methods Clin Dev*. 2021;22:183–95.

[53] Kavaklı K, Antmen B, Okan V, Şahin F, Aytaç S, Balkan C, Berber E, Kaya Z, Küpesiz A, Zülfikar B. Gene therapy in haemophilia: literature review and regional perspectives for Turkey. *Ther Adv Hematol*. 2022;13:20406207221104591. https://doi.org/10.1177/20406207221104591

SUPPLEMENTARY MATERIAL

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