

Gene Therapy

A Practical Guide

Book

September 2022

Disclaimers: The EHC produces this publication primarily as an educational tool for our NMOs. The information contained, and the views expressed herein, constitute the collective input of the EHC Steering Committee, Medical Advisory Group, and international experts in the field of haemophilia. The EHC does not engage in medical practice and under no circumstances recommends a particular treatment for specific individuals. The EHC makes no representation, express or implied, on the therapeutic candidates or class references in this publication. The EHC strongly recommends that individuals seek advice, information, and dialogue with other experts and sources of experience in tandem with this publication. The EHC does not endorse any particular treatment product or manufacturer; any reference to a therapeutic candidate, product, or treatment class is not an endorsement by the EHC.

How to use this document

This Guidebook was put together by the EHC to help support and guide our National Member Organisations (NMOs) through the introduction of gene therapy as a therapeutic option in their countries.

It contains important information, questions, and emerging areas for consideration and food for thought. It also outlines sources of additional information, resources, existing good practices, templates, and recommended actions.

With this, the EHC hopes to provide its NMOs with the information they need to help:

- *Navigate national patient communities and individual patients considering gene therapy through crucial questions and issues, and*
- *Engage nationally with all stakeholders, including clinicians, health agencies, reimbursement bodies, and haemophilia care networks, on the broader systems that need to be put into place to ensure the safest and most optimal outcomes possible.*

Acronyms

AAV	Adeno-associated viral
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CAR-T	Chimeric antigen receptor T cells
CSA	Chromogenic factor activity assay
EAHAD	European Association for Haemophilia and Allied Disorders
EHC	European Haemophilia Consortium
EMA	European Medicines Agency
EUHANET	European Haemophilia Network
EUHASS	European Haemophilia Safety Surveillance
FDA	Food and Drug Administration
FVIII	Factor 8
FIX	Factor 9
GCP	Good clinical practice
GT	Gene therapy
GTR	Gene therapy registry
HCP	Health care provider
HTA	Health Technology Assessment
IU	International Units
ml	Millilitres
N	Number
NHF	National Hemophilia Foundation
MDT	Multi-disciplinary team
NMO	National Member Organisation
OSA	One stage assay
REMS	Risk evaluation and mitigation strategy
RMP	Risk Management Plan
SDM	Shared decision-making
sH	Severe haemophilia
SmPC	Summary of Product Characteristics (sometimes also 'SPC')
WFH	World Federation of Hemophilia

Contents

Background	5
Are we ready to include gene therapy in the national haemophilia strategy?	7
What is the need for gene therapy?	8
Is gene therapy effective? And if so, for how long?	10
How should patients decide whether to take gene therapy?	18
Should patients take gene therapy now or wait for the 'next generation version'?	23
How do we integrate	25
gene therapy into the current national haemophilia treatment model?	25
What are the right laboratory assays to measure factor activity of gene therapy?	31
Is it (economically) worth investing in gene therapy when other therapeutic options are available?	33
How do we pay for gene therapy?	36
Conclusions & recommended actions	38
References	40
Appendix 1	45
Appendix 2	47

Background

The haemophilia community has been awaiting gene therapy for many years, expecting it to be a ‘cure’. In the past few years, we started to see promising results from the late stages of clinical trials for gene therapy in haemophilia A and B.

We learned that the reality of gene therapy will differ from original hopes and expectations; that gene therapy is a promising new option but ‘it depends’ for whom and when.

We also learned that we collectively still have a lot of work to ensure its safe and optimal introduction into patients’ treatment options and choices.

State of approvals

For haemophilia A, a positive opinion for Conditional Marketing Authorisation (CMA) was granted in June 2022 by the European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP) for BioMarin’s Roctavian® (Valoctocogene Roxaparvec, an experimental gene therapy for haemophilia A)¹. Announcement of the European Commission decision to agree with this decision followed from the EMA on August 24th, 2022². The final publication of the license is expected in the September 2022.

For haemophilia B, following positive results in the HOPE-B phase III trial for CSL Behring’s Etranacogene Dezaparvec (an experimental gene therapy for haemophilia B), the company announced that the EMA had accepted Marketing Authorization Application (MAA) under an accelerated assessment process³. We may expect another positive opinion from the EMA for marketing authorisation in the coming months.

What to expect next

This news may give rise to many questions: on the mode of action, safety, efficacy, durability, toxicity, and suitability of these gene therapies for various patients.

These questions may come from the patient community but also clinicians or government officials.

We need to consider what role national haemophilia patient organisations should play in the coming months to help navigate their members and community through this.

Compared to other rare diseases, haemophilia benefits from many therapeutic options, many of which have a long track record of safety and efficacy. Therefore, it seems natural that potential questions may include:

- *Are we ready to include gene therapy in national haemophilia treatment strategies?*
- *What is the need?*
- *Is it effective? And if so, for how long?*
- *How should patients decide whether to take it?*
- *How should patients deal with the uncertainty that comes with taking a novel therapy such as this one?*
- *Should patients take gene therapy now or wait for the 'next generation' version?*
- *How do we integrate gene therapy into the current national haemophilia treatment model?*
- *What are the right laboratory assays to measure the factor activity following infusion?*
- *Is it (economically) worth taking this therapy when other therapeutic options are available?*
- *How do we pay for this?*

European level

The European Haemophilia Consortium (EHC) has been addressing many of these questions for the past five years at European level.

We published several thought pieces on the above and included regular gene therapy clinical trial updates in all our New Products Newsletters⁴.

We engaged with all stakeholders and participated in all relevant gene and cell therapy policy discussions.

During the past five years, we have strived to engage our National Member Organisations (NMOs) on this topic through tailored education, multi-media information, and expert-based trainings.

These issues were covered in our workshops on New Technologies in Haemophilia Care, workshops on Tenders and Procurement, Round Tables of Stakeholders, and in our annual EHC Conferences.

The goal was to help prepare our NMOs to take active part in national conversations on gene therapy.

National level

With the recent licensing, we expect that these conversations will become more pressing and move to national levels.

The EHC believes that its NMOs must be prepared to actively engage on this topic, because:

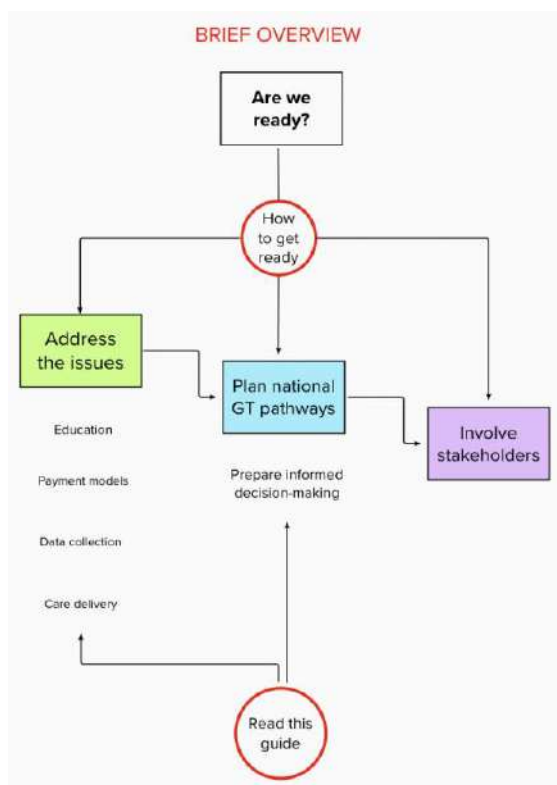
- *This will shape the future of haemophilia care in their countries.*
- *This is the moment to ensure full commitment to shared decision-making.*
- *The current EMA approval is conditional meaning that the community plays an important role in affecting the future of this therapy.*

Are we ready to include gene therapy in the national haemophilia strategy?

At the time of writing this document, for most European countries the answer is likely a 'No'.

With preparation, however, it could quickly become a 'Yes.'

This document outlines the issues that need addressing, the plans that need to be made, and the stakeholders that need to be involved.



The European health care landscape is diverse and fragmented. Conversations about gene therapy are ongoing in some countries and have not yet started in others.

In this guide, we offer food for thought on things to consider when thinking about gene therapy, and recommendations on what NMOs can address and with whom.

At a national level, for informed decisions to be made about gene therapy, stakeholders will need to address all the issues on education, payment models, data collection, and care delivery. If that does not happen, we risk uninformed gene therapy uptake or no gene therapy at all.

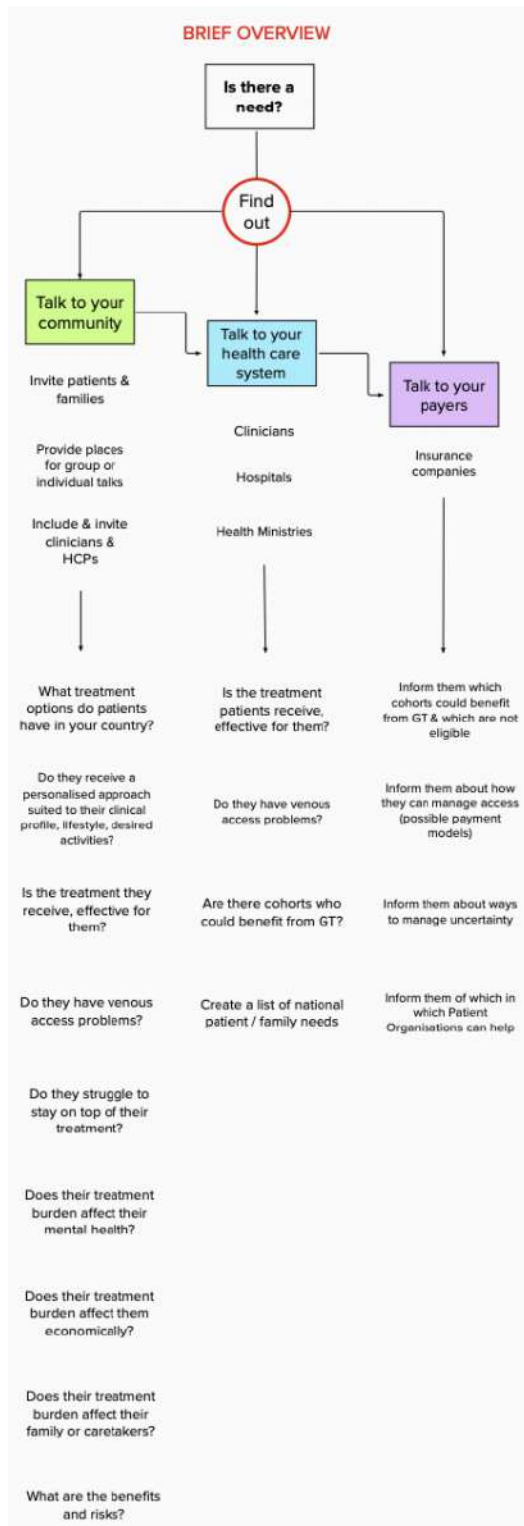
At an individual patient level, patient organisations and stakeholders will need to address issues such as answering questions, ensuring patient education programs, and enabling all patients to be offered the same opportunities and the same awareness of all aspects of the potential journey they may want to start.

The international support and expertise exist. The EHC, WFH, EAHAD and ISTH are working toward supporting the implementation of frameworks that will make gene therapy accessible and delivered as safely as possible.

We encourage NMOs not to hesitate to reach out and to attend, in particular, the EHC workshops on Health Economics and on New Technologies to further explore the points addressed in the document.

Crucially, it will be up to patient organisations to make their voices heard and ensure due diligence in the development process of national gene therapy pathways.

What is the need for gene therapy?



Haemophilia is an ideal condition for gene therapy because it is a single gene disorder requiring the replacement of only one clotting factor. Additionally, patients do not need to achieve 'normal' factor levels to reduce overall bleeding risks⁵.

Since the late 1990s, the global haemophilia research, clinical, and patient communities have been working on gene therapy⁶.

In the last decade, there have been several successful (and some failed) phase I-II clinical trials in haemophilia gene therapy^{7,8}. These trials demonstrated that an adeno-associated viral (AAV) vector could deliver the gene containing the information to produce the missing clotting factor to the liver, the organ that produces clotting factors.

A single infusion delivers the gene to the liver. Unfortunately, at the time of writing, this infusion cannot be repeated.

Gene therapy research and development occurred in parallel to the development of a wide array of other treatment options for haemophilia.

- First came the extended half-life coagulation factors for haemophilia A and haemophilia B.
- In haemophilia A, the bispecific antibodies were then licensed initially for people with inhibitors and then in people without inhibitors.
- In addition, many other non-replacement therapies are still progressing in their clinical development pathway for haemophilia A and B⁹⁻¹¹.

Therefore, a natural question is whether additional treatment options for people with haemophilia are still needed.

Here, we outline several issues that available treatment still don't address:

- Current replacement therapy requires frequent intravenous infusions, which can be a significant burden on the patient's day-to-day life¹². Intravenous infusions are limited by venous access. Venous access can be difficult for some and becomes more difficult with frequent use.
- Current replacement therapy achieves peaks to trough protection, not continuous protection¹³. Peak-to-trough versus continuous protection may leave the patient more prone to trauma, spontaneous bleeds, or subclinical bleeds, which in the long run can cause joint damage. While this trade off could potentially be less of a concern in haemophilia B, than in haemophilia A, due to the extension in half, it is still heavily reliant on access and adherence to replacement therapies.
- Advances in non-replacement therapies for haemophilia A have greatly improved the standard of care. The only currently licensed non-replacement therapy, a bi-specific antibody, mimics a steady state of an estimated 12-20 FVIII IU/ml¹⁴. This treatment provides a significant improvement in baseline protection and reduces the infusion burden thanks to subcutaneous injections. However, it does not involve the whole FVIII protein. Also, clinical studies suggest that a small percentage of patients (approx. 3-5%) on this treatment develop anti-drug antibodies (ADAs)^{15,16}. In addition, some researchers question the long-term effect on bone health due to absence of the FVIII protein¹⁷. Finally, some patients may require a higher level of protection to engage in certain physical activities¹⁸.
- The treatment burden of a chronic and life-long condition is not negligible, even in a small cohort of patients. While treatment adherence in haemophilia is generally high, a proportion of patients struggle to maintain it lifelong¹⁹⁻²¹. Unlike in some other burdensome therapeutic areas, in haemophilia it is not possible to consider 'treatment interruption' for concordance and mental health (such as e.g., in HIV) because in haemophilia, absence of treatment results in bleeding, swelling, and long-term joint damage with life-long consequences²².

Gene therapy is not without its own associated burdens.

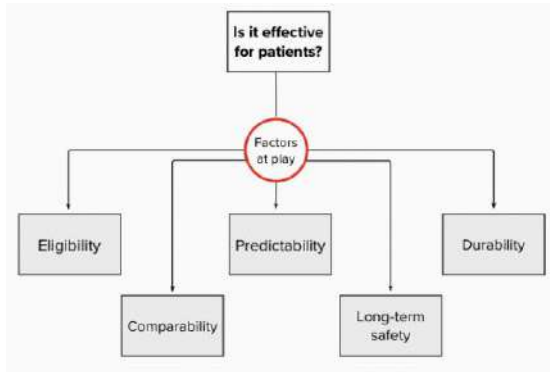
The importance of long-term follow up and, in the first year, frequent visits to the clinic, should not be minimized.

However, gene therapy may offer some patients a viable treatment alternative that, in the long term, does not involve weekly/monthly commitment to a treatment regimen.

Although these patients may also have difficulties with the demands of short- and long-term follow-up due to gene therapy, they could also reap the most benefits from this therapeutic approach.

Is gene therapy effective? And if so, for how long?

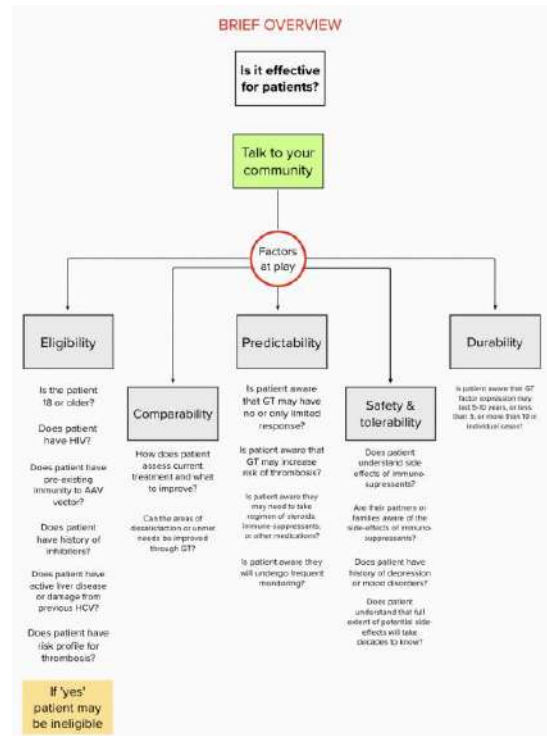
There is significant variation in results between and within clinical trials.



Performance criteria for gene therapies exist, but some are better characterized than others.

We have broken them into five categories

Eligibility	<ul style="list-style-type: none"> Who can receive gene therapy?
Predictability	<ul style="list-style-type: none"> What proportion of patients will achieve reasonable factor expression after gene therapy? How do we define reasonable?
Durability	<ul style="list-style-type: none"> How long will the factor expression last?
Safety and tolerability	<ul style="list-style-type: none"> How safe is gene therapy both in the short and long term?
Comparability	<ul style="list-style-type: none"> How does gene therapy compare to available treatment?



Eligibility

This is a well-defined criterion.

Based on the clinical trials, we can expect haemophilia gene therapy to be licensed for adults (≥ 18 years old)^{23,24}. Those < 18 years (children, adolescents) are not eligible for gene therapy.

Final language is awaited to understand if there may be a gender restriction at this point.

HIV is not likely to be an exclusion criterion, but it may be required to be controlled before entry, and other aspects such as concomitant use of some medications may need to be reviewed²⁵.

For haemophilia A, the eligible adult population is limited to severe (< 1 IU/ml). For haemophilia B, the eligible adult population is limited to severe/moderately severe (< 2 IU/ml).

Exclusion criteria include a patient with a history of inhibitors, a pre-existing liver disease, and pre-existing immunity to the AAV vector (with the exclusion of CSL Behring's

Etranacogene Dezaparvovec for FIX, which does not exclude patients in clinical trials)^{26,27}.

Studies have shown that 30 to 60% of the haemophilia population (depending on the AAV serotype and geography) have neutralising anti-AAV antibodies^{28,29}.

This pre-existing immunity against AAV is a problem because it completely excludes patients from a specific gene therapy or potentially from an entire class of gene therapy due to cross reactivity, which may limit their outcome and increase their need for other medications like corticosteroids.

In the Etranacogene Dezaparvovec trial for haemophilia B, patients with AAV antibodies were eligible and are likely to be eligible after licensing with a potential upper limit of neutralizing antibodies³⁰.

Other exclusion considerations may include a patient's predisposition or risk profile for thrombosis (e.g., a family history, previous cardiac events, age).

National patient organisations have a crucial role to play in informing their members about inclusion / exclusion criteria and supporting them if they are not eligible for gene therapy at this stage.

Before considering the idea of gene therapy, patients should check if their medical situation even allows them eligibility for this approach.

If all patients did this, it would make it easier to identify an eligible population and to target education and information efforts specifically with them, initially.

Patient organisations need to work closely with clinicians and hospitals to enable appropriate access to laboratory

assays for AAV antibodies in a hub or a spoke centre.

It is advisable that patients make decisions about actual rather than potential options, and that patient organisations have clear definitions on who to support, initially.

Predictability

Results from clinical trials show that the majority (>80%) of people treated with gene therapy achieve, as an initial response, factor levels within the target therapeutic range, which confers protection from bleeding and potential long-term joint damage^{31,32}.

However, within those, range, results demonstrated significant variability between individual factor level responses, especially in haemophilia A.

In terms of the therapeutic range for haemophilia, we would consider that:

- A level of 3-5 FVIII IU/ml may reduce likelihood of spontaneous bleeds, unless joints have been badly damaged by repeated hemarthrosis³³,
- A level of ≥ 12 FVIII IU/ml may reduce traumatic bleeds^{18,34}, and
- A level of ≥ 30 FVIII IU/ml may reduce chronic synovitis, a key contributor to the development of joint pain and loss of motion³⁵.

People in the gene therapy clinical trials who did not respond or had only a partial response may continue to require factor concentrate replacement therapy or non-replacement therapy, either prophylactically or on-demand.

In haemophilia A, a small cohort of participants in one clinical trial responded with FVIII levels above the normal (50-150 FVIII IU/ml) FVIII range (>150 FVIII IU/ml)³¹.

These patients may need monitoring for an (as yet unknown) amount of time to prevent thrombosis.

Whilst anticoagulation medicines were not used in Valoctogene Roxaparovec clinical trials, it may be feasible that patients achieving an above-normal range of FVIII levels may be managed with such medication.

It could also be expected that anticoagulation medication will be incorporated into the clinical protocols of other or future haemophilia gene therapy trials.

So far, all haemophilia A gene therapy trial participants have 'naturally' dropped out of this region and entered the normal FVIII range.

In haemophilia B, the leading gene therapy candidate, Etranacogene Dezaparovec has not produced results >150IU/ml FIX³².

The Phase I/II dose escalating study of the FLT180a gene therapy trial from Freeline, produced one case of high FIX level expression^{36,37}.

The result in this case, is that the dose being brought forward. in the Phase III trial is reduced for future participants.

This type of response may be potentially more problematic in FIX gene therapy than in FVIII gene therapy, as levels may remain higher for an extended period.

The range of possible initial responses vary greatly in individuals. Patients, clinicians, and payers need to be aware of this issue in their planning for access to gene therapy.

Patient organisations need to collaborate with all stakeholders and put plans in place to ensure that the value of gene therapy achieves its potential benefits.

Additionally, when a patient does not respond or has a supra-normal factor expression, processes need to be in place to help patients manage.

Durability

The long-term durability varies between haemophilia A and haemophilia B gene therapies.

In haemophilia A, the clinical trials have shown factor expression levels dropping over time³¹.

Valoctogene Roxaparovec has shown a mean drop of 14-27% FVIII IU/ml year-on-year, although individual response varies greatly.

Investigators reported two-year data at the 2022 Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), which states that³⁸:

- Twenty (15%) patients had a factor expression of > 40IU/ml (normal range), there were no bleeds, and no patients were on prophylaxis.
- Thirty-five (26%) patients had a factor expression between 15-40IU/ml, which should provide steady state protection greater than any currently available treatments. Ninety-seven per cent of patients in this cohort had no bleeds, and no patient re-started prophylaxis.
- Forty-six (35%) patients had a factor expression between 5-15IU/ml. This range is potentially lower than that provided by bispecific antibodies but does not have the burden of treatment with regular infusions (as discussed above). In these 46 patients, 85% of them had zero bleeds, and one patient re-started prophylaxis.
- Thirteen (10%) patients had a factor expression between 3-5IU/ml. In this group, 77% of patients were bleed-

free, and one patient re-started prophylaxis.

- Eighteen (14%) of patients had a factor expression between 0-3IU/ml. Of these, 28% were bleed-free, and four patients re-started prophylaxis. The lowest level of FVIII quantification is 3IU/ml, using the assay that BioMarin used in their trial results. It is therefore unclear what the actual level below 3IU/ml might be.

Based on this outcome, it is reasonable to expect that most patients who opt for this first-generation haemophilia A gene therapy would, by year two, have adequate factor levels greater than or equal to those provided by currently available treatment options. However, considering the year-on-year FVIII level drops shown above, it does not seem likely that these therapeutic levels would last more than eight years. Long-term follow-up of these patients will be needed to secure evidence for this.

In haemophilia B, the original clinical trial data have shown sustained factor expression levels for at least ten years³⁹.

During the EAHAD Conference 2022, data was available on 18-month post-infusion indicating, a stable expression with a 3% drop in mean factor IX expression³⁰.

However, at the time of writing is document, it is unclear whether there is a FIX expression loss or assay discrepancies in small sample sizes. We await additional data on responses 2-year post infusion.

Based on the data published so far, we can reasonably expect the average individual factor FIX expression response to fall in the normal (40-

100IU/ml) or mild (5-40 U/ml) haemophilia B range, and to last up to 10 years or more. Long-term follow-up of these patients will be needed to secure evidence for this.

We note that, as a condition for marketing authorisation, the EMA has asked for 15-year follow-up of patients dosed with haemophilia gene therapy⁴⁰. This is a similar EMA position as with other types of gene therapy⁴¹.

Safety / Tolerability

Here we address two safety and tolerability issues. The first regards liver health and the second regards long-term safety.

Liver inflammation

Data from clinical trials show that in the short term (<1 year), some haemophilia gene therapy participants developed liver inflammation.

These are measured with two biomarkers: aspartate aminotransferase (AST) or alanine aminotransferase (ALT). A rise in one or both biomarkers in blood samples indicates liver inflammation.

In the haemophilia A clinical trials, we note an ALT increase in 85.5% of the trial participants, whereas in the haemophilia B clinical trials, an ALT increase occurred only in 17%^{31,42}.

An increase in ALT may be accompanied by a loss of factor expression. To prevent this, investigators treated those patients, who showed an increase in liver biomarkers, with corticosteroids and/or immunosuppressive medication.

The duration of steroids and immune suppression treatment varies greatly between the different trials, and ranges from six weeks to one year.

In BioMarin's Valoctocogene Roxaparvec trial, the average use of these medications was approximately seven months³⁸.

Unfortunately, it is not yet possible to identify which patients might need this medication after being infused with gene therapy.

This is an issue as long courses of steroids and immune suppression can be difficult to manage in patients' day-to-day lives.

In the haemophilia A trial, a total of 110 participants out of 132 HIV-negative participants (82%) were given steroid treatment to manage liver inflammation.

Of these, 79 (71.8%) reported adverse events due to the steroid treatment and not due to the gene therapy.

The most reported symptoms were acne, insomnia, Cushing syndrome, and weight gain³¹.

Of these, three developed a severe adverse event due to the steroid treatment.

In the haemophilia B trial, 24% of adverse events reported were related to the use of steroids and not related to the gene therapy itself⁴².

Although it is possible to manage the side effects of corticosteroids and immune suppressants, it is critical to provide patients who consider gene therapy, and their families, with information about liver inflammation and its treatment.

The gene therapy journey should not be undergone alone.

Professionally, clinical teams and patient organisations should be ready to support patients choosing gene therapy.

Privately, a patient's whole family and particularly partners or carers are important to include and to be made aware of the potential side effects.

Partners will also need to be aware of the need from barrier contraception and avoiding pregnancy for a period of time.

A long-term course of steroids and immune suppression treatment can be difficult to manage.

Below is a range of quotes from the Exigency Study related to the use of corticosteroids and immune suppressants to manage liver inflammation in a haemophilia gene therapy clinical trial⁴³.

Trial patient using steroids who had had mild side effects:

"It's hard to explain, but when I was on steroids, I probably had the best time of my life. Yes, so I was lucky there weren't any side effects. But then, almost overnight, taking steroids, my ankle pain was pretty much..., I wouldn't say it was gone..., but it was certainly eased."

Trial patient using steroids who had a more severe side effect:

"I'm feeling genuinely manic. Like, I'm going out for runs at three o'clock in the morning; (and) I had this hypersensitivity in my hands."

Family member of a trial participant:

"He got angry about it all the time, saying, 'I regret it. Why did I do this stupid thing?' - all the time. So, it was a really dark time."

Integration (potential cancer risks)

Integration means that the gene therapy delivery system, the viral vector, combines with the DNA of the gene therapy recipient.

This integration can be a concern, especially when the vector integrates close to genes that are more susceptible to causing cancers (i.e., oncogenes).

The delivery system of first-generation haemophilia gene therapy, AAV, was originally thought not to integrate⁴⁴.

However, preliminary studies in dogs and humans have shown that there is, in fact, a small amount of integration⁴⁵⁻⁴⁷.

The issue is that we do not yet know whether AAV integration in DNA locations close to oncogenes will cause cancer in the long term.

At the time of writing this document, we know of four cancer cases across multiple gene therapy trials of over 200 patients: one in the blood, one in the tonsils, one in the salivary gland, and one in the liver^{38,48,49,50}.

For all four, research investigators who reviewed the clinical trial data determined it to be unlikely that the gene therapy administered in the trials caused these cancers.

- In the case of the tonsil cancer, this occurred in a haemophilia B gene therapy trial which had 8 patients⁴⁹. Investigators carried out a biopsy and reported no evidence of gene therapy vector integration in the tumour. They therefore concluded that there was “no causal link to the haemophilia B gene therapy”. The trial has since been discontinued due to a lack of gene therapy effect.
- In the case of the liver cancer, this occurred in a haemophilia B gene

therapy clinical trial⁴⁸. Investigations indicated that “any causal link between the gene therapy and the cancer was highly unlikely”, and noted that due to the patient’s medical history, there was a pre-existing risk of developing liver cancer.

- In the case of the salivary gland cancer, this occurred in the Phase 2 trial a haemophilia A gene therapy with 13 patients³⁸. An investigation reported “no integration of the haemophilia gene therapy vector into portions of the genes known for causing this type of cancer”. Investigators concluded that the cancer was unlikely to be related to the haemophilia A gene therapy. In Phase 3 portion with 134 patients of this trial a second case of the blood cancer occurred⁵⁰. At the time of writing this report, investigators are waiting for results from the whole genome sequencing analysis but the company initially reported no difference between the amount of vector between the healthy blood cells and the cancer blood cells.

There is insufficient evidence currently to indicate any short-term cancer risk associated with gene therapy.

The potential long-term risk of cancers, linked to vector integration events, also remains unknown. It will require data on many patients, over many years, to assess a gene therapy cancer risk compared to the cancer risk rate in the haemophilia and general populations.

As mentioned above, regulators are requiring companies to collect long-term follow-up data (15 years) for those receiving gene therapy. We must remain vigilant and follow that data.

Comparability

Many gene therapies are developed for other conditions where there is significantly reduced quality of life and low life expectancy⁵¹.

In most cases, these conditions have little adequate or no alternative treatment options available.

In contrast, therapeutic developments in haemophilia have been significant, with multiple safe and effective products available for on-demand or prophylactic regimes¹⁰.

These reduce mortalities and morbidities and improve the quality of life of patients towards that of the general population.

Gene therapy is an addition to these treatment options.

Regulators have awarded Conditional Marketing Approval to the first gene therapy in our space (for haemophilia A, see above)⁵².

This means that the benefit/risk of this therapeutic approach for this patient population is considered positive⁵³.

The license is awarded initially for one year, with data reported regularly to the regulators as part of a risk minimisation plan.

An assessment will then be made on whether the license gets renewed or withdrawn.

The EMA makes available the risk minimisation plans for a specific product, which can be found on that product's page on the EMA website.

This approach is used in all gene therapies for any condition and many other medicines to understand the benefits and monitor any potential issues arising in the real-world setting.

The main difference between gene therapy and other medicinal products is that gene therapy is a one-time treatment, no matter what response is achieved.

Therefore, patients must receive consistent and structured information thereby providing them every opportunity to weigh up the advantages and disadvantages of this approach based on their own lives and experiences.^{54,55}

In practice, this means that the eligible gene therapy patient population will almost certainly be greater than those who decide to undergo the treatment.

Various stakeholders are developing multiple approaches to ensure a shared decision-making process for those considering gene therapy⁵⁶⁻⁵⁹.

Gene therapy candidates should make this choice being fully aware of the potential lack of initial response, potential use of steroid/immunosuppression regimens, potential short- and long-term side effects, and the loss of factor expression over time.

Ensuring real patient awareness of the full spectrum of outcomes (positive and negative) can be challenging, but NMOs should make every effort to support each patient in fully considering all aspects towards making the best-informed decision they can make.

NMOs should also work closely with centres to ensure that all issues are addressed, including potential remorse and loss of identity.

Gene therapy candidates need to be aware that no decision is final until the gene therapy is infused.

Despite all possible side-effects and unknowns, patients in gene therapy clinical trials generally report a measurable improvement in quality of life^{60,10}.

The definition of gene therapy success is different for each gene therapy candidate, and each person thinking of taking this treatment should form a clear idea of what that would be for them.

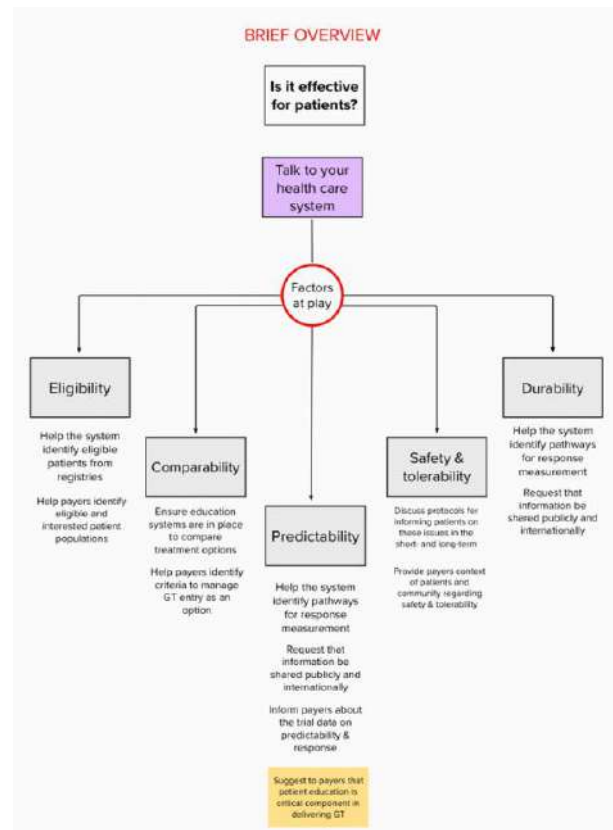
For this reason, there is an onus on healthcare system, healthcare professionals, and patient organisations to ensure that each gene therapy candidate has time to discuss all available options and their pros and cons.

Gene therapy candidates must not feel pressured to undergo any treatment without fully understanding its consequences.

These individuals will need help and information so that they can make the best choice suited to their profile and lifestyle.

Gene therapy candidates that choose to be treated should also continue to receive this support after their infusion and as they move through their pathway to regularly manage their expectations.

Patient Organisations need to work with all stakeholders to ensure that these needs are met to assist in this process.



How should patients decide whether to take gene therapy?

There is increasing recognition that shared decision-making (SDM) is the way forward for choosing treatment and care in healthcare systems^{62–65}.

SDM is a methodology to address a medical question based on medical evidence and the patient's preferences and experiences. It is a collaborative approach between clinicians and patients that puts people at the centre of the decision about their treatment and care.

The aim of SDM is to:

- Make explicit that a decision needs to be taken and why and introducing a choice.
 - Guide the patient towards understanding and ranking the available treatment or care options based on both:
 - The evidence and their personal preferences, beliefs, and experiences
- The benefits and risks based on what is important to them and what they value.
- The degree of (un)certainly regarding their preferences.
- Explain the steps in the decision-making process and the stages of communication with other stakeholders (doctors, family, relatives) to help them explore their preferences and make decisions.

SDM is not just a tool/methodology used in a clinic setting. It also consists of empowering people to develop the knowledge, skills, and confidence they need to manage and make informed decisions about their health and health care towards patient autonomy⁶⁶.

SDM can be applied in rare diseases such as haemophilia where we have enough data to compare between treatments options⁶⁷.

Irrespective of the therapy chosen, Shared Decision Making (SDM) can change the culture of the patient-clinician relationship and transform it into a partnership rather than a one-way flow of directing or prescribing.

When patients and clinicians make decisions together, they both understand what is important to the other.

Patients should feel empowered to make an informed choice, and their treatment and care plan should take account of their perspective.

Health and other care professionals can tailor the care or treatment to the needs and preferences of the individual, ensuring a better outcome.

The importance of SDM mechanisms in gene therapy

For people with haemophilia considering taking gene therapy, the SDM process should:

- Respect the patient's right to be involved in discussions and decision-making about their own treatment and care, together with health care professionals.
- Include care and support in consideration of the patient's needs and preferences.
- Endeavour to make the patient feel empowered to clarify any issues relating to their treatment and care, together with health care professionals.
- Be an ongoing process as the patient's needs and preferences will evolve.
 - Therefore, any treatment and care decisions should be continuously reviewed.
 - Patient and clinician should take a joint decision on future approaches.
- Involve partners or other family members when needed, especially regarding barrier contraceptives or if other medications become necessary that affect the patient's family.
 - Including them will enhance the patient's support during the treatment period.
- Respect the patient's right to change their mind or refuse gene therapy at any time prior to infusion and support them in exercising that right if they choose to.
 - Although this seems obvious, external pressures could make the patient feel uncomfortable during the SDM process.
 - Ultimately, this is a potentially life-changing decision that remains with the patient for the rest of their and their families' lives.
 - Expression of agreement in the form of a signed memorandum of understanding by the patient may be helpful for the final decision. Depending on national legislation this can be non-binding but may help the patient to make a final decision.

For clinicians considering administering gene therapy, the SDM process should help to:

- Manage the responsibility of recommending the right therapy for a patient for the 'right' time of their lives.
- Present the available data as neutrally as possible.
- Navigate patient who have difficulties with bleeding, poor pharmacokinetic profile, venous access, physical activity, treatment burden, etc., through:
 - Making treatment decisions based on a balance between their needs and their expectations. (For example, what is appropriate for an older individual would not necessarily be appropriate for a younger, more active individual.)
 - Eligibility for treatment, concerns about potential side-effects, concerns about the risks and benefits, and awareness of a spectrum of possible outcomes.
- Move beyond the assessment of patient treatment response based predominately on clinical outcomes, towards incorporating patient relevant outcomes and perspective. This more holistic approach enables:
 - A patient's quality of life be the primary focus.
 - An understanding of potential short- and long-term risks and benefits.
- Find a way to lead comprehensive and comprehensible conversations tailored to the patient's initial level of knowledge, interest, and education about these treatment options. (For example, by using a "teach back" method to assess the degree of understanding of the information imparted.)

In the context of gene therapy, this approach is fundamental.

Gene therapy candidates should have multiple opportunities to engage in discussions, to be

informed about gene therapy, and to check their understanding.

These patients should have the possibility to hold meetings with peers who have gone through or are considering this therapy, either one-on-one or as a group.

Patient organisations should work with haemophilia treatment centres to ensure that the decision pathway for all people with haemophilia, who are considering gene therapy, is optimised. These may vary depending on individuals' pre-GT level of knowledge, education or prior engagement.

Patient organisations and haemophilia treatment centres should work together with a psychologist and/or gene counsellor as part of the decision pathway to ensure that critical topics are addressed at different stages of the SDM process.

Importantly, the SDM process does not stop when the gene therapy is infused.

It should continue after the infusion to help individuals address their new normality.

For most, this may not be a problem, but there are case reports of loss of identity, regret over lost opportunity, concerns over loss of factor levels, and lost connection with the health care system.

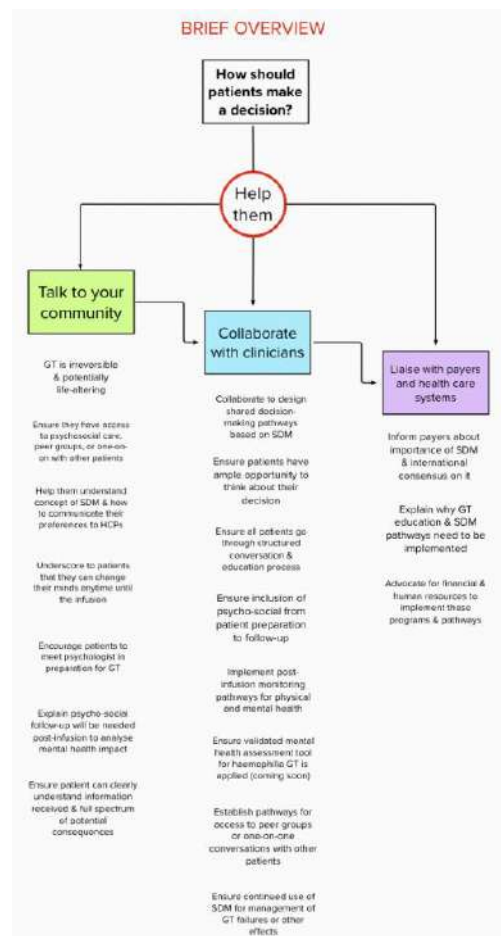
These concerns are often easily addressed but not dealing with them early can lead to problems for the individual. It is crucial for the patient organisation and treatment centre to provide a support system.

In some therapeutic areas, regulators suggest specific education programs recognition of informed decision-making is captured through signing agreements of understanding.

For example, in Portugal, when a patient switches from one treatment class to another, there is a legal requirement for a discussion and a signed agreement. In other countries, there is no legal requirement, but the practice still exists to ensure that the information was provided and discussed by both parties as part of a SDM process.

Patient organisations in conjunction with national clinicians should develop the education models and practices around SDM for all therapies, but especially for gene therapy.

These practices should be carried out in the clinic and supported outside the clinic to assist all stakeholders in ensuring a fully informed patient decision.



How should patients deal with uncertainty?

Gene therapy is an irreversible one-off therapy which may confer significant benefits to many individuals.

However, a calm consideration of benefits, risks, unknowns, and uncertainties should be made by each country and indeed by each individual contemplating treatment with gene therapy.

It is a milestone to have the first haemophilia gene therapy licensed, and to have data that demonstrates significant factor expression in most clinical trial participants, which may confer very significant amelioration of their haemophilia for several years.

Yet we must also be aware of significant uncertainties with this as outlined throughout this document, and other potential haemophilia gene therapies.

People with haemophilia, clinicians, patient organisations, and payers will all have to deal with these uncertainties and factor them into their decision-making process.

Patients will need to acquire a sufficient degree of knowledge on the benefits, risks, and uncertainties, and sufficient self-awareness to identify their own decision drivers and their expectations. They will have to prepare for a range of possible outcomes and be comfortable with these to make a fully informed decision.

Clinicians will need to ensure that every person who is eligible for and interested in gene therapy is provided with all the information they require to allow them to be aware of the uncertainties and make a fully informed decision.

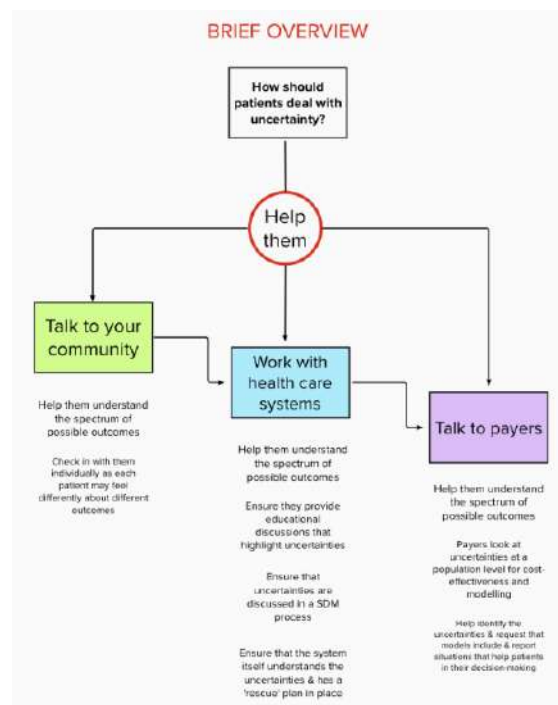
Payers do not like uncertainty. Access programs and payment models may need to adapt to ensure an element of risk sharing between the company marketing the gene therapy and the payer.

Budget impact could be very significant and may limit access or the number of people who may have access in a country.

Payers will not want to pay full cost for a therapy which may not work or stop working for some people.

An outcome-based annual payment model with defined outcomes (such as factor expression, treatment use, or requirement for return to prophylaxis) for an agreed or flexible period would deal with many of these economic uncertainties.

Countries may state that they do not currently have mechanisms to achieve this but now is the time for this work to get underway.



Patient organisations have a strong role with all stakeholders.

With patients they play a strong role in the education of people with haemophilia, in providing information on all aspects of the therapies, in testing understanding and comprehension via workshops or other suitable interactions, and in working closely with clinicians and hub-and-spoke centres to ensure that patients enter into these momentous personal decisions well prepared with knowledge, an understanding of the benefits, risks and uncertainties, and a clear understanding and commitment to the follow-up and monitoring required.

With clinicians on working to define best practices for the delivery of gene therapy and ensuring shared decision making is a key component of assessment.

Finally with payers, to help address the concerns about economic uncertainties, and developing payment methods that address the needs of the payers, deal with the unknowns of the clinicians and not make the entire process too burdensome for a patient to access.

Should patients take gene therapy now or wait for the ‘next generation version?’

As discussed throughout this document, we are living in an era of robust and rapid scientific advances.

Since gene therapy was first imagined, the haemophilia community has waited for the opportunity to be ‘cured’.

The recent advances and impending regulatory approvals for AAV gene therapy to treat haemophilia are to be celebrated. They hold the promise of a meaningful functional cure or an extended period of haemophilia-free life for many, but not all.

For whom they are right, and who should say ‘yes’ is a scientific and a personal decision.

There are important differences between haemophilia A and haemophilia B gene therapy.

While both therapies offer hope for a reduced burden of treatment and improved quality of life, the gene therapy clinical trial results reported to date suggest that people with haemophilia B are closer to achieving a durable, functional cure, a treatment that may relieve them from the need for ongoing prophylaxis, than people with haemophilia A.

Whether to receive the first-generation gene therapy now or wait for the next requires carefully informed and thoughtful discussion.

While there is no certainty that any clinical trial will lead to a marketable therapy, additional or second-generation gene therapy options will likely be available for haemophilia A and B over the next decade.

How they will compare to the first approvals is unknown.

There is still much we do not know about gene therapy. Additional research is needed on many unanswered questions around safety, variability, and durability of response. Unknowns also exist. Most certainly, we do not know all the questions we need research to answer.

Considering this uncertainty, education, thoughtful discussion, and shared decision-making between the person living with haemophilia, their family, and their health care provider are essential.

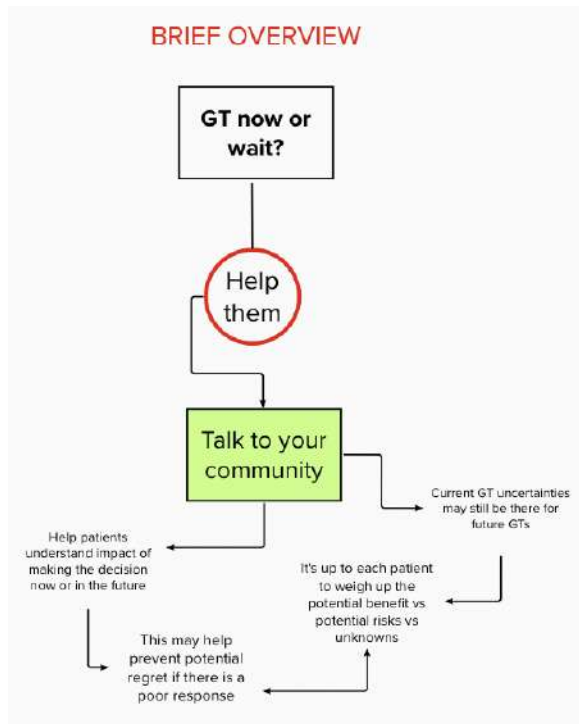
Reaching a decision is made through an iterative process.

While one may decide to wait for a future generation of gene therapy with the hope of greater certainty of outcome, it does not mean there are no reasons to consider gene therapy or other opportunities to improve your treatment and quality of life today.

Each person will need to consider personal treatment goals carefully, how living with haemophilia impacts our lives today, and whether it is interfering with our ability to achieve our life goals tomorrow. We will each have a different risk tolerance and comfort with uncertainty.

Patient organisations will have to deal with these questions and there is no simple answer. This will take time and engagement with patients and clinicians to work through these questions and concerns.

Patient organisations should workshop these issues through with patients assisting in weighing up the options and their preferences in collaboration with multidisciplinary team connected with the gene therapy.



How do we integrate gene therapy into the current national haemophilia treatment model?

In this section we consider seven aspects requiring the attention of all stakeholders nationally.

Hub-and-spoke approach

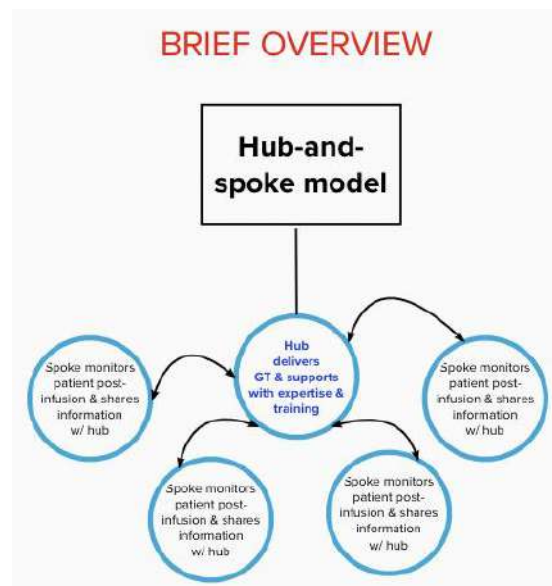
The introduction of gene therapy, once it is licensed, will be unlike the introduction of any other treatment product the haemophilia community has seen arrive thus far.

Because it is a vastly different and highly complex new therapy, it must be introduced, used, and monitored in an optimal way.

The joint recommendation of the European haemophilia patient (EHC) and health care provider (EAHAD) for the initial introduction of this therapy is contained in two EHC-EAHAD position statements and one paper^{68,69}. These state that:

- Gene therapy should be prescribed and managed exclusively by expert haemophilia comprehensive care centres (as the national hubs).
- Patients receiving gene therapy should be monitored by haemophilia treatment centres in close collaboration and communication with the primary expert haemophilia comprehensive care centres (as spokes to the national hubs).
- These haemophilia comprehensive care centre hubs should ideally have previous experience with gene therapy trials and specialists who can promptly provide expertise in gene therapy research, education, and monitoring, including laboratory monitoring, to maximize the long-term benefits of gene therapies for patients.

- The comprehensive care hub centres and the haemophilia treatment spoke centres should manage adverse events to provide the most timely and current state-of-the-art treatment options to maximise long-term benefits.
- All adverse events should be logged into a centralised reporting scheme.
- In countries that have expert haemophilia comprehensive care centres but have not had clinical trials, education and knowledge transfer programs should be considered with locations that have had such clinical trial experience.



Countries like France, Ireland, Sweden, and the United Kingdom already have hub-and-spoke haemophilia structures in place pertaining to services like orthopaedic care, patients with inhibitors, or reference centres for von Willebrand Disease (VWD), remote patients or rare bleeding disorders.

The EHC-EAHAD recommended approach for gene therapy would be an extension of these types of already existing structure, with a greater emphasis on centre-to-centre communication in the pre-infusion and follow-up phases.

In The Netherlands and Germany there are national plans underway toward creating this structure for gene therapy.

For more information on this model, please see the:

- 2020 joint EHC-EAHAD position statement on 'promoting hub-and-spoke model(s) for the treatment of haemophilia and rare bleeding disorders using gene therapies⁶⁸.
- 2021 joint EAHAD-EHC publication on the 'delivery of AAV-based gene therapy through haemophilia centres – a need for re-evaluation of infrastructure and comprehensive care⁶⁹; and
- 2022 joint EAHAD-EHC publication on 'gene therapy of haemophilia: hub centres should be haemophilia centres⁷⁰.

Patient Organisations need to work with stakeholders on the structure for the delivery of gene therapy within the healthcare system.

This will involve discussions on how centres will coordinate between each other to ensure patient needs are met and that patients are aware of the pathway.

To assist you in discussions this document has provided a list of potential points for discussion with stakeholders on criteria for hubs, spokes and liaison required to ensure consistent care (see Appendix 1). These are not exhaustive and will vary from country to country.

National Engagement

In July 2022, the National Hemophilia Foundation (NHF) in the United States submitted a citizen's petition to the Food and

Drug Administration (FDA) about the pending approval of two gene therapy treatments⁷¹.

In the document ([click here](#) or see Appendix 2), the NHF requested the FDA make the creation of a risk evaluation and mitigation strategy (REMS) a condition for approving these gene therapies.

They also requested the FDA to include the eligibility (inclusion and exclusion) criteria used in the clinical trials on the drug label. The NHF-specific requests to the FDA were:

- Provide training and education for physicians and health care providers (HCPs) on gene therapy and the management of people with haemophilia who receive a gene therapy product.
- Provide training and education on SDM for physicians and HCPs who will evaluate, administer, and follow people with haemophilia who are candidates to receive a gene therapy product.
- Certify medical facilities administering gene therapies.
- Mandate that gene therapies are only to be administered at a federally recognized haemophilia treatment centre with knowledge and expertise in evaluating, administering, and managing people with haemophilia who have received investigational gene therapy products.
- Mandate that individuals receiving gene therapies should be enrolled in a registry to collect robust data, including on adverse events of interest.

The EHC has endorsed the NHF's rationale behind the REMS request for the US given the context of the American healthcare system. The NHF's request is in line with patients' interests.

In the European context, the REMS program is equivalent to the Risk Management Plan (RMP) which is mandated for all products centrally licensed in the EU since 2010.

This information is publicly available on the EMA webpage for each specific product, in conjunction with the Summary of Product Characteristics (SmPC) which outlines the license requirements.

The NHF request for designated centres is equivalent to the EAHAD-EHC joint recommendations on hub-and-spoke models.

The difference in this case is the US request would be a requirement within the license and would require discussions between the regulator and company to identify qualifying criteria and carry out assessments.

This approach is an option that the EMA could use, as they have in other gene and cell therapies in the past.

The EHC have taken the position that it is within a national competency to define the criteria, in collaboration with patients and clinicians, without specific qualification coming from the company.

It is prudent for Patient Organisations to read the NHF request and adapt it to national context, for delivery structures and define a national set of criteria for centres with the haemophilia network.

Other elements that are in place in Europe or should be established nationally, including the following:

Safety surveillance

In Europe, the EMA runs EudraVigilance a post-marketing surveillance system, which is the counterpart to the FDA Adverse Events Reporting System (FAERS)^{72,73}.

This system is fed with information from national medicines surveillance systems in which individuals can directly report any adverse event they experience.

In addition, the European Haemophilia Surveillance System (EUHASS) collects prospective adverse events for haemophilia and other rare bleeding disorders.

This system has been in place since 2008⁷⁴. EUHASS is part of the European Haemophilia Network (EUHANET) project, which has a Rapid Alert System enabling health professionals treating patients with haemophilia or other congenital bleeding disorders to be notified immediately in case of unexpected or serious adverse events⁷⁵.

This system is being updated to account for gene therapy-specific adverse event data collection.

Patient Organisations should work with clinicians to ensure that these systems are reported to appropriately and in a timely and efficient manner, as it is through this engagement early detection signals, if any, will be identified and addressed within the license.

A comprehensive care approach for delivering gene therapy in haemophilia

The comprehensive care model for managing people with haemophilia and other rare bleeding disorders is well established. It is enshrined in the European Principles of Care for Haemophilia⁷⁶.

The concept is a multidisciplinary approach to ensure a patient's needs are addressed by healthcare professionals with an understanding of the clinical challenges arising from the bleeding disorder.

Typically, the patient is followed by a haematologist who will liaise with other healthcare professionals (such as orthopaedic surgeons, physiotherapists, and specialized nurses, among others) to achieve optimal patient management and treatment outcomes.

As described above, patients thinking of embarking on gene therapy will need adequate information and psychological support from healthcare professionals and peers to decide whether to undergo gene therapy.

Patients who receive gene therapy will also need continued psychological support post-infusion to help with any mental hurdles they may face and to document any mental health impact of gene therapy, which may be useful in ongoing decision making.

Psychological support is one of the health care specialties that should be available in the haemophilia comprehensive care model – and it is an essential component of the decision-making pathway for gene therapy candidates.

However, from regular surveys^{76–78} on implementing the principles of care, this service is often missing or very difficult to access.

Patient Organisations should strongly encourage, in conjunction with their national clinicians, that this service is in place, accessible, and adequately funded to support, monitor, and follow up gene therapy patients.

A soon-to-be-validated gene therapy mental health assessment tool may be a useful addition to outcome measurements in this area⁷⁹.

Currently haemophilia treatment centres can seek certification through the EUHANET project⁷⁵.

However, the certification process is voluntary and based on information provided by the treatment centre itself.

Based on EHC surveys, this information does not always reflect the reality of patients seeking access to various medical services.

Talks are ongoing about auditing EUHANET certified centres by independent experts. If these occur, special attention should be given to centres dispensing gene therapy and following-up gene therapy patients to guarantee access to all the required support services for these patients, including psychological support.

International Collaborative Registry

The World Federation of Hemophilia (WFH), in collaboration with the International Society on Thrombosis and Hemostasis (ISTH), EHC, NHF, the American Thrombosis and Haemostasis Network (ATHN), industry developer partners, and regulatory liaisons, developed a global gene therapy registry⁸⁰.

This registry will use a core data set with input from a multi-stakeholder steering committee. Guidance from the FDA and EMA has informed the registry on specific data elements.

The gene therapy registry project aims to provide a core data set integrated into a robust, scientifically valid registry, available to all clinicians treating people with haemophilia who receive gene therapy.

The data stemming from this registry will provide robust surveillance of the safety and efficacy of gene therapy in both the short and the long term.

All stakeholders should recommend engagement with this registry to help answer old questions and identify new ones.

Patient Organisations should work with all stakeholders, align with the WFH Gene Therapy Registry for the overall improvement in the care and long-term monitoring of patients who have received gene therapy.

Adverse Event (AE) Reporting

Gene therapy and other novel agents will need consistent reporting practices than is currently in place for structures like EudraVigilance and EUHASS to identify potential early signals⁸¹.

For example, a health care professional reporting an adverse event can state "unrelated to drug X" and request that authorities do not contact them for further information.

This data is subsequently difficult to access in detail. This is a significant problem when assessing if an event is or is not an early safety signal. Clear, consistent, timely, and transparent reporting will be needed.

Recent lessons in the communication on adverse events in haemophilia and other areas have demonstrated not just the need for coordinated reporting of adverse events, but importantly, the need for clear, transparent, and timely communication of those directly to relevant patient organisations.

The speed of information through social media and the lack of ability at times to adequately distinguish between N=1, N=100 or N=1000 result in misinformation and misinterpretation of the treatment's actual risks and benefits, especially for gene therapies.

Patient Organisations in collaboration with healthcare professionals should provide adequate training and information to all those administering and following up gene therapy to identify protocols on reporting of events, related, suspected, or unrelated, to gene therapy.

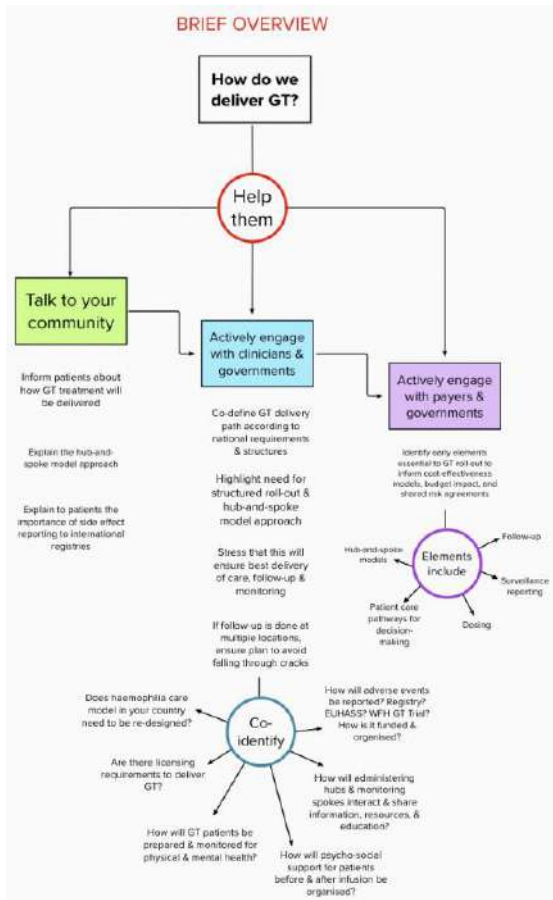
This will maximize awareness of the known concerns and respond in a timely manner for the unknown concerns.

Health Technology Assessment and reimbursement requirements

Many European Health Technology Assessment (HTA) bodies and reimbursement agencies may place strict limitations on specified centres that may deliver high-cost medications such as gene therapy⁸².

These agencies' structured requirements may help guide gene therapy's introduction nationally, and similar points to those listed above could be recommended by these agencies.

Patient Organisations should engage early in dialogue with Health Technology Assessment and reimbursement agencies to ensure that the appropriate approach for the delivery of gene therapy is indicated not just by the license but also the national structures on access to coalesce data collection, delivery and ensured value for all stakeholders.



and the formal involvement of the national haemophilia patient organisation in each country.

- Follow-up and monitoring of gene therapy patients by secondary centres where appropriate (for example, closer to patients' homes) as to maintain close communication with the primary prescribing centres.

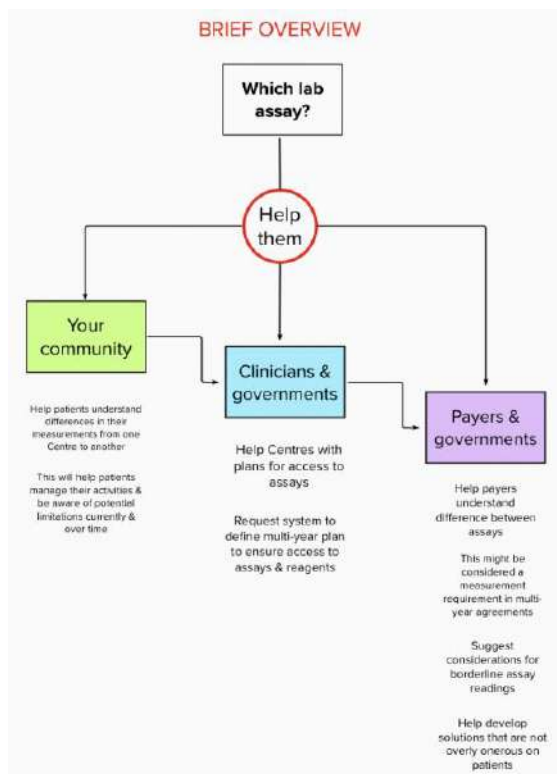
Although the US and European healthcare systems vary, patients' goals remain the same.

It is for this reason that in Europe, NMOs must work towards ensuring that, in a manner appropriate to each unique national or regional system, the same goals are met, namely the:

- Safe introduction, use, monitoring, and follow-up of first-generation gene therapies in the haemophilia population of the country.
- The prescription and management of haemophilia gene therapies exclusively by expert centres, which should be defined by each European country, with the active involvement of expert clinicians

What are the right laboratory assays to measure factor activity of gene therapy?

There is no simple answer to this question. Instead, it is important to be mindful that interpreting gene therapy trial data may be challenging for patients, clinicians, and payers.



This is because therapeutic response to gene therapy is assessed by measuring factor levels using a one-stage or chromogenic substrate assay.

The fundamental difference between these two assays is that the one-stage assay measures clotting time whereas the chromogenic assay quantifies clotting activity.

However, these assays are set up in different ways, so they show different limitations in estimating coagulation.

This means that either of them can overestimate or underestimate coagulation when the FVIII or FIX created by gene therapy is not identical to that typically found in people.

In haemophilia A gene therapy trials, the one-stage assay has consistently shown higher FVIII levels by ~1.6-fold because the FVIII produced by gene therapy is beta-domain deleted (BDD), which speeds up early activation of factor X but does not increase overall thrombin generation⁸. Hence, the chromogenic assay seems more reliable.

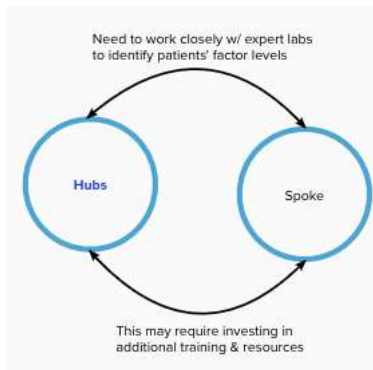
In haemophilia B gene therapy trials, we have seen more significant discrepancies (~2-fold), but these appear to be linked to FIX-Padua enhanced kinetics⁸³.

The assays were optimized for measuring standard half-life normal FVIII and FIX and clotting factor concentrates.

At the current state of the art, these uncertainties complicate the interpretation of trial results and should be kept foremost in mind when considering informing patients on their response, clinical reporting in trials, publications and congress reports, and potential contracting obligations by payers.

Patient organisations need to be aware of these issues for three reasons:

- *To ensure that the gene therapy dosing centres have access to both assays, that systems are in place to reduce differences between centres, and that data is collected consistently for reporting.*



- *Where a hub-and-spoke approach is used, and a patient may be measured with one assay at the hub and a different assay at the spoke. This awareness needs to be designed into the system when talking to patients to avoid confusion or concern. It may be important to know a gene therapy patient's day-to-day coagulation factor level, but for any surgeries or trauma it would be more prudent to base clinical decisions on a lower level. We will need to gain more clarity on this in the long term.*
- *Where contracting is based on factor levels, to ensure clear rules for consistent reporting with the same reagents in the long term, to avoid issues such as, for example, lack of ability to obtain rebates.*

Is it (economically) worth investing in gene therapy when other therapeutic options are available?

Now that a haemophilia gene therapy has been granted a conditional marketing authorisation, the discussion on price, value, cost-effectiveness, and budget impact will ensue come up quickly.

The reported net price of the first gene therapy for haemophilia A is a net cost of €1.5m.

While this is not the most expensive gene therapy on the market, we should consider whether a publicly stated price is a valid price.

In haemophilia gene therapy, the reimbursement decision will be less about price and more about mitigation of uncertainty using outcome based contractual agreements.

This section looks at two components of this population and the calculation of the Incremental Cost Effectiveness Ratio (ICER).

The eligible population for gene therapy in haemophilia may appear relatively well defined. However, the eligible population does not account for information on:

AAV neutralising antibodies in the patients choosing gene therapy,
Underlying conditions which may put patients at higher risk,
Patients' perceived success of current therapy regimens, and most importantly,
The personal choice of wanting gene therapy.

Patient organisations and clinicians will need to ensure more discussions within the haemophilia community to better quantify this in the coming years.

For health technology assessment (HTA) and reimbursement bodies, this population uncertainty puts the financial risk on the health care system and places the cost somewhere between zero (no uptake) to 5-10 times the current annual patient cost per year (in line with the 5-10 years of expected outcome).

To manage this type of uncertainty, payers would view that the costs per year should be approximately the same as the current annual cost of treatment, which is paid for over an extended period.

For example: if the current factor concentrate costs per year are €200,000 and the list price is €1m, then payers would pay €200,000 per year for five years.

Or if the current annual costs are €100,000, then payers could pay that amount over ten years.

This is an easy solution as, in the short term, it maintains budget neutrality for the payer and, in the long term, it may be potential cost saving. In addition, the company recovers the cost of their product.

An issue with this model may be the inability of certain countries to legally engage in and conclude these types of agreements.

In some countries, like France, lawmakers have requested legal changes to conclude such agreements.

Other countries may require special purpose vehicles or other novel mechanisms to be put in place.

Another problem with this model is the contract duration. The recent report of €1.5m net cost based on outcome-based contracts is an interesting price point².

With the likelihood that Germany will be the first launch country in Europe, this is

approximately 5 years the annual cost of factor concentrate prophylaxis.

With a contract duration of six to eight years at the top end, this is within the range discussed by payers.

However, what happens if the annual haemophilia treatment costs €100,000?

If the contract maximum is eight years and the current annual costs are fixed variables in the equation, a gap of €700,000 needs to be overcome in negotiations to get reimbursement.

This situation will be an issue, especially with the current lack of efficacy data over eight years, which means an even greater financial risk of uncertainty for the health care system.

Considering the current level of prophylactic treatment provided, the national net price should be a combination of upper-end contract duration and the annual prophylactic treatment costs as shown below:

Gene Therapy (GT) cost= (4-8 years) x (current national cost of factor or non-replacements)

The greater the difference between the national net price for gene therapy and a multiple of annual prophylactic costs beyond 8 years, the greater the delays in access we might expect.

Gene therapy can potentially reduce annual spending on patients with severe haemophilia.

The budgetary cost is lower in the short term as the evidence is relatively well understood. In the long term, the potential for savings is much higher, but with limited available evidence, the budgetary risk is

also much higher, so payers may aim to limit the exposure to the health system.

National or international groups will look at cost-effectiveness to inform this question.

The basic equation for this is the incremental cost-effectiveness ratio (ICER) below:

$$ICER = \frac{Cost\ New\ Therapy - Cost\ Old\ Therapy}{Effect\ New\ Therapy - Effect\ Old\ Therapy}$$

Effects

Cost-effectiveness analysis can include several effects.

Four are factor expression, joint health, infusion rate, and the disease-specific or generic health-related quality of life questionnaires. These can significantly benefit the patient's understanding of the differences between therapies and may help make an informed decision.

These effects should be included in the cost-effectiveness model, and HTA bodies should put them into their reports as information for patients and clinicians.

There are measurable effects for gene therapy patients, but it can be challenging to determine the level of evidence acceptable to be included in these models and, in addition, payers do not often understand outputs like these appropriately.

The effects, with enough evidence (annual bleed rates and EQ-5D), may show little difference especially compared to rising standards of care.

As a result, the difference in effects is likely to be minor, and the certainty around each number with current evidence is problematic, as shown by the ICER report on haemophilia gene therapy in haemophilia A⁸⁴.

Costs

A cost-effectiveness model is based on a point in time, so the starting annual costs of factor or non-factor therapy are fixed and decrease over time using discounting.

The annual cost per adult patient can have a wide cost range. From a heavier patient with a low half-life to a lighter one with a long half-life or a patient with limited capacity for prophylaxis, this gives a relatively wide range of costs on the current standard of care.

The gene therapy cost element of the equation is easy to calculate because gene therapy is a fixed cost.

However, independently of an individual's gene therapy response, the equation must include the potential for treatment failure or lack of efficacy.

As described above, there is currently no way to predict individual gene therapy responses.

Therefore, the potential for any individual (heavy or light, higher or lower dose achieved, good or poor venous access) must be calculated into the model, leading to a higher degree of uncertainty, not because of the efficacy of gene therapy, but because of the unknown cost risk in the event of no or partial response.

Companies worked with payers to implement rules to reduce the uncertainty of a new therapy cost, such as gene therapy, to account for these uncertainties.

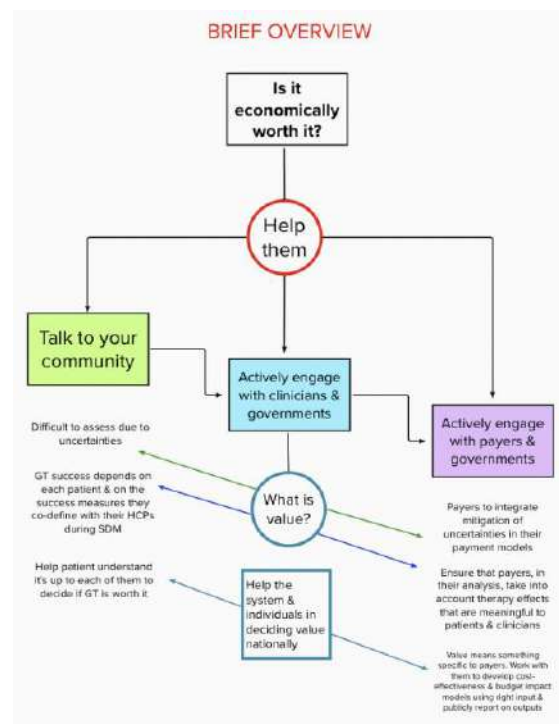
The 'no response=no payment rules' were used for pricing CAR-T therapies.

The same could be implemented in haemophilia gene therapies. A partial response could get a reduced payment, for example, in the event of a reduction in factor expression or an increase in treatment consumption.

Gene therapies in haemophilia can improve care and potentially generate significant savings for the healthcare system.

Undoubtedly, there is a high degree of uncertainty around aspects of the population, efficacy, and cost.

However, Patient Organisations with early dialogue, good risk planning, stakeholder collaboration, and funded data collection, can readily manage these uncertainties in the short and long term, creating the certainty that those with severe haemophilia can achieve a spontaneous life.



How do we pay for gene therapy?

There are several challenges in ensuring haemophilia gene therapies are accessible, including financial challenges such as payment timing and affordability, therapeutic performance risk, and actuarial risk⁸⁵.

We expect these challenges to be met differently across the health care system and disease areas.



GT-dosed patients should pay attention to this aspect & be aware that honouring follow-up visits, tests & exams will help build a stronger case for making GT more widely available

We should tailor proposed financial solutions to create a 'precision financing' approach.

Potential financial solutions include options such as one-off payments, subscription payments, leasing/warranty models, annual payments, or performance-based payments. Each provides different benefits in ease of administration, short/long term budget impact, population size, data sharing requirements, and their response to risk sharing for uncertainty.

One-off payments have significant merit in ease of administration and minimal data sharing requirements but have a significant budget impact and do not account for uncertainty or provide a risk-sharing

arrangement for cases of sub-optimal outcomes.

Also, the one-off payment approach limits access to gene therapy as the budget impact will limit the number of candidates treated annually.

Subscription models work very well, as demonstrated in the hepatitis C space. The more people receive the treatment, the cheaper it becomes.

However, in this model tangible benefits come with a large population and ability/need for re-treatment, which is not currently possible in haemophilia.

The leasing/warranty model has the potential of buying a gene therapy, and if it does not work, the company provides factor or non-factor replacement therapy for the same annual amount.

Key disadvantages are higher prices for security and loss of discretion in choosing replacement therapies or a company being unable to provide such an approach as they do not have a licensed replacement/non-replacement product for the condition.

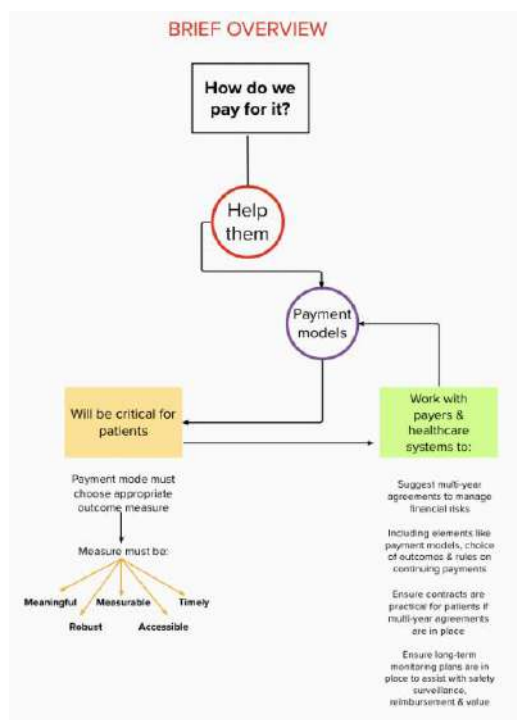
Performance-based payments require significant monitoring and data sharing.

Another important aspect of multiyear payment models is choosing the appropriate outcome measures.

The metrics should be⁸⁶:

- **Meaningful:** The outcomes matter to the patient or strongly correlate to overall treatment effectiveness.
- **Measurable:** The outcomes are measurable and offer clear and unambiguous results.
- **Timely:** The outcomes are highly likely to happen during the contract duration.

- **Robust:** The outcomes should reduce insensitivity to potential biases, such as patient selection, interpretation of test results, availability of test results, and other confounding variables.
- **Accessible:** The outcomes should be accessible to both parties at no and or low cost, and the metric should be in structured data rather than free text.



A set of core measurable outcomes has been developed for haemophilia gene therapy, including annual reduction in factor use, breakthrough bleeding rates (although definitions of a bleed have a significant subjective component), and circulating factor levels⁸⁷.

There are inter-individual differences in bleeding risk based on activity level, bleeding phenotype, personal definitions of a bleed on a background of joint damage, making it difficult on an individual, but not population level to provide reliable data on the performance criteria.

Factor activity levels are an important option over time, which can be used as a performance

criterion. However, factor activity levels have shown to vary in repeated measurements on individuals during clinical trials^{7,8}.

Quality of life and joint scores such as the Hemophilia Joint Health Score (HJHS) are also essential measurable long-term outcomes for a population if performed in a uniform way⁸⁸⁻⁹⁰. These can be difficult to incorporate into models for reimbursement in the near term due to the long duration required to measure benefits⁹¹.

The need for consistency and uniformity when assessing efficacy and durability of different gene therapy treatments is essential.

Working from common outcome sets, such as CoreHEM and incorporating these into a global registry collecting post-marketing data on individuals who undergo gene therapy, is critical to provide uniform data on reliability, efficacy, durability, and most importantly, safety if these therapies are to provide value to the system.

Finally, there are several other considerations such as, but not limited to, death, liver failure, loss to follow-up, patient mobility and alcohol use that could require a risk mitigation plan for clarity of all parties involved.

When choosing outcome measures, payers need to consider other aspects, such as if the aim is to use a defined factor level, then with what assay and what reagents, and demand an independent adjunction plan in the event of disagreement.

The elements of these types of agreements should not be discussed just with hospital or national contracting bodies. These conversations need to involve clinicians and patient organisations so that the burden of the data collection is practical and expectations for payers, patients, and the health system are win-win-win.

Conclusions & recommended actions

Gene Therapy offers additional and new challenges as a one-off irreversible therapeutic option for patients with haemophilia.

This document has outlined the issues that need addressing, the plans that need to be made, and the stakeholders that need to be involved.

Patient Organisations will have to deal with these questions and there is no simple answer. This will take time and engagement with all stakeholders to work through.

We strongly encourage our NMOs to plan and prepare to play a strong role in the coming months to help navigate their members, community, and health systems through this.

We believe that NMOs must be active in this area because:

- At a community level, no gene therapy journey should not be undergone alone. Individual patients – and their families and caregivers – will need help, guidance, and support from their Patient Organisations. NMOs play a strong role in the education of people with haemophilia, in providing information on all aspects of the therapies, in testing understanding and comprehension via workshops or other suitable interactions, and in working closely with clinicians and hub-and-spoke centres to ensure that patients enter into these momentous personal decisions well prepared with knowledge, an understanding of the benefits, risks and uncertainties, and a clear understanding and commitment to the follow-up and monitoring required.
- At an organisational level, advance therapies such as this one will shape the future of haemophilia care in their countries. Patient organisations need to collaborate with all stakeholders and put plans in place to ensure that the value of gene therapy achieves its potential benefits.
- At a political level, this is the moment to ensure full commitment to shared decision-making. Irrespective of the therapy chosen, SDM can change the culture of the patient-clinician relationship and transform it into a partnership rather than a one-way flow of directing or prescribing.
- At a stakeholder level, the current EMA approval is *conditional* meaning that the community plays an important role in affecting the future of this therapy.

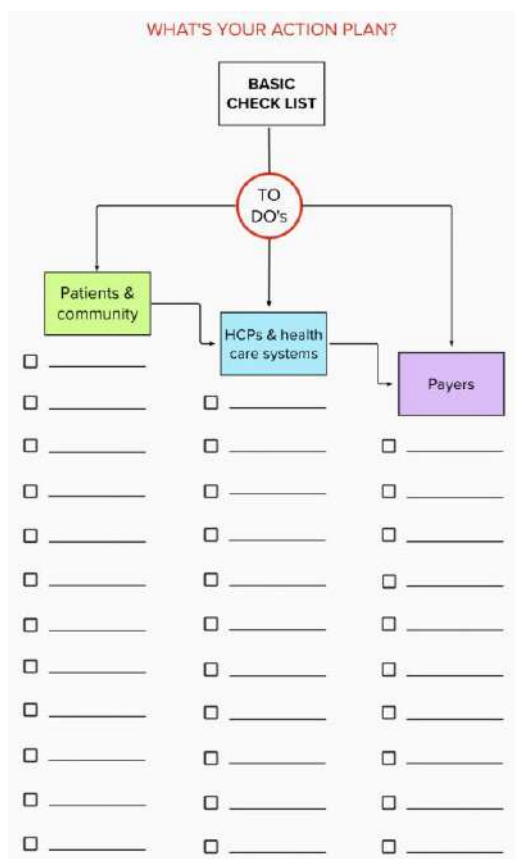
Crucially, it will be up to Patient Organisations to make their voices heard and ensure due diligence in the development process of national gene therapy pathways.

Compared to other geographies, Europe has several important elements already in place which can help the provision of gene therapy in haemophilia:

- Increasing recognition and development of shared decision-making models within national health systems,
- Strong European network of haemophilia centres with further development of the hub-and-spoke model,
- Good collaboration between clinicians and patient organisations at national and international level,
- EUHASS and EudraVigilance capacity for surveillance,
- WFH Gene Therapy Registry with core outcomes already identified, and
- Adapted structures in payment models for gene therapy.

European NMOs can build on this foundation, bring to bear their decades of advocacy and partnership experience, and their detailed knowledge of developments in haemophilia therapy, to add weight to their recommendations and proposals with all stakeholders.

It is vital that Patient Organisations engage fully on these issues at this time in our history, to ensure that the future tide of haemophilia treatment develops in line with patients' interests, and that the European patient voice remains impactful for decades to come.



References

1. Committee for Medicinal Products for Human Use Committee for Medicinal Products for Human Use. Roctavian: Pending EC decision | European Medicines Agency. *Eur Med Agency*.
2. Biomarin. First Gene Therapy for Adults with Severe Hemophilia A, BioMarin's ROCTAVIAN™ (valoctocogene roxaparvovec), Approved by European Commission (EC) - Aug 24, 2022.
3. CSL Behring. EMA Commences Review of Novel Gene Therapy Candidate EtranaDez for People with Hemophilia B. <https://www.cslbehring.com/newsroom/2022/ema-commences-review-of-novel-gene-therapy-candidate-etranadez-for-people-with-hemophilia-b>, Accessed 09/09/2022
4. Novel Treatment Products Newsletter. *European Haemophilia Consortium*, <https://www.ehc.eu/novel-treatment-products-newsletter/>, Accessed 09/09/2022
5. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26(S6):1-158.
6. Pierce GF. Uncertainty in an era of transformative therapy for haemophilia: Addressing the unknowns. *Haemophilia*. 2020;27(S3):hae.14023.
7. 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):2215-27.
8. Rangarajan S, Walsh L, Lester W, et al. AAV5–Factor VIII Gene Transfer in Severe Hemophilia A. *N Engl J Med*. 2017;377(26):2519-30.
9. Weyand AC, Pipe SW. New therapies for hemophilia. *Blood*. 2019;133(5):389-98.
10. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet*. 2021;397(10274):630-40.
11. Ling G, Nathwani AC, Tuddenham EGD. Recent advances in developing specific therapies for haemophilia. *Br J Haematol*. 2018;181(2):161-72.
12. Pedra G, Christoffersen P, Khair K, et al. The impact of factor infusion frequency on health-related quality of life in people with haemophilia. *J Haemoph Pract*. 2020;7(1):102-9.
13. Jiménez-Yuste V, Auerswald G, Benson G, et al. Achieving and maintaining an optimal trough level for prophylaxis in haemophilia: the past, the present and the future. *Blood Transfus*. 2014;12(3):314-19.
14. Lenting PJ. Laboratory monitoring of hemophilia A treatments: new challenges. *Blood Adv*. 2020;4(9):2111-18.
15. Schmitt C, Emrich T, Chebon S, et al. Low immunogenicity of emicizumab in persons with haemophilia A. *Haemophilia*. 2021;27(6):984-92.
16. Paz-Priel I, Chang T, Asikanius E, et al. Immunogenicity of Emicizumab in People with Hemophilia A (PwHA): Results from the HAVEN 1-4 Studies. *Blood*. 2018;132(Supplement 1):633-633.
17. Manco-Johnson M, Briones N, Tran A, Thornhill D, Baird C, Jacobson L, Warren B, Kuldaneck S, Ambruso D KG. Emicizumab: Will it Suffice for Bone Metabolism? [abstract]. *Res Pr Thromb Haemost*. 2021;5(2).
18. Martin AP, Burke T, Asghar S, et al. Understanding minimum and ideal factor levels for participation in physical activities by people with haemophilia: An expert elicitation exercise. *Haemophilia*. 2020;26(4):711-17.

19. Dover S, Blanchette VS, Wrathall D, et al. Hemophilia prophylaxis adherence and bleeding using a tailored, frequency-escalated approach: The Canadian Hemophilia Primary Prophylaxis Study. *Res Pract Thromb Haemost.* 2020;4(2):318-25.
20. Mizrahi T, St-Louis J, Young NL, et al. Adherence to treatment regimen and bleeding rates in a prospective cohort of youth and young adults on low-dose daily prophylaxis for severe hemophilia A. *BMC Hematol.* 2016;16(1):26.
21. Thornburg C, Duncan N. Treatment adherence in hemophilia. *Patient Prefer Adherence.* 2017; Volume 11:1677-86.
22. Josefson D. Breaks from antiretroviral treatment are not the answer for HIV patients. *BMJ.* 2003;6(327):7414.
23. HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients - Full Text View - ClinicalTrials.gov.
24. Gene Therapy Study in Severe Haemophilia A Patients (270-201) - Full Text View - ClinicalTrials.gov.
25. Ragni V, Majerus E, Giermasz A, Fong S, Yates B, Scheeler, Razon B, Liu S, Yu H, Reddy DB, Robinson M. Valoctocogene roxaparvec gene transfer in participants with HIV. *Haemophilia.* 2022;28(Suppl 1):101 (PO146).
26. Male C, Andersson NG, Rafowicz A, et al. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: a PedNet study. *Haematologica.* 2020;106(1):123-29.
27. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia.* 2003;9(4):418-35.
28. Klamroth R, Hayes G, Andreeva T, et al. Global Seroprevalence of Pre-existing Immunity Against AAV5 and Other AAV Serotypes in People with Hemophilia A. *Hum Gene Ther.* 2022;33(7-8):432-41.
29. Rajavel K, Ayash-Rashkovsky M, Tang Y, et al. Co-Prevalence of Pre-Existing Immunity to Different Serotypes of Adeno-Associated Virus (AAV) in Adults with Hemophilia. *Blood.* 2019;134(Supplement_1):3349-3349.
30. CSL Behring. Final Analysis of Pivotal HOPE-B Study Demonstrates Durable and Sustained Therapeutic Effect of Etranacogene Dezaparvec Gene Therapy in Hemophilia B – Data Presented at EAHAD 2022. 2022.
31. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvec Gene Therapy for Hemophilia A. *N Engl J Med.* 2022;386(11):1013-25.
32. Pipe SW. First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing. In: 62nd ASH Annual Meeting, Late-Breaking Abstracts, LBA-6. American Society of Hematology; 2020.
33. Peyvandi F, Kreuth V: European consensus proposals for treatment of haemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies. *Haemophilia.* 2020; In press.
34. Den Uijl IEM, Fischer K, Van Der Bom JG, et al. Analysis of low frequency bleeding data: The association of joint bleeds according to baseline FVIII activity levels. *Haemophilia.* 2011;17(1):41-44.
35. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood.* 2015;125(13):2038-44.
36. Chowdary P, Shapiro S, Davidoff AM, et al. A Single Intravenous Infusion of FLT180a Results in Factor IX Activity Levels of More Than 40% and Has the Potential to Provide a Functional Cure

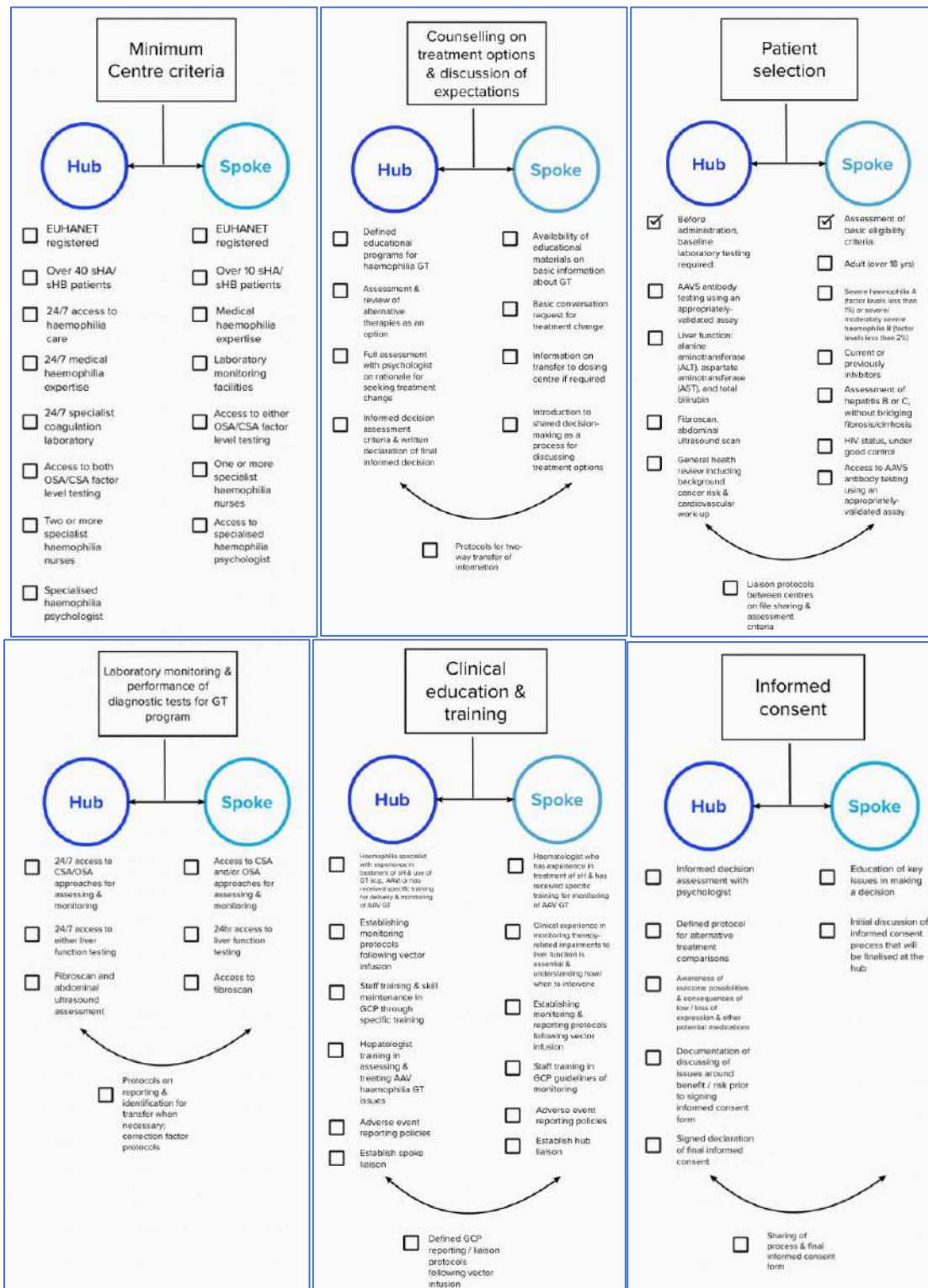
- for Patients with Haemophilia B. *Blood*. 2018;132(Supplement 1):631-631.
37. Chowdary P, Shapiro S, Makris M, Evans G, Boyce S, Talks K, Dolan G, Reiss U, Phillips M, Riddell A, Peralta MR, Quaye M, Tuddenham E, Krop J, Short G, Kar AS, Nathwani AA, Novel Adeno Associated Virus (AAV) Gene Therapy (FLT180a) Achieves Normal FIX Activity Levels in Severe Hemophilia B (HB) Patients (B-AMAZE Study). *Res Pr Thromb Haemost*. 2021;5(Suppl 2).
 38. Mahlangu JN. Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe haemophilia A: Results from the GENER8-1 two-year analysis. In: EAHAD Oral Presentation. ; 2022.
 39. Nathwani AC. Gene therapy for hemophilia. *Hematology*. 2019;2019(1):1-8.
 40. European Medicines Agency. First gene therapy to treat severe haemophilia A. 2022. <https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia>, Accessed 09/09/2022
 41. European Medicines Agency. EMA finds no evidence linking viral vector in Zynteglo to blood cancer 2021. <https://www.ema.europa.eu/en/news/ema-finds-no-evidence-linking-viral-vector-zynteglo-blood-cancer>. Accessed 09/09/2022
 42. W Pipe S, Leebeek FW, Recht M, S Key N, Lattimore S, Castaman G, K Sawyer E, Verweij S, Colletta V, Cooper D, Dolmetsch R, Miesbach W, W Pipe S, Leebeek FW, Recht M, S Key N, Lattimore S, Castaman G, K Sawyer E, Verweij S, Colletta V, Cooper D, Dolmetsch MW. 52 Week Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderate-severe Hemophilia B: Data from the Phase 3 HOPE-B Gene Therapy. *Res Pr Thromb Haemost*. 2021;5((Suppl 2)).
 43. Fletcher S, Jenner K, Pembroke L, et al. The experiences of people with haemophilia and their families of gene therapy in a clinical trial setting: regaining control, the Exigency study. *Orphanet J Rare Dis*. 2022;17(1):155.
 44. Grimm D, Büning H. Small But Increasingly Mighty: Latest Advances in AAV Vector Research, Design, and Evolution. *Hum Gene Ther*. 2017;28(11):1075-86.
 45. Batty P, Lillicrap D. Hemophilia Gene Therapy: Approaching the First Licensed Product. *HemaSphere*. 2021;5(3):e540.
 46. Batty P, Fong S, Franco M, Gil-Farina I, Mo AM, Harpell L, Hough C, Hurlbut D, Pender A, Sardo Infirri S, Winterborn A, Schmidt M LD. Frequency, Location and Nature of AAV Vector Insertions After Long-Term Follow up of FVIII Transgene Delivery in a Hemophilia A Dog Model [abstract]. *Res Pr Thromb Haemost*. 2020;4((Suppl 1)).
 47. Nguyen GN, Everett JK, Kafle S, et al. A long-term study of AAV gene therapy in dogs with hemophilia A identifies clonal expansions of transduced liver cells. *Nat Biotechnol*. 2021;39(1):47-55.
 48. M. Schmidt, G.R Foster, M. Coppens, H. Thomsen, D. Cooper, R. Dolmetsch, E.K Sawyer, L. Heijink S. P. Liver Safety Case Report from the Phase 3 HOPE-B Gene Therapy Trial in Adults with Hemophilia B. In: ISTH Congress, OC67.4.; 2021.
 49. 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):763-74.
 50. BioMarin announced an additional serious adverse event in its gene therapy clinical trial for haemophilia A, European Haemophilia Consortium Statement, <https://www.ehc.eu/biomarin-announced-an-additional-serious-adverse-event-in-its-gene-therapy-clinical-trial-for-haemophilia-a/>, Accessed 15/09/2022
 51. Gene, Cell, & RNA Therapy Landscape, Q1 Report.; 2021. <https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx>, Accessed 09/09/2022
 52. First gene therapy to treat severe haemophilia A | European Medicines Agency.

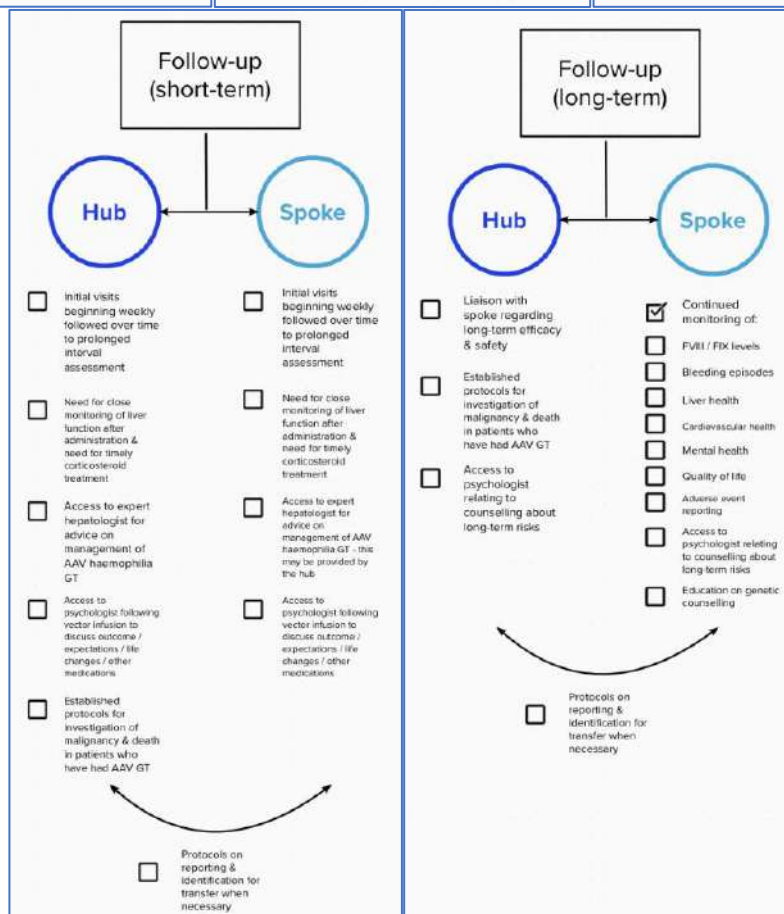
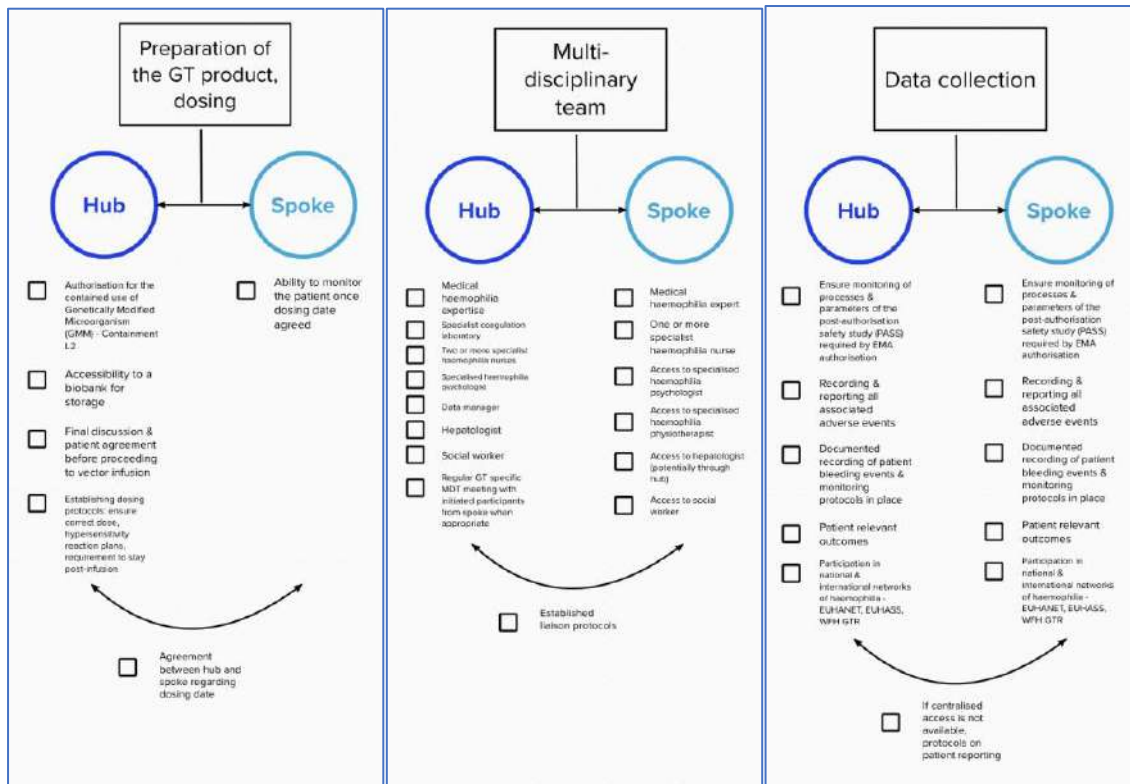
- <https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia>,
Accessed 09/09/2022
53. European Medicines Agency. Conditional marketing authorisation. <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation>. Accessed 09/09/2022
 54. Pipe SW. Delivering on the promise of gene therapy for haemophilia. *Haemophilia*. 2021;27(S3):114-21.
 55. Woollard L, Gorman R, Rosenfelt DJ. Addressing patient education priorities in the era of gene therapy for haemophilia: Towards evidence-informed shared decision-making. *Haemophilia*. 2021;27(2).
 56. 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; Volume 16:1439-47.
 57. LA Valentino, V Blanchette, C Negrier, B O'Mahony, V Bias, T Sannié MW Skinner, et al. Personalising haemophilia management with shared decision making. *J Haemoph Pract*. 2021;8(1):69-79.
 58. Miesbach W, O'Mahony B, Key NS, et al. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. May 2019; hae.13769.
 59. Nossair F, Thornburg CD. The role of patient and healthcare professionals in the era of new hemophilia treatments in developed and developing countries. *Ther Adv Hematol*. 2018;9(8):239-49.
 60. O'Mahony B, Mahlangu J, Peerlinck K, et al. Health-Related Quality of Life Following Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A in the Phase 3 Trial GENE8-1. *Blood*. 2021;138(Supplement 1):4916-4916.
 61. R. Itzler, J. Miller, R. Robson PM and SP. Improvements in Health-Related Quality of Life in Adults with Severe or Moderately Severe Hemophilia B After Receiving Etranacogene Dezaparvovec Gene Therapy. In: ISTH Congress; OC01.2. ; 2022.
 62. Bravo P, Härter M, McCaffery K, et al. Editorial: 20 years after the start of international Shared Decision-Making activities: Is it time to celebrate? Probably.... *Z Evid Fortbild Qual Gesundheitswes*. 2022;171:1-4.
 63. Shared Decision Making: NICE Guideline [NG197].; 2021.
 64. Agency for Healthcare Quality. The SHARE Approach—Essential Steps of Shared Decision making: Quick Reference Guide. 2014.
 65. Moumjid N, Durand M-A, Carretier J, et al. Implementation of shared decision-making and patient-centered care in France: Towards a wider uptake in 2022. *Z Evid Fortbild Qual Gesundheitswes*. 2022;171:42-48.
 66. Coulter A. WHO Policy Brief: Where Are the Patients in Decision-Making about Their Own Care?; 2008.
 67. Athale A, Giguere A, Barbara A, et al. Developing a two-sided intervention to facilitate shared decision-making in haemophilia: decision boxes for clinicians and patient decision aids for patients. *Haemophilia*. 2014;20(6):800-806.
 68. EAHAD – EHC Statement on Gene Therapies Hub-and-Spoke Model – EAHAD.
 69. 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):967-73.
 70. Miesbach W, Baghaei F, Boban A, et al. Gene therapy of hemophilia: Hub centres should be haemophilia centres: A joint publication of EAHAD and EHC. *Haemophilia*. 2022;28(3).
 71. National Hemophilia Foundation. National Hemophilia Foundation Requests Risk Evaluation

- and Mitigation Strategy for Pending Gene Therapy Treatments.2022.
72. FDA Adverse Events Reporting System (FAERS). <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>, Accessed 09/09/2022
 73. Eudra/Vigilance - European Database of suspected adverse drug reaction reports. <https://www.adrreports.eu>. Accessed 09/09/2022
 74. Calizzani G, Lassila R, Hay CRM, et al. EUHASS: The European Haemophilia Safety Surveillance system. *Thromb Res.* 2010;127:S22-25.
 75. Makris M, Calizzani G, Fischer K, et al. The European Haemophilia Network (EUHANET). *Blood Transfus.* 2014;12 Suppl 3(Suppl 3): s515-8.
 76. Noone D, O'Mahony B, Peyvendi F, et al. Evolution of Haemophilia Care in Europe: 10 years of the principles of care. *Orphanet J Rare Dis.* 2020;
 77. O'Mahony B, Noone D, Giangrande PLF, et al. Haemophilia care in Europe: A survey of 19 countries. *Haemophilia.* 2011;17(1).
 78. O'Mahony B, Noone D, Giangrande PLFLF, et al. Haemophilia care in Europe - a survey of 35 countries. *Haemophilia.* 2013;19(4).
 79. E. Clearfield, H.-Y. Chang, T. Majid MWS. Responses to Anxiety and Depression Items in People with Hemophilia who Tested a Patient Reported Outcome Measure: The coreHEM MH Study. In: ISTH Congress; PB0662. ; 2022.
 80. Konkle BA, Coffin D, Pierce GF, et al. World Federation of Hemophilia Gene Therapy Registry. *Haemophilia.* 2020;26(4):563-64.
 81. Peyvandi F, Garagiola I, Mannucci PM. Post-authorization pharmacovigilance for hemophilia in Europe and the USA: Independence and transparency are keys. *Blood Rev.* 2021;49:100828.
 82. Eurordis. Rare Impact.2022. <https://rareimpact.eu/>, Accessed 09/09/2022
 83. Robinson M, George LA, Samelson-Jones BJ, et al. Activity of a FIX-Padua Transgene Product in Commonly Used FIX:C One-Stage and Chromogenic Assay Systems Following PF-06838435 (SPK-9001) Gene Delivery. *Blood.* 2018;132(Supplement 1):2198-2198.
 84. Hemophilia A Update: Evidence Report.
 85. Goodman C, Berntorp E, Wong O. Alternative payment models for durable and potentially curative therapies: The case of gene therapy for haemophilia A. *Haemophilia.* 2022;28(S2):27-34.
 86. Precision Financing Solutions for Durable / Potentially Curative Therapies (White Paper).; 2019.
 87. 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(4): e167-72.
 88. O'Mahony B, Dolan G, Nugent D, et al. Patient-centred value framework for haemophilia. *Haemophilia.* 2018;24(6):873-79.
 89. Skinner MW, Nugent D, Wilton P, et al. Achieving the unimaginable: Health equity in haemophilia. *Haemophilia.* 2019;26(July):1-8.
 90. Osooli M, Steen Carlsson K, Baghaei F, et al. The association between health utility and joint status among people with severe haemophilia A: findings from the KAPPA register. *Haemophilia.* 2017;23(3): e180-87.
 91. Beeton K, DE Kleijn P, Hilliard P, et al. Recent developments in clinimetric instruments. *Haemophilia.* 2006;12(s3):102-7.

Appendix 1

Discussion points on hub-and-spoke criteria (non-exhaustive check list)







Appendix 2

NHF Citizen's Petition Letter to the national regulator (FDA)

(see next page)



NATIONAL HEMOPHILIA FOUNDATION

for all bleeding disorders

July 1, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam,

The National Hemophilia Foundation (NHF) respectfully submits this Citizen Petition pursuant to 21 U.S.C. §§ 10.25 and 10.30 to request that if it approves the products, the U.S. Food and Drug Administration (FDA) require a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval for both valoctocogene roxaparvovec, a BioMarin investigational gene therapy under regulatory review for the treatment of severe hemophilia A, and etranacogene dezaparvovec, a CSL Behring investigational gene therapy currently under review for the treatment of hemophilia B. NHF is the nation's leading advocacy organization working to ensure that individuals affected by hemophilia and related inherited blood disorders have timely access to high quality medical care and services and safe and effective products to treat their disease, regardless of financial circumstances or place of residence.

About Hemophilia

Hemophilia is a rare, chronic blood disorder affecting approximately 35,000 males in the US. There are also similar inherited bleeding disorders, such as von Willebrand disease (VWD), that affect an estimated three million Americans, the majority of whom remain undiagnosed and without care, leading to excessive healthcare expenditures, morbidity, and mortality. Others are affected by rare factor deficiencies or inherited platelet disorders. Currently, hemophilia treatments involve patients infusing high-cost clotting factor therapies to replace missing or deficient blood proteins or, in the case of coagulation factor VIII deficiency, injection of a monoclonal antibody to replace the deficient clotting factor activity. It is an exciting time for the hemophilia community, with gene therapy products on the horizon.

Most people with hemophilia receive care at the national network of hemophilia treatment centers (HTCs). Since 1974, Congress has authorized and funded the hemophilia program at the Health Resources and Services Administration (HRSA). HTCs, authorized under section 501(a)(2) of the Social Security Act, deliver integrated, patient-centered care, reduce morbidity and mortality, and lower overall healthcare costs associated with this patient population. Studies have consistently demonstrated the value of the HTC network at improving patient outcomes. For example, a recent study from 2019 found that there was 47.1% lower frequency of emergency department use among patients being cared for at an HTC compared to patients cared for outside of the HTC network, and that HTC patients are 30% more likely to be treated with prophylaxis, the current standard of care.ⁱ In 2020, the CDC published a Mortality and Morbidity Weekly Review article with an evaluation of the history of the HTC program.ⁱⁱ There is a growing need for more specialized clinical care as spelled out in a recent publication, Integrated Hemophilia Patient Care via a National Network of Care Centers in the United States: A Model for Rare Coagulation Disorders.ⁱⁱⁱ

Action Requested

NHF respectfully urges that the FDA:

1. **Require a REMS as a condition of approving valoctocogene roxaparvovec and etranacogene dezaparvovec.**
2. **Include the eligibility (inclusion and exclusion) criteria utilized in the clinical trials on the drug label.**

Statement of Grounds

FDA should require a REMS as a condition of approving valoctocogene roxaparvovec and etranacogene dezaparvovec. Specifically, the REMS should include Elements to Assure Safe Use (ETASU) that include the following elements:

1. Training and education for physicians and health care providers (HCPs) on gene therapy and the management of people with hemophilia who receive a gene therapy product.
2. Training and education on shared decision making for physicians and HCPs who will evaluate, administer, and follow people with hemophilia who are candidates to receive a gene therapy product.
3. Facilities administering valoctocogene roxaparvovec and etranacogene dezaparvovec must be certified.
4. Valoctocogene roxaparvovec and etranacogene dezaparvovec are only to be administered at a federally recognized hemophilia treatment center with knowledge and expertise in evaluating, administering, and managing people with hemophilia who have received investigational gene therapy products.
5. Individuals receiving valoctocogene roxaparvovec and etranacogene dezaparvovec be enrolled in a registry in order to collect robust data, including on adverse events of interest.

The Federal Food, Drug, and Cosmetic Act authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (21 U.S.C. § 355-1(a)). In making this determination, FDA is required to consider six factors. The discussion below lays out the six factor and how they apply to both products.

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

Both known and unknown adverse events exist. Steroid use should be an outcome of interest, given the reported required use of glucocorticoids in the two-year data analysis for valoctocogene roxaparvovec (79.1% of participants received steroids for a median treatment duration of 230 days), and the high proportion of related adverse events.^{iv} Additionally, recent events with adeno-associated virus (AAV) therapy including thromboses, requirement for prophylactic anticoagulant treatment, as well as three reports of cancer (deemed unrelated to the vector) highlight the many unknowns.^v Lastly, NHF directs the FDA to the coreHEM core outcome set for an updated list of adverse events of interest within gene therapy. These are grouped in three domains: short-term adverse events (liver toxicity, short term immune response to FVIII/FIX, immune response to gene therapy, thrombosis), long-term adverse events (development of other disorders, vector integration into host genome, duration of vector-neutralizing response) and mortality.^{vi}

2. The expected benefit of the drug with respect to the disease or condition;

The goal is for each treatment to be a one-time therapy that relieves patients from the treatment burdens of ongoing prophylaxis and/or factor VIII trough levels that place them at significant risk of bleeding when their circulating FVIII activity level drops below a therapeutic level. However, the gene therapy requires rigorous adherence to a demanding follow-up regimen, which includes significant lifestyle modifications including abstinence from alcohol ingestion and use of barrier contraception. Currently, the efficacy data demonstrates similar impacts on bleeding rates compared to factor replacement therapy in adherent individuals.

3. The seriousness of the disease or condition that is to be treated with the drug;

Hemophilia is a life-long inheritable bleeding disorder due to the deficiency of the activity of coagulation factor VIII (hemophilia A) or IX (hemophilia B). The life expectancy for people with hemophilia has dramatically improved over the past five decades due to the combination of the availability of integrated comprehensive care delivered by a network of care centers and therapeutic drug innovations. Without treatment, people with hemophilia can bleed internally, sometimes as a result of trauma, but sometimes simply from everyday activities. This bleeding can lead to severe joint damage and permanent disability, or can even lead to death, if a bleed involves major organs and/or the brain.

Individuals living with hemophilia have complex, lifelong medical needs. They depend on the ongoing use of prescription biologic medications (clotting factor or other novel therapies) to avoid and/or treat painful bleeding episodes, that if left untreated, could lead to permanent joint damage and debilitating lifelong pain, and as mentioned above, even death. These biologic medications, derived from human blood plasma or created by recombinant technology, are highly effective, but extremely expensive. Since there are no less expensive generic or biosimilar equivalents, the annual cost can exceed several hundred thousand dollars annually.

4. Whether the drug is a new molecular entity;

As set forth by FDA, a new chemical entity (NCE) is “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act (21 CFR 314.108(a)). Under this definition, both valoctocogene roxaparvovec, a BioMarin investigational gene therapy under regulatory review for the treatment of severe hemophilia A, and etranacogene dezaparvovec, a CSL Behring investigational gene therapy currently under review for the treatment of hemophilia B, should both be considered a new chemical entity.

The durability of effect on factor activity levels and/or annualized bleed rates of valoctocogene roxaparvovec and etranacogene dezaparvovec is unknown. We do know, however, that AAV gene therapy can be administered only a single time. At this time, the immune response will preclude re-administration of any other currently identified AAV vectors. At present, no solution exists for this problem, meaning that if a patient gets a suboptimal response or loses activity over a comparatively short period, they have lost their opportunity for subsequent AAV gene therapy.^{vii} In that respect, the duration of the effects of the treatment are lifelong.

5. The estimated size of the population likely to use the drug.

Finally, approximately 35,000 males in the U.S. have hemophilia A and B with approximately one-fifth of that number having hemophilia B. Clinical trials have imposed exclusionary criteria that reduce the eligible population – such as excluding women with hemophilia, people with mild hemophilia, people with pre-existing immunity to AAV 5, prior history of an inhibitor, and/or significant liver disease, along with other exclusion criteria. In addition, many people with hemophilia will choose not to receive gene therapy at this time. Therefore, the NHF estimates that not more than 2,000 people with hemophilia A and a fraction of those with hemophilia B will choose to receive a commercial gene therapy product.

In order to ensure the optimal outcomes for people who do wish to receive a gene therapy product, FDA should authorize/approve the products use in the same population as studied in the controlled clinical trials precluding off-label use.

Environmental impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

Economic Impact

Petitioner will submit information on the economic impact if requested by the FDA.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.

Thank you for your consideration.

Sincerely,

Leonard A. Valentino, MD
President & Chief Executive Officer
National Hemophilia Foundation

7 Penn Plaza Suite 1204,
New York, NY 10001
212-328-3760

-
- ⁱ Okolo AI, Soucie JM, Grosse SD, et al. Population-based surveillance of haemophilia and patient outcomes in Indiana using multiple data sources. *Haemophilia*. 2019;25:456–462. <https://doi.org/10.1111/hae.13734>
- ⁱⁱ Schieve LA, Byams VR, Dupervil B, et al. Evaluation of CDC’s Hemophilia Surveillance Program — Universal Data Collection (1998–2011) and Community Counts (2011–2019), United States . *MMWR Surveill Summ* 2020;69(No. SS-5):1–18. DOI: <http://dx.doi.org/10.15585/mmwr.ss6905a1>
- ⁱⁱⁱ Valentino, L. A., Baker, J. R., Butler, R., Escobar, M., Frick, N., Karp, S., Koulianos, K., Lattimore, S., Nugent, D., Pugliese, J. N., Recht, M., Reding, M. T., Rice, M., Thibodeaux, C. B., & Skinner, M. (2021). Integrated Hemophilia Patient Care via a National Network of Care Centers in the United States: A Model for Rare Coagulation Disorders. *Journal of blood medicine*, 12, 897–911. <https://doi.org/10.2147/JBM.S325031>
- ^{iv} Ozelo, M.C., Mahlangu, J., Pasi, K.J., Giermasz, A., Leavitt, A.D., Laffan, M., Symington, E., Quon, D.V., Wang, J.-D., Peerlinck, K., Pipe, S.W., Madan, B., Key, N.S., Pierce, G.F., O’Mahony, B., Kaczmarek, R., Henshaw, J., Lawal, A., Jayaram, K., Huang, M., Yang, X., Wong, W.Y., Kim, B., 2022. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. *New England Journal of Medicine* 386, 1013–1025. doi:10.1056/nejmoa2113708
- ^v Pierce, GF, Iorio, A. Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes. *Haemophilia*. 2018; 24(Suppl. 6): 60- 67. <https://doi.org/10.1111/hae.13489>
- ^{vi} Iorio A, Skinner MW, Clearfield E, et al.; for the coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. *Haemophilia*. 2018;24:e167–e172. <https://doi.org/10.1111/hae.13504>
- ^{vii} Kaczmarek et al., Eliminating Panglossian thinking in development of AAV therapeutics, *Molecular Therapy* (2021), <https://doi.org/10.1016/j.ymthe.2021.10.025>