THERAPEUTIC ADVANCES in
Hematology

Review

How to translate and implement the current science of gene therapy into haemophilia care?

Ther Adv Hematol

2023, Vol. 14: 1–14

DOI: 10.1177/20406207221145627

Cedric Hermans, **Yves Gruel**, **Laurent Frenzel** and **Evelien Krumb**

***Abstract*:** Gene-based therapy opens an entirely new paradigm in managing people with haemophilia (PWH), offering them the possibility of a functional cure by enabling continuous expression of factor VIII (FVIII) or factor IX (FIX) after transfer of a functional gene designed to replace the PWH's own defective gene. In recent years, significant advances in gene therapy have been made, resulting in clotting factor activity attaining near-normal levels, as reflected by 'zero bleeding rates' in previously severely inflicted patients following a single administration of adeno-associated viral (AAV) vectors. While this new approach represents a major advancement, there are still several issues that must be resolved before applying this technology in clinical practice. First, awareness, communication, and education about the therapeutic potential and modalities of gene therapy must be further strengthened. To this end, objective, unbiased, transparent, and regularly updated information must be shared, in an appropriate way and understandable language with the support of patients' organizations. Second, healthcare providers should adopt a patient-centred approach, as the 'one size fits all' approach is inappropriate when considering gene therapy. Instead, a holistic patient view taking into account their physical and mental dimensions, along with unexpressed expectations and preferences, is mandatory. Third, the consent procedure must be improved, ensuring that patients' interests are maximally protected. Finally, gene therapy is likely to be first delivered in a few centres, with the highest expertise and experience in this domain. Thus, patients should be managed based on a hub-and-spoke model, taking into account that the key to gene therapy's success lies in an optimal communication and collaboration both within and between haemophilia centres sharing their experiences in the frame of international registries. This review describes recent progress and explains outstanding hurdles that must be tackled to ease the implementation of this paradigm-changing new therapy.

Keywords: adeno-associated virus, gene therapy, haemophilia, patient education, shared decision-making

Received: 18 September 2022; revised manuscript accepted: 28 November 2022.

Correspondence to:
Cedric Hermans
Haemostasis and Thrombosis Unit, Division of Adult Haematology, Cliniques universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Avenue Hippocrate 10, 1200 Brussels, Belgium.
cedric.hermans@uclouvain.be

Yves Gruel
Centre Régional de Traitement de l'Hémophilie, Hôpital Trousseau, CHRU de Tours, Tours, France

Laurent Frenzel
Laboratory of Cellular and Molecular Mechanisms of Hematological Disorders and Therapeutical Implications, Labex GR-Ex, Imagine Institute, Inserm, Paris Descartes – Sorbonne Paris Cité University, Paris, France

Hematology unit care, Hemophilia Center, Necker Hospital, Paris, France

Evelien Krumb
Haemostasis and Thrombosis Unit, Division of Adult Haematology, Cliniques universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium

Introduction

Progress in haemophilia treatment

In the past, haemophilia A (HA) or B (HB) management has focused on replacing missing coagulation factors in order to treat and prevent bleeding, initially with whole blood, followed by fresh frozen plasma (FFP) or cryoprecipitates, before switching to plasma-derived concentrates, enabling early bleeding control and home therapy. This greatly enhanced life expectancy for people with haemophilia (PWH). Still, the contamination of clotting factor concentrates (CFCs) using non-virally inactivated pooled plasma caused high morbidity and mortality rates among PWHs, with the need for safer procedures.[1] Accordingly, effective viral inactivation procedures were then implemented, followed by recombinant DNA technology,[2] which paved the way for implementing prophylaxis.[3] Meanwhile,

extended half-life factors have reduced the dosing frequency for prophylaxis, further boosting patient quality of life. Over the last decade, nonfactor therapies that increase thrombin (FIIa) generation by either simulating a missing protein or inhibiting endogenous anticoagulant mechanisms have also been developed. A potential yet unresolved risk in PWHs is the development of inhibitors. Managing these inhibitors is challenging and costly, as grounded on repeated high CFC dosing, along with immune tolerance induction (ITI), to eradicate the inhibitor.[4] Further progress has occurred since bispecific humanized monoclonal antibodies like emicizumab have been developed. Subcutaneous emicizumab partially mimics the function of missing FVIII by bridging FIXa and FX, so restoring haemostasis control,[5] and has been approved in many countries for routine prophylaxis in HA patients, with or without inhibitors.[6,7] Alternative therapies focusing on coagulation pathway inhibitors like fitusiran are also being explored.[8] While all these agents effectively improved haemophilia outcomes, they do not eliminate breakthrough bleedings.[9–11] Still, unprecedented progress is now on the horizon with gene therapy, which likely offers the potential of a phenotypic cure by re-establishing FVIII or FIX levels via the transfer of cDNA fragments that encode the missing protein. This has opened up an entirely new dimension in haemophilia management.

Basic principles of gene therapy

Gene therapy seeks to introduce relevant genetic material into the target cells, with the goal of durably treating, preventing, or potentially even curing disease. Most gene therapy studies have used vectors based on recombinant adeno-associated virus (AAV) serotypes to selectively deliver the clotting factor (CF) cDNA into hepatocytes.[12–14] AAVs exhibit a simple structure, are not associated with any disease, and do not integrate into the genome.[15] The FIX cDNA (~1.6 kb) is easily packaged into the AAV-vector particles, whereas the FVIII cDNA (~8 kb) exceeds this system's capacity. All FVIII transgenes used in AAV gene protocols are thus B-domain deleted.[16]

Largest gene therapy clinical trials to date

Gene therapy relies on the delivery of liver-directed FVIII or FIX transgenes using recombinant non-integrating AAV, and this approach is likely to alter the haemophilia treatment paradigm. In the first trials, certain AAV serotypes proved to be hepatotoxic, and more immunogenic,[17] yet significant progress has since been made. Great optimism has been garnered from large gene therapy studies recently conducted in adult patients with both HA and HB.[18] The Phase 3, open-label, single-dose, single-arm HOPE-B trial, which included 54 male participants with severe or moderate haemophilia B, demonstrated that etranacogene dezaparvovec produced mean FIX activity of 39.0 IU/dL at 6 months and 36.9 IU/dL at 18 months post-infusion. After the 6-month lead-in period post-infusion, the adjusted annualized bleeding rate (ABR) (1.51) for all bleeds was reduced by 64% ($p = 0.0002$) and was reduced by 77% (3.65–0.83; $p < 0.0001$) for all FIX-treated bleeds over months 7–18. In addition, 98% of subjects treated with a full dose of etranacogene dezaparvovec discontinued prophylaxis with FIX concentrates.[19] Analysis of the HOPE-B trial revealed that overall, 37/54 (68.5%) patients had any treatment-related adverse event (AE) post-treatment, the majority of which were mild (81.5%). No deaths occurred and no treatment-related serious adverse events (SAEs) were reported. The most frequent treatment-related AEs were headache (13.0%) and influenza-like illness (13.0%). All patients discontinued steroid use prior to week 26, with FIX activity was preserved in the mild range. No inhibitors to FIX were reported.[20] The largest gene study ever conducted in the HA setting involved 134 participants with severe HA who were treated with valoctocogene roxaparvovec, an AAV5-based gene therapy vector.[21] In this study, valoctocogene roxaparvovec provided endogenous FVIII production and significantly reduced bleedings, amounts of FVIII concentrates required for prophylaxis, and FVIII infusions/year. The risk–benefit profile was favourable, and most participants displayed FVIII levels in the mild (5 to <40 IU/dL) or non-haemophilia (≥40 IU/dL) range. All the participants had at least one adverse event; 22 of 134 (16.4%) reported serious adverse events. Elevations in alanine aminotransferase levels occurred in 115 of 134 participants (85.8%) and were managed with immune suppressants. The other most common adverse events were headache (38.1%), nausea (37.3%), and elevations in aspartate aminotransferase levels (35.1%). Of note is that many participants received prolonged courses over many months of corticosteroids. No development of factor VIII

(FVIII) inhibitors or thrombosis occurred in any of the participants.

Are we ready for gene therapy?

Flashback to haemophilia management in the past

To date, the journey to improved haemophilia care has been grounded in incremental research developments, starting with a better disease understanding to the introduction of prophylaxis treatment, initially with standard CFCs, then extended half-life CFCs, followed by CF mimetics, and eventually leading to the advent of gene therapy.[22,23] Although the properties of existing therapeutic agents differ, they all have well-known characteristics in common (Table 1). So far, the transition from one step to the next has been fairly smooth, with each stepwise innovation building on the last, bringing us a step closer to the ultimate goal of finding a cure.[23] In contrast with this, gene therapy is a completely innovative, unprecedented, though highly complex approach. The progress made over the last five decades in haemophilia care has been illustrated in Figure 1. As such, many questions remain unanswered with regard to the true clinical and economic value of gene therapy, particularly concerning its safety, sustainability, and durability.

Transition to gene therapy

The question that the scientific community often discusses is: Are we ready for gene therapy?[24,25] In other words, how can we insure a smooth transition from existing practice to gene therapy?

What is known about gene therapy? Based on recent research, we can state that gene therapy is actually feasible based on the results of several ongoing or completed clinical trials,[26] causing significant endogenous CF generation (Table 2), and improved clinical outcomes in terms of bleeding rates and CF requirements. Nevertheless, with only a few patients eligible for this procedure, the production of FVIII or FIX has proven to be highly variable and unpredictable. Certain patients do not respond to gene therapy. Moreover, monitoring liver integrity is paramount to controlling rejection reactions, and many patients need immunotherapy, with intense follow-up over the first post-infusion months, and at times years.

Most approaches that have enabled successful gene therapy in haemophilia were first tested in HB patients, and many of these can possibly be extrapolated to gene therapy in HA patients. Nevertheless, biological differences between FVIII and FIX explain specific obstacles in the development of gene therapy for HA. Indeed, FVIII is a significantly larger protein than FIX, 280 kDA *versus* 55 kDA, respectively, leading to AAV-vector packaging problems.[27] More problematic, however, is the fact that FVIII is intrinsically less efficiently secreted even when compared to similar-size genes.[28,29] Consequently, normal plasma concentrations of FVIII are generally lower than those of FIX. Moreover, it has been shown that FVIII is exclusively expressed in endothelial cells rather than in hepatocytes, as for FIX. All these discrepancies likely account for differences noted in HA-gene therapy recipients *versus* HB-gene therapy recipients, with likely lower durability, less requirement of corticosteroids or immunosuppressant agents, and a lower percentage of eligible candidates in HA *versus* HB.

What is not known about gene therapy? Given that factor production decreases over time, it is still unknown how long the therapeutic effects will last (Table 3). Although we have now a decent understanding of the pharmacodynamics and pharmacokinetics of CFCs employed for treating haemophilia patients, our knowledge with regards to several variables between vector infusion and sustained therapeutic expression is scarce. Moreover, the impact of gene therapy on the patients' life is not yet clearly grasped; in brief, the patients' overall satisfaction from psychological, personal, and family perspectives is still unknown.[26] Other unidentified features include

Table 1. Coagulation factor concentrates VIII and IX.

Key known properties
• Mechanism of action
• Established haemostatic efficacy
• Proven safety excepting inhibitor development
• Low inter-individual variability in haemostatic response
• Highly predictable effect
• Ubiquitous use by all patients
• Reversible and transitory effect
• No particular precautions required

Table 2. What is known about gene therapy in 2022?

Key known properties
• Gene therapy in haemophilia A and B is possible
• Many exclusion criteria exist; only few patients are eligible
• Gene therapy results in the synthesis of endogenous FVIII or FIX, with a major reduction in bleedings and infusion requirements
• Not all patients do respond to gene therapy
• Patient response is unpredictable
• Corticosteroid therapy is often required over months
• Regular long-term follow-up is mandatory
• Certain restrictions are imposed (alcohol; sexuality, and so on)
• Response duration and sustainability still unknown

FIX, factor IX; FVIII, factor VIII.

Table 3. What is still unknown about gene therapy in 2022?

Key unanswered questions
• Number of patients eligible for gene therapy
• Gene therapy's perceived impact on patients apart from bleedings and factor levels
• Patients' experience of the process
• Overall patient satisfaction (experience *vs* expectation)
• Psychological, personal, and family impact
• Tolerance and acceptability of corticosteroid therapy
• Acceptability of follow-up requirements over many months
• Acceptability of certain imposed restrictions (alcohol, sexuality, and so on)
• Management of undesirable effects and treatment failures

the tolerance and acceptability of corticosteroid or immunosuppressant therapy, certain life restrictions regarding alcohol consumption, sexuality, and so on, and how undesirable effects and treatment failures should be managed.

Patient-centred therapy

The appeal but also the confusion surrounding gene therapy for PWH is both exciting and worrying.[26] Consequently, patient-centred care is paramount. This means that medical care must be focused on the patients and their individual needs to empower them to actively contribute to their own care. This requires healthcare providers to actually become patient advocates. They must ensure that patients perfectly understand the information they receive so they can participate more actively in shared decision-making. This is easier said than done, given that numerous basic requirements must be followed, as outlined below. In the haemophilia setting, there are three pillars from a triptych management approach that must be considered (Figure 2): (1) Who is the candidate?, (2) What do we know about his potential treatment?, and (3) What outcome is to be expected? We are thus faced with a triptych patient management schedule, with at one side, the patient and his history and background, including haemophilia type, presence of inhibitor, comorbidities, as well as his lifestyle, ambitions, and expectations. In the middle, there is often a new treatment, meaning its type along with its modalities. Last but not least, we have the treatment outcomes, which must be better apprehended. In other words, what outcomes are we looking at in terms of bleeding rates, infusion requirements, perceived pain, medical visits, and patient quality of life? In fact, patient perspectives are paramount, especially when defining the real value of these therapies in terms of improved quality of life (QoL); based on this, we must determine what constitutes a fair price.[30] Patient contribution in collecting follow-up data is paramount with respect to these therapies' effectiveness on a long-term and real-world basis.

Patient profiling

It is crucial for healthcare providers to establish a precise patient profile, encompassing their physical features, including age, inhibitor history, concomitant HIV infection, and other comorbidities, in addition to their liver and joint health, as well as their ongoing treatments (Table 4). In addition, the patients' psychological and mental conditions must be considered, including their expectations, understanding, and ambitions, as must be their acceptability of restrictions, their

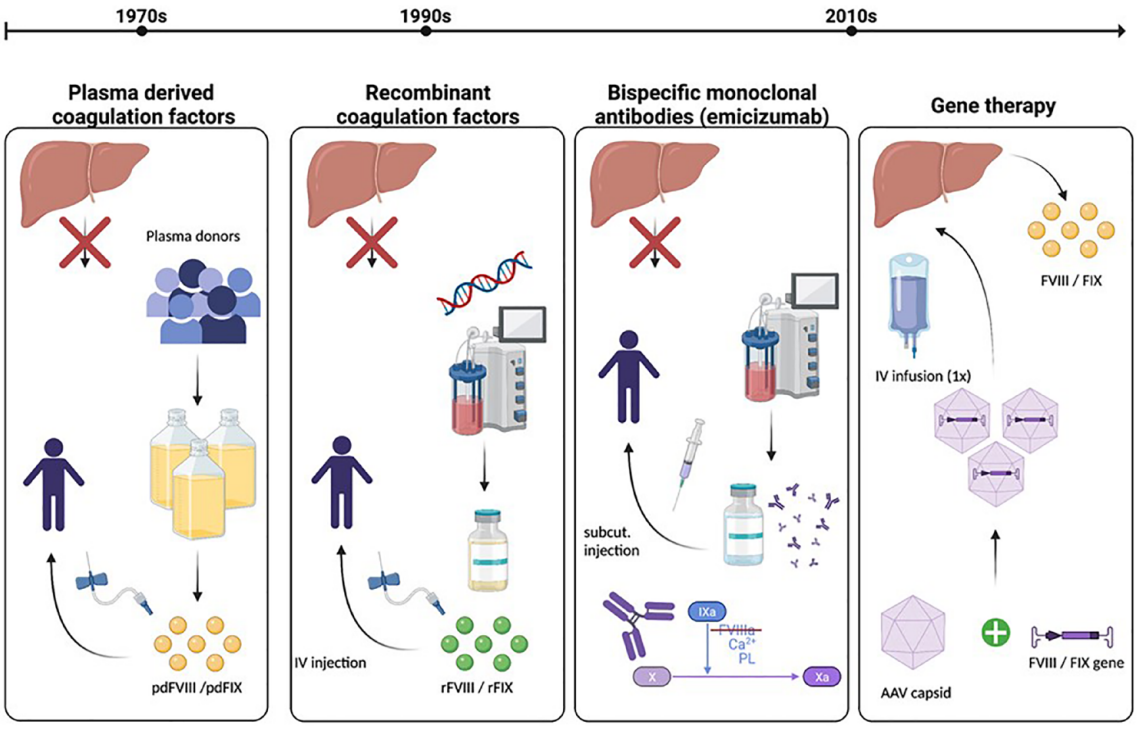

Figure 1. Progress made in haemophilia care over the last five decades (created with BioRender).

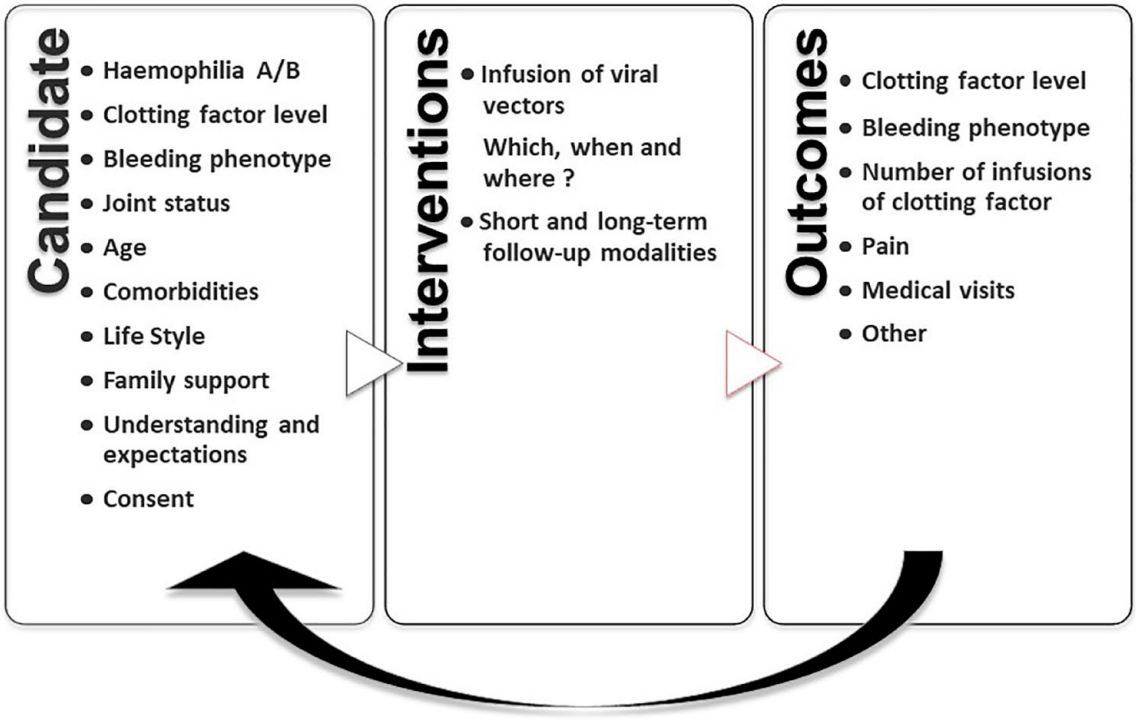

Figure 2. Multistep management approach of gene therapy of haemophilia.

Table 4. Necessity of profiling each candidate's physical and psychological dimensions.

Patient profiling	
Physical dimensions	**Psychological dimensions**
• Patient age	• Patient's expectations
• Inhibitor history	• Patient's understanding
• Human immunodeficiency virus infection	• Patient's ambitions
• Comorbidities	• Patient's acceptability of restrictions
• Liver status (hepatitis C and alcohol)	• Management of uncertainty
• Joint status (limitations and pain)	• Support of environment
• Ongoing therapies (efficacy and compliance)	• Patient's capacity of tolerating restrictions
	• Patient's ability of failure management

capacity of tolerating restrictions and dealing with failures, and the question must be raised what support they have in their environment.

At present, pre-existing antibodies against the various AAV serotypes still pose a significant hurdle to the universal application of AAV gene therapy.[31] However, recent advances in the development of new AAV variants with different immunological profiles, chemical vector modification, immunosuppression, and plasmapheresis indicate that it is likely that AAV gene therapy can be extended to a significant number of patients that currently would have to be excluded because of pre-existing, especially if the different modalities can be combined.

What are the patients' expectations with regard to gene therapy?

Patients' expectations are rather individual. Several papers have attempted to shed light on these attitudes.[32–34] Specific inputs from patients are urgently needed, as they help define the best gene therapy-delivering system, facilitating cross-border mobility, and patients' access to these therapies. Patients must approach gene therapy with realistic expectations regarding the expected risks and potential benefits, for which they require basic knowledge enabling them to make informed decisions. In an attempt to assess patient preferences, the PAVING survey was conducted in Belgium, investigating the trade-offs that PWH were willing to make when preferring gene therapy to standard CFC infusions.[32] Several tools for estimating patient expectations were generated for this study. Its final results clearly confirmed the large heterogeneity in preferences for novel treatments among the Belgian PWH population. The authors additionally analysed the factors that contributed to preference heterogeneity and quantified the minimum acceptable benefit needed to switch from standard prophylaxis to gene therapy. According to their analysis, the most accepted (88%) gene therapy profile turned out to be zero bleeds per year (*vs* six for standard prophylaxis), 90% probability of stopping prophylaxis, no impact on quality of life, and a 10-year follow-up (*vs* 30 years for standard prophylaxis) for identifying rare undesirable effects. Most importantly, the authors strongly stressed the relevance of patient education with regard to therapy acceptance.[34]

From the healthcare side, the ultimate goal is to free PWH from their disease, not only its muscular and skeletal consequences but also its burden on patients' minds. Indeed, PWH rarely have their minds free of haemophilia, despite major improvements in haemophilia care.[35] This goal has now become reality for several gene therapy–treated patients, at least for those who, several months following factor infusion, have achieved sufficient endogenous FIX or FVIII production, and are no longer burdened by the limitations of gene therapy study protocols.[32]

How many patients are eligible?

This question is still difficult to answer. Considering the breakthrough study from *The New Engl J Med*,[21] it would have been interesting to know the

total number of candidates available for the trial who were not considered as good candidates at screening. Today, numerous patients are still being barred from participating in gene therapy trials, including those with detectable viral loads of hepatitis C or hepatitis B and those with portal hypertension, splenomegaly or liver fibrosis. The potential challenge posed by liver damage following gene therapy must be considered, and there are still questions about the risk of ongoing liver inflammation or even hepatocellular carcinoma (HCC). Consequently, patients must be closely followed-up. The only case of HCC reported in an HB gene therapy trial involved a patient with several risk factors, including prior hepatitis C and B infection.[36] After full investigation and given that HCC occurred so early after gene therapy, it was concluded that gene therapy was unlikely to have contributed to this severe adverse event.[16]

Cost of gene therapy

Undoubtedly, the upfront costs of gene therapy are exorbitant, owing to the highly complex treatment process, costly production of the gene shuttles, operating procedures that are individually tailored to each patient, low patient numbers, complex and long studies, in addition to high safety requirements. Yet, these costs are likely to come down in the future. Nevertheless, owing to their added clinical benefits, haemophilia gene therapies offer the prospects of large cost offsets from reduced need for chronic, high-cost standard-of-care therapies. Questions are being raised as to how the cost offsets generated by gene therapy could be assessed and eventually be incorporated into value-based pricing. These issues that are still being debated exceed the scope of this article. Of note, attention should be focused on ensuring adequate availability and equitable access to this emerging gene therapy in low- and middle-income countries.[37]

Requirements for implementing gene therapy

The ultimate goal of gene therapy is to support the patient's ability to 'forget' about their disease and to focus on other life goals, such as family, education, career, and other societal activities. For healthcare providers, it is crucial to investigate, for each patient, what are his expectations, and what changes would be necessary to satisfy him: No more bleeding? No pain? For every single patient, these questions must be asked and eventually answered.

In the coreHem project, Iorio *et al.*[38] sought to determine the outcome measurement set that would be needed to assess efficacy, safety, and value of gene therapy versus other therapeutic alternatives. Then, a core outcome set was developed in collaboration with representatives of all relevant parties. Of the six core outcomes identified, only frequency of bleeds turned out to be a 'legacy' outcome consistently applied in past haemophilia trials. Its inclusion as core outcome will thus enable healthcare providers and others like funding partners or patient associations, to compare the effectiveness of gene therapy with that of existing treatments, in addition to computing derived measures, such as impact on target joints or patient quality of life. Due to massive patient involvement in the coreHem project, the outcomes were deemed meaningful and relevant to most PWH.[37,38] This also means broad acceptance and uptake of these core outcomes are anticipated in forthcoming clinical trials.[37,38]

Patient selection, information, and education

To achieve this challenging goal, several requirements must be satisfied. The decision to undergo gene therapy is deeply personal, requiring detailed and multi-stage decisions. Today, it is still difficult to estimate the proportion of PWH who would be eligible for gene therapy once such treatment has become commercially available. The accurate number of patients deemed ineligible by the investigators involved among those selected for screening is mostly left unreported. In a single-centre study conducted in our haemophilia clinic in Brussels, there were 87 adult patients with severe HA or HB.[39] Of these, most individuals with severe haemophilia could not be enrolled, almost half due to partly modifiable psychosocial reasons (49.4%). Of note is that the number of patients who would accept gene therapy in the absence of strict clinical trial requirements was estimated at 36 (41.4%), irrespective of any exclusion criteria. In this single-centre study, there were actually only seven out of 87 patients left deemed eligible for entering a gene therapy trial. Nevertheless, the proportion of candidates should substantially increase in the future as eligibility criteria are likely to change and more data on long-term efficacy and safety of gene therapy will be available.

Among the PWH community, patient education and clear information play a key role in the successful adoption of complex technologies like gene

therapy. It is thus paramount for healthcare providers to set realistic expectations of eligibility and treatment goals.[40] Hence, healthcare providers must be adequately equipped to provide their patients with sound information, so that the latter can fully weight up the various risks and benefits.[41] An international study evaluated the knowledge and perception of a variety of healthcare professionals concerning gene therapy for PWH. Among them, 59% were directly involved in the care of PWH; yet 35% lacked the ability to explain the science to their patients, and 40% felt rather uncomfortable answering patient questions.[42] It must be mentioned that most patients surveyed, based on World Federation of Hemophilia (WFH) membership, self-reported that they had only a 'basic' understanding of gene therapy ($n = 69$; 68%). As a result, it was stressed that considerable involvement from patient advocacy groups would be needed for providing patient education in haemophilia.[40] Some pharmaceutical companies have already created their own platforms and apps to help visualize the vector delivery process.[43]

Discussing gene therapy with patients

Before proceeding with gene therapy, potential study participants must be given enough information to enable them to understand and consent in an informed way to the risks of the investigational therapy.[44] In two recent papers, Sidonio *et al.*[45] and Miesbach *et al.*[46] have provided a nice review of the fundamentals of AAV-mediated, liver-directed gene transfer in the haemophilia setting. These basics were primarily meant to facilitate discussion between healthcare providers, patients, and their families and advocates, should a trial of investigational gene therapy be considered. Some PWH have difficulty in finding the right information on new therapies on the Internet; they therefore still prefer to turn to their treating primary physicians or nurses for appropriate updates.[47] In contrast, other PWH, referred to as 'empowered' or 'e-patients', have become much more informed and, thus, more involved in decision-making. The successful adoption and translation of gene therapy will depend heavily on addressing barriers relating to knowledge and acceptability. Implementing multi-level interventions targeting healthcare providers, patients, caregivers, and patient advocates to communicate the gene therapy's benefits and risks will clearly improve acceptance of this innovative therapy.

Various national and international societies like the WFH have generated a number of didactics including web-based videos and webinars, which can be used to improve gene therapy knowledge. Nevertheless, these materials are mainly focused on healthcare providers, whereas gene therapy education should accommodate different level learners, including the patients. For the latter, it is essential to create educational material that takes into account their health literacy, while simultaneously taking a deep dive in patients' fears, beliefs, anxieties, and expectations so as to obtain their informed consent for such innovative approaches. Adult learner therapy suggests that the focus should be directed on educational events in small patient groups in order to allow for discussion, interaction, and reflection.[48]

Evidence-informed shared decision-making

Patient engagement is gaining increasing notice among all the disciplines, including the haemophilia field. In clinical practice, PWH are usually well instructed about their treatments, though they would rather not be engaged in conversation, discussion, and decision-making.[49,50] More often than not, true discordance exists between the physicians' perception of their patients' comprehension and patients' actual understanding. Such communication issues can often cause non-adherence to treatments and poorer outcomes.[51] Adequate and individualized communication is, in fact, paramount. The best approach is referred to as patient-centricity, meaning that patients must be actively engaged to achieve the best possible outcomes for themselves and their families.[45] Shared decision-making will most likely reduce the knowledge imbalance between healthcare providers and patients, and gene therapy thus represents a unique opportunity for healthcare providers to embark on patient-centred decision-making.[45]

Another key element of patient-centred care is the use of appropriate language. It is recommended that physicians avoid basic assumptions of 'low' or 'high' patient health literacy. They should omit using technical jargon and unnecessary details, but rather implement what is called the 'teach-back' method in order to ensure patients' full understanding. The preparation of written materials, with key points and several graphics, may prove highly useful for this purpose.

Improved patient consent for haemophilia gene therapy

Gene therapy is an entirely new therapeutic paradigm. Unsurprisingly, there are still many unanswered questions and uncertainties. Several prerequisites must be satisfied for communication with your patients to become highly efficient, as shown in Table 5. The quality of physician-patient communication has proven to significantly impact patient outcomes.

Table 5. Requirements for good patient information about gene therapy.

Criteria for optimal patient information
• Objective information (based on facts and evidence)
• Updated information (within a rapidly changing environment)
• Unbiased information (neutral and reliable)
• Ubiquitous information (for any patient anywhere in the country)

Informed consent is meant to be an active process between healthcare professionals and either a patient or research participant, culminating in the latter's decision to accept or refuse a specific therapeutic intervention or trial participation.[52] In the gene therapy setting, physicians or nurses must figure as primary educators for PWH, with the responsibility to explore patient expectations regarding their eligibility, access to treatment, and outcomes. In a mixed methods study involving 63 healthcare providers, nurses were seen as the most trusted source for advice relative to gene therapy.[53] Presently, the basis for an ethically designed informed consent process relies on good, clear, and transparent information, as the patient is unable to grasp what is not disclosed to him.[54] In a 2021 UK report, six PWH were retrospectively asked about their experiences while receiving investigational gene therapy. They all noted that at pre-infusion, they had been rather worried about potential unwanted effects. Given this background, experts in haemophilia, including representatives of the patient and clinical communities, published best-practice recommendations for patient–physician discussions prior to patient inclusion into an investigational gene therapy trial.[55] In 2019, the European Commission released new guidelines on good clinical practice requirements for advanced therapy medicinal products (ATMPs) like gene therapy. This publication clearly emphasized that participants receive comprehensive information on the expected benefit–risk ratio, along with explicit instruction with regard to the irreversible nature of gene therapy. In 2021, the US Food and Drug Administration (FDA) published further guidance on informed clinical consent.[56]

Long-term follow-up

The duration of benefit derived from AAV gene therapy is still unknown, essentially due to the small number of patients having participated in Phase 1 or 2 trials. In line with the longest ongoing human AAV gene therapy trial, it appears that CF levels of at least >0.05 IU/mL, once achieved, would likely persist for 5–10 years, and possibly longer. There have been concerns that patients could be lost to follow-up by their treatment centres.[16] There is a wide consensus that indefinite long-term patient monitoring is required. It is only now that experts are actually beginning to better appreciate the long-term outcomes of AAV-mediated gene therapy. First, assessment of plasmatic CF levels must be regularly conducted to check for persistent expression of the transgenic protein, and the patients' clinical status should be meticulously monitored in terms of ABRs and infusion requirements. The potential of hepatotoxicity must be followed-up, as well as the host genotoxicity.[57] Regular liver imaging must ensure that there is no ongoing cancer development.

Long-term considerations of AAV therapeutics

The major hypothesized long-term safety concerns of systemic AAV-vector administration remain the risks of liver toxicity and target organ toxicity in addition to genotoxicity. While AAV is predominantly non-integrating, sequencing data in animals and humans post-environmental AAV exposure or vector administration demonstrates low-frequency AAV integration events with a proclivity for sites of active transcription. Evidence of AAV integration and clonality post-systemic AAV vector was also recently demonstrated in a large-animal HA model. Importantly, however, the same animals were followed-up for 10 years without evidence of tumorigenesis; nonetheless, this study provides the first large-animal data to highlight the risk of AAV-mediated integration.[58]

Haemophilia care centres

Gene therapy should ideally be carried out in comprehensive haemophilia treatment centres. AAV-vector administration is accomplished by peripheral vein infusion, meaning patients are not required to be admitted overnight. While acute undesirable effects are quite rare with AAV-vector delivery, subsequent follow-up over the next months, or even years, appears mandatory.

Hub centres

Today, expertise in gene therapy is still highly localized. Significant work is still required to prepare haemophilia treatment centres for gene therapy. Considering the limited number of comprehensive care centres (CCCs) that already conduct investigational gene therapy trials, it is possible to transfer PWH from their own care centre to other CCCs already involved in gene therapy. Such move could possibly unsettle the foundations required for patients to ask questions, to feel confident, and to discuss gene therapy issues with the newly assigned physicians. For these reasons, coordinated and integrated models, which are also referred to as 'hub-and-spoke', have been charged to oversee all the different steps of the care pathway designed for gene therapy.[59]

The 'hub and spoke' model was proposed in a joint statement published by the European Association for Haemophilia (EAHAD) and the European Haemophilia Consortium (EHC). This model is meant to ensure the safe introduction, use, monitoring, and optimal learning of gene therapies over time. Given this setting, the EAHAD and EHC jointly called for all first-generation gene therapies to be managed using this 'hub and spoke' model, meaning that

1. Gene therapies should be managed and prescribed exclusively by expert haemophilia CCCs, as national hubs.
2. Gene therapies should be monitored by haemophilia treatment centres in close communication with the primary expert hub, as spokes linking into that hub.

Any adverse events should be managed by both the expert 'hubs' as well as the treatment centre 'spokes' to provide the timeliest state-of-the-art options to patients and maximize long-term benefits.

The proposed 'hub-and-spoke' model will likely enable patients to be treated in centres with the greatest experience in gene therapy, with the follow-up still provided by their own spoke centre, which works hand in hand with the respective hub centre.[60]

Multidisciplinary approach and integrated care

Comprehensive integrated care by a multidisciplinary expert team has been proven to ameliorate outcomes.[61,62] It is widely recommended for PWH in both the United States and Europe alike.[63] Nevertheless, the approval of gene therapy for managing PWH within the next years will not only alter the disease course, but also necessitate an adaptation in haemophilia care. This is anticipated to significantly impact haemophilia care models and networks. In the short-term, haemophilia treatment centres will require additional resources to coordinate care and follow-up of gene therapy recipients.[58] Both physicians and nurses will become heavily involved in patient education; additional investment in psychosocial support may be required, as will be new processes for ordering, storing, and handling gene therapy products, with possible repercussion on the pharmacists. During the first months following gene therapy, the liver health must be closely monitored, with additional workload on hepatologists. Moreover, physiotherapists must continue to monitor joint health in gene therapy recipients, using physical assessment tools and muscular and skeletal ultrasound, as necessary.[64] Here, competencies will likely evolve, and physiotherapists in primary care and specialist treatment centres must work along with haematologists to develop more sensitive tools for detecting early joint changes. These physiotherapists will need to play a crucial role in counselling, physically coaching, and monitoring the musculoskeletal status of PWH.[65] Nurses will need to adapt to this rapidly changing environment. They must be aware of gene therapy's potential risks and be able to answer the patients' numerous questions. In brief, the key to success of the gene therapy journey will likely rely on a strong collaboration and communication among and between healthcare providers and patients.

Gene therapy registry

A growing number of studies are seeking to assess the the impact of gene therapy on the lives of

those who have already undergone the procedure. With most registries primarily focused on positive outcomes, including liberation from a debilitating disease or ability to participate in risk sports, they have not always addressed the respective concerns, including the undesirable effects associated with immunosuppressive therapy or post-vector infusion transaminitis, which is now a recognized undesirable effect linked with gene therapy.

The world gene therapy registry is currently being developed by the WFH. This registry primarily seeks to collect long-term data on safety, and variability and durability of efficacy on all PWH who receive gene therapy.

Surveillance of gene therapy in PWH requires a global reach, as patients are dispersed throughout countries and continents. A global strategy is required to ensure a large enough patient pool to allow for robust evaluation and for detecting low-incident events. If events are captured in disparate registries, it would be technically challenging to combine such data. As gene therapy continues to progress and advance, a growing set of long-term safety and efficacy data must urgently be entered into an international or global gene therapy registry. Such precious data collection will ultimately define gene therapy's future in haemophilia.

Conclusion

The world is still getting ready for gene therapy, as we are at the forefront of transformative developments in haemophilia care. Although the resources, expertise, and experiences required to evaluate gene therapy are not yet available in all countries, promoting national and international collaboration is a MUST for healthcare providers, manufacturers, authorities, and payers alike, eventually providing access to gene therapy to all who need it. With continuing advances and increasing evidence of gene therapy's cost-effectiveness *versus* CFC infusions, the future will hopefully bring about more efficient, safe, and durable factor expression in resource-rich but also resource-poor countries where CFCs are hardly available.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Cedric Hermans: Conceptualization; Methodology; Visualization; Writing – original draft.

Yves Gruel: Conceptualization; Validation; Writing – review & editing.

Laurent Frenzel: Conceptualization; Writing – review & editing.

Evelien Krumb: Conceptualization; Validation; Visualization; Writing – original draft; Writing – review & editing.

Acknowledgements

Writing support was provided by Gabrielle Cremer working at Cremer Consulting SAS, Strasbourg, France.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CH has received research support from Bayer, Shire, Pfizer, and Novo Nordisk; CH has obtained consultant fees from Pfizer, Bayer, Shire, Novo Nordisk, CSL Behring, Octapharma, Sobi Biogen, LFB, CAF-DCF, and Roche; CH has been invited to give guest lectures at different conferences by Pfizer, Bayer, Shire, Novo Nordisk, CSL Behring, Octapharma, Sobi Biogen, LFB, CAF-DCF, Roche; and Kedrion. YG has received research support from Roche and consultant fees from Bayer, Octapharma, and LFB. LF received consultant fees from SOBI, Roche and Pfizer. EK has received research support from Sobi and CSL Behring. These funders had no role in the writing of this manuscript. The Associate Editor of *Therapeutic Advances in Haematology* is an author of this paper; therefore, the peer-review process was managed by alternative members of the Board and the submitting Editor was not involved in the decision-making process.

Availability of data and materials

Data sharing not applicable – no new data generated

ORCID iDs
Cedric Hermans https://orcid.org/0000-0001-5429-8437

Evelien Krumb https://orcid.org/0000-0001-8270-8819

References

1. Saito H, Matsushita T and Kojima T. Historical perspective and future direction of coagulation research. *J Thromb Haemost* 2011; 9(Suppl. 1): 352–363.
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al*. Guidelines for the management of hemophilia. *Haemophilia* 2013; 19: e1–e47.
3. O'Hara J, Hughes D, Camp C, *et al*. The cost of severe haemophilia in Europe: the CHESS study. *Orphanet J Raredis* 2017; 12: 106.
4. Hay CR, DiMichele DM and International Immune Tolerance Study. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood* 2012; 119: 1335–1344.
5. Blair HA. Emicizumab: a review in haemophilia A. *Drugs* 2019; 79: 1697–1707.
6. Oldenburg J, Mahlangu JN, Kim B, *et al*. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med* 2017; 377: 809–818.
7. Cafuir L, Kruse-Jarres R, Mancuso ME, *et al*. Emicizumab for hemophilia A without inhibitors. *Expert Rev Hematol* 2019; 12: 515–524.
8. Franchini M and Mannucci PM. Non-factor replacement therapy for haemophilia: a current update. *Blood Transfus* 2018; 16: 457–461.
9. Kruse-Jarres R, Oldenburg J, Santagostino E, *et al*. Bleeding and safety outcomes in persons with haemophilia A without inhibitors: results from a prospective non-interventional study in a realworld setting. *Haemophilia* 2019; 25: 213–220.
10. Mahlangu J, Oldenburg J, Paz-Priel I, *et al*. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med* 2018; 379: 811–822.
11. Callaghan MU, Negrier C, Paz-Priel I, *et al*. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1–4 studies. *Blood* 2021; 137: 2231–2242.
12. Grimm D and Büning H. Small but increasingly mighty: latest advances in AAV vector research, design, and evolution. *Hum Gene Ther* 2017; 28: 1075–1086.
13. High KA and Anguela XM. Adeno-associated viral vectors for the treatment of hemophilia. *Hum Mol Genet* 2016; 1525: 36–41.
14. Arruda VR and Xiao W. It's all about the clothing: capsid domination in the adeno-associated viral vector world. *J Thromb Haemost* 2007; 5: 12–15.
15. High KA. AAV-mediated gene transfer for hemophilia. *Ann N Y Acad Sci* 2001; 953: 64–74.
16. Batty P and Lillicrap D. Gene therapy for hemophilia: current status and laboratory consequences. *Int J Lab Hematol* 2021; 43(Suppl. 1): 117–123.
17. Verdera HC, Kuranda K and Mingozzi F. AAV vector immunogenicity in humans: a long journey to successful gene transfer. *Int J Mol Ther* 2020; 28: 723–746.
18. Von Drygalski A, Giermasz A, Castaman G, *et al*. Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B. *Blood Adv* 2019; 3: 3241–3247.
19. Purdue J and Behring CSL. Final analysis of Pivotal HOPE-B study demonstrates durable and sustained therapeutic effect of Etranacogene Dezaparvovec Gene Therapy in Hemophilia B – Data Presented at EAHAD 2022. (2022, accessed 23 December, 2022).
20. Pipe SW, Recht M, Key NS, *et al*. First data from the phase 3 HOPE-B gene therapy trial: efficacy and safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in adults with severe or moderate-severe Hemophilia B treated irrespective of pre-existing anti-capsid neutralizing antibodies. *Blood* 2020; 136(Suppl. 2): LBA–6. https://doi.org/10.1182/blood-2020-143560
21. Ozelo MC, Mahlangu J, Pasi KJ, *et al*. Valoctocogene roxaparvovec gene therapy for hemophilia A. *N Engl J Med* 2022; 386: 1013–1025.
22. Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica* 2020; 105: 545–553.
23. O'Mahony B, Wong O, Eichler H, *et al*. Preparing for tomorrow: defining a future agenda. *Haemophilia* 2022; 28(Suppl. 2): 35–41.
24. Garrison LP and Kleinermans D. Is the world ready for gene therapy? *Haemophilia* 2022; 28(Suppl. 2): 5–8.
25. Thornburg CD. Prepare the way for hemophilia A gene therapy. *N Engl J Med* 2022; 386: 1081–1082.

26. Hermans C. Haemophilia gene therapy: experiences and lessons from treated patients. *Orphanet J Rare Dis* 2022; 17: 154.

27. Marder VJ, Aird WC, Bennett JS, *et al*. *Hemostasis and thrombosis: basic principles and clinical practice*. 6th ed. Philadelphia, PA: Lippincott Williams &Wilkins, 2013.

28. Arruda VR and Samelson-Jones BJ. Obstacles and future of gene therapy for hemophilia. *Expert Opin Orphan Drugs* 2015; 3: 997–1010.

29. Pipe SW. Functional roles of the factor VIII B domain. *Haemophilia* 2009; 15: 1187–1196.

30. Hollak CEM, Sirrs S, van den Berg S, *et al*. Registries for orphan drugs: generating evidence or marketing tools? *Orphanet J Rare Dis* 2020; 15: 235–241.

31. Louis Jeune V, Joergensen JA, Hajjar RJ, *et al*. Pre-existing anti–adeno-associated virus antibodies as a challenge in AAV gene therapy. *Hum Gene Ther Methods* 2013; 24: 59–67.

32. Van Overbeeke E, Michelsen S, Hauber B, *et al*. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. *Haemophilia* 2022; 27: 129–136.

33. van Overbeeke E, Hauber B, Michelsen S, *et al*. Patient preferences for gene therapy in haemophilia: results from the PAVING threshold technique survey. *Haemophilia* 2021; 27: 957–966.

34. Khair K, Steadman L, Chaplin S, *et al*. Parental perspectives on gene therapy for children with haemophilia: the exigency study. *Haemophilia* 2021; 27: 120–128.

35. Krumb E and Hermans C. Living with a 'hemophilia–free mind' – the new ambition of hemophilia care. *Res Pract Thromb Haemost* 2021; 5: e12567.

36. Davé UP and Cornetta K. AAV joins the rank of genotoxic vectors. *Mol Ther* 2021; 29: 418–419.

37. Garrison LP, Pezalla E, Towse A, *et al*. Hemophilia gene therapy value assessment: methodological challenges and recommendations. *Value Health* 2021; 24: 1628–1633.

38. Iorio A, Skinner MW, Clearfield E, *et al*. Core outcome set for gene therapy in haemophilia: results of the coreHEM multistakeholder project. *Haemophilia* 2018; 24: e167–e172.

39. Krumb E, Lambert C and Hermans C. Patient selection for hemophilia gene therapy: real-life data from a single center. *Res Pract Thromb Haemost* 2021; 5: 390–394.

40. Pierce G and Coffin D and Members of the WFH Gene Therapy Round Table Program Committee and Organizing Committee. The 1st WFH gene therapy round table: understanding the landscape and challenges of gene therapy for haemophilia around the world *Haemophilia* 2019; 25: 189–194.

41. Woollard L, Gorman R and Rosenfelt DJ. Addressing patient education priorities in the era of gene therapy for haemophilia: towards evidence-informed shared decision-making. *Haemophilia* 2021; 27: e302–e304.

42. Peyvandi F, Lillicrap D, Mahlangu J, *et al*. Hemophilia gene therapy knowledge and perceptions: Results of an international survey. *Res Pract Thromb Haemost*. 2020; 4(4): 644–651.

43. Spark Therapeutics. Turning genes into medicine. https://www.sparkgenetherapyeducation.com (2019, accessed 22 December, 2022).

44. Bolous NS, Bhatt N, Bhakta N, *et al*. Gene therapy and hemophilia: where do we go from here? *J Blood Med* 2022; 13: 559–580.

45. Sidonio RF Jr, Pipe SW, Callaghan MU, *et al*. Discussing investigational AAV gene therapy with hemophilia patients: a guide. *Blood Rev* 2021; 47: 100759.

46. Miesbach W, O'Mahony B, Key NS, *et al*. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia* 2019; 25: 545–557.

47. van Balen EC, Wesselo ML, Baker BL, *et al*. Patient perspectives on novel treatments in haemophilia: a qualitative study. *Patient* 2020; 13: 201–210.

48. Dionyssopoulos A, Karalis T and Panitsidis ZA. Continuing medical education revisited: theoretical assumptions and practical implications: a qualitative study. *BMC Med Educ* 2014; 14: 1051.

49. Wang M, Negrier C, Driessler F, *et al*. The hemophilia gene therapy patient journey: questions and answers for shared decision-making. *Patient Prefer Adherence* 2022; 16: 1439–1447.

50. Hermans C, Noone D, Benson G, *et al*. Hemophilia treatment in 2021: choosing the 'optimal' treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians. *Blood Rev* 2021; 1: 100890.

51. Safeer RS and Keenan J. Health literacy: the gap between physicians and patients. *Am Fam Physician* 2005; 72: 463–468.

52. Woollard L, Gorman R and Rosenfelt DJ. Improving patient informed consent for heamophilia gene therapy: the case for charge. *Ther Adv Rare Dis* 2021; 2: 1–16.

53. Khair K, Steadman L, Chaplin S, *et al*. Parental perspectives on gene therapy for children with haemophilia: the exigency study. *Haemophilia* 2021; 27: 120–128.

54. Kahn J. Informed consent in human gene transfer clinical trials. *Hum Gene Ther* 2008; 19: 7–8.

55. Hart DP, Branchford BR, Hendry S, *et al.* Optimizing language for effective communication for gene therapy concepts with hemophilia patients: a qualitative study. *Orphanet J Rare Dis* 2021; 16: 189.

56. US Food & Drug Administration and Center for Biologics Evaluation and Research. Long term follow-up after administration of human gene therapy products; guidance for industry, https://www.fda.gov/media/113768/download (2020, accessed 21 June 2022).

57. Monahan PE, Négrier C, Tarantino M, *et al.* Emerging immunogenicity and genotoxicity considerations of adeno-associated virus vector gene therapy for hemophilia. *J Clin Med* 2021; 10: 2471.

58. Samelson-Jones BJ and George LA. Adeno-associated virus gene therapy for hemophilia. *Annu Rev Med*. Epub ahead of print 14 September 2022. DOI: 10.1146/annurev-med-043021-033013.

59. Athanasopoulos A. EAHAD-EHC statement on gene therapies hub-and-spoke model, https://eahad.org/eahad-ehc-statement-on-promoting-hub-and-spoke-model-using-gene-therapies/(2020, accessed 21 June 2022).

60. Miesbach W, Baghael F, Boban A, *et al*. Gene therapy of hemophilia: hub centers should be hemophilia centers: a joint publication of EAHAD and EHC. *Haemophilia* 2022; 28: e86–e88.

61. Colvin BT, Astermark J, Fischer K, *et al.* European principles of haemophilia care. *Haemophilia* 2008; 14: 36174.

62. Noone D, O'Mahony B, Peyvandi F, *et al.* Evolution of haemophilia care in Europe. *Orphanet J Raredis* 2020; 15: 184.

63. Miesbach W, Pasi KJ, Pipe SW, *et al*. Evolution of haemophilia integrated care in the era of gene therapy: treatment centre's readiness in United States and EU. *Haemophilia* 2021; 27: 511–514.

64. Lobet S, Detrembleur C, Massaad F, *et al.* Three-dimensional gait analysis can shed new light on walking in patients with haemophilia. *ScientificWorldJournal* 2013; 2013: 284358.

65. Lobet S, Merel T, Königs C, *et al.* The role of physiotherapy in the new treatment landscape for haemophilia. *J Clin Med* 2021; 10: 2822.