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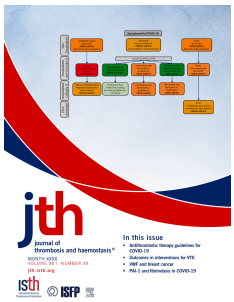

A comprehensive care pathway of gene therapy for hemophilia based on current guideline documents and Summary of Product Characteristics (SMPCs); Communication from the ISTH SSC Working Group on Gene Therapy

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Title: A comprehensive care pathway of gene therapy for hemophilia based on current guideline documents and Summary of Product Characteristics (SMPCs); 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 multi-stakeholder preparedness and clear guidelines. In addition to pharmaceutical Summaries of Product Characteristics (SMPCs), various (inter)national guidance documents have been published. However, no guidance document or SMPC covers the entire gene therapy care pathway.

Study objectives: To provide 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 eleven (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 two approved gene therapy products and between the SMPCs issued by the two regulatory authorities, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). (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: Hemophilia; gene therapy; care pathway; guideline; implementation;

1. Introduction

Over the past years the therapeutic landscape for hemophilia has expanded as new non-factor 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 adeno-associated viral vectors (AAV) 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 FIX activity of 40-100 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 hemophilia A patients, 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 pre-existing 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 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 hemophilia A.[15,19] Therefore, 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 ISTH SSC together have proposed a (core) data set 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 (Roctavian®, hemophilia A) and etranacogene dezaparvovec (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 necessitates 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 multi-stakeholder 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 aims 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 treaters 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 1st 2024 and January 31st 2025. Relevant search terms included "hemophilia", "gene therapy" and "guideline" in various configurations. Moreover, SMPCs and United States Prescribing Information (USPIs) of approved gene therapies from respectively the EMA and FDA were collected, from here 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 valoctocogene roxaparvovec (VR) and etranacogene dezaparvovec (ED).[23-26] In addition, eleven published national and international guidance documents and recommendations, including publications from scientific societies, were gathered, and two articles on (core) data sets 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 (site preparation, screening, administration and/or follow-up),[31-33,35,37] others focused on care delivery models and required preparational steps towards 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 e.g. 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 which are systematically outlined below, we have developed a care pathway for AAV-based hemophilia gene therapy delivery, visualized in a Metro Map (Figure 1).[39] Metro Mapping is a service design tool for co-designing 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 supplement, allowing for modification of the care pathway according to local practice.

Within the care pathway five different phases can be identified:

(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 therapy product and preparation for infusion. Day of infusion consists of gene therapy administration, post-infusion 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, the Spoke is a follow-up center, usually patients' home center, that 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; post-infusion 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. 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; and 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 re-education 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 AAV-5. Patients should have a negative *history* of FVIII inhibitors according to the EMA,[23] or have absent *active* inhibitors according to the FDA.[26]

ED is available for adults with severe and moderately severe hemophilia B. Factor IX activity levels are not specified in SMPCs, but according to the FDA patients should currently use factor IX 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 should have a negative history of FIX inhibitors to 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 is limited and one 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 two weeks in case of a positive 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 only required by FDA), with possibly required retesting for some tests according to the EMA. Additionally, VR requires assessment of gamma-glutamyl transferase (GGT) and international normalized ratio (INR).[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 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 1.5-1.6-fold higher result compared to 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 (UK) 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) 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 pre- and post-infusion, and should also be extended to individuals who are deemed ineligible or who choose not to proceed. Pre-infusion 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 and HIV status[32,33], as well as measurement of alpha feto-protein (AFP).[31,37]

3.3.4. Shared decision making: patient information and discussion topics

The screening phase includes consultations with healthcare professionals in which information on gene therapy is provided to the patient. Gene therapy should be presented as one option 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 UK,[32] a comprehensive overview of information that should be covered according to SMPCs and available guidance documents is displayed in Supplement 1.[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, thrombo-embolism, 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-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. Healthcare 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 2-8°C for 3 days after thawing.[23,26] The recommended dose of VR is a single dose of $6x10^{13}$ vg/kg.[23,26] After preparation the infusion should be completed within 10 hours at 25°C. ED stored at 2-8°C and the recommended dose is $2x10^{13}$ gc/kg.[24,25] After preparation the infusion should be completed within 24 hours.

During preparation and administration personal protective equipment is recommended, only the 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 min by 1mL/min to a maximum of 4 mL/min and flushed afterwards at the same rate.[23,26] ED is infused continuously at 500 mL/hour (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]

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, 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, MASAC, United States (US), and UK 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 US and UK 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] MASAC, the US and UK 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 UK 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 (CPK) is recommended by the EMA to evaluate for alternative causes of ALT elevation,[23,24] which the FDA only recommends 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 AFP 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 UK recommend follow-up schedules according to SMPCs,[30-32] although the UK 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 onwards.[33] Moreover, GTH recommends the measurement of lactate dehydrogenase (LDH), GGT, ALP 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 US highlights continuation of follow-up care to monitor potential long-term risks, also 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 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 UK and US recommend immunosuppressive approach based on the product specific SMPC,[32,37] while GTH aligns with 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 six 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 enough to prevent spontaneous bleeding.[23,24]

Reinitiation of FVIII/FIX concentrates is recommended if FVIII/FIX activity is consistently below 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 2-5% for at least two 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 (GTR),[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 data set for longitudinal data collection in the WFH GTR and a minimum data set to enhance data collection and ensure documentation of most essential data.[20,22] This subset includes data on efficacy and safety among others, e.g. 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]

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 two regulatory authorities FDA and EMA respectively, e.g. regarding inclusion and exclusion criteria, diagnostic assessment for gene therapy eligibility and recommended follow-up regimen. Differences were also found between the two 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 e.g. the geographical distribution of HTCs and HTCs possibility to administer gene therapy, as available facilities may differ.[27,45] Moreover, with two 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 intra- and inter-individual 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 complicates interpretation and comparability of long-term collected data in registries to evaluate safety. Data with immunosuppression other than corticosteroids is 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 above 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 (NCT 06003387).

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 qualitied treatment centers.[53] Besides, the higher prevalence of hepatitis B and C infections and pre-existing 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 it becomes available.

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 between 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:

Caroline M.A. Mussert: study design, data collection, data analysis, data interpretation, original draft, review process, writing

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WM: Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, sobi, Takeda/Shire, uniQure.

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FP has served on the advisory committee of CSL Behring, Biomarin, Roche, Sanofi, Sobi and Pfizer; and has participated in educational meetings and symposia for Takeda, Sanofi and Kedrion.

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GP is an advisor to ASC Therapeutics, BioMarin, Inovio, Novo Nordisk, Regeneron, Roche/Genentech, Sanofi, St. Jude Children's Hospital, Third Rock Ventures, Typewriter. He is a member of the Scientific advisory boards of Be Bio, Frontera, hC Bio, Metagenomi, US National Bleeding Disorders Fdn (NBDF) Medical and Scientific Advisory Council (MASAC).

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Figure 1. *Proposed care pathway for gene therapy delivery in hemophilia*

Table 1. *Overview of current SMPCs 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 haemophilia in Australia.	Australian Haemophilia Centre Directors' Organisation [28]	2022	Australia	Both
Delivery of gene therapy in haemophilia treatment centers in the United States: Practical aspects of preparedness and implementation.	Pipe [37]	2023	United States	Both
Perspectives and perception of haemophilia gene therapy by French patients.	Pietu [36]	2023	France	Both
Laying the foundations for gene therapy in Italy for patients with Haemophilia: A Delphi consensus study. Gene therapy for people with haemophilia B: a proposed care delivery model in Italy.	Castaman [30] Castaman [31]	2022 2024	Italy	Hemophilia A Hemophilia B
UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults.	Chowdary [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 [38]	2024	Spain and Portugal	Both
International guidance documents and scientific societies				
Evolution of haemophilia integrated care in the era of gene therapy: Treatment centre's readiness in United States and EU.	Miesbach [34]	2021	United States and EU	Both
Gene therapy for haemophilia: recommendations from the German, Austrian, and Swiss Society for Thrombosis and Haemostasis Research (GTH).	Miesbach [33]	2022	Germany, Austria, 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 [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 [20]	2020	WFH	Both
Recommendations for a minimum data set for monitoring gene therapy in hemophilia:	Miesbach [22]	2023	ISTH	Both

Communication from the ISTH SSC Working Group on Gene Therapy.				

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)* - No detectable antibodies to AAV-5	- Severe and moderately severe hemophilia B *who* ** Currently use factor IX prophylaxis (FDA)* ** Have current or historical life-threatening hemorrhage (FDA)* ** Have repeated, serious spontaneous bleeding episodes (FDA)* - Adult patients *- No history of FIX inhibitors (EMA) or no presence of active FIX inhibitors (FDA)*
Exclusion criteria	*- History of FVIII inhibitors (EMA), presence of active FVIII inhibitors (FDA)* - Anti-AAV-5 antibodies - Age < 18 years - Hypersensitivity to the product excipients - Active infections (acute or uncontrolled chronic) - Significant hepatic fibrosis or cirrhosis	- Presence of FIX inhibitors - Age < 18 years *- Hypersensitivity to the product excipients (EMA)* *- Active infections (acute or uncontrolled chronic) (EMA)* *- Advanced hepatic fibrosis or cirrhosis (EMA)*

Differences between SMPCs of EMA and USPIs of FDA are highlighted in italic.

Table 3. *Diagnostic assessment for gene therapy eligibility*

Valoctocogene roxaparvovec (HemA) [23,26]	**Etranacogene dezaparvovec (HemB)** [24,25]
FVIII inhibitors	FIX inhibitors (1x repeated within 2 weeks if positive)
Liver function: * - ALT ** - AST - GGT - Total bilirubin - INR - *Alkaline Phosphatase (FDA)*	Liver function: * - ALT ** - AST - Total bilirubin - Alkaline phosphatase
Anti-AAV antibodies	Anti-AAV antibodies *(encouraged to be tested in antibody study – FDA)*
Fibrosis assessment: liver ultrasound and elastography or laboratory assessment ***	Fibrosis assessment: liver ultrasound and elastography ***

* Within 3 months according to the EMA

** 1x repeated according to the EMA. Regarding valoctocogene roxaparvovec an average of prior measurements can be used for baseline value according to the EMA.

*** Within 6 months according to the EMA

Differences between SMPCs of EMA and USPIs of FDA are highlighted in italic.

Table 4. *Additional assessments before gene therapy*

Medical history	**Assessments**	**Additional diagnostic assessments**
- Hemophilia specific history: o Current treatment o Current bleed control o Inhibitor history o Factor 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: o Joint score (HJHS) o Joint ultrasound o Optional: HEAD-US score o Optional: 6-minute walk test o Optional: timed up and go - Psychological/psychosocial assessment (by a psychologist or social worker) - Quality of life measures: o Haemophilia Activities List (HAL) o EQ5D	- Full blood count - Renal function - Alpha feto-protein - Virology (hepatitis B/C/HIV)

Table 5. *Preparation and handling of gene therapy*

	Valoctocogene roxaparvovec (HemA) [23,26]	**Etranacogene dezaparvovec (HemB)** [24,25]
Shelf-life	*3 years (EMA)*	*24 months (EMA)*
Dose	6 x 10^{13} vg/kg	2 x 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 days 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)* 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, mask (EMA)*	*Gloves, safety goggles, protective clothing, mask (EMA)*

Differences between SMPCs of EMA and USPIs of FDA are highlighted in italic.

Table 6. *Monitoring of hepatic function and FVIII/FIX 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)* and FIX:Act	
First 26 weeks	Once per week	First 3 months	Once per week
Weeks 26-52	*Every 2-4 weeks (EMA)* *Every 1-2 weeks (FDA)*	*Months 4-12 (EMA)* *Year 2 (EMA)*	*Every 3 months* *FIX:Act > 5 IU/dl: every 6 months*
Year 2	FVIII:Act > 5 IU/dl: every 3 months FVIII:Act ≤ 5 IU/dl: more frequently		*FIX:Act ≤ 5 IU/dl: more frequently*
After year 2	FVIII:Act > 5 IU/dl: every 6 months FVIII:Act ≤ 5 IU/dl: more frequently	*After year 2 (EMA)*	*FIX:Act > 5 IU/dl: annually* *FIX:Act ≤ 5 IU/dl: more frequently*
FVIII inhibitors *		FIX inhibitors *	
*In patients with preexisting risk factors** for hepatocellular carcinoma: Regular (annually) liver ultrasound screening and AFP monitoring for at least 5 years (FDA)*		In patients with preexisting risk factors** for hepatocellular carcinoma: Regular (annually) liver ultrasound screening and AFP monitoring for at least 5 years	

* Especially if bleeding is not controlled or plasma FVIII/FIX activity decreases

** Such as hepatic fibrosis, hepatitis C or B, non-alcoholic fatty liver disease

Differences between SMPCs of EMA and USPIs of FDA are highlighted in italic.

Table 7. *Initiation of corticosteroids and recommended treatment regimen*

Valoctocogene roxaparvovec (HemA) [23,26]	**Etranacogene dezaparvovec (HemB)** [24,25]
Start corticosteroid treatment: - ALT > upper limit of normal - ALT > 1.5x baseline - Absence of other cause for ALT increase	**Start corticosteroid treatment:** - ALT > upper limit of normal - ALT > 2x baseline
Starting dose: * 60 mg/day prednisone or equivalent dose of another corticosteroid Week 1-2: 60 mg/day Week 3-5: 40 mg/day Week 6: 30 mg/day Week 7: 20 mg/day Week 8: 10 mg/day 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	**Starting dose:** 60 mg/day prednisolone or prednisone Week 1: 60 mg/day Week 2: 40 mg/day Week 3: 30 mg/day Week 4: 30 mg/day After week 4: 20 mg/day maintenance dose until ALT level returns to baseline level
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/week.

* ALT test should be repeated within 24-48 hour to confirm ALT elevation prior to initiation of corticosteroid treatment.

Differences between SMPCs of EMA and USPIs of FDA are highlighted in italic.

Hemophilia gene therapy care pathway

METRO MAPPING

The purpose of this medical Metro Map is to describe the care pathway for patients with hemophilia undergoing gene therapy. It describes the care pathway regarding site preparation and readiness, referral, screening, handling and preparation of gene therapy product, day of infusion, follow-up, and treatment and follow-up in case of transaminase elevations.

This medical Metro Map is based on gene therapy product SMPCs and published (inter)national guidance documents and recommendations.

This medical Metro Map has been developed by Caroline Mussert and Frank Leebeek in collaboration with the ISTH SSC Working Group on Gene Therapy.

Colours

P	Light grey: Site preparation and readiness
R	Dark grey: Referral
S	Fuchsia: Screening
HP	Handling and preparation
I	Yellow: Day of infusion
F	Green: Follow-up
ELE	Blue: Treatment and follow-up in case of transaminase elevation

Legend

- Treatment path of the patient
- Preceding trajectory
- Step without participation or presence of the patient
- Treatment step (no consultation)
- Consultation – discussion with patient (possibility to adjust treatment path)
- Discussion with the patient and planned shared decision making moment: patient choise required
- Phase transfer: patient will continue path in another metro line
- Consultation or treatment step that is repeated several times
- Multiple consultations or treatment steps that are repeated several times
- Stop: The patient stops treatment or exits the Metro line
- Switch-over: patient switches to another phase in the current Metro line or switches to another Metro line
- Duration

Site preparation and readiness

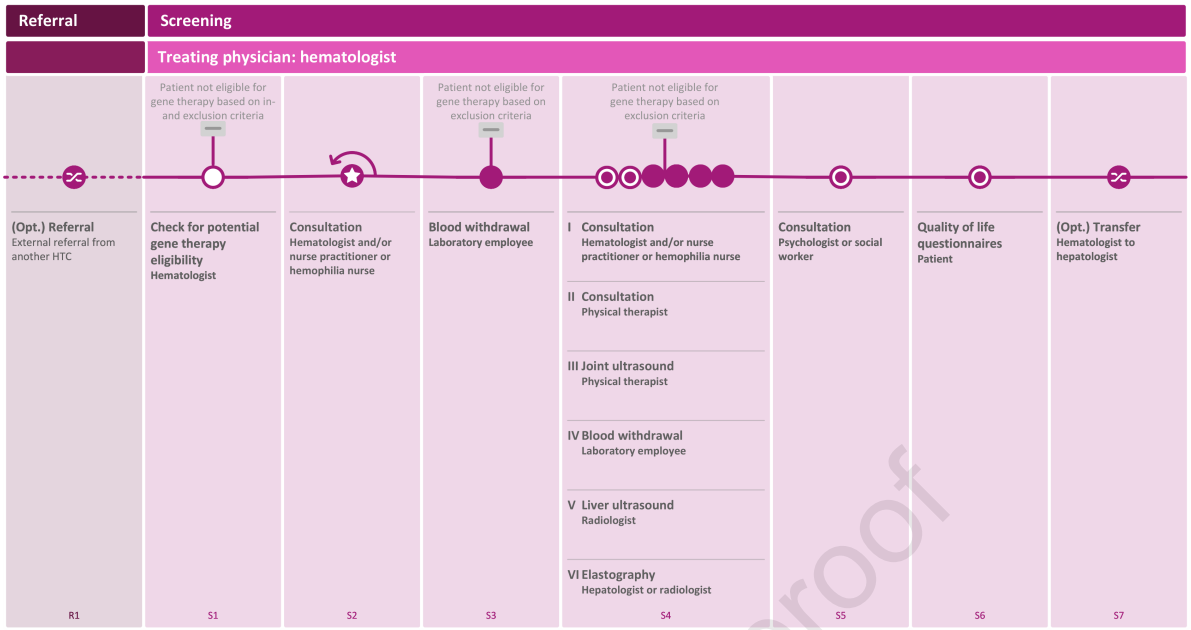
Medical Metro line

P1	P2	P3	P4	P5
(Opt.) Accreditation for gene therapy treatment center HTC director	Assessment of gene therapy quality register HTC director	Biological risk assessment Biosafety officer	I Prepare necessary facilities and equipment HTC director II Development of protocols, SOPs and guidance documents HTC director	I Training and education of personnel Multidisciplinary care team II Annual retraining Multidisciplinary care team III Documentation of training Data manager

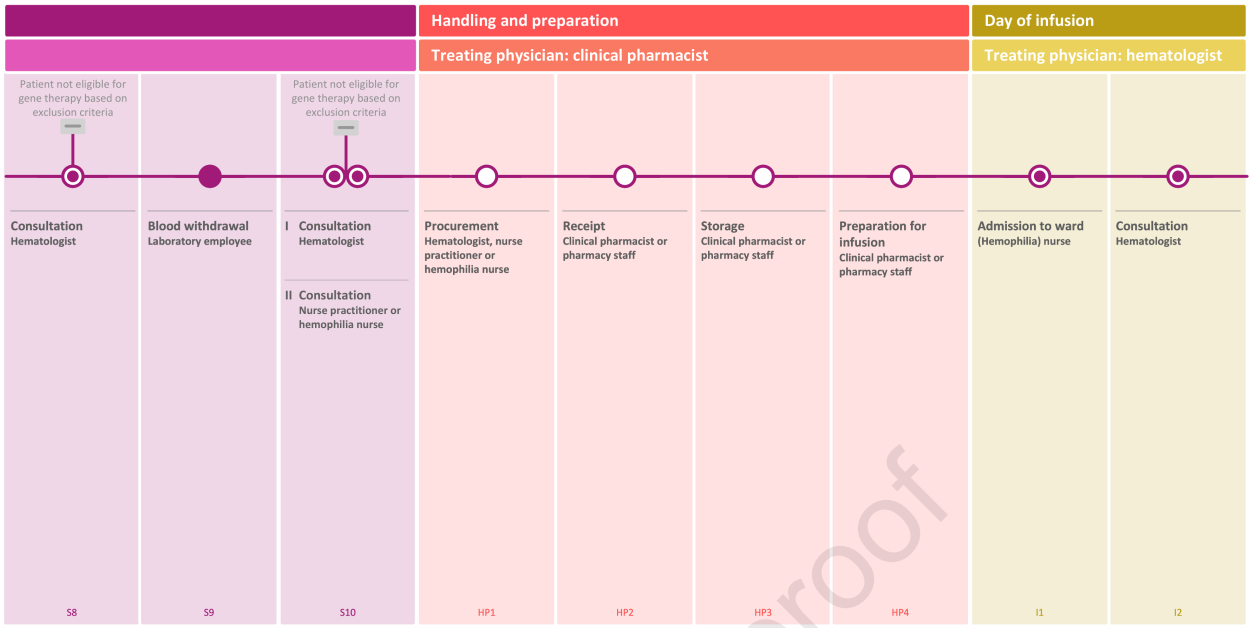
Context

	In some countries accreditation is required.		I) Necessary facilities and equipment for gene therapy product handling, preparation and administration should be available. II) SOPs for gene therapy procurement, receipt, storage, preparation and administration. Guidelines and guidance documents with regard to: - Insurance authorization and reimbursement - Patient eligibility - Patient screening - Patient information and education - Day of infusion - Follow-up - Data collection and sharing between registries - Framework with hub and spoke responsibilities if they are different institutions	All involved members of the multidisciplinary care team should receive training and education on gene therapy, based on their role and activities. Specific educational models should be completed, for which different programs and online modules are available. Multidisciplinary core team consists of: hematologists, nurse practitioners, (hemophilia) nurses, physical therapists, psychologists, social workers, pharmacy staff and clinical pharmacists, and hemophilia laboratory team. Additional team members: hepatologists, immunologists, orthopedists, anesthesiologists, data managers and financial administrators

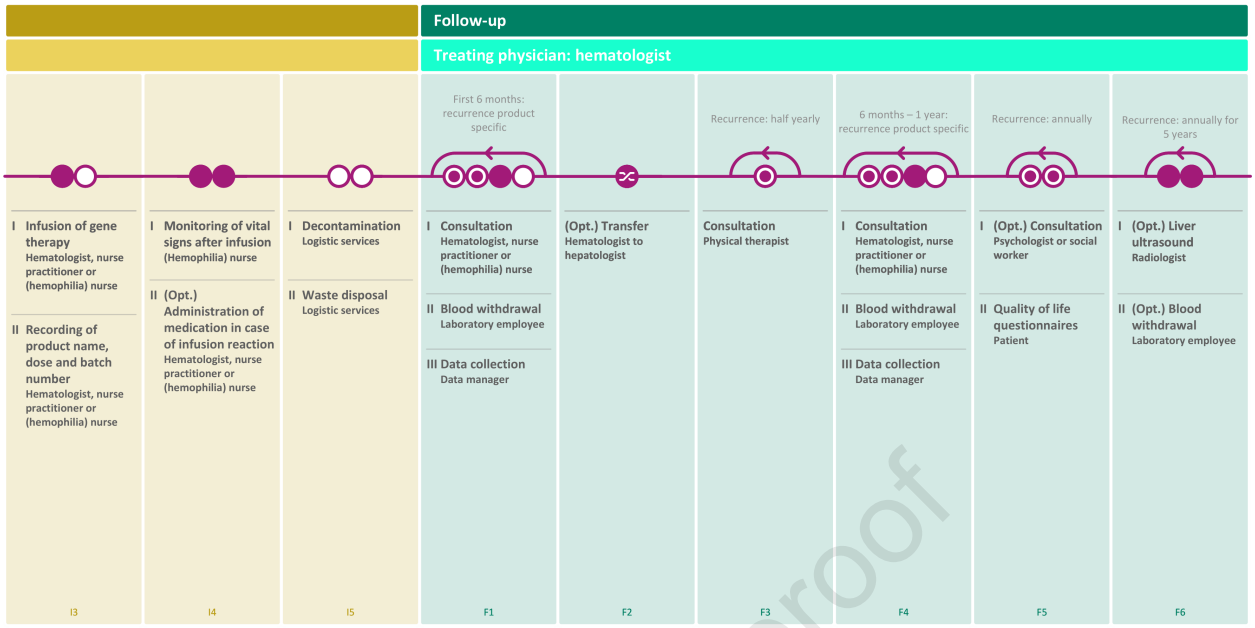
Content consultation | Discussed information



	Check product-specific inclusion and exclusion criteria according to SMPC for potential gene therapy eligibility.	Discuss gene therapy as treatment option within the therapeutic landscape for hemophilia and provide information to the patient. Discussions on gene therapy should have a shared decision making approach and information should be given over multiple visits to ensure an informed decision making. Provide patient with comprehensive written information.	Early assessment of AAV antibodies to reduce patient disappointment and delays.	I) - Medical history - Physical examination - Height and weight - Vital signs II-III) Musculoskeletal assessment: HJHS and joint ultrasound. Optional: - HEAD-US score - 6-minute walk test - Timed up and go IV) According to SMPC - Full blood count - FVIII/FIX inhibitors - Hemostasis: PT, APTT, FVIII or FIX activity (chromogenic and one-stage) - Liver function: ALT, AST, GGT, total bilirubin, alkaline phosphatase, INR, alpha feto-protein (AFP) - Renal function - Virology: Hepatitis B/C, HIV	Consultation with psychologist or social worker for psychological or psychosocial assessment.	Quality of life assessment with hemophilia specific questionnaires: - Haemophilia Activities List - EQ5D Quality of life questionnaires can be completed by the patient at home.	Referral to hepatologist for evaluation of hepatic function and/or hepatitis B/C and HIV testing.
		Hematologist Information provision according to table x: (1) gene therapy basics; (2) benefits; (3) risks including infusion reactions, hepatotoxicity and possible requirement of corticosteroids, thrombo-embolism, development of FVIII/ FIX inhibitors, malignancy in relation to vector genome integration, horizontal and germline transmission, and details on how these risks can be minimized; (4) treatment response including unpredic-tive variability and possibility of non-respondence; (5) potential outcomes and unpredictability of long-term treatment effect; (6) long-term safety and mission information; (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. Check understanding and expectations.		**Hematologist** Medical history: hemophilia specific (current treatment, current bleed control, inhibitor history, FVIII/FIX mutation), joint procedures to date, allergies, previous allergies to blood products, vaccinations, mean alcohol consumption, medical comorbidities, concomitant medication and medicinal herbs use,	**Psychologist or social worker** Discuss implications of treatment on identity/social life.		



	In case of a positive FVIII/FIX inhibitor test: repeated within 2 weeks if positive. Repeat liver function tests: ALT, AST, GGT, total bilirubin, alkaline phosphatase, INR.	These consultations take place after all test results are back. Usually a few weeks after the first consultation. Transition to next phase after patient consent for gene therapy treatment.		**Shelf life:** - Roctavian: 3 years (EMA) - Hemgenix: 24 months (EMA)	Gene therapy products should be stored upright in the original package in order to protect it from light. Storage temperature is product specific and should be according to SMPC. After thawing of frozen products intact vials can be refrigerated at 2-8 °C for 24 hour or 3 days according to SMPC.	Gene therapy dose is product specific and should be prepared according to SMPC. Preparation of gene therapy according to SMPC. Add in-line filter while priming infusion system. After preparation infusion should be completed within limited tine according to SMPC. Personal protective equipment should be used during preparation according to SMPC.	Patient is admitted to the hematology ward for gene therapy infusion.	Reconfirm patient agreement, and review patient's fitness for infusion and eligibility requirements: - Physical examination - Vital signs - Review laboratory and liver assessments
	Hematologist Discuss (blood) test results, eligibility for gene therapy and next steps. Question and answer.	**Hematologist** Discuss test results, eligibility for gene therapy and next steps. Information provision according to table x: (1) gene therapy basics; (2) benefits; (3) risks including infusion reactions, hepatotoxicity and possible requirement of corticosteroids, thrombo-embolism, development of FVIII/FIX inhibitors, malignancy in relation to vector genome integration, horizontal and germline transmission, and details on how these risks can be minimized; (4) treatment response including unpredic-tive variability and possibility of non-respondence; (5) potential outcomes and unpredictability of long-term treatment effect; (6) long-term safety and mission information; (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. Check understanding and expectations. Question and answer. Patient consent.						**Hematologist** Anamnesis, reconfirmation of patient agreement, review patient's fitness for infusion, check eligibility requirements. Final question and answers. Immediate side effects of infusion: allergic reactions, headache, nausea, flu-like illness and fatique.



I) During gene therapy infusion hematologist and nurse should be present.

Infusion rate is product specific and should be according to SMPC.

In case of an infusion reaction infusion should be stopped or slowed down and may be restarted at a slower rate when infusion reaction is resolved (according to SMPC).

Infusion line should be flushed after gene therapy infusion.

II) Gene therapy product name, dose and batch number should be recorded.

I) After infusion patients should be monitored for at least 3 hours.

II) In case of an infusion reaction medication (antihistamines, corticosteroids) is administered if necessary. Treatment may be according to local guidelines.

I) Decontamination procedures after gene therapy infusion according to SMPC.

II) Waste should be disposed in compliance with local guidelines for pharmaceutical waste.

During first 6 months

Roctavian:
- First 26 weeks: once per week

Hemgenix:
- First 3 months: once per week
- Month 4-6: every 3 months

III)
- Full blood count
- FVIII/FIX:Act
- FVIII/FIX inhibitors
- Liver function: ALT, AST, CPK
- Renal function

IV) Data collection in national and/or WFH registry

Referral to hepatologist in case of transaminase elevation and immunosuppressive management if necessary.

Musculoskeletal assessment: HJHS and joint ultrasound with optional HEAD-US score

During month 6-12

Roctavian:
- Week 26-52: every 2-4 weeks (EMA)/ every 1-2 weeks (FDA)

Hemgenix:
- Month 6-12: every 3 months

III)
- Full blood count
- FVIII/FIX:Act
- FVIII/FIX inhibitors
- Liver function: ALT, AST, CPK
- Renal function

IV) Data collection in national and/or WFH registry

I) Patients should be offered psychological and psychosocial support throughout all gene therapy phases.

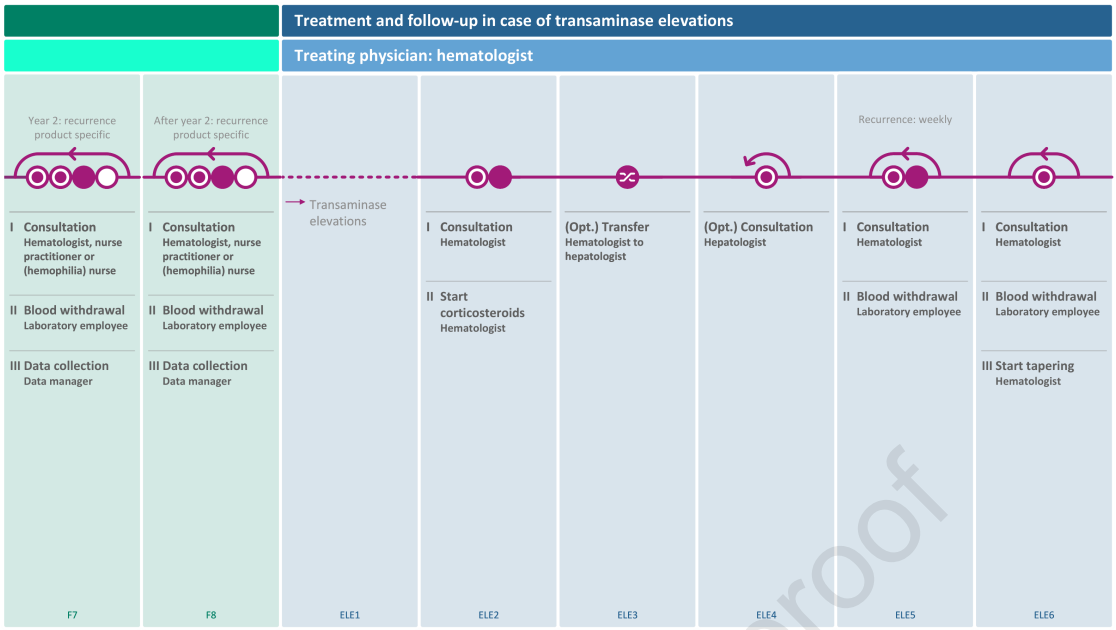
II) Quality of life assessment with hemophilia specific questionnaires:
- Haemophilia Activities List
- EQ5D

Quality of life questionnaires can be completed by the patient at home.

In patients with preexisting risk factors for hepatocellular carcinoma: annual liver ultrasound screening and AFP monitoring for at least 5 years.

Hematologist
Discuss side effects, effectiveness of gene therapy (new FVIII/FIX level), factor concentrate use, other medication, bleeding, psychosocial problems, lifestyle modifications (barrier contraceptives, restriction on alcohol consumption), importance of follow-up. Adjust hemophilia treatment plan (based on new FVIII/FIX level).
Data required for WFH registry.

Hematologist
Discuss side effects, effectiveness of gene therapy (new FVIII/FIX level), factor concentrate use, other medication, bleeding, psychosocial problems, lifestyle modifications (barrier contraceptives, restriction on alcohol consumption), importance of follow-up. Adjust hemophilia treatment plan (based on new FVIII/FIX level).
Data required for WFH registry.



F7	F8	ELE1	ELE2	ELE3	ELE4	ELE5	ELE6
During year 2 **Roctavian:** Every 3 months, more frequently if FVIII:Act ≤ 5 IU/dl **Hemgenix:** Every 6 months, more frequently if FIX:Act ≤ 5 IU/dl III) - Full blood count - FVIII/FIX:Act - FVIII/FIX inhibitors - Liver function: ALT, AST, CPK - Renal function IV) Data collection in national and/or WFH registry	**After year 2** **Roctavian:** Every 6 months, more frequently if FVIII:Act ≤ 5 IU/dl **Hemgenix:** Annually, more frequently if FIX:Act ≤ 5 IU/dl III) - Full blood count - FVIII/FIX:Act - FVIII/FIX inhibitors - Liver function: ALT, AST, CPK - Renal function IV) Data collection in national and/or WFH registry	If liver dysfunction occurs within 12 weeks after the infusion of gene therapy this is often due to an immunological response against the vector. This immunological response may lead to a reduction in expression of the coagulation factor.	II) Treatment with corticosteroids should be initiated according to SMPC indications. Starting dose: 60 mg/day prednisone or prednisolone. Dosing regimens are product specific, dosing regimen according to SMPC.		Patient has an optional consultation with the hepatologist in case of transaminase elevation and necessary initiation of immunosuppressive therapy. Follow-up consultations with hepatologist if necessary.	I-II) Weekly monitoring of transaminases until levels return to baseline. II) Liver function: ALT, AST, CPK Optional: LDH, bilirubin, ALP, GGT	II) Liver function: ALT, AST, CPK Optional: LDH, bilirubin, ALP, GGT III) Start tapering according to product-specific SMPC.
Hematologist Discuss effectiveness of gene therapy (new FVIII/FIX level), factor concentrate use, other medication, bleeding, psychosocial problems, importance of follow-up. Adjust hemophilia treatment plan (based on FVIII/FIX level). Data required for WFH registry.	**Hematologist** Discuss effectiveness of gene therapy (new FVIII/FIX level), factor concentrate use, other medication, bleeding, psychosocial problems, importance of follow-up. Adjust hemophilia treatment plan (based on FVIII/FIX level). Data required for WFH registry.		**Hematologist** Immunosuppression: rationale, medications used (steroids), duration of treatment, side effects of immunosuppression (weight gain, indigestion, problems sleeping, feeling restless, changes in mood), review current medications and switch to less hepatotoxic medications if appropriate and feasible, causes elevated liver enzymes (exercise, alcohol, immune response).				