Journal of Blood Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

# Gene Therapy and Hemophilia: Where Do We Go from Here?

Nancy S Bolous[1], Nidhi Bhatt[2], Nickhill Bhakta[1], Ellis J Neufeld[2], Andrew M Davidoff[3], Ulrike M Reiss[2]

[1]Department of Global Pediatric Medicine – St. Jude Children's Research Hospital, Memphis, TN, USA; [2]Department of Hematology – St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Department of Surgery – St. Jude Children's Research Hospital, Memphis, TN, USA

Correspondence: Nancy S Bolous, Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 721, Memphis, TN, 38105, USA, Tel +1 901 595 1968, Fax +1 901 595 5319, Email nancy.bolous@stjude.org



**Abstract:** Gene therapy for hemophilia using adeno-associated virus (AAV) derived vectors can reduce or eliminate patients' disease-related complications and improve their quality of life. Broad implementation globally will lead to societal gains and foster health equity. Several vector products each for factor IX (FIX) or factor VIII (FVIII) deficiency are in advanced clinical development. Safety data are reassuring. Efficacy data for up to 8 and 5 years, respectively, vary considerably among vector types and among individuals, but indicate significant reduction in bleeds and factor use. Products will soon be approved for marketing. This review highlights the relevant considerations for implementation of hemophilia gene therapy, specifically across a broad range of socioeconomic backgrounds globally, based on recent publications and our own experience. We address the current efficacy and safety data and relevant aspects of vector immunology. We then discuss pertinent implementation steps including pre-implementation and readiness assessments, considerations on cost, cost-effectiveness and payment models, approaches to education and informed consent, and the operational needs as well as the need for monitoring of health outcomes and implementation outcomes. To prevent a lag or complete lack of establishing access to this life-changing therapy option for all patients with hemophilia worldwide, adaptable pathways supported by collaborative and international efforts of all stakeholders are needed.

**Keywords:** global health, health equity, cost-effectiveness, adeno-associated virus vector, factor VIII, factor IX

## Introduction

Hemophilia A and hemophilia B are monogenic, x-linked bleeding disorders that occur due to a decrease or lack of function of the respective clotting factor, factor VIII (FVIII) or factor IX (FIX), respectively.[1,2] Persons with hemophilia (PWH) experience frequent provoked or spontaneous bleeds into joints, or soft tissue, and, occasionally, intracranial or internal bleeds. Chronic hemarthropathy or recurrent intracranial bleeding can lead to lifelong disability or early death.[3,4] The standard of care for bleed treatment or prevention includes factor replacement with plasma-derived or recombinant concentrates by intravenous infusion at intervals between every day to every 2 weeks, or a recently developed non-factor product given subcutaneously every 1–4 weeks.[5]

The standard of care varies for PWH in different socioeconomic environments. In high-income countries (HIC), standard dose prophylaxis is recommended, which aims to reduce bleeding episodes and prevent or at least minimize joint damage, significantly improving patients' quality of life. HIC health systems are well equipped to regularly supply these high-cost products and, therefore, consume more than 60% of the global factor supply.[6]

While these agents and treatment approaches are available in most HIC, access varies for PWH in resource-limited socioeconomic environments. In many low- and middle-income countries (LMIC), where more than 75% of PWH live, constrained resources limit the options, and clotting factor concentrate is not available or not affordable. Often PWH have to rely on fresh frozen plasma or cryoprecipitate, which make it harder to reach the desired factor level due to the risk of volume overload in addition to the risk of infection with blood-borne diseases. The financial burden associated

Received: 26 May 2022
Accepted: 22 September 2022
Published: 6 October 2022

with factor concentrate in these settings has forced guidelines predominantly in LMICs to recommend low-dose prophylaxis or even low dose on-demand treatment to control bleeding episodes.[5] Hence, the variability in the treatment approach and intensity across countries contributes drastically to the discrepancy in the quality of life and life expectancy for hemophilia patients globally.[7,8]

AAV-mediated gene therapy for hemophilia A or B has the potential to cure the disease after a single peripheral vein infusion.[9] The clinical development of several FVIII or FIX gene transfer products is now at the critical junction of moving from the clinical trial environment to marketing and commercial availability. Although regulatory approvals are still pending, preparations for provider and patient education, clinical infrastructure, and manufacture scale up including pricing and reimbursement plans are well on their way in high-income countries (HIC). In contrast, there is minimal preparative activity in low- and middle-income countries (LMIC); only 7 of 137 (4%) LMIC (Brazil, Bulgaria, China, India, South Africa, Thailand, Turkey) have been participating in hemophilia gene therapy trials, and only China is sponsoring its own trials.[10] Therefore, most LMIC have only limited knowledge and experience, in addition to their lower economic capacity, regarding introducing these new and expensive drugs. The recently announced proposed price tag of US$ 1,000,000–3,000,000/dose has the potential to worsen the existing health outcomes gap among PWH worldwide.

Gene therapy offers an exciting opportunity to reduce health inequity in PWH globally and contribute to improved quality of life, societal and global gains. Adaptation of gene therapy implementation in LMIC versus HIC is essential and requires the use of an implementation science framework. This review highlights the needs to be addressed for equitable, global implementation of hemophilia gene therapy. After summarizing the current evidence from hemophilia A and B gene therapy trials, we address the important considerations in this process: pre-implementation assessment and readiness; education of patients and providers; establishment of infrastructure and clinical delivery processes; monitoring for implementation and health outcomes; and cost, cost-effectiveness and payment models.

# Current Experience with AAV-Mediated Gene Therapy for Hemophilia A and B

## Efficacy and Safety of Gene Therapy Products in Development

Three initial clinical trials of AAV-mediated gene therapy in patients with hemophilia B laid the groundwork for today's 10 or more gene transfer products in ongoing development (Tables 1 and 2). The first trial administered an AAV2-FIX vector intramuscularly with no clinical complications, but without sufficient expression levels in plasma, although persistence of local transgene expression in muscle cells, as assessed by immunohistochemical staining of transduced myocytes, was present after 3.7 years.[11,12] A subsequent study of AAV2-FIX delivered via intrahepatic artery injection, showed only temporary FIX expression, up to 12% in one participant, but uncovered the possible role of vector-induced, CD8 T-cell mediated immune response targeting transduced liver cells causing reduction or loss of factor expression post infusion.[13,14] Subsequently, the trial of an AAV2/8-FIX vector introduced close monitoring post infusion for vector-induced transaminitis and, as indicated, the use of transient immunosuppressive treatment with oral prednisone or prednisolone. This study has reported stable long-term FIX expression for at least 8 years without late toxicity.[15–17]

Following these trials, nine different AAV-FIX vectors have entered Phase 1/2 trials of which five are currently continuing in active research and development phases, four of these using a higher specific activity variant of FIX, termed FIX-Padua: AMT061 (etranacogene dezaparvovec, etranadez), SPK9001 (fidanacogene elaparvovec), FLT180a (vebrinacogene setparvovec), BBM-H901, and VGB-R04 (Table 1).[10,18] AMT061 achieved a mean FIX activity of 36.9% (± 21.4, range 4.5–122.9) at 1.5 years in 54 Phase 3 participants using a dose of $2\times10^{13}$ vg/kg; preliminary data show that the initial vector construct, a wild-type FIX-containing vector AMT060, has been stably expressed without long-term toxicity up to 5 years.[19–22] AMT061 is currently under accelerated review by the European Medicines Agency. SPK9001 therapy has resulted in mean FIX activity of 22.9% (±9.9) at a dose of $5\times10^{11}$ vg/kg in 15 Phase 2 subjects after 1 year.[23,24] FLT180a treatment has resulted in FIX activity levels between 50% and 180% at a dose of $8.3\times10^{11}$ vg/kg in 4 subjects having received the final dose level of the phase 1/2 trial.[25] Interestingly, the final vector doses vary up to 40-fold between the different vectors. Overall, 20–70% of the patients experienced vector-induced transaminitis requiring

**Table 1** Clinical Trial Results for AAV-Mediated Gene Therapy for Factor IX Deficiency

| Vector Product | NCT | Trial Phase | Vector Dose | Number Treated | FIX (%) at Year: 0.5–1y | 1.5–2y | 2.5–3y | 4y | 5y | 6y | Transaminitis Rate | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *CHOP/Avigen* | | | | | | | | | | | | |
| rAAV2-FIX (intramuscular) | | I | 0.2 to 1.8 $\times 10^{12}$ | 8 | 0 | | | | | | | [11,12] |
| *CHOP/Avigen* | | | | | | | | | | | | |
| rAAV2-FIX-WT (intra-hepatic artery) | NCT00515710 | I/2 | 0.08 to $2\times 10^{12}$ | 7 | 0 | | | | | | | [13] |
| *St. Jude/UCL* | | | | | | | | | | | | |
| rAAV8-FIX-WT | NCT00979238 | I/2 | $2\times 10^{12}$ | 6 | 1.4–7.2 | 5.1±1.7 | | | | 5.1 | 4/6 (67%) | [15–17] |
| *Uniqure/CSL Behring* | | | | | | | | | | | | |
| AMT060, rAAV5-FIX-WT | NCT02396342 | I | $2\times 10^{13}$ | 5 | 6.9 (2.6–11.3) | 7.1 | 8.4 | 7.4 | 5.2 | | 2/5 (40%) | [19,20] |
| AMT061, (etranacogene dezaparvovec, rAAV5-FIX-R338L) | NCT03489291 | 2 | $2\times 10^{13}$ | 3 | 47 (33–57) | | 50 (37.1–58.6) | | | | 0/0 (0%) | [21] |
| | NCT03569891 | 3 | $2\times 10^{13}$ | 54 | 39±18.7 (8.2–97.1) | | 36.9±21.4 (4.5–122.9) | | | | 0/0 (0%) | [22] |
| *Pfizer/Spark* | | | | | | | | | | | | |
| SPK9001, (fidanacogene elaparvovec, SPK100-FIX-R388L) | NCT02484092 | 2 | $5\times 10^{11}$ | 15 | | 22.9±9.9 | | | | | 3/15 (20%) | [23,24] |
| | NCT03861273 | 3 | n/a | n/a | | | | | | | | |
| *UCL/Freeline* | | | | | | | | | | | | |
| FLT180a, (AAVS3-FIX-R388L) | NCT03369444 | I | $8.3\times 10^{11}$ | 4 | 50–180 | | | | | | n/a | [25] |
| | NCT05164471 | I/2 | $7.7\times 10^{11}$ | I | | | | | | | n/a | |
| *IHBDH/SBDB* | | | | | | | | | | | | |
| BBM-H901, AAV843-FIX-WT | NCT04135300 | I/2 | $5\times 10^{12}$ | 10 | | | | | | | n/a | |

(*Continued*)


https://doi.org/10.2147/JBM.S371438 DovePress

**Table 1** (Continued).

| Vector Product | NCT | Trial Phase | Vector Dose | Number Treated | FIX (%) at Year: 0.5–1y | 1.5–2y | 2.5–3y | 4y | 5y | 6y | Transaminitis Rate | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *HBDH/FIX Variant* | | | | | | | | | | | | |
| VGB-R0-4 | NCT05152732 | 2 | n/a | n/a | | | | | | | n/a | |
| *Dimension/Ultragenics* | | | | | | | | | | | | |
| DTX101, AAVrh10-FIX-WT | NCT02718915 | 1 | $5\times10^{12}$ | 3 | 0 | | | | | | n/a | [27] |
| *Baxalta/Takeda* | | | | | | | | | | | | |
| BAX335, rAAV8-FIX-R388L | NCT01687608 | 1 | $3\times10^{12}$ | 2 | 45.3 (32–59) | 20 (n=1) | | | | | n/a | [26] |
| *Takeda/Baxalta/Shire* | | | | | | | | | | | | |
| SHP648, rAAV8-FIX-R388L | NCT04394286 | 1 | n/a | | | | | | | | | |

**Table 2** Clinical Trial Results for AAV-Mediated Gene Therapy for Factor VIII Deficiency

| Vector Product | NCT | Trial Phase | Dose | Number Treated | FVIII (%) at Year: 0.5y | 1y | 2y | 3y | 4y | 5y | Transaminitis Rate | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Biomarin* | | | | | | | | | | | | |
| BMN270, Roctavion | NCT02576795 | 1/2 | $6\times10^{13}$ | 7 | - | 93±48 | 36 | 33 | – | 11.6±12.2 | 7/7 (100%) | [30–32] |
| | | | $4\times10^{13}$ | 6 | - | 21 | 15 | – | 5.6 | | 4/6 (66%) | [30–32] |
| | NCT03370913 | 3 | $6\times10^{13}$ | 134 | - | 42.9±45.5 | 24.4±29.2 | | | | 106/134 (79%) | [29] |
| | NCT03392974 | 3 | $4\times10^{13}$ | 1 | - | | | | | | | |
| *Spark* | | | | | | | | | | | | |
| SPK8011, AAV-LK03-coBDD-F8 | NCT03003533 | 1/2 | $5\times10^{11}$ | 2 | - | | | | | | | [35] |
| | | | $1\times10^{12}$ | 3 | - | | | | | | | [35] |
| | | | $1.5\times10^{12}$ | 4 | - | All four doses: | | | | | | [35] |
| | | | $2\times10^{12}$ | 9 | - | 6.9±3.8 (3.0–14.3)* | | | | | 13/18 (72%) | [35] |
| SPK8016, AAV-coBDD-F8 | NCT03734588 | 1/2 | $5\times10^{11}$ | 4 | - | 10.4 (6.2–21.8) | | | | | 3/4 (75%) | [36] |
| *UCL/St. Jude* | | | | | | | | | | | | |
| GO8, scAAV2/8 HLP-FVIII-V3 | NCT03001830 | 1 | $6\times10^{11}$ | 1 | - | 7 | | | | | 0/1 | [39] |
| | | | $2\times10^{12}$ | n/a | - | | | | | | | |
| | | | $4\times10^{12}$ | n/a | - | | | | | | | |
| | | | $6\times10^{12}$ | n/a | - | | | | | | | |
| *Pfizer/Sangamo* | | | | | | | | | | | | |
| SB525, PF07055480, giroctocogene fitelparvovec | NCT03061201 | 1/2 | $3\times10^{13}$ | 5 | - | 42.6 | 25.4 | | | | 4/5 (80%) | [37] |
| | NCT04370054 | 3 | $3\times10^{13}$ | n/a | - | | | | | | | |
| *Bayer/Ultragenix* | | | | | | | | | | | | |

(*Continued*)


https://doi.org/10.2147/JBM.S371438 DovePress

**Table 2** (Continued).

| Vector Product | NCT | Trial Phase | Dose | Number Treated | FVIII (%) at Year: 0.5y | 1y | 2y | 3y | 4y | 5y | Transaminitis Rate | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bay2599023, DTX201, AAVhu37-BDD-F9 | NCT03588299 | 1/2 | $0.5\times10^{13}$ | 2 | - | ≥5 | | | | | | [38] |
| | | | $1.0\times10^{13}$ | 2 | - | 2–10 | | | | | 1/2 | [38] |
| | | | $2.0\times10^{13}$ | 4 | 10–45 | | | | | | 2/2 | [38] |
| | | | $4.0\times10^{13}$ | n/a | - | | | | | | | |
| *Takeda/Shire/Baxalta* | | | | | | | | | | | | |
| TAK754, SHP654, BAX888, AAV8-BDD-F8 | NCT03370172 | 1/2 | $2\times10^{12}$ | n/a | - | | | | | | | |
| | | | $6\times10^{12}$ | n/a | - | | | | | | | |
| | | | $1.2\times10^{13}$ | n/a | - | | | | | | | |

**Note**: *Two participants lost expression and their FVIII values are not included here.

transient reactive and/or prophylactic immunosuppressive treatment in the first months after vector infusion, except with the use of AMT061, an AAV5-FIX Padua construct (see discussion below). The trials of BBM-H901 and VGB-R04 have no results reported yet. Other vectors have failed due to early loss of expression possibly related to immune response by introduced CpG oligonucleotides (BAX335 or AAV8-hFIX)[26] or capsid-specific immune attack not responsive to immunosuppression (DTX101 or AAV-rh10-FIX),[27] or the program has been suspended for other reasons (SHP648). In summary, one vector showed stable expression at low levels for up to 8 years, two vectors report stable FIX levels in the mild hemophilia range up to 1.5 years, and the others are in earlier trial stages.

Seven FVIII-AAV-derived vector constructs have been in clinical evaluation since 2015 with six in ongoing research and development (Table 2).[28] The furthest developed vector, BMN270 or roctavion, has completed phase 3 enrollment of 134 participants administering a dose of $6\times10^{13}$ vg/kg resulting in a mean FVIII activity of 42.9% (±45.5) at 1 year, and 24.4% (±29.2) at 2 years after infusion.[29] A similar decline of factor activity has been observed in the related phase 1/2 trial where the reduction of factor expression slowed over time.[30–32] However, by end of the published observation period of 5 years the mean post-infusion FVIII level was 11.6% (±12.2). This trend of declining FVIII expression is continuing.[32] Therefore, in contrast to FIX, the durability of AAV-mediated FVIII gene therapy remains unclear. Several potential reasons are being considered, but related supporting data are limited.[33] These include characteristics of the vector construct including the oversized (for AAV) nature of the expression cassette, the type and conditions of the vector production platform, post-translational modifications, ongoing subclinical inflammation or damage of the liver, turnover of transduced hepatocytes, and instability of episomal AAV-DNA. A small number of liver biopsy tissue evaluations did not find evidence of stress to the endoplasmic reticulum.[34] Eighty-six percent of patients developed increased transaminases and 79% were treated with reactive transient immunosuppression, with resolution in 96% of the cases.[29] This vector product is currently under review by regulatory authorities in Europe and the United States (US). The other vector products have reported phase 1/2 trial results up to 2 years in less than 10 participants each for a given dose. SPK8011 and SPK8016 vectors achieved mean FVIII levels of 6.9% (dosing range $0.5–2\times10^{12}$ vg/kg) and 10.4% (at $2\times10^{12}$ vg/kg) in 16 and 4 participants, respectively, with 13/18 and 3/4 patients experiencing abnormal liver function tests and, therefore, receiving oral steroids.[35,36] Giroctocogene fitelparvovec, or SB525, treatment of 5 patients with $3\times10^{13}$ vg/kg has resulted in 42.6% and 25.4% mean FVIII activity at 1 and 2 years post infusion, with 4 experiencing transaminitis and being treated with steroids.[37] BAY2599023 or DTX201 achieved FVIII activity in the range of 25–40% in 4 participants at 2 years using a vector dose of $2\times10^{13}$ vg/kg.[38] The trials of the GO8 vector, scAAV2/8-HLP-FVIII-V3,[39] and the TAK754 and BAX888 vectors have reported only limited or no results yet. In summary, similar to FIX products, the vector doses reaching meaningful FVIII expression have varied widely between $0.2\times10^{13}$ and $6\times10^{13}$ vg/kg, a 30-fold difference. While most gene transfer products resulted in a state of mild hemophilia with significant reduction in bleed rate and factor use, only one product has been monitored up to 5 years and is showing a continuous decline in FVIII expression.

None of the vectors has been approved by regulatory agencies yet, because additional follow-up data were requested. For both, FVIII and FIX vectors, achieved levels vary significantly among vector types and among individuals given the same vector, indicating only limited predictability. Variability may be influenced by the subject's subclinical or clinical immune response to the vector, such as vector-induced transaminitis, and its response to immunosuppression.[40] However, other causes could include details of the vector construct, manufacturing methods, vector titering methods, transduction efficiency including AAV binding and internalization at cell surface, escape from endosomes, entry into the nucleus, DNA annealing or second-strand synthesis, episome and concatemer formation, mRNA transcription, and translation and post-translational processing – much of this is not well understood.[34,41]

## AAV Antibodies and AAV Vector-Induced Transaminitis

An appreciation for the immunologic aspects of adeno-associated virus (AAV) infection is critical for ensuring its successful use as a vehicle for affecting gene transfer. Yet, there is only a limited understanding of the role of cellular immunity and its contribution to the post-vector administration liver inflammation. The latter generally manifests as asymptomatic transaminitis in many, but not all, recipients of systemically administered AAV vectors, in a dose-dependent manner. Better understood is the humoral (antibody) response to naturally occurring infection with wild-

type AAV or recombinant AAV vectors used for gene transfer, which generates long term, serotype-specific neutralizing antibodies. The significant consequence is that these neutralizing antibodies, unless somehow abrogated, generally would prevent subsequent successful liver-targeted gene transfer with systemic, intravenous administration of recombinant AAV vectors of the same serotype.[42] However, while pre-clinical animal models did not predict cross-reactivity of neutralizing antibodies between different serotypes, some degree of cross-reactivity was shown in studies on human blood samples, including from persons with hemophilia after AAV-mediated gene therapy.[14,43–45]

Critical then, for most rAAV vector products, is to confirm the absence of serotype-specific neutralizing antibodies in PWH under consideration for enrollment on a gene therapy trial of liver-targeted, AAV-mediated transfer of the therapeutic gene encoding clotting factor VIII or IX. In fact, the lack of success of the early liver-targeted AAV-mediated gene therapy protocols was due, at least in part, to the failure to appreciate the problematic nature of low-titer pre-existing neutralizing antibodies in addition to the then-unanticipated potential of a cellular T-cell response via CD8 T-helper cells. The percentage of people with measurable neutralizing antibody titers varies between 20% and 70% depending on AAV serotype.[46–48] A number of methods have been tested in preclinical studies in an attempt to circumvent these neutralizing antibodies including pheresis, immunosuppression, B cell depletion, immune signaling blockade, coating of AAV particles, modifying the immunogenic portions of the capsids and giving an excess of empty AAV particles to act as a decoy, but no strategy has clearly worked consistently well.

An exception may be vectors derived from AAV5. With AMT-061, an AAV5-FIX-Padua vector, only one participant with a very high anti-AAV5 antibody titer failed to show factor expression, while all other trial participants with low positive or negative titers did express factor successfully and had no evidence of vector-induced transaminitis.[22] A phase 1/2 trial of BMN270, roctavion, an AAV5-FVIII vector, is currently further exploring the efficacy in patients with anti-AAV5 antibodies.[49]

Not all serotypes have the same incidence of prior exposure, and the incidence varies with geographic location. Therefore, screening of specific potential recipients is required. A variety of methods have been used to screen for the presence of pre-existing neutralizing antibodies, using both in vitro and in vivo assays. To detect the presence of AAV-binding antibodies within a serum sample, the in vitro assay involves antibody capture in tissue culture plates that have been pre-coated with recombinant AAV vector of a specific serotype. The binding detection step is then achieved with commercial antibodies to human IgG performed after several washing steps. Although simple, inexpensive and high throughput, this method may not prove the identified antibodies to be functionally neutralizing. To detect neutralizing anti-AAV antibodies, two types of cell-based assays are used: in vitro (eg, human embryonic kidney 293 (HEK293) cells as targets for transduction) or in vivo (murine hepatocytes). These assays involve demonstrating inhibition of transduction of the target cells by human test serum given prior to administering the particular recombinant AAV vector.[15,23,50] Transgene expression resulting in 70% or greater of expected factor activity is generally considered to demonstrate a lack of the presence of a neutralizing antibody. Another option is an in vitro assay in which proband serum is incubated with AAV-luciferase of a specific serotype and then added to cells. Luciferase is quantified to determine the level of transduction and resultant transgene expression compared to the control informing the titer of the neutralizing antibody. Although more expensive and time consuming, the in vivo assay using mice is generally preferred because it is a functional assay that demonstrates the presence of neutralizing antibodies. Typical negative and positive controls for these assays are serum samples from a human prior to and after successful transduction with AAV vector, respectively.

With most vector types, the prevention of transaminitis is approached with immunosuppressive therapy to modify immune reactivity by using prednisone or prednisolone prophylaxis with or without tacrolimus. Breakthrough transaminitis is typically treatable with a high-dose corticosteroid regimen if recognized promptly and managed with frequent monitoring of liver function tests such as 2–3 times per week for the first 6–9 months after vector infusion. This is a significant burden on the patient and provider clinic, but typically only occurs in this early post-infusion period. Point-of-care laboratory testing of liver function tests and remote clinical management should be explored in the future to support widespread access.

## Long-Term Toxicity

No long-term liver toxicity has been reported after AAV-mediated gene therapy for hemophilia in clinical trials. Toxicity by vector genome integration into chromosomes and potential resultant oncogenesis remains an ongoing theoretical concern.[51] AAV-mediated gene transfer primarily results in episomal persistence of vector genomes, but chromosomal vector genome integration has been described at very low frequency at random locations. In preclinical studies in different animal models, the oncogenicity of AAV-mediated gene transfer has been reported, but the significance of these findings in humans is not clear.[52] A small number of patients after AAV administration, with diagnoses of hemophilia, acute intermittent porphyria and lipoprotein lipase deficiency, had liver biopsies revealing a low frequency of integrations, but no concern for integration at oncogenic sites and no evidence of abnormal pathology.[34,53,54] To date, no AAV vector-related malignancy has been identified across all trials in hemophilia. A single case of hepatocellular carcinoma (HCC) in an AAV vector-treated patient with hemophilia B was determined highly unlikely associated with the vector, because the patient had multiple known clinical risk factors for HCC. Tissue evaluations found several HCC-related mutations and only a very low, random vector genome integration frequency at chromosomal locations unlikely to support vector-related oncogenesis.[55]

Overall, long-term follow-up of efficacy and safety outcomes, including liver health and tissue evaluations when indicated, by participation of treatment centers and treated patients in globally accessible observational studies or registries, such as the one established by the World Federation of Hemophilia,[56] will be critical to further elucidate vector-related effects.

# Considerations for Successful Implementation of Gene Therapy Worldwide

The new treatment paradigm of gene therapy for hemophilia offers the opportunity to prospectively plan for successful equitable access for all PWH globally. The latter will depend on an integrated approach to implementation adaptable to various settings. The adoption of an implementation science framework will guide the stakeholders and extended community. Drawing from multiple implementation constructs synthesized in the Consolidated Framework for Implementation Research (CIFR) and from our own experience in conducting clinical gene therapy trials, we will discuss the most relevant considerations in the following sections: the assessment of the pre-implementation context and readiness; a methodological approach to effective communication, education and training; cost and cost-effectiveness analysis for planning of sustainable pricing and reimbursement; resource-adjusted operational planning; and monitoring of health outcomes and implementation outcomes throughout the process.[57,58]

## Pre-Implementation Context Assessment and Readiness

For introducing a novel treatment concept, an interested and supportive environment is needed. All stakeholders should be identified, including the hemophilia providers, the target patient group which ideally includes either all local PWH or the potentially eligible patients, leaders of the patient advocacy groups, the healthcare institutions and local health authorities. A local leader of the process should be determined. This network of supporters may also include other groups currently supporting the care of patients in different ways, such as groups from programs of the World Federation of Hemophilia, pharmaceutical industry, or other local or international organizations. Depending on local preferences, additional legal or ethics consultants can provide valuable input.

An assessment of the regulatory and policy requirements may necessitate additional discussions with authorities and potentially need amendments or the establishment of new regulatory guidelines for drug manufacturing or procurement and approval. Policies and systems for regulation of clinical gene therapy are largely in place in North America and Europe, where most of the clinical trial activity has been conducted and pharma has established vector manufacturing. An industry guidance has been published by the Food and Drug Administration (FDA), and both FDA and European Medicines Agency (EMA) oversee robust regulatory processes.[59,60] To foster global access, the WHO has published a White Paper draft in December 2021 addressing the need for regulatory convergence for cell and gene therapy.[61] A recent

article supported by ASGCT discusses global regulatory challenges and tries to provide solutions considering the goal of providing access to gene therapy globally.[62]

Notably, some LMICs are establishing their own regulatory and infrastructure frameworks for hemophilia gene therapy, either by developing and/or manufacturing their own vector products or participating in internationally sponsored gene therapy trials.[63,64] These countries include Brazil, China, India, Nepal, Peru, South Africa, Thailand, Sri Lanka, and Vietnam, if not more. Beyond participating in international trials, another pathway of establishing a new regulatory framework for gene therapy in a given country is through interaction, exchange and harmonization of established framework templates between countries or regions and with the regulatory bodies in countries with more advanced frameworks such as in the US, Europe, and Japan.

Another important context dimension to explore are the financial resources in relation to cost and payment models. Current payment or reimbursement pathways may not be feasible and new arrangements and agreements will need to be created (see Cost, Cost-Effectiveness, and Payment Models). Further, any gap in current and required operational capacities needs to be evaluated and addressed as feasible to create a locally efficient process (see The Iterative Process of Implementing Hemophilia Gene Therapy). In a final step, checking the readiness for implementation should document the implementation plan, the availability of resources, and the commitment and motivation of all stakeholders to engage on the journey of change.

## Addressing Barriers to Knowledge and Acceptability

The successful adoption and translation of gene therapy in LMIC will depend heavily on addressing barriers relating to knowledge and acceptability. Introducing multi-level interventions targeting healthcare providers, patients, caregivers and patient advocates to communicate the benefits and risks of gene therapy will clearly improve acceptance of gene therapy. Effective communication around the concept of a complex treatment option such as gene therapy may assuage fears and provide salient information to equip patients and providers in shared decision-making. The process of informed consent and steps taken to educate patients with hemophilia will set the stage for many other gene therapy products.

Various national and international societies such as the World Federation of Hemophilia (WFH), National Hemophilia Foundation (NHF), International Society of Thrombosis and Hemostasis and American Society of Gene and Cell Therapy (ASGCT) have generated a series of didactics including web-based videos and webinars, which can be used to improve gene therapy knowledge.[65–68] These are excellent resources that provide basic information with excellent visuals for patients; however, most of the material is focused on educating providers. These resources lack detailed explanation in plain language and individualization for patients.

Gene therapy education should be approached at multi-level, focusing separately on providers and patients. Delivering education to providers has its own challenges such as different learning styles, competing professional priorities, implicit biases and lack of dedicated time. Physicians are often overburdened by a "culture of excellence" which leads to hesitancy in admitting knowledge deficiencies.[69] To design interventions that accommodate different level learners and to promote supportive learning environment, adult learner theory suggests that we focus on small group educational events to allow dialogue, interaction, and reflection.[69]

Additionally, creation of education material for patients that can be used in obtaining informed consent needs to take into account health literacy, and take a deep dive in patients' beliefs, fears, and expectations about the treatment. Although some progresses have been made in North America and Europe to map out patients' perspectives and identify their fears, the same cannot be said about LMICs where no material has been published to our knowledge.

A summary of the conducted studies includes a small US-based qualitative study which used phone-based semi-structured interviews with 21 hemophilia A and B patients and found that prevention of bleeding and improvement in quality of life were the major advantages of gene therapy that patients looked forward to. Failure of gene therapy and financial burden of these treatments were amongst the biggest worry of the patients. The study called for clear information to be provided regarding safety and efficacy of gene therapy.[70] A multicenter study performed in the United Kingdom, North America and Australia conducted a discrete choice experiment to investigate the relative importance and differential preferences patients provided for gene therapy attributes via a survey of 183 hemophilia A and B participants. Patients prioritized reduction in bleeding rate (31%), and reduction in dose frequency and durability

of gene therapy (26%). Uncertainty regarding potential short- and long-term safety issues and impact on daily life were weighed at 17% and 11%, respectively.[71] A qualitative study in Belgium with 20 hemophilia participants demonstrated a positive attitude towards gene therapy with 40% of patients "very willing" (N=8) or 35% "willing" (N=7) to receive gene therapy. Annual bleeding rate, factor level, uncertainty of long-term risk, impact on daily life and probability to stop prophylaxis were found to be the important factors to discuss.[72] Review of this literature shows that despite the relatively similar cultural context, priorities and fears about gene therapy may differ considerably between individuals. These findings will probably vary significantly for participants in LMICs.

Ideally, creative, and practical approaches through multimedia and interactive formats can have numerous benefits for presenting information in more user-friendly ways, and can aid in optimizing discussion, through personalization and consolidation of the information to avoid excessive information. The multimedia format however should not be substituting robust conversation with patients about benefits, known and unknown risks, efficacy, and long-term effects of gene therapy.[73,74] The education material must also address the psychosocial burden on the participant, which may affect a patient's willingness to undergo gene therapy.[75] Multiple guidelines are published on how to discuss gene therapy with patients, provide lists of helpful vocabulary or pictorial representation of the basic process of gene therapy, and highlight topics of discussion related to safety and efficacy.[76–78] These tools can help guide face-to-face discussions with each patient and should be individualized based on their priorities and fears (Table 3).

More research is required to evaluate the methods of obtaining informed consent and implementing educational programs regarding gene therapy in LMIC. Language barriers, cultural differences and socioeconomic disparities invariably pose challenges to the provision of clear and accurate information. Creating education packages that can be

**Table 3** Guide for Physicians for Discussing Gene Therapy with Persons with Hemophilia

| Topic | Sub-topics |
|---|---|
| Fundamentals of gene therapy | What is a vector?<br>What is a functional gene?<br>How is the vector delivered?<br>How does the body react to the vector?<br>Anti-vector antibodies |
| Expectations after gene therapy<br>Efficacy | Treatment of bleeding events<br>Frequency of bleeding events<br>Pain management<br>Factor expression (level and duration) |
| Safety (short- term) | Side effects (ie, transaminitis, inhibitor development, thrombosis, anti-vector antibodies)<br>Treatment of side effects |
| Safety (long-term) | Risk of developing cancer or other disorders<br>Possibility of unknown side effects<br>Long-term monitoring and annual follow-up for many years |
| Eligibility for gene therapy | Severity of disease (factor level ≤2%)<br>Adults or young adults<br>Patients without inhibitors<br>Patients without neutralizing antibodies to AAV capsid |
| Current clinical trials | Status of ongoing clinical trials<br>Major findings of clinical trials |
| Other things to consider | Psychological functioning and emotional maturity<br>Social support<br>Family planning |

rapidly adapted across cultures and countries with differing resources must account for variations in understanding of gene therapy across all stakeholders such as patients, caregivers, community leaders, and healthcare providers.

## Cost, Cost-Effectiveness, and Payment Models

### Pricing Approaches and Cost-Effectiveness Simulation Models

Although contextual factors that may limit adoption and acceptability of gene therapy in LMIC are critical, the prices proposed for gene therapy remain perhaps the largest impediment to global access. It is difficult to determine a price for gene therapy because of complex pricing considerations, the need to scale out or up, lack of transparency on initial research and development (R&D) investments and production costs, the combination of fixed indirect and variable direct costs, lack of agreement on whether prices of therapies should be value, procedure, or R&D based, and limited clinical evidence at the time payers need to make decisions.[79]

Although multiple factors should be considered when pricing novel treatments, manufacturers often follow value-based pricing in which they choose the highest price point that the market could bear based on the comparative cost of the alternative approach.[80] The comparative outcome of cost-effectiveness models is often expressed in incremental cost–effectiveness ratio (ICER), which is calculated by dividing the additional cost of the new intervention compared to the standard one, by the additional effects generated by the new intervention. The effects are usually measured in quality-adjusted life years (QALYs), a unit of measure that combines the expected years of life lived (ie, life expectancy) with quality-of-life metrics. If the cost is cheaper and the QALYs exceed that of the standard intervention, then the new intervention is considered dominant. In the opposite scenario, the new intervention is considered dominated and should be rejected. In case the new intervention is more expensive, yet yields additional QALYs, then the ICER is compared against a country-specific threshold to determine whether or not it is cost-effective compared to the standard intervention.

As pricing remains tentative and clinical trials are ongoing, investigators have developed five cost-effectiveness models using simulated data to evaluate the cost-effectiveness of gene therapy in hemophilia. Four models evaluated gene therapy from the perspective of PWH in the US and one in the Netherlands.[81–85] None of the models were conducted using perspectives from LMICs, demonstrating one more time the extent to which these countries have been overlooked. Our study[84] was the first and so far the only model focused on hemophilia B while the remaining four models assess the cost-effectiveness of treatment options for hemophilia A. Table 4 summarizes the key input parameters and the results of each of the five cost-effectiveness models. Although all five models reach the same conclusion, suggesting that gene therapy is less costly and more effective (dominant) compared to the alternative treatment, the final results – gene therapy lifetime cost and QALYs, comparator lifetime cost and QALYs – are very different. Driving these differences are several factors and key assumptions that should be carefully considered when interpreting the results of each model. Each of these parameters are also critical to understanding what, if any, role gene therapy may have to play in LMICs.

The first major determinant is the time-horizon, models with a 10-year time-horizon cannot be compared to those with a lifetime horizon. Furthermore, lifetime horizon models starting at 18 years of age are not comparable to those starting at 30. The perspective used while considering costs is another key factor. Societal perspective takes into account all incurred cost categories regardless of the payer, this includes productivity losses for both patient and caregiver. Conversely, healthcare perspective disregards all costs not paid by the healthcare system. Additionally, the discounting factor might play a role in the final results when accumulated over a long period of time. Different countries recommend different discounting factors. Finally, each model's parameters have a direct impact on the outcomes of the model and thus should be critically evaluated by the reader (Table 4).

Results of the five models are presented in Table 4. Machin et al and Ten Ham et al[81,85] conducted a 10-year time horizon starting at approximately 30 years of age. Cook et al[82] presented the latter as a scenario analysis which we use here for comparability purposes. These three models concluded that over the 10-year period, the gene therapy arm cost (in US$) was $1,022,249, $2,526,897 and $3,469,487, while prophylaxis with standard half-life FVIII cost was $1,693,630, $2,923,374 and $8,502,702, respectively. These differences could be explained by the assumed price of the gene therapy vector at $850,000, $1,891,250 and $2,000,000, the probability of developing bleeding under different treatment scenarios and the cost to treat a bleed when one occurred. Differences in costs to control and treat bleeds were

**Table 4** Summary of Cost-Effectiveness Models Comparing Gene Therapy to Alternative Treatments for Hemophilia

| | Machin 2018[81] | Cook 2020[82] | Rind 2020[83] (ICER Report) | Bolous 2021[84] | Ten Ham 2021[85] |
|---|---|---|---|---|---|
| **Model Outline** | | | | | |
| Model type | Markov state-transition model | Microsimulation Markov model | Markov model | Microsimulation Markov model | Markov state-transition model |
| Disease | Severe hemophilia A | Severe hemophilia A | Severe hemophilia A | Severe hemophilia B | Severe hemophilia A |
| Intervention | Gene therapy (No brand specified) | Valoctocogene roxaparvovec | Valoctocogene roxaparvovec | Gene therapy (No brand specified) | Valoctocogene roxaparvovec |
| Comparator | FVIII prophylaxis | FVIII prophylaxis<br>- SHL (base case)<br>- EHL (scenario analysis) | FVIII prophylaxis<br>- SHL<br>- EHL | 1) FIX prophylaxis<br>2) On-demand treatment<br>- SHL (for both options)<br>- EHL (for both options) | 1) FVIII prophylaxis<br>2) Emicizumab |
| **Model Specifications** | | | | | |
| Time horizon | 10 years starting at 30 | Lifetime starting at 30 | Lifetime starting at 18 | Lifetime starting at 18 | 10 years starting at 31 |
| Perspective | US healthcare perspective (Assumed 2018 USD) | US healthcare perspective (2019 USD) | US healthcare perspective (2019 USD) | US healthcare perspective (2020 USD) | Dutch societal perspective (2019 Euro) |
| Discounting | 3% | 3% | 3% | 3% | Costs 4%<br>QALYs 1.5% |
| **Model Input Parameters** | | | | | |
| Gene therapy cost | $850,000 | $2,000,000 | $2,500,000 | $2,000,000 | €2,125,000 ($1,891,250) |
| Clotting factor unit cost | $1/IU | $1.63/IU WAC | Advate net: $1.08/IU<br>Eloctate net: $1.82/IU<br>Net price was used in base case<br>Advate WAC: $1.69/IU<br>Eloctate WAC: $2.23/IU | Benefix WAC: $1.41/IU<br>Alprolix WAC: $3.24/IU | FVIII: €0.89/IU ($0.79/IU) (11% discount from WAC for base case)<br>Emi: €2476 per 30 mg/mL vial ($2204) |
| Mean weight | 88.7 kg for 30-year-old | 90.2 kg for 30-year-old | 81.4 kg for 18-year-old | 89.3 kg for 30-year-old | 85 kg for 31-year-old |

(*Continued*)


https://doi.org/10.2147/JBM.S371438 DovePress

**Table 4** (Continued).

| | Machin 2018[81] | Cook 2020[82] | Rind 2020[83] (ICER Report) | Bolous 2021[84] | Ten Ham 2021[85] |
|---|---|---|---|---|---|
| Dosing | Prophy: 33 IU/kg 3 times weekly<br>Bleed: 50 IU/kg/d 2 or 4 days | Prophy: 40 IU/kg 3 times a week<br>Bleed: 50 IU/kg 2 doses | Not stated | Prophy: 40 IU/kg twice weekly<br>Bleed (minor): 50 IU/kg 3 doses per episode | Prophy: 30 IU/kg 3 times a week.<br>Emi: 3 mg/kg biweekly.<br>Bleed: 25 IU/kg then twice daily 15IU/kg for 3.5 days. |
| Effectiveness of gene therapy | Effective for 10 years.<br>Success rate 90%, complications 1% for first 12 months. | 90% mean 12.43 years and median 11.33 years.<br>10% mean 11.13 years and median 10.73 years.<br>Move back to prophylaxis below 5 IU/dL.<br>No joint bleeds above 15IU/dL | FVIII ≥1% for 12 years (7 and 15 years in conservative and optimistic scenarios) | 31 years >3%, switch all patients to prophylaxis at 3% (worst case scenario 4 years) | Mean 11.5 years before dropping below 1% and switching to prophylaxis.<br>15% limited response (FVIII<5% after 2 years). |
| **Results** | | | | | |
| Gene therapy cost over entire time horizon | $1,022,249 | $16,700,000<br>(10 years: $3,469,487) | $13,693,000 | SHL: $6,293,502<br>EHL: $7,315,914 | €2,839,210 ($2,526,897) |
| Gene therapy QALYs | 8.33 QALYs | 18.07 QALY<br>(10 years: 6.88 QALY) | 19.091 QALYs | SHL: 23 QALYs<br>EHL: 23.04 QALYs | 7.03 QALYs |
| Comparator cost over entire time horizon | $1,693,630 | $23,500,000<br>(10 years: $8,502,702) | $18,722,000 | OD SHL: $11,596,617<br>OD EHL: $7,917,721<br>Pro SHL: $15,109,058<br>Pro EHL: $20,324,299 | Prophy: €3,284,690 ($2,923,374)<br>Emi: €4,252,167 ($3,784,428) |
| Comparator QALYs | 6.62 QALYs | 17.32 QALYs<br>(10 years: 6.37 QALYs) | 19.087 QALYs | OD SHL: 11.81 QALYs<br>OD EHL: 12.20 QALYS<br>Prophy SHL: 20.95 QALYs<br>Prophy EHL: 21.57 QALYs | Prophy: 6.38 QALYs<br>Emi: 6.90 QALYs |
| ICER | Dominant | Dominant | Dominant | Dominant | Dominant |

**Note**: ICER is calculated by the following formula: Costs $^{\text{New Intervention}}$ – Costs $^{\text{Standard Intervention}}$/QALYs $^{\text{New Intervention}}$ – QALYs $^{\text{Standard Intervention}}$.

**Abbreviations**: ICER Report, Institute for Clinical and Economic Review Report; SHL, standard half-life; EHL, extended half-life; USD, United States dollar; QALYs, quality-adjusted life years; WAC, wholesale acquisition cost; Emi, emicizumab; OD, on-demand treatment; Prophy, prophylaxis; ICER, incremental cost-effectiveness ratio of the intervention being investigated versus the alternative, in costs per added QALY.

driven by major variations in 1) the dosing protocol which varied in the number of units and number of administered doses for prophylaxis and different types of bleeds (Table 4), 2) the assumed weight of the prototypical patient which ranged between 81.4 and 90.2 kg, 3) the FVIII unit cost which ranged between $0.79/IU (discounted) and $1.63/IU (Wholesale Acquisition Cost), and 4) the costing perspective and discounting rate used in the model. Ten Ham et al[85] was the only model that adopted a societal perspective meaning that more cost categories like productivity loss were considered. However, it was also the only model that discounted costs at an annual rate of 4% compared to 3% for the two other models.

For the three models ordered as above, the QALYs were 8.33, 7.03 and 6.88 for the gene therapy arm and 6.62, 6.38 and 6.37 for the prophylaxis arm, respectively. Effects attributed with the gene therapy arm differed based on the assumptions made regarding its treatment effects which lasted for a period that ranged between 10 and 12.4 years, and the quality of life assigned to patients after receiving it. Machin et al[81] assigned a perfect health utility of 1 to patients who received gene therapy which is an overestimation.

On the other hand, our study[84] and the report generated by the Institute for Clinical and Economic Review (ICER)[83] both analyzed an 18 years old to death time horizon. However, the results are incomparable because each assessed gene therapy for a different type of hemophilia, hemophilia B for the former and hemophilia A for the latter, with very different assumptions regarding the long-term effectiveness of gene therapy. Lifetime cost associated with gene therapy was $6,293,502 and $13,693,000, respectively. The key model input that led to this significant difference in the results was the assumption made regarding the number of years during which gene therapy was sufficient to prevent bleeds, which was 31 and 12 years, respectively. The assumed price of gene therapy, $2,000,000 and $2,500,000, also had an impact, but played a less drastic role compared to the difference in effectiveness. Lifetime cost for prophylaxis with the standard half-life factor concentrate was $15,109,058 and $18,722,000 for FIX and FVIII, respectively. QALYs for gene therapy were 23.00 QALYs and 19.091 QALYs and those for prophylaxis using standard half-life factor concentrate were 20.95 QALYs and 19.087 QALYs, respectively. In the future, cost-effectiveness models that will be tailored for LMICs will need to consider totally different treatment approaches. In most of these countries, access to prophylaxis is scarce and, in many cases, patients rely on low-dose protocols and fresh frozen plasma or cryoprecipitate instead of factor concentrate. This means that the cost and yielded effects of gene therapy will be compared to significantly cheaper but also less effective alternatives than those available in HICs.

## Challenges Encountered with the Traditional Health Economic Approach

In the case of hemophilia, recombinant clotting factor unit cost is distorted in the US and multiple other countries due to industry monopolization, exacerbated by failure of the government to regulate the price and by buyer insensitivity due to coverage by their insurance.[80] This distortion led to the high suggested commercial price of $1,000,000–$3,000,000 for hemophilia gene therapy, which was based on the cost of the alternative treatment in high-income countries, but did not take into account LMICs. In LMICs, available treatment options are limited and constrained by finances, therefore, a single-dose subsidized, gene therapy may significantly improve patients' outcomes if negotiations and international collaborations enabled a reasonable pricing.[64] For analyses using the ICER, analysts should adjust distorted clotting factor market prices in their calculations to represent social opportunity cost and avoid generating evidence demonstrating a false sense of cost savings.[80]

Moreover, there is a need to reconsider economic evaluation methods as a whole because they may not be equally applicable to every type of medical intervention. Patients with rare genetic diseases present a unique set of conditions that warrant equally unique analytic approaches to estimating value for money.[86] Gene therapies have a number of particular characteristics, taken individually, none of them is exclusive to gene therapy; however, it is the confluence of these various characteristics that leads to specific methodological challenges making assessment of both costs and effects controversial.[87]

Treatment effects are hard to evaluate when the only clinical data available are generated by small and single-arm trials, spanning a short period of time, lacking information on long-term durability or adverse consequences.[87,88] This particularly imposes a challenge in conducting a lifetime horizon. Table 4 shows heterogeneity of model assumptions regarding the time horizon analyzed. Two of the 5 currently published models chose to limit their time horizon to 10

years starting approximately at 30 years of age, to minimize the extent of extrapolation needed. Nonetheless, one of the advantages of simulation models is the ability to envision plausible scenarios and use rational assumptions to predict future outcomes. Accordingly, the other three models chose 18 or 30 years old till death time horizons. These models relied on clinical trial data that span less than a decade, to predict the time at which decline in factor activity will necessitate switching back to prophylaxis.

To extend the time horizon even further, simulation models are yet to explore administration of gene therapy in the pediatric population which to-date remains an area for scientific aspiration. Theoretically, the earlier gene therapy is administered, the better the outcomes should be, in both costs and quality of life, given that joint damage develops in childhood. LMICs, in particular, could benefit from this, and payers could potentially have the incentive to invest in early years replacement therapy which would be less of a financial burden, yet would offer patients the opportunity to avoid long-term joint damage. Simulation models can play an important role in highlighting the potential gains yielded by achieving this scientific breakthrough, which in turn can help direct efforts in the right direction.

Another challenge is that there is no consensus over the definition of "cure". This is superimposed by the limitations of traditional generic quality of life (utility) measures which may not capture the true impact of hemophilia.[88] On the other hand, costing is complicated by the perspective used in the evaluation whether it is only inclusive of healthcare costs or encompasses societal costs, the extent to which long-term cost-offsets should be counted against the large up-front payment and pricing of gene therapy given the uncertainty of treatment effect.[88]

Special considerations are proposed to address these challenges such as using data from previous clinical trials of alternative treatments or real-world evidence to construct synthetic historic cohorts of patients as comparators, extrapolating the effects of clinical trials, and collecting post-approval real-world registry data.[87,88] Additional suggestions include adding hemophilia-specific questions to generic quality of life surveys, using a comprehensive set of outcomes (coreHEM) beyond mere quality of life, conducting several time horizons, analyzing both healthcare and societal study perspectives, utilizing multiple discounting rates, including all treatment options available and exploring alternative payment models.

In November 2019, a new framework was proposed by the US-based, private, non-profit Institute for Clinical and Economic Review (ICER) for single or short-term therapies (SSTs).[89] To date, this is the first and only attempt to tailor a health economic approach for the purpose of gene therapy. This SSTs' model assessed several scenarios assuming multiple clinically plausible outcomes, ranging from conservative to optimistic, in addition to the conventional base-case and sensitivity analyses to reflect uncertainty about the benefits of gene therapy. For cost offsets, several hypothetical "cost-sharing" scenarios were included. Moving forward, analysts should develop future simulation models assessing novel technologies, such as gene therapy, guided by the template carved out by ICER and the recommendations highlighted by Drummond et al,[87] Garrison et al[88] and others.

## Payment and Reimbursement Schemes

After 30 years of official clinical trials, the total number of completed and ongoing gene therapy clinical trials exceeds 4000[90] with at least 22 gene therapies approved by drug regulatory agencies globally.[91] Based on the pipeline and the clinical success rates of products, the FDA predicts approving 10 to 20 cell and gene therapy products every year by 2025.[92] So far only a few have gained reimbursement in some countries and two (Glybera and Zynteglo) have since been withdrawn from the market due to market access and reimbursement challenges.[79] Fair pricing and functional reimbursement models are necessary to allow patients equitable access to the full potential of gene therapies.

Similar to cost-effectiveness models, reimbursement schemes should be conceived thoughtfully to ensure sustainability. Multiple gene therapies may enter the market simultaneously, and payers could face a steep, untenable financial burden that requires considering unconventional payment schemes.[93] Alternative payment models have been classified into two main categories: outcomes-based and finance-based schemes. The former links payments to an agreed upon target clinical outcome. Payments can be made either per achievable milestone, or by annuity if the desired result lasts, or by rebating part or all of the paid price if the outcome declines after initial full payment. In this type of model, an agreed upon clinically relevant outcome must be identified and consensus needs to be reached how to objectively measure it. This can be difficult and resource consuming, making it less feasible outside a highly controlled context.

Finance-based schemes have fewer logistical considerations; they are suitable when patient outcomes are predictable, but the number of potential patients is large or unpredictable.[93] Sometimes, a capitation is applied regardless of the number of beneficiaries. This can be implemented in a subscription fashion with a fixed amount covering an unlimited number of patients per year, or a volume-based approach in which the price per patient decreases after reaching a preset number. Other times, payments are spread over several years rather than paid up-front, or the risk is minimized by diluting it to multiple payers or transferring some of the liability to reinsurers.

In addition to the dilemma of payment schemes, the question of who will pay for this expensive new therapy remains a major concern. Given the devastating consequences of the disease and the burdensome costs associated with its treatment, ideally, funding should ultimately come as part of governmental responsibility. This would align with the goal of universal health coverage, a World Health Organization strategic priority. Unfortunately, out-of-pocket payments remain the main funding source in many LMICs, resulting in significant patient and family-level financial hardship. Country-specific strategies will need to be tailored to fit the local context. For example, in a high-income country like the US, formal drug discount programs such as that provided by section 340B of the Veterans Affairs act of 1993 help somewhat to control costs, and simultaneously allow for hemophilia center funding. Similar programs should be nestled within healthcare systems to fund gene therapy. In LMICs, it will be more challenging. However, scientifically sound cost-effectiveness models, budget impact analyses, and return on investment reports that would highlight the potential gains throughout the lifetime of the patient are all valuable tools that governments could rely on to make informed decisions. Moreover, while not sustainable over the long-term, existing hemophilia civil society organizations in the private sector such as global or local foundations must continue to play a vital funding and advocacy role to bridge existing gaps.

Unlike regulators who created novel approval pathways to ensure appropriate assessments of gene therapies, payers have not adapted distinct payment and reimbursement pathways.[79] Given the unique set of circumstances associated with gene therapies, most importantly that they usually require one or only a limited number of administrations and, thus, very high short-term cost have been quoted for them, gene therapies will necessitate novel payment and reimbursement models requiring multi-stakeholder engagement and risk-sharing arrangements between industry, patients, providers and payers.[94]

## The Iterative Process of Implementing Hemophilia Gene Therapy

The implementation plan for establishing gene therapy for hemophilia in HIC or LMIC will vary by country, region or even clinical centers and by existing level of experience through previous trial sponsorship, trial participation as a site, or having had only minimal to no exposure to clinical gene therapy activities. After the abovementioned pre-assessments, changes to existing infrastructure and processes may be needed, and the team may proceed along the sequential and iterative activities of planning, engaging, executing, and monitoring, evaluating and revising.

In theory, the clinical delivery of gene therapy is relatively simple. Screening for eligibility before and monitoring after vector infusion requires standard laboratory blood tests and the capacity for liver ultrasound. Factor activity assays should be established for easy accessibility and quick turnaround time, while the few other, non-urgently and infrequently required specialty lab tests can be arranged with remote specialty labs if not available locally. The possibility of use of immunosuppression after vector infusion requires screening of patients for history of hepatitis or other past or current infections. It also requires establishing access to the immunosuppressive medication, for most vector products a corticosteroid, but tacrolimus has also been used in some clinical trials. Required screening and monitoring evaluations and the use of immunosuppression may vary depending on the vector product.

The gene therapy administration itself first includes a pathway for vector procurement from the manufacturer and establishing a shipping process under frozen, temperature-controlled and trackable conditions. At the infusion center, the vector product requires storage in a −65°C freezer. Specific steps for thawing and reconstitution under sterile conditions (using a laminar flow hood) for administration will be provided by the manufacturer. In the US, biosafety level 1 is required for AAV vectors, defined for agents not known to consistently cause disease. It recommends the use of laboratory coat, gloves and eye protection, and standard microbiological practices within a room with doors for access control, easy to clean bench and sink for hand washing. However, the stakes are high since contamination or damage to

the product during thawing would be a grievous loss owing to its expensive list price. The administration to the patient is a peripheral vein infusion over about 1 hour in an outpatient setting with the ability to treat potential, infusion-associated allergic reactions.

Treaters will be required to have specific knowledge allowing skilled communication of the characteristics of all aspects of the treatment and follow-up. To maximize expertise of providers and optimize vector management for clinical administration but also provide broad access to PWH to gene therapy, a "hub-and-spoke" model has been suggested.[95] The "hub" center will perform the vector infusion and maintains a high level of skill and knowledge, whereas peripheral "spoke" sites or home hemophilia treatment centers (HTC) offer screening and conduct post-infusion monitoring in close collaboration with the "hub".

Two very important responsibilities of the treater-patient team are the short-term and long-term follow-up collaboration. Short-term, the timely and effective prevention and/or treatment of vector-induced transaminitis is critical to avoid treatment failure and requires strict regular assessments one to three times per week for the initial 6–9 months after vector infusion, depending on the individual vector product. Long-term follow-up should evaluate for known and unknown outcomes, including liver health, provide comprehensive care for persistent, pre-existing hemophilia-related complications and provide ongoing psychosocial support to the patient whose hemophilia-related medical needs and life experiences have now been altered.

Health outcomes are important to assess on a regular basis throughout the process. The data generated will inform about safety and efficacy of gene therapy in the local setting and support further establishment of this novel treatment. At the same time, the monitoring of the methods and outcomes of implementation of this new treatment will inform necessary improvements and guide other centers in earlier stages. Specifically, the operational processes of vector management including shipping, storage, and reconstitution, the procedure of vector infusion, and the efficiency of follow-up monitoring and the compliance with these processes are important to be scrutinized for the patients to have a successful health outcome. Collecting and analyzing data on real-life cost and requirements for infrastructure and funding in each socioeconomic setting will be of great importance to develop a sustainable therapeutic offer.

## Summary and Conclusion

Gene therapy has made great strides and has the potential to revolutionize treatment and transform the lives of a vast number of patients affected by hemophilia as well as other genetic diseases, through introducing a normal copy of the defective gene to restore its function for a prolonged time such as years or potentially decades.[18,28,90] Current evidence indicates that eligible PWH can achieve a state of mild hemophilia or a normal clotting state for at least 5–8 years, if not longer, after a single-gene therapy infusion. For patients worldwide to realize the full potential of gene therapy, we have summarized the challenges needing to be addressed at the current stage of development. Specifically, relevant clinical, educational, regulatory, and financial aspects need to be tackled and at times reinvented to cultivate a broadly accessible landscape for this novel treatment technology, dissimilar to any previous one. Particularly, PWH in countries with limited access to current standard hemophilia treatments have an opportunity for significant improvements in mortality and morbidity. This review points to the directions to take for effective, international capacity building by all stakeholders to work and collaborate towards improved health equity for patients with hemophilia.

## Funding

St Jude Children's Research Hospital which is supported by the American Lebanese Syrian Associated Charities funded this study. The funding organization had no role in the study design, data collection, analysis, interpretation or writing the report.

## Disclosure

NB receives research support from Pfizer. EJN has served on advisory boards for BioMarin, Genentech, Novo Nordisk and Octapharma, and on data monitoring boards for Merck, Agios and Sobi; was consultant to Pfizer and Bayer, and has received honoraria from Octapharma, Novo Nordisk and Takeda. AMD has contributed to the design of the shortened LP1 promoter of the scAAV2/8-FIX-Padua vector and is entitled to receive a share of net license income if this vector is

commercialized. He also reports a patent design of gene therapy vectors for producing FVIII, FIX licensed to BioMarin, a patent design of gene therapy vectors for producing FVIII, FIX licensed to UniQure. UMR receives resaerch support from Pfizer. The other authors report no conflicts of interest in this work.

## References


1. Konkle BA, Huston H, Nakaya Fletcher S, et al. Hemophilia A. In: Adam MP, Ardinger HH, Pagon RA, editors. *Genereviews(R)*. Seattle WA: University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle; 1993.
2. Konkle BA, Huston H, Nakaya Fletcher S, et al. Hemophilia B. In: Adam MP, Ardinger HH, Pagon RA, editors. *Genereviews(R)*. Seattle WA: University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle; 1993.
3. Hay CRM, Nissen F, Pipe SW. Mortality in congenital hemophilia A - A systematic literature review. *J Thrombosis Haemostasis*. 2021;19 (Suppl1):6–20. doi:10.1111/jth.15189
4. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007;110(3):815–825. doi:10.1182/blood-2006-10-050435
5. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1–158. doi:10.1111/hae.14046
6. World Federation of Hemophilia. The report on the WFH annual global survey 2020; 2021. Available from: https://www1.wfh.org/publications/files/pdf-2045.pdf. Accessed September 22, 2022.
7. Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia*. 2010;16(1):20–32. doi:10.1111/j.1365-2516.2009.02127.x
8. Stonebraker JS, Bolton-Maggs PH, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia B prevalence around the world. *Haemophilia*. 2012;18(3):e91–94. doi:10.1111/j.1365-2516.2011.02588.x
9. Nathwani AC. Gene therapy for hemophilia. *Hematol Am Soc Hematol Educ Program*. 2019;2019(1):1–8. doi:10.1182/hematology.2019000007
10. NIH U.S. National Library of Medicine; 2022. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/. Accessed April 25, 2022.
11. Manno CS, Chew AJ, Hutchison S, et al. AAV-mediated factor IX gene transfer to skeletal muscle in patients with severe hemophilia B. *Blood*. 2003;101(8):2963–2972. doi:10.1182/blood-2002-10-3296
12. Jiang H, Pierce GF, Ozelo MC, et al. Evidence of multiyear factor IX expression by AAV-mediated gene transfer to skeletal muscle in an individual with severe hemophilia B. *Mol Ther*. 2006;14(3):452–455. doi:10.1016/j.ymthe.2006.05.004
13. Manno CS, Pierce GF, Arruda VR, et al. Successful transduction of liver in hemophilia by AAV-factor IX and limitations imposed by the host immune response. *Nat Med*. 2006;12(3):342–347. doi:10.1038/nm1358
14. George LA, Ragni MV, Rasko JEJ, et al. Long-term follow-up of the first in human intravascular delivery of AAV for gene transfer: AAV2-hFIX16 for severe hemophilia B. *Mol Ther*. 2020;28(9):2073–2082. doi:10.1016/j.ymthe.2020.06.001
15. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;365(25):2357–2365. doi:10.1056/NEJMoa1108046
16. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014;371 (21):1994–2004. doi:10.1056/NEJMoa1407309
17. Nathwani AC, Reiss UM, Tuddenham EG, et al. Adeno-associated mediated gene transfer for hemophilia B: 8 year follow up and impact of removing "empty viral particles" on safety and efficacy of gene transfer [abstract]. *Blood*. 2018;132:491. doi:10.1182/blood-2018-99-118334
18. Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. *Blood*. 2021;138 (11):923–931. doi:10.1182/blood.2019003777
19. Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. *Blood*. 2018;131(9):1022–1031. doi:10.1182/blood-2017-09-804419
20. Miesbach W, Meijer K, Coppens M, et al. Five year data confirms stable FIX expression and sustained reductions in bleeding and factor IX use following AMT-060 gene therapy in adults with severe or moderate-severe hemophilia B [abstract]. *Res Pract Thrombosis Haemostasis*. 2021;5:90.
21. 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(21):3241–3247. doi:10.1182/bloodadvances.2019000811
22. Miesbach W, Leebeek FWG, Recht M, et al. Final analysis from the pivotal phase 3 Hope-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe hemophilia B [abstract]. *Haemophilia*. 2022;28:99–100.
23. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. *N Engl J Med*. 2017;377 (23):2215–2227. doi:10.1056/NEJMoa1708538
24. George LA, Sullivan SK, Rasko JEJ, et al. Efficacy and safety in 15 hemophilia B patients treated with the AAV gene therapy vector fidanacogene elaparvovec and followed for at least 1 year [abstract]. *Blood*. 2019;134:3347. doi:10.1182/blood-2019-124091
25. Chowdary P, Shapiro S, Makris M, et al. Phase 1–2 trial of AAVS3 gene therapy in patients with hemophilia B. *N Engl J Med*. 2022;387(3):237–247. doi:10.1056/NEJMoa2119913
26. Konkle BA, Walsh CE, Escobar MA, et al. BAX 335 hemophilia B gene therapy clinical trial results: potential impact of CpG sequences on gene expression. *Blood*. 2021;137(6):763–774. doi:10.1182/blood.2019004625
27. Calcedo R, Kuri-Cervantes L, Peng H, et al. Immune responses in 101HEMB01, a phase 1/2 open-label, single ascending dose-finding trial of DTX101 (AAVrh10FIX) in patients with severe hemophilia B [abstract]. *Blood*. 2017;130:3333.
28. Pipe SW, Gonen-Yaacovi G, Segurado OG. Hemophilia A gene therapy: current and next-generation approaches. *Expert Opin Biol Ther*. 2022;2022:1–17.
29. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *N Engl J Med*. 2022;386(11):1013–1025. doi:10.1056/NEJMoa2113708
30. Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. *N Engl J Med*. 2017;377(26):2519–2530. doi:10.1056/NEJMoa1708483

31. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382(1):29–40. doi:10.1056/NEJMoa1908490
32. Pasi KJ, Laffan M, Rangarajan S, et al. Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A. *Haemophilia*. 2021;27(6):947–956. doi:10.1111/hae.14391
33. Arruda VR. Why is AAV FVIII gene therapy not approved by the US Food and Drug Administration yet? *Blood Adv*. 2021;5(20):4313. doi:10.1182/bloodadvances.2021004760
34. Fong S, Yates B, Sihn CR, et al. Interindividual variability in transgene mRNA and protein production following adeno-associated virus gene therapy for hemophilia A. *Nat Med*. 2022;28(4):789–797. doi:10.1038/s41591-022-01751-0
35. George LA, Monahan PE, Eyster ME, et al. Multiyear factor VIII expression after AAV gene transfer for hemophilia A. *N Engl J Med*. 2021;385 (21):1961–1973. doi:10.1056/NEJMoa2104205
36. Sullivan SK, Barrett JC, Drelich DA, et al. SPK-8016: preliminary results from a phase 1/2 clinical trial of gene therapy for hemophilia A [abstract]. *Haemophilia*. 2021;27:129. doi:10.1111/hae.14190
37. Vishweshwar N, Harrington TJ, Leavitt AD, et al. Updated results of the Alta study, a phase 1/2 study of giroctocogene fitelparvovec (PF-07055480/SB-525) gene therapy in adults with severe hemophilia A [abstract]. *Blood*. 2021;138:564. doi:10.1182/blood-2021-148651
38. Pipe SW, Hay C, Sheehan J, et al. Evolution of AAV vector gene therapy is ongoing in hemophilia. Will the unique features of BAY 2599023 address the outstanding needs? [abstract]. *Res Pract Thrombosis Haemostasis*. 2021;5:1–7.
39. Nathwani AC, Tuddenham EG, Chowdary P, et al. GO-8: preliminary results of a Phase I/II dose escalation trial of gene therapy for haemophlia A using a novel human factor VIII variant [abstract]. *Blood*. 2018;132:489. doi:10.1182/blood-2018-99-118256
40. Verdera HC, Kuranda K, Mingozzi F. AAV vector immunogenicity in humans: a long journey to successful gene transfer. *Mol Ther*. 2020;28 (3):723–746. doi:10.1016/j.ymthe.2019.12.010
41. Zou C, Vercauteren KOA, Michailidis E, et al. Experimental variables that affect human hepatocyte AAV transduction in liver chimeric mice. *Mol Ther Methods Clin Dev*. 2020;18:189–198. doi:10.1016/j.omtm.2020.05.033
42. Davidoff AM, Gray JT, Ng CY, et al. Comparison of the ability of adeno-associated viral vectors pseudotyped with serotype 2, 5, and 8 capsid proteins to mediate efficient transduction of the liver in murine and nonhuman primate models. *Mol Ther*. 2005;11(6):875–888. doi:10.1016/j.ymthe.2004.12.022
43. Halbert CL, Rutledge EA, Allen JM, Russell DW, Miller AD. Repeat transduction in the mouse lung by using adeno-associated virus vectors with different serotypes. *J Virol*. 2000;74(3):1524–1532. doi:10.1128/JVI.74.3.1524-1532.2000
44. Calcedo R, Vandenberghe LH, Gao G, Lin J, Wilson JM. Worldwide epidemiology of neutralizing antibodies to adeno-associated viruses. *J Infect Dis*. 2009;199(3):381–390. doi:10.1086/595830
45. Li C, Narkbunnam N, Samulski RJ, et al. Neutralizing antibodies against adeno-associated virus examined prospectively in pediatric patients with hemophilia. *Gene Ther*. 2012;19(3):288–294. doi:10.1038/gt.2011.90
46. Boutin S, Monteilhet V, Veron P, et al. Prevalence of serum IgG and neutralizing factors against adeno-associated virus (AAV) types 1, 2, 5, 6, 8, and 9 in the healthy population: implications for gene therapy using AAV vectors. *Hum Gene Ther*. 2010;21(6):704–712. doi:10.1089/hum.2009.182
47. Kruzik A, Fetahagic D, Hartlieb B, et al. Prevalence of anti-adeno-associated virus immune responses in international cohorts of healthy donors. *Mol Ther Methods Clin Dev*. 2019;14:126–133. doi:10.1016/j.omtm.2019.05.014
48. Erles K, Sebökovà P, Schlehofer JR. Update on the prevalence of serum antibodies (IgG and IgM) to adeno-associated virus (AAV). *J Med Virol*. 1999;59(3):406–411. doi:10.1002/(SICI)1096-9071(199911)59:3<406:AID-JMV22>3.0.CO;2-N
49. Biomarin. Gene therapy study in severe hemophilia A patients with antibodies against AAV5 (270-203). MNLM identifier: NCT03520712. 2021.
50. Scallan CD, Jiang H, Liu T, et al. Human immunoglobulin inhibits liver transduction by AAV vectors at low AAV2 neutralizing titers in SCID mice. *Blood*. 2006;107(5):1810–1817. doi:10.1182/blood-2005-08-3229
51. Monahan PE, Négrier C, Tarantino M, Valentino LA, Mingozzi F. Emerging immunogenicity and genotoxicity considerations of adeno-associated virus vector gene therapy for hemophilia. *J Clin Med*. 2021;10(11):2471. doi:10.3390/jcm10112471
52. Sabatino DE, Bushman FD, Chandler RJ, et al. Evaluating the state of the science for adeno-associated virus integration: an integrated perspective. *Mol Ther*. 2022;30(8):2646–2663. doi:10.1016/j.ymthe.2022.06.004
53. D'Avola D, López-Franco E, Sangro B, et al. Phase I open label liver-directed gene therapy clinical trial for acute intermittent porphyria. *J Hepatol*. 2016;65(4):776–783. doi:10.1016/j.jhep.2016.05.012
54. Kaeppel C, Beattie SG, Fronza R, et al. A largely random AAV integration profile after LPLD gene therapy. *Nat Med*. 2013;19(7):889–891. doi:10.1038/nm.3230
55. Uniqure.com. UniQure announces findings from reported case of hepatocellular carcinoma (HCC) in hemophilia B gene therapy program; 2021. Available from: https://wwwuniquregcom/PR_HCC%20Investigation%20Findings%20_3_29_21_FINALpdf. Accessed September 22, 2022.
56. Konkle B, Pierce G, Coffin D, et al. Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thrombosis Haemostasis*. 2020;18(11):3074–3077. doi:10.1111/jth.15023
57. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci*. 2009;4:50. doi:10.1186/1748-5908-4-50
58. Pfadenhauer LM, Gerhardus A, Mozygemba K, et al. Making sense of complexity in context and implementation: the Context and Implementation of Complex Interventions (CICI) framework. *Implement Sci*. 2017;12(1):21. doi:10.1186/s13012-017-0552-5
59. US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Human gene therapy for hemophilia. Guidance for industry; 2020. Available from: https://wwwfdagov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances. Accessed September 22, 2022.
60. Agency EM. EMA's scientific guidelines on gene therapy; 2022. Available from: https://wwwemaeuropaeu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy. Accessed September 22, 2022.
61. World Health Organization. WHO considerations on regulatory convergence of cell and gene therapy products; 2021:1–22. Available from: https://cdnwhoint/media/docs/default-source/biologicals/ecbs/who-public-consultation_cgtp-white-paper_16_dec_2021pdf?sfvrsn=18f6c549_5. Accessed September 22, 2022.

62. Drago D, Foss-Campbell B, Wonnacott K, Barrett D, Ndu A. Global regulatory progress in delivering on the promise of gene therapies for unmet medical needs. *Mol Ther Methods Clin Dev*. 2021;21:524–529. doi:10.1016/j.omtm.2021.04.001
63. Reiss UM, Mahlangu J, Ohmori T, Ozelo MC, Srivastava A, Zhang L. Haemophilia gene therapy - update on new country initiatives. *Haemophilia*. 2022;28:61–67. doi:10.1111/hae.14512
64. Reiss UM, Zhang L, Ohmori T. Hemophilia gene therapy-new country initiatives. *Haemophilia*. 2021;27(Suppl 3):132–141. doi:10.1111/hae.14080
65. World Federation of Hemophilia. Gene therapy for hemophilia; 2019. Available from: https://elearning.wfh.org/resource/gene-therapy-for-hemophilia/. Accessed September 22, 2022.
66. National Hemophilia Foundation. Gene and innovative therapies education. Available from: https://www.hemophilia.org/educational-programs/education/gene-and-innovative-therapies-education. Accessed March 10, 2022.
67. American Society of Gene and Cell Therapy. Hemophilia. Available from: https://patienteducation.asgct.org/disease-treatments/hemophilia. Accessed October 22, 2020.
68. International Society on Thrombosis and Hemostatis. Gene therapy in hemophilia an ISTH education initiative. Available from: https://genetherapy.isth.org/. Accessed September 29, 2021.
69. Dionyssopoulos A, Karalis T, Panitsides EA. Continuing medical education revisited: theoretical assumptions and practical implications: a qualitative study. *BMC Med Educ*. 2014;14:1051. doi:10.1186/s12909-014-0278-x
70. Vasquez-Loarte TC, Lucas TL, Harris-Wai J, Bowen DJ. Beliefs and values about gene therapy and in-utero gene editing in patients with hemophilia and their relatives. *Patient*. 2020;13(5):633–642. doi:10.1007/s40271-020-00442-7
71. Witkop M, Morgan G, O'Hara J, et al. Patient preferences and priorities for haemophilia gene therapy in the US: a discrete choice experiment. *Haemophilia*. 2021;27(5):769–782. doi:10.1111/hae.14383
72. van Overbeeke E, Michelsen S, Hauber B, et al. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. *Haemophilia*. 2020;27:129–136.
73. Tingley K, Coyle D, Graham ID, et al. Stakeholder perspectives on clinical research related to therapies for rare diseases: therapeutic misconception and the value of research. *Orphanet J Rare Dis*. 2021;16(1):26. doi:10.1186/s13023-020-01624-0
74. Anderson EE, Newman SB, Matthews AK. Improving informed consent: stakeholder views. *AJOB Empir Bioeth*. 2017;8(3):178–188. doi:10.1080/23294515.2017.1362488
75. Krumb E, Lambert C, Hermans C. Patient selection for hemophilia gene therapy: real-life data from a single center. *Res Pract Thrombosis Haemostasis*. 2021;5(3):390–394. doi:10.1002/rth2.12494
76. Sidonio RF, Pipe SW, Callaghan MU, Valentino LA, Monahan PE, Croteau SE. Discussing investigational AAV gene therapy with hemophilia patients: a guide. *Blood Rev*. 2021;47:100759. doi:10.1016/j.blre.2020.100759
77. Hart DP, Branchford BR, Hendry S, et al. Optimizing language for effective communication of gene therapy concepts with hemophilia patients: a qualitative study. *Orphanet J Rare Dis*. 2021;16(1):189. doi:10.1186/s13023-020-01555-w
78. Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. 2019;25(4):545–557. doi:10.1111/hae.13769
79. van Overbeeke E, Michelsen S, Toumi M, et al. Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions. *Drug Discov Today*. 2020;26:399–415. doi:10.1016/j.drudis.2020.11.024
80. Garrison LP, Jiao B, Dabbous O. Gene therapy may not be as expensive as people think: challenges in assessing the value of single and short-term therapies. *J Manag Care Special Pharm*. 2021;27(5):674–681. doi:10.18553/jmcp.2021.27.5.674
81. Machin N, Ragni MV, Smith KJ. Gene therapy in hemophilia A: a cost-effectiveness analysis. *Blood Adv*. 2018;2(14):1792–1798. doi:10.1182/bloodadvances.2018021345
82. Cook K, Forbes SP, Adamski K, Ma JJ, Chawla A, Garrison LP. Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A. *J Med Econ*. 2020;23:1–12. doi:10.1080/13696998.2019.1678170
83. Rind D, Walton S, Agboola F. *Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value; Evidence Report*. Institute for Clinical and Economic Review; 2020.
84. Bolous NS, Chen Y, Wang H, et al. The cost-effectiveness of gene therapy for severe hemophilia B: a microsimulation study from the United States perspective. *Blood*. 2021;138:1677–1690. doi:10.1182/blood.2021010864
85. Ten Ham RM, Walker SM, Soares MO, et al. Modeling benefits, costs, and affordability of a novel gene therapy in hemophilia A. *HemaSphere*. 2022;6(2):e679. doi:10.1097/HS9.0000000000000679
86. Marsden G, Towse A, Pearson S, Dreitlein B, Henshall C. Gene therapy: understanding the science, assessing the evidence, and paying for value. 2017.
87. Drummond MF, Neumann PJ, Sullivan SD, et al. Analytic considerations in applying a general economic evaluation reference case to gene therapy. *Value Health*. 2019;22(6):661–668. doi:10.1016/j.jval.2019.03.012
88. Garrison LP, Pezalla E, Towse A, et al. Hemophilia gene therapy value assessment: methodological challenges and recommendations. *Value Health*. 2021;24(11):1628–1633. doi:10.1016/j.jval.2021.05.008
89. Institute for Clinical and Economic Review. Value assessment methods for "single or short-term transformative therapies" (SSTs); 2019. Available from: https://icerorg/wp-content/uploads/2020/10/ICER_SST_ProposedAdaptations_080619-2pdf. Accessed September 22, 2022.
90. Maldonado R, Jalil S, Wartiovaara K. Curative gene therapies for rare diseases. *J Community Genet*. 2020;11:1–10. doi:10.1007/s12687-019-00448-1
91. Ma C-C, Wang Z-L, Xu T, He Z-Y, Wei Y-Q. The approved gene therapy drugs worldwide: from 1998 to 2019. *Biotechnol Adv*. 2020;40:107502. doi:10.1016/j.biotechadv.2019.107502
92. FDA. *Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.d., Director of the Center for Biologics Evaluation and Research on New Policies to Advance Development of Safe and Effective Cell and Gene Therapies*. FDA; 2019.
93. Goodman C, Berntorp E, Wong O; Council IHAS. Alternative payment models for durable and potentially curative therapies: the case of gene therapy for haemophilia A. *Haemophilia*. 2022;28:27–34. doi:10.1111/hae.14425
94. Noone D, Coffin D, Pierce GF. Reimbursing the value of gene therapy care in an era of uncertainty. *Haemophilia*. 2020;27:12–18.
95. Miesbach W, Chowdary P, Coppens M, et al. Delivery of AAV-based gene therapy through haemophilia centres-a need for re-evaluation of infrastructure and comprehensive care: a joint publication of EAHAD and EHC. *Haemophilia*. 2021;27(6):967–973. doi:10.1111/hae.14420