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Infrastructural considerations of implementing gene therapy for hemophilia in the Nordic context

Jan Astermark, Fariba Baghaei, Karin Strandberg, Petra Gabric Toplican, Maj Friberg Birkedal, Emma Engman Grahn, Charlotta Hansson, Peter Kampmann, Anna-Elina Lehtinen, Kinga Täckström, Pål Andre Holme and Maria Magnusson

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Correspondence to:
Jan Astermark
Department of Translational Medicine, Lund University, Malmö, Sweden

Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Jan Waldenströms gata 14, Malmö, SE-205 02, Sweden
Jan.astermark@med.lu.se

Fariba Baghaei
Department of Medicine, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Karin Strandberg
Division of Laboratory Medicine, Department of Clinical Chemistry and Pharmacology, Coagulation, University and Regional Laboratories Region Skåne, Malmö, Sweden

Petra Gabric Toplican
Radiopharmacy Unit, Karolinska University Hospital, Stockholm, Sweden

Maj Friberg Birkedal
Department of Pediatric Hematology/Oncology, Rigshospitalet, Copenhagen, Denmark

Emma Engman Grahn
Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden

Charlotta Hansson
Kinga Täckström
BioMarin (Europe) Limited, Dublin, Ireland

Peter Kampmann
Department of Hematology, Rigshospitalet, Copenhagen, Denmark

Anna-Elina Lehtinen
Coagulation Disorders Unit, Department of Hematology, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland

Abstract

Background: Despite improvements in hemophilia care, challenges remain, including treatment burden and impaired quality of life. Gene therapy may overcome these. However, its introduction presents a challenge.

Objectives: To outline a function-based gene therapy working model describing critical milestones associated with gene therapy handling, administration, and follow-up to facilitate and implement an effective infrastructure for gene therapy introduction.

Design: Literature review and consensus discussion among Hemophilia Comprehensive Care centers (HCCCs) in the Nordic region.

Methods: Representatives from six HCCCs sought to pinpoint milestones and key stakeholders for site readiness at the pre-, peri-, and post-infusion stages, including authority and genetically modified organism (GMO) product requirements, awareness, medical eligibility, logistics and product handling for infusion, laboratory monitoring, and follow-up.

Results: A gene therapy transit map was developed with key stakeholders identified. The approach to prepare the vector will differ between the Nordic centers, but the contracted pharmacy unit will be a key stakeholder. Therefore, a pharmacy checklist for the implementation of gene therapy was developed. For the future, Advanced Therapy Medicinal Product centers will also be implemented. Patients' expectations, commitments, and concerns need to be addressed repeatedly and education of patients and the expanded health-care professionals team will be the key to successful and optimal clinical management. Eligibility testing according to the product's summary of product characteristics and frequent follow-up and monitoring post-infusion according to the World Federation of Hemophilia chart will be crucial.

Conclusion: The approach to deliver gene therapy in the Nordic region will differ partly between the hemophilia centers, but the defined road map with checklists for the implementation of this advanced therapy will be applicable to all. The map may also serve as a platform for the use of future GMO product options both within and outside the area of hemophilia.

Plain language summary

Implementing gene therapy for hemophilia in the Nordic context

Why was this study done?

- Despite improvements in hemophilia care, challenges remain including treatment burden and impaired quality of life.
- Gene therapy may overcome these challenges.
- The introduction of gene therapy presents a challenge in many ways.

Pål Andre Holme
Department of Hematology, Oslo University Hospital, Oslo, Norway

Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Maria Magnusson
Coagulation Unit, Department of Hematology, Karolinska University Hospital, Stockholm, Sweden

Clinical Chemistry and Blood Coagulation Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

What did the researchers do?

- We, as representatives from six Hemophilia Comprehensive Care Centers in the Nordic region, sought to pinpoint milestones and key stakeholders for site readiness at the pre-, peri- and post-infusion stages, including authority and genetically modified organism (GMO) product requirements, awareness, medical eligibility, logistics and product handling for infusion, laboratory monitoring, plus follow-up.

What did the researchers find?

- We developed a gene therapy transit map and identified key stakeholders.
- The approach to prepare the vector will differ between the Nordic centers, but the pharmacy unit will be a key stakeholder. We therefore developed a pharmacy checklist for the implementation of gene therapy.
- For the future, Advanced Therapy Medicinal Product centers will be implemented.
- Patients' expectations, commitments and concerns need to be addressed repeatedly.
- Education of patients and the expanded health care professionals team will be the key to successful and optimal clinical management.
- Eligibility testing according to the product's summary of product characteristics and close follow-up and monitoring post-infusion according to the World Federation of Hemophilia chart will be crucial.
- Access to both chromogenic and one-stage factor activity assay results from a specialized coagulation laboratory with a short turn-around time is important.

What do the findings mean?

- The approach to delivering gene therapy in the Nordic region will differ partly between the hemophilia centers, but the defined road map with checklists for the implementation will be applicable to all.
- The map may also serve as a platform for the use of future GMO product options both within and outside the area of hemophilia.

Keywords: gene therapy, hemophilia, implementation, Nordics, pharmacy, stakeholders

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Introduction

Hemophilia is an X-linked recessive condition caused by a deficiency of factor (F) VIII (hemophilia A) or IX (hemophilia B).[1] For decades, the current standard treatment has been replacement therapy with standard half-life clotting factor concentrates. More recently, extended half-life factor concentrates and nonfactor therapy, for example, emicizumab, have become available, improving both treatment efficacy and convenience for the patient. However, despite these significant improvements in treatment, challenges remain including breakthrough bleeds, progressive joint damage, impaired quality of life, and treatment burden with the need for regular injections.[2] Accordingly, there are unmet needs with the current treatment options, and subsequently, there is hope for even better future therapeutic options, health equity, and normal hemostasis.[3,4] Gene therapy has proved to be effective in hemophilia patients and may offer the potential to overcome these limitations and unmet needs of current therapeutic options.[4–7] However, the introduction of gene therapy presents a challenge for current hemophilia care, requiring extensive preparation and reorganization of infrastructure.[8,9] It requires knowledge and adherence to hospital and authority genetically modified organism (GMO) product requirements, extensive collaboration between different stakeholders and implementation of new structures that are fit for purpose to maximize the benefits and minimize the risks of the new advanced therapies.[10] To address this in the Nordic region, a preparatory project was defined

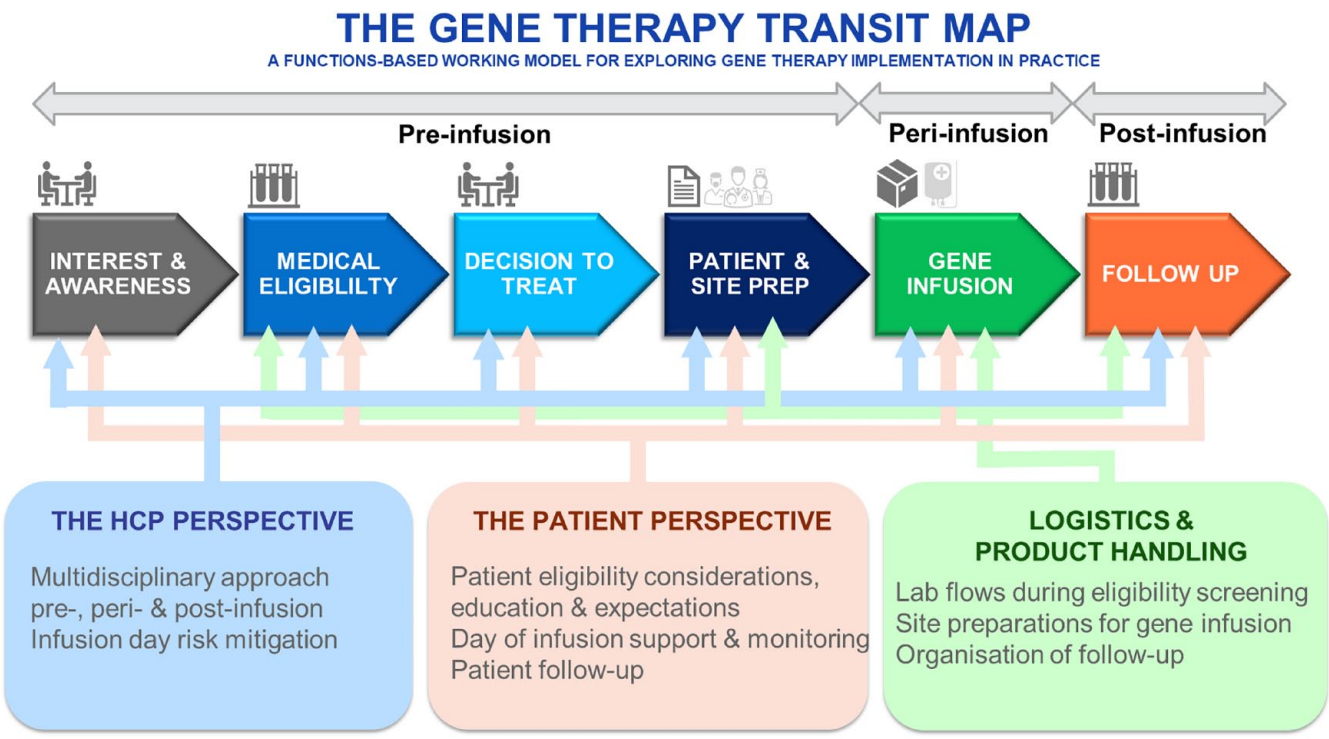

Figure 1. The gene therapy transit map. A function-based working tool for exploring gene therapy implementation in practice.

and initiated in order to facilitate and implement an effective infrastructure for gene therapy introduction. The objectives were to outline a function-based gene therapy working model describing critical milestones associated with gene therapy handling, administration, and follow-up. In addition, the model should identify and address potential gaps and suggest solutions within the current Nordic hemophilia health-care setting in order to prepare efficiently for the seamless and safe introduction of gene therapy. The process and reporting of this project, including the guidelines and recommendations provided, essentially conform along the lines of the Standards for Quality Improvement Reporting Excellence (Squire 2.0) statement.[11]

Nordic hemophilia health care is characterized by a centralized organized care system managed largely within a few highly specialized and multidisciplinary Hemophilia Comprehensive Care Centers (HCCCs), according to the criteria of the European Association for Haemophilia and Allied Disorders (EAHAD).[12] This is despite there often being long geographical distances between patient and center in the Nordic countries. There are three such centers in Sweden (Stockholm, Gothenburg, and Malmö), two in Denmark (Aarhus and Copenhagen), one in Norway (Oslo), and one in Finland (Helsinki). In Finland only, hemophilia care is also managed outside the HCCCs at four university hospitals *via* networking with some of the central hospitals.

By creating a gene-therapy-function-based working model (i.e., gene therapy transit map; see Figure 1), we pinpointed critical milestones for site readiness during the gene therapy journey chronologically at the pre-, peri-, and post-infusion stages. We began with initial authority and GMO product requirements, followed by interest and awareness, aspects of medical eligibility, practical aspects of logistics and product handling for vector infusion, and laboratory monitoring, as well as follow-up. All milestones, outlined and discussed in this paper, were addressed from a key stakeholder's functional point of view, that is, 'patient perspective,' 'health-care professionals' (HCP) perspective,' and 'logistics and product handling perspective,' including the pharmacy, to ensure alignment, and enable a multilayered and overarching

Table 1. Summary of GMO requirements and AAV or biosafety group 1 vector preparation approach in six Nordic hemophilia treatment centers.

Site (country)	GMO requirements	How the vector will be prepared
Malmö (Sweden)	No permits required for the routine use within approved indications of a therapeutic GMO agent after EU marketing authorization, but a risk assessment should be performed according to the Swedish Work Environment Authority requirements.	In an isolator or safety cabinet at the Hospital pharmacy located within the University hospital area (by external part).
Stockholm (Sweden)	As above.	In a safety cabinet in a dedicated cleanroom at the Radiopharmacy unit at the Karolinska University Hospital.
Gothenburg, (Sweden)	As above.	In a safety cabinet located in a dedicated cleanroom at the Radiopharmacy unit at the Sahlgrenska University Hospital *or* in a single-use isolator at the ward.
Copenhagen (Denmark)	New identified risks need to be specified in a GMO permit despite EU approval.	In a single-use isolator at the hospital ward by the Pharmacy, serving as an external actor outside the University hospital.
Helsinki (Finland)	No permits required for the routine use within approved indications of a therapeutic GMO agent after marketing authorization in the EU.	In a safety cabinet in a cleanroom at the University hospital pharmacy.
Oslo (Norway)	No permits required for the routine use within approved indications of a therapeutic GMO agent after marketing authorization in the EU.	In an isolator in a cleanroom at the Hospital Pharmacy unit.

AAV, Adeno-Associated Virus; GMO, Genetically Modified Organism.

approach to preparations for the introduction of gene therapy.

Pre-infusion phase

Authorities and GMO product requirements

Different guidelines and laws apply to handling gene therapy in the Nordic countries, depending on whether the product will be used in clinical trials or has gained marketing authorization and is used within therapeutic indications. Basically, as outlined in Table 1, no application to and/or registration with the Work Environmental Authority is required for the routine use of a GMO product within approved indications after EU marketing authorization, except in Denmark, and only new identified risks need to be specified in the GMO product permit.

In Sweden, the pharmacies will also be obliged to inform the Medical Products Agency and to perform a risk assessment according to the Swedish Work Environment Authority requirements.

Health technology assessments (HTAs) containing cost-utility analyzes are performed in all Nordic countries upon introduction of a new therapy, and then, recommendations for its clinical use are issued based upon the assessment report and negotiations. However, the national structure differs. In Sweden, the New Therapies (NT) Council initiates health economic assessments of drug therapies by the Dental and Pharmaceuticals Benefits Agency for products used in hospital care. The NT Council is commissioned to make recommendations to the Swedish Regions on the use of new drug therapies. In Norway, the Norwegian Medicine Agency is the regulatory authority that performs the HTA of the new product. This is used to inform further decision-making during the New Methods process, which is the national system for the managed introduction of new health technologies in

the specialist health-care sector. The Norwegian Directorate of Health is responsible for further coordination of the recommendation with the national clinical guidelines. In Denmark, the Danish Medicines Council is the authority that provides guidance on new medicines for use in the Danish hospital sector. The Danish Medicines Council does this through two separate processes: assessment of the new medicine, where a new compound is compared to the standard therapy used in Denmark, and the development of guidelines with a prioritized list of medicines to be used for patients. Finally, in Finland, the Finnish Medicines Agency (FIMEA) performs the HTA of the product that sets the basis for a recommendation prepared by COHERE Finland (Council for Choices in Health Care in Finland). The COHERE Finland recommendation based on the FIMEA assessment constitutes a basis for further decision making and negotiations with the joint national procurement ring. The National Advisory Committee on Pharmaceuticals, which represents the hospital districts, commits itself to the recommendation arising from the negotiation process. These differences in HTA setup and national processes may impact upon the timeline and introduction of gene therapy in each country, but several additional factors, such as which payment model(s) and financing infrastructure are to be used, will be of major importance. At the hospital level, several institutions/departments need to be involved, depending on the local organization.

Pharmacy

A key stakeholder for the implementation of gene therapy in the routine clinic will be the directly involved pharmacy unit within each hospital. The setup will differ between sites and countries, but in all cases similar routines need to be established and implemented. Table 2 shows a checklist for the pharmacy unit to follow to prepare for correct vector storage, preparation, and management of the approved drug. As far as possible, the gene therapy product should be handled in the same way as any other medicine, but with a key person responsible for the entire process. It is also preferable that the gene therapy medicine will be delivered directly to the hospital pharmacy, and this is especially important for drugs that are sensitive to temperature variation.

Hemophilia center organization

The 'hub-and-spoke' model has been proposed as a framework for all aspects of gene therapy and has been promoted by the EAHAD and the European Haemophilia Consortium (EHC).[10] It is associated with the best cost-effective and resource utilization[13] and addresses all aspects of gene therapy.[10] According to this initial model, tasks, and responsibilities are divided between a gene therapy delivering center or the infusion center (hub) and a management center from which the patient is referred (spoke).[9,10] The hub center needs to have in-depth knowledge and experience of gene therapy and the facilities to order, store, prepare, and administer the gene therapy product, as well as the ability to perform and interpret diagnostic tests for eligibility and follow-up. In addition, the hub center should be knowledgeable regarding the timely diagnosis and management of adverse events. The spoke centers will manage the long-term follow-up of the patient in close communication with the hub. An alternative hub-and-spoke scenario has been suggested, in which the spoke center also has experience of gene therapy and the availability of different gene therapy platforms. In this situation, not all centers will have all platforms open, and patients may, therefore, be transferred to another center to receive their treatment and then return to their 'home' center for their subsequent management. The strength of a hub-and-spoke model for managing gene therapy is to enable standardized treatment and adequate registration, regardless of the center or even country in which the patient is located. In addition, quality criteria could be established and approved to ensure a robust informed decision, with the maximum benefit of gene therapy and the least possible side effects.

Based on the structure of the health care in the Nordics with a centralized care system and only a few HCCCs, the original hub-and-spoke model will not be fully applicable. For the time being, only the Malmö center in Sweden has delivered the vector in clinical trials, but in the near future, all HCCCs in the Nordic area plan to become infusion centers. This still means long-distance travel for many patients living far from the center in both Sweden and in Norway and also requires blood sampling locally by mobile teams and/or testing at the local hospital with a defined alert

Table 2. Checklist for the pharmacy.

	1. GMO CONSIDERATIONS
1	Any additional certification/notification to handle the specific GMO agent required?
2	Routines and conditions for GMO preparation established?
3	Have personnel received the required knowledge to manage GMO agents?
4	Management and disposal for GMO-contaminated materials established?
5	Personal protective equipment available?
6	Spill boxes easily available in all areas where GMO agent will be managed?
	2. PRODUCT HANDLING AND LOGISTICS
7	Define capacity to receive and store product according to the SPC?
8	Define the high/low temperature range and temperature set point of the refrigerator/freezer.
9	Make sure the refrigerator/freezer is alarmed and monitored.
10	Make sure the refrigerator/freezer has a back-up power source in case of a power outage.
11	Back-up refrigerator/freezer available?
12	Define whether and how the carrier may deliver the product all the way to the refrigerator/freezer location.
13	Experience for in handling temperature- monitoring devices, such as web logger?
14	Establish how to unpack/load the product into the refrigerator/freezer within 5 minutes upon delivery.
15	Define the preferred disposal method of any unused product and/or waste.
	3. ASSIGNED RESPONSIBILITIES
16	Identify contact person(s) and routines for product ordering and reception.
17	Identify contact person(s) from the pharmaceutical company that holds marketing authorization.
18	Identify contact person(s) from the clinic that who will be ordering the GMO agent from the hospital pharmacy.
19	Establish and define the transport of the product from the hospital pharmacy to the clinic in accordance with the local legislative.
20	Inform the responsible person at the clinic that they need to establish routines for waste management and have spill boxes available (clinical personnel need to be educated and trained on this matter).

system for the responsible hemophilia team (see also below). In Finland, which has one HCCC in Helsinki, four university hospitals with a defined hemophilia center, and two central hospitals with attending hemophilia patients, the situation will be slightly different. A modified hub-and-spoke model will apply in Finland with all infusions delivered at the HCCC in Helsinki, but with patient follow-up in the post-infusion phase at the local center and *ad hoc* consultation. In this scenario, and in agreement with the published Gesellschaft für Thrombose- und Hämostaseforschung e.V. (GTH) and Italian recommendations, a pre-infusion collaborative agreement needs to be established between the hub-and-spoke centers with appropriate educational activities and checklists defined in order to enable an appropriate and timely discussion with the patient.[8,9] An approach of value to prepare for the introduction of a GMO product at the site will be to perform a risk assessment for each step, from shipment of the drug to its administration, and subsequent management of the patient post-infusion. Importantly, the assessed risk is not based on the pathogenicity of the particular

biological agent alone (biosafety group of the agent), but on the likelihood and consequence of an incident occurring – in other words, the risk of exposure to, and/or release of, the biological agent during handling of a GMO product.[14]

Vector delivery

The pharmacy plays a key role in the preparation and administration of the vector at each Nordic center, but the setup will differ between countries (see Table 1). An isolator, safety cabinet, or a single-use isolator will be used and, in most cases, this entity will be located in a dedicated cleanroom. For the future management of a GMO product, Advanced Therapy Medicinal Product centers are currently being organized and implemented in several of the University hospitals. These centers will presumably be involved in vector preparation and GMO product delivery in the future, and be supervised by, and in close collaboration with, the multidisciplinary hemophilia care team.

Patient information/selection

Adeno-associated virus (AAV)-mediated liver-directed gene therapy is possibly one of the most complex investigational therapies ever developed.[15] The phase leading up to the delivery of gene therapy is a time in which concerns and questions regarding safety, possible side effects, impact on comorbidity, and expected efficacy, need to be addressed. Key points identified by patients with hemophilia considering undergoing gene therapy and their clinicians include effect of the therapy on factor activity level, uncertainty regarding long-term risks, impact on daily life, frequency of monitoring, impact on ability to participate in physical activity, and uncertainty regarding long-term benefits.[16] Early information and counseling about treatment options and reasonable expectations of gene therapy should be provided on several occasions to all potentially eligible patients and through different channels during the pre-dosing process. Regarding the interest in gene therapy, the patient should preferentially approach the doctor and not *vice versa*. The doctor should make it clear that research is ongoing and there are gaps in knowledge, such as long-term safety and duration of treatment effect.[2] It will be crucial to manage patient expectations of gene therapy, particularly in the early days following treatment. Patients should understand that although gene therapy may convert them from a 'severe' phenotype to a 'mild' category, they should not be considered as 'cured,' and they will continue to need clinical monitoring independent of the expression level.[2] In addition to what is stated in the summary of product characteristics (SPC) about contraindication/cautiousness for vector delivery and the review of therapeutics and comorbidities, for example, malignancies, liver diseases, active viral infections, autoimmune diseases, all candidates must be given sufficient information in order to understand and consent to the commitments and potential risks involved. Alcohol consumption, and the requirement post-infusion for abstinence from alcohol for at least a year after the vector is administered, needs an extra focus and discussion, as does the need for the use of barrier and effective contraception throughout the period of vector shedding (see below). The likelihood of a cytotoxic immune response occurring and the subsequent need for treatment with immunosuppressive agents (mainly corticosteroids) for several weeks post-infusion should also be addressed. The information provided to the patient should be based on published phase III data for patients with hemophilia A and B, respectively.

The nurses involved in gene therapy should be well educated and have up-to-date knowledge at a level enabling informed patient education. They will also play a key role in the interpretation of patients' motivations and expectations for receiving gene therapy, as well as for the identification of the patients' individual internal and external recourses.

Patient education should take individual health, literacy, diverse social, and educational background, language barriers, and learning mechanisms into account. A broad pallet of educational tools should be provided, including face-to-face sessions, and the provision of written and visual aid materials are of paramount importance in providing equal access to gene therapy. General information about gene therapy and additional risk-minimization materials, developed jointly by the industry and the Nordic HCCCs, will be presented locally and discussed with the patient/family. Special attention should be paid to including all the patient's family members, for example, partners and children. Communicating effectively

and presenting highly technical and complex therapeutic information to the patient/family is challenging, and the patient's judgment can easily be clouded by both the disease burden and its treatments. In addition, the desire for improved health-related quality of life (HRQoL) can undermine the patient's decisional capacity.[17] Relevant outcome measures for gene therapy have been provided by the coreHEM panel, including mental health aspects of HRQoL.[18] However, it is difficult to measure HRQoL in hemophilia patients undergoing gene therapy, and it has been highlighted that none of the currently used hemophilia-specific quality-of-life instruments are likely to fully capture HRQoL in hemophilia patients treated with gene therapy, as they were developed in a pre-gene therapy era.[19]

An informed decision-making process based on a designed pre-infusion checklist according to Table 3 has been defined. This will ensure that all preparatory work has been performed and that adequate information has been provided to the patient/family. Hopefully, this will also contribute to an increased understanding and stronger commitment to such therapy and confirm the patient's determination to go through with the gene therapy including the follow-up requirements. In addition, it may help in the dialogue with all family members. Importantly, patients should also be made aware that they can change their mind at any time during the pre-infusion phase, but after this, once the infusion has been administered, it cannot be undone. To optimize the informed decision-making process and to minimize the risk of psychological drawbacks after the treatment, the preparation for gene therapy should, if possible, also include a psychological evaluation.

The multidisciplinary hemophilia care team

Another important aspect of future hemophilia care with GMO products in the toolbox will be deciding how the team should be compiled. Dealing with a new treatment modality with a lifelong impact and requiring extensive follow-up, as well as carrying several unknowns, the psychological aspects of hemophilia care will again be an important part of clinical management. Ideally, the multidisciplinary team will include a hematologist, nurse, physiotherapist, psychologist, social worker, and hepatologist. Unfortunately, most hemophilia centers in the Nordics will not have immediate access to a dedicated psychologist with specific knowledge of hemophilia, and this may require a collaboration between centers on a national level. The role of the social worker may also be reviewed. Another key member of the hemophilia team, with whom there is a need for close collaboration in the era of gene therapy, will be the hepatologist.[20] Patients will be followed for a long time after treatment with a focus on transaminitis and various liver comorbidities, which may impact upon liver function and the expression levels. The access to laboratory analyzes, in particular factor activity analyzes, needs to be discussed with the appropriate coagulation laboratories. This is because the requirements for common chemistry analyses and the availability of both the one-stage clotting assay (OSA) and the chromogenic substrate assay (CSA) within 24 h from blood sampling require a certain organization.

Eligibility testing

Besides the general routines and laboratory work-up in association with the patient's annual visits to the hemophilia center, additional eligibility testing for gene therapy will be topical and crucial, that is, AAV antibody testing and liver assessment.

AAV testing. Based on the design of most trials and current knowledge, pre-existing immunity to AAV will, for the time being, eliminate approximately 50% of hemophilia A patients who would otherwise be eligible for gene therapy.[21] However, at least in the case of patients with hemophilia B, the impact of pre-immunity to AAV5 is not clear, since of patients with pre-immunity who were enrolled in a recent phase III gene therapy trial, all but one – with a very high antibody titer – had an equal outcome and expression to those without pre-immunity.[22] Hence, the eligibility criteria for gene therapy may differ, but should follow the guidelines in the relevant SPC.[22] In any case, accurate measurement of anti-AAV antibodies will be crucial. To this end, the manufacturer of each drug will presumably offer mandatory companion diagnostics, preferentially including enzyme-linked immunosorbent-assay-based total antibody measurement against a specific serotype, including both neutralizing and non-neutralizing AAV antibodies. In the Nordics, based on the size of the population,

Table 3. Pre-infusion checklist. Date: Patient:

1. PATIENT HAS BEEN SCREENED AND FOUND ELIGIBLE FOR GENE THERAPY

1.1 Patient is informed of the potential outcomes:

- ☐ Expected expressed factor level
- ☐ Discontinuation of factor concentrate prophylactic regimen
- ☐ On-demand treatment of bleeds
- ☐ Concomitant medicine (potential restrictions)
- ☐ Lifestyle modifications
- ☐ Financial impact

1.2 Patient is informed of risks/potential side-effects:

- ☐ Transient liver toxicity; frequency, timing, symptoms and management
- ☐ Side-effects of steroids/immunosuppressants
- ☐ Risk of loss of expression of the transgenic protein and AAV capsid-specific cytotoxic T cells
- ☐ Symptoms of treatment failure
- ☐ Symptoms of thromboembolism in case of overexpression
- ☐ Potential risk of vector integration and malignancy
- ☐ Risk of vertical transmission
- ☐ Gaps in scientific knowledge and evidence

1.3 Patient is informed of the peri- and post-infusion procedures:

- ☐ Duration and schedule of infusion day
- ☐ Agreement on sampling and monitoring over an extended time period
- ☐ Agreed upon schedule of short- and long-term follow up appointments

2. MANAGEMENT OF PATIENT MOTIVATIONS AND EXPECTATIONS

- ☐ The patient's motivations for gene therapy have been explored
- ☐ Unrealistic expectations, positive and/or negative, have been addressed

3. PATIENT EDUCATION AND CLARIFICATION OF INDIVIDUAL CONCERNS

3.1 Patient is informed of the following conditions:

- ☐ Willingness to abstain from alcohol for at least 12 months
- ☐ Agreement to use double-barrier and effective contraception methods to prevent transfer of vector particles (vector shedding) until the vector is no longer detectable in semen
- ☐ Agreement to discuss with the hemophilia team before any donation of blood, cells, semen, tissue or organs from the time of gene therapy administration and onwards
- ☐ Refrain from any elective major and/or orthopedic surgery for at least 6 months post-dosing

4. IDENTIFICATION OF PATIENT RESOURCES

4.1 Patient is informed of the potential mental challenges of possible success or failure:

- ☐ Change of self-perception
- ☐ Management of disappointments
- ☐ Management of morbidity in case of liver toxicity
- ☐ Potential impact on work situation
- ☐ Potential change in interactions with patient advocacy groups

4.2 Patient is informed of the possibilities of support at the hemophilia treatment center (HTC):

- ☐ Social worker and/or psychologist

4.3 Patient has been encouraged to disclose his gene therapy:

- ☐ Family and/or friends
- ☐ Workplace/Educational institution
- ☐ Any other potential healthcare providers

5. EVALUATION OF UNDERSTANDING

- ☐ The patient can explain the basic mechanisms of gene therapy and potential risks, at a level that allows for the patient to take relevant action in response to symptoms
- ☐ The patient can account for the lifestyle restrictions post-infusion
- ☐ The patient has received written patient information about gene therapy

6. INFORMED DECISION MAKING

The patient and the physician confirm that information has been provided and understood

Date:	Patient:
Date:	Physician:

and since the process for evaluating patient eligibility will be relatively long with the need for repeated testing, the plan will be to validate a centralized method for AAV-serotype testing at one of the Nordic centers. This will also enable the possibility of testing for different serotypes of AAV independent of the product manufacturer, as more options emerge in the future and allow long-term monitoring of the immune response post-infusion. At least some of the companion diagnostics to gene therapy will only provide a 'yes' or 'no' to AAV testing and, for vector delivery, a negative result will be required. However, antibody titers are not a black-and-white case, and a binary test result may, therefore, give a false sense of security and *vice versa*. Therefore, the central AAV testing laboratory will provide the actual antibody titers to the referred doctor at either the hub or the spoke center. The information about titers toward the various subtypes may also, in the future, be of value for choosing the most appropriate vector, as well as the use of immunosuppression and/or re-infusion. From the Nordic hemophilia centers' perspectives, all these aspects, including the possibility of an initial first screening in the early phase of

communication, even before the recommended time of 3 months prior to infusion,[8] further encourage the centers to have access to a centralized validated testing system as a complement to the companion diagnostics provided by the manufacturer. This latter testing, which needs to take place closer to the time of dosing, will, however, be crucial as it will be highly specific to the vector of interest and will always be performed before reaching a final decision and the ordering of the vector.

A web-based portal to order AAV testing and to receive the results will be used, but firewalls or local information technology restrictions may complicate the data transfer. Thus, the optimal communication platform should be chosen early in the site readiness phase.

Liver assessment. An accurate and appropriate liver assessment for evaluating patient eligibility will be crucial for the outcome of gene therapy, and a close collaboration with the hepatologist needs to be established.[20] Laboratory work-up should include alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (γGT), prothrombin time/international normalized ratio, and protein profile including albumin. The decision limit of liver enzyme levels for eligibility for gene therapy should follow the guidance that is stated in the relevant SPC, but all pathological findings need to be scrutinized, and it is important to keep in mind the fact that the enzymatic levels will correlate to the volume of hepatocytes. Active hepatitis B or C infections need to be ruled out, and subjects who have been treated and cured of hepatitis C virus infection must have two negative viral assays performed by polymerase chain reaction at least 6 months apart. Fibroscan, liver ultrasound and fibrosis-4 score for liver fibrosis (based on age, ALT, AST, and platelets) should be performed on all eligible patients to screen for advanced liver fibrosis or liver cirrhosis.

Peri-infusion phase

The peri-infusion phase will be an extraordinary phase for both patients and HCP. It will start the day before infusion and, in most cases, end the day afterward. Any final potential obstacles and concerns from the patient's view should be identified. There should also be a confirmation by the pharmacy the day before the infusion on how and when the drug will be delivered.

A general working sheet or checklist for the preparation and performance of the peri-infusion phase should be established. This needs to be adjusted to the local organization and setup at each center, but should include contact with the patient and planning of all logistics, contact with the ward and intensive care unit as well as the submission of the prescribed GMO product dose to the pharmacy ahead of dosing – usually around 2 weeks before. An early discussion to divide the responsibilities between team members on the day of the infusion is also advisable. In addition, in case of the development of infusion reactions, the routine for, and availability of, emergency equipment and drugs should be identified and confirmed.

On day 1 post-infusion before discharge, the procedure should be reviewed with the patient, follow-up discussed and the commitments confirmed, as well as any post-infusion thoughts/concerns identified.

Post-infusion phase

Organization of follow-up

Follow-up visits will generally be performed at the individual HCCC, that is, the dosing center, and include a general laboratory work-up including liver assessment and inflammatory markers, but will also include the measurement of factor activity levels, including inhibitor testing, whenever indicated at the specialized coagulation laboratories. The content and minimal timing of these visits/sampling time points will mainly follow the recommendations of the World Federation of Hemophilia (WFH), as outlined in Table 4, but during the first 3–6 months, sampling and monitoring will be performed more frequently, basically every week. In addition, AAV testing may be considered at certain intervals at least annually to follow and better appreciate the immune response to gene therapy.

Regarding the sampling and laboratory flow for patients living far away from the center, blood sampling will be performed at the patient's local hospital and/or by mobile teams in Sweden,

Table 4. Follow-up chart data entry schedule.

Assessments	Baseline	Treatment Day	Week 2	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	Annually
Information	X										
Shared decision making is confirmed	X										
Hemophilia details – Medical history	X										
Comorbidities[a]	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X
Vital signs/Height and Weight	X	X	X	X	X	X	X	X	X	X	X
Liver ultrasound	X					X		X	X	X	X
Liver fibrosis testing/Fibroscan	X										
AAV NaB	X							X		X	X
Vector infusion details[b]		X									
Factor VIII/IX activity[c]	X	X	X	X	X	X	X	X	X	X	X
Inhibitor testing	X	X	X	X	X	X	X	X	X	X	X
Liver transaminases	X	X	X	X	X	X	X	X	X	X	X
Vector shedding[d]					X	X					
PROBE	X					X		X		X	X
EQ5D-5L	X					X		X		X	X
HJHS/ (Joint ultrasound)	X							X		X	X
Adverse events of special interest[e]		X	X	X	X	X	X	X	X	X	X
Bleeds requiring treatment			X	X	X	X	X	X	X	X	X
Use of factor or nonfactor treatments			X	X	X	X	X	X	X	X	X
Concomitant medication[f]	X		X	X	X	X	X	X	X	X	X
Pain Visual Analog Scale	X					X		X		X	X
Surgeries			X	X	X	X	X	X	X	X	X
Mortality			X	X	X	X	X	X	X	X	X

[a]Liver disease, hepatitis B or C, HIV, history of malignancy, renal disease, diabetes, deep vein thrombosis, atrial fibrillation, coronary artery disease, autoimmune disorder, thromboembolic events (pulmonary embolism, deep venous thrombosis, myocardial infarction, nonhemorrhagic stroke, thrombotic microangiopathy, other).
[b]Vector infusion details: dose, type.
[c]One-stage clotting assay (OSA) and Chromogenic substrate assay (CSA).
[d]Optional, but may be required depending on gene therapy product used. Not included in register.
[e]Thromboembolic events (pulmonary embolism, deep vein thrombosis, myocardial infarction, nonhemorrhagic stroke, thrombotic microangiopathy, etc.), autoimmune disorders, malignancies, liver disease, hypersensitivity reaction, hepatitis B or C (new or reactivation).
[f]Including immunosuppression, anticoagulation, platelet inhibition.

Norway, and Finland. An agreement, between the mobile unit/nurses and the responsible University or Central hospital (hub or spoke), will be signed and responsibilities defined. In Denmark, the geographical distances are less and all sampling will be performed at the University hospital. Importantly, when local hospitals are engaged, reporting and alert systems will be defined to ensure proper and timely management of the patient. Thus, as for AAV testing, the optimal communication platform needs to be settled in an early preparatory phase and a contact person at each center, usually the hemophilia nurse as well as a dedicated biomedical scientist for the logistic handling of samples and test results, will be identified.

Factor activity assays. Factor analysis will be carried out at least weekly during the first 3 months at the specialized coagulation laboratories after validation for gene therapy products with external controls or similar material with assigned values, followed by analysis every 1–2 weeks for the next 3-month period. This is mainly in agreement with the German guidelines,[9] but is more frequent than that suggested in the consensus paper from Italy.[8] The preference for the chromogenic test for monitoring factor activity has been highlighted previously.[8,9] However, within the Nordic region, the activity levels, as measured by both the OSA and CSA assays, will be recorded for optimal information in case of, for example, the need for an acute surgical intervention. This is because of the described assay discrepancy between the two tests.[23,24] Depending on the clinical phenotype and/or if factor activity values show an unexpected decline, inhibitor testing according to the Nijmegen-Bethesda assay should also be performed.

For follow-up, a turnaround time (TAT) of 24 h for both factor activity analyzes and liver enzymes will be required, and availability of these analyzes at weekends may require extra consideration, since the difference between getting the result on a Friday or the following Monday may have a significant impact on the final decision to start immunosuppression.

Liver assessment. ALT, AST, ALP, and γGT should be measured on a routine basis according to the particular SPC, but at least weekly, as for the factor activity, with a similar TAT (24 h) for the first 3 months following the infusion and with successively longer intervals thereafter (Table 4), that is, mainly in line with the GTH recommendations.[9] Some patients living far away from the hemophilia center will require the liver assessment to be performed and analyzed at a local hospital with a defined reporting system to secure appropriate awareness and timely action by the responsible HCCC.

In addition to the plasma laboratory work-up, and irrespective of any fibroscanning, ultrasound of the liver is recommended – as for all other patients with a history of hepatitis B and/or C infection – every 6–12 months, since these patients, independent of gene therapy, will carry a risk of hepatocellular carcinoma and the early identification is associated with a very good prognosis for cure.[25]

Vector shedding. According to the SPC of each approved GMO product, patients must agree to use double barrier and effective contraception methods including condoms to prevent the transfer of vector particles for at least 6 months post-infusion. This also applies to vasectomized patients. During this time frame, the patient should also not donate any cells and/or tissues including semen. Sampling will be optional for the registration in the Gene Therapy Registry (see below), but in the Nordic region sampling for analyzes of blood, urine and semen will be recommended until negative samples have been achieved – usually up to 6 months, but longer if required. The patient should also be aware of the fact that the time period for vector shedding in various tissues will vary and that analyzes may need to be performed for a longer interval.

Registry

An important part of the follow-up will be proper data collection and registration in the national registries. The Nordic centers use different platforms and will not have a common Nordic registry, but will communicate with each other and harmonize the parameters to be documented based on consensus discussion within the Nordic Hemophilia Council. In addition, all centers will join the WFH Gene Therapy Registry and transfer the data required, either manually or automatically, as well as be part of the gene therapy actions and certification process planned by the EAHAD.

The HCCCs in each country will be responsible for data collection and reporting.

Concluding remarks

Based on the data in clinical trials and by the approval of gene therapy vectors for routine use in both patients with hemophilia A and B by the European Medicines Agency and the US Food and Drug Administration over the last months, the relevance of initiating the discussion and preparatory work for the potential use of GMO products in hemophilia centers outside clinical trials becomes highly relevant. However, the process is burdensome and involves several stakeholders, as outlined in this paper. The infrastructural considerations will have both similarities and differences between countries including within the Nordic area, but our collaborative work has provided common guidelines, useful tools, and a similar approach for the implementation of gene therapy in the different HCCCs. Whenever established, the road map for gene therapy in hemophilia may facilitate and serve as a platform for the use of additional future GMO product options, both within and outside the area of hemophilia.

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Consent for publication

Not applicable.

Author contributions

Jan Astermark: Conceptualization; Data curation; Investigation; Writing – original draft.

Fariba Baghaei: Project administration; Writing – review & editing.

Karin Strandberg: Methodology; Writing – review & editing.

Petra Gabric Toplican: Methodology; Writing – review & editing.

Maj Friberg Birkedal: Methodology; Writing – review & editing.

Emma Engman Grahn: Methodology; Writing – review & editing.

Charlotta Hansson: Conceptualization; Methodology; Visualization; Writing – original draft.

Peter Kampmann: Methodology; Project administration; Writing – review & editing.

Anna-Elina Lehtinen: Methodology; Project administration; Writing – review & editing.

Kinga Täckström: Conceptualization; Methodology; Project administration; Visualization; Writing – review & editing.

Pål Andre Holme: Methodology; Project administration; Writing – review & editing.

Maria Magnusson: Methodology; Project administration; Writing – review & editing.

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Availability of data and materials

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