Understanding gene therapy for haemophilia

The Haemophilia Society

UKHCDO
UNITED KINGDOM HAEMOPHILIA CENTRES DOCTORS' ORGANISATION

Haemophilia Nurses Association UK

Contents

Funding in form of a grant was originally supplied by BioMarin UK Ltd and Spark Therapeutics to create gene therapy materials for patients. This booklet has been created using these original materials. Neither company has been involved in the development of the content of this booklet.

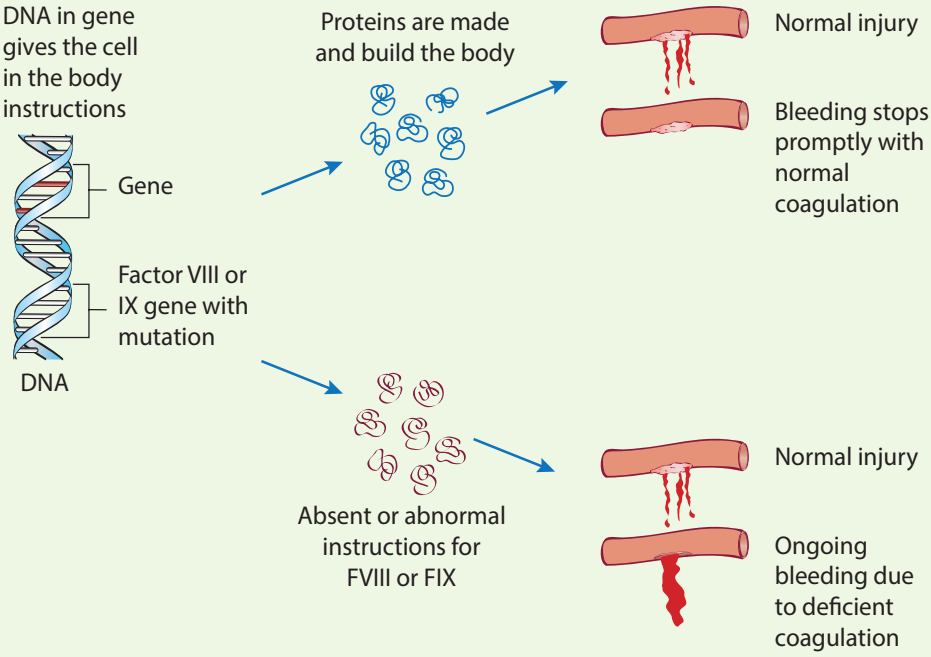
Haemophilia

Why do people with haemophilia bleed?

Haemophilia is an inherited condition where the blood doesn't clot properly because it lacks certain proteins. If you have haemophilia, your body has difficulties stopping bleeding, both externally, like with a cut, and internally, such as inside your muscles or joints.

Your blood contains proteins called clotting factors that help stop bleeding by forming clots. In haemophilia, you are either missing or have low levels of one of these factors. The most common types are:

- Haemophilia A is a deficiency of factor VIII
- Haemophilia B is a deficiency of factor IX



Why is haemophilia an inherited disease?

Haemophilia is usually inherited and is passed down from parents to children through genes.

Your genetic material or DNA makes you unique. A gene is a small portion of your DNA that acts like a blueprint within your body, instructing it how to make specific proteins or substances to perform vital functions. Genes are inherited from your parents, so you may share traits with them, such as hair or eye colour or some health issues. Errors in these genes can lead to conditions like haemophilia.

In haemophilia A, the factor VIII (8) gene has an error in its structure or is missing; in haemophilia B, it is the factor IX (9) gene.

How is haemophilia currently managed?

Haemophilia is primarily managed by replacing the missing clotting factors in the blood. This is done through injections of clotting factors or drugs that act in a similar way, either on-demand to treat bleeds or as a preventative measure (prophylaxis) to reduce future bleeding episodes.

- **Replacement Therapy:** Regular infusions of the clotting factor that is missing into a vein to help manage and prevent bleeding episodes.
- **Non-Factor Therapies:** These drugs are administered as an injection under the skin and correct the bleeding tendency by correcting the coagulation through different clotting mechanisms.
- **Bypassing Agents:** These also help blood clot and are used when factor replacement is ineffective, such as when an inhibitor has developed. They are antibodies to clotting proteins that have been given for treatment.

Haemophilia gene therapy – the science

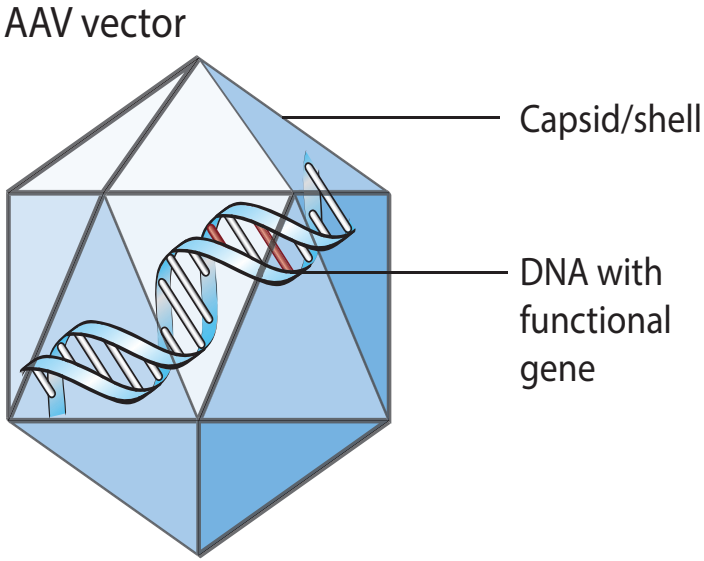
What is haemophilia gene therapy?

Gene therapy for haemophilia requires the introduction of a functioning gene into the liver cells, enabling your body to produce its clotting factor. This method of gene therapy is called gene transfer.

This gene is designed to produce stable and sufficient messages for protein production. The modified gene is called the transgene. The gene has a start switch, which ensures it activates only in the liver. It also has sticky ends on both sides, so that they form circular loops in the cell. All this content is often called the expression cassette.

How is the functioning gene introduced into the cell?

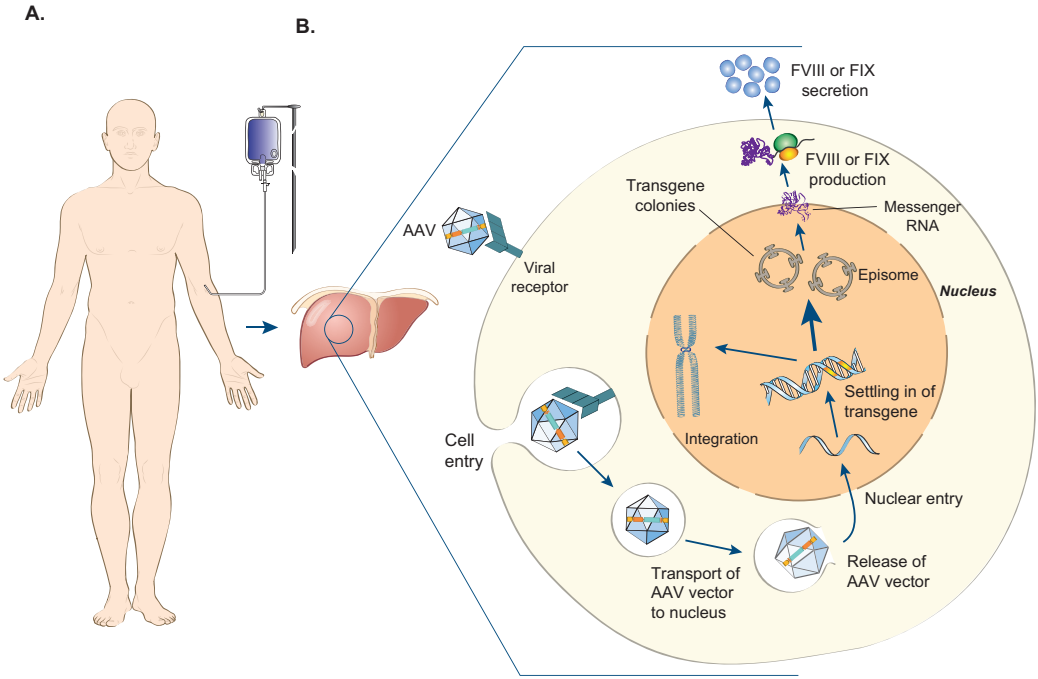
Gene therapy uses naturally occurring viruses to enable this. The gene and linked structures are packaged in a virus shell. This shell called the capsid has proteins that allows it to home onto specific targets. In the case of haemophilia gene therapy, the virus shell targets the liver.



What types of viruses are used for haemophilia gene therapy?

The most used viruses in haemophilia gene therapy are called adeno-associated viruses (AAV). These viruses cannot multiply by themselves as they require the help of other viruses.

The infections caused by these naturally occurring viruses usually have no clinical effects. AAV viruses are commonly used across rare disorders and are not associated with known diseases.



What is a viral vector?

The term vector often refers to the virus shell with the functioning gene/expression cassette. The shell and the expression cassette are manufactured together in cell cultures to produce a viral vector. The functioning gene is often present only in a limited number of viral particles.

What happens once the vector reaches the liver cells?

After the vector is injected, it travels to the liver via the bloodstream. The vector is taken up by the liver cell. It travels to the nucleus of the cell; this is the part of the cell that contains all the DNA. The protein shell breaks down and the transgene is placed in the nucleus. This transgene forms small groups with other transgenes and generates messages carried into the cell to manufacture the clotting factors.

Not all viral vectors reach the liver; the immune system removes some.

What other types of gene therapy are there?

Other methods are being tried to enable the body to produce the missing factor VIII and factor IX. In one method, there is an attempt to correct genetic error, called gene editing. Research is also ongoing to see if cells with functioning genes can be introduced into the body, which is called cellular therapy.

Is gene therapy only used in haemophilia?

Gene therapy is being investigated for many inherited conditions, and the NHS has made a number of these available to date. It is the only treatment available for some people with severe, life-limiting diseases.

Is gene therapy a cure for haemophilia?

Gene therapy is not a cure for haemophilia as it does not remove the abnormal gene from the body and does not correct the genetic error that leads to haemophilia. If you undergo gene therapy, it's important to understand that it won't prevent the passing of the haemophilia gene to your daughters, who can then pass it on to their children.

Gene therapy does have the potential to provide long-term relief from disease symptoms. The risk of bleeds and the need for treatment may be significantly reduced, but the duration of the effect is not known or guaranteed.

Haemophilia gene therapy – benefits and risks

How do I know if the gene therapy has worked?

Your haemophilia centre team will measure your factor levels frequently to see if the gene therapy is working. They may be able to stop prophylaxis because factor levels have increased enough to stop spontaneous bleeding. You may notice a change in bleeding pattern with a reduction in bleeding episodes.

Does gene therapy work in all patients?

Gene therapy may not work for some people. The number of people it does not work for varies between studies. The current treatments appear to work in more people with haemophilia B than with haemophilia A.

How long before gene therapy starts to work?

Factor levels usually rise within 2-3 weeks of the gene therapy infusion. Once certain levels are reached, usually around 5%, prophylaxis is stopped. Factor levels are anticipated to be stable by 6-12 months after infusion.

What are the benefits of gene therapy?

The key benefits of gene therapy are better control of haemophilia by reducing the need for regular injections to prevent bleeds, and it also decreases treatment burden in the long term. The extent of these benefits depends on how effective the gene therapy is in an individual as assessed by the factor levels.

How much benefit can I expect?

The exact benefit depends on the actual stable factor levels achieved after the infusion of gene therapy. In rare cases, if

someone gets no response to gene therapy and their factor levels do not increase, they will continue with their previous treatment.

Near Normal Levels (30-50%): If the levels are near normal after gene therapy, regular prophylaxis is not required and can be stopped. No further treatment for minor procedures (such as dental work) or most injuries will be needed. Treatment will be required for major surgery or in the event of a major accident. You might not need to carry additional treatment when you are travelling.

Levels in the "mild haemophilia" range (6-30%): Prophylaxis can be stopped if the levels are in the mild range. The decision around treatment for minor procedures or injuries will depend on the exact procedure and exact level achieved after gene therapy, which your haemophilia team will determine. Treatment will be required for major surgery or in the event of a major accident. Dental care may not require any treatment.

Levels in the "moderate haemophilia" range (1-5%): The decision to stop prophylaxis requires a discussion with your clinician. This decision is very personal, and the issues considered are the number of bleeds over 6 - 12 months and the types of physical and sporting activities you are involved with. If there is only an occasional non-joint bleed, prophylaxis may not be required. This decision is usually reviewed every six months.

How many bleeds do you have after haemophilia gene therapy?

Even after gene therapy, there remains a risk of bleeding from everyday activities such as cutting yourself, shaving or in the kitchen. The duration of bleeding will depend on the factor levels achieved.

It is essential to remain vigilant and contact your haemophilia centre if you are concerned about bleeding.

Will I still need factor if I receive gene therapy to cover an injury or surgery?

It depends on your actual factor level and the type of procedure. Once a stable level has been achieved, your haemophilia will be different from before, and you need to relearn about your disease with input from your haemophilia centre. The amount of factor required (if any) for an injury or surgery will be decided on a case-by-case basis in conjunction with your centre.

What happens if I undergo gene therapy and my factor levels get too high?

While gene therapy aims to raise clotting factor levels to a normal range and prevent bleeding episodes, it is possible that factor levels might go higher than expected. If they do, your centre will discuss the risk of excessive clotting and monitor you closely.

What are the immediate side effects of gene therapy?

Some patients may develop allergic reactions to the gene therapy. It is a recombinant (synthetic) product, and traces of various proteins can cause an allergic reaction up to two days after the infusion. These are usually mild and respond to antihistamines and paracetamol. Sometimes, they also cause fever, transient rashes and chest discomfort. Because of the possibility of allergic reactions, you will be in the hospital for at least a few hours after the infusion. The haemophilia centre team will instruct you on who to call if you feel unwell at home.

Some patients have noted headaches, flu-like symptoms, dizziness, itchy eyes, stomach discomfort, feeling sick and tired or unwell.

What are the potential long-term side effects?

The gene is in the nucleus outside of your DNA. We know some of the transgenes can insert themselves into the DNA of the liver cells. This is the case with both naturally occurring viruses and with gene therapy. These are random or chance events, and in some instances, there is the theoretical concern that they may contribute to the development of cancer, particularly liver cancer. Safety data is being accumulated across all gene therapies in rare disorders. The reason it is believed to be more theoretical is related to the fact that natural infection has not been associated with liver cancer. This uncertainty is being addressed through long-term monitoring.

Regular follow-up appointments with your haemophilia centre team are important after gene therapy to monitor your progress and detect potential risks or side effects. The follow-up will also look at your overall liver health. While there may be other risks associated with gene therapy that are not yet known, your doctor will guide you on what to look out for at each appointment and may order regular testing to ensure everything is okay following your gene therapy. Attending all follow-up appointments and sharing any concerns with your doctor is essential.

Gene therapy – who and when?

Who can have gene therapy?

Currently, gene therapy for haemophilia A is only offered in clinical trials for those with severe haemophilia A, with factor VIII levels below 1%.

Gene therapy for haemophilia B is now licensed and available across the NHS.

- There must also be a case for clinical and personal benefit from the treatment.
- Having HIV is not automatically disqualifying, but it requires a careful review of your treatment to avoid drug interactions. Participation might be possible if your HIV is well-controlled with medication.
- You must also adhere to the recommendations for the follow-up period.

Who cannot have gene therapy?

- People are not eligible if they have a current inhibitor or antibody against FVIII or FIX. Clinical trials are underway to see if gene therapy can be used in patients with inhibitors. It is not likely in haemophilia B but may be possible in haemophilia A. You may be eligible if you have had a previous transient inhibitor in haemophilia A.
- People with severe liver disease: This includes serious liver problems, like acute hepatitis, uncontrolled chronic hepatitis, severe fibrosis, or cirrhosis.
- Current active infections, new or ongoing.
- Recent immunosuppression (use of medications that suppress the immune system in the preceding 30 days).
- Any allergy to ingredients in the therapy.
- Young participants (under 18 years of age).

- Pregnancy potential in women i.e. women who can currently bear children are not eligible.
- Limited life expectancy due to active cancer or other long term conditions where benefits are unclear.
- The presence of antibodies against the AAV virus does not automatically exclude people from receiving treatment. This will be product specific, and will be discussed by the team. In some studies the presence of antibodies was associated with lack of response to treatment but not in other studies.

Can children have gene therapy?

Not yet, as children haven't been included in clinical trials of gene therapy for haemophilia and the regulatory authorities have not licensed it for use in children. Gene therapies are currently being used in some children with other serious, life-limiting diseases.

The key reason is that a child's liver is still growing and developing until around age 12. If the liver is still growing, the effects of the gene therapy might be diluted or less effective over time. More research is needed to determine the safety and efficacy of gene therapy in children with growing bodies.

If I undergo gene therapy and it stops working, can I try again in the future?

At present, we don't know. After gene therapy, antibodies develop to the AAV vector used, which may make any further AAV-gene therapy given at a later date ineffective.

Will I still be able to go to my haemophilia centre?

Yes, please do! The whole haemophilia multi-disciplinary team will still be available to you. You must be checked for changes in overall physical health and monitored for any issues you had before gene therapy (e.g., joint problems).

Will I still have haemophilia if I have normal factor levels?

No, although you will still carry the gene that causes haemophilia after gene therapy. Therefore, you will still pass on this gene to your daughters.

Will I still be part of the bleeding disorders community?

The bleeding disorders community is warm and welcoming, regardless of a change in your health status. You will always be a member of the community. You have much to offer and your experience and knowledge can benefit others.

Will gene therapy affect my ability to have children?

Gene therapy does not affect fertility or the ability to conceive. To ensure safety, it is recommended to use barrier contraception (condoms) until the semen is free of AAV. The exact duration will be defined by the product used. It will be a minimum of six months and no more than 12 months.

If I have children after gene therapy, will it prevent them from getting haemophilia?

If you have gene therapy and then have children, the gene is still passed onto your daughters and they will be carriers of haemophilia. Remember that the original gene in your sperm is not being corrected.

Can I drink alcohol after gene therapy?

After having your gene therapy infusion, you will be asked not to drink alcohol for up to 6 months. As gene therapy involves the liver and monitoring is being done to look for immune response, any alcohol can mimic the immune response and result in treatment when none is needed. Also, during this time, the liver is stressed, and additional strains are not good for the overall outcome.

Will I be able to work after gene therapy?

Yes, but you must make time available to attend clinic appointments. You might also need time off if you have troublesome side effects from steroid treatment. The appointments are very frequent in the first few weeks and months after gene therapy, and your haemophilia team will do their best to accommodate times that suit you and to liaise with your employer if necessary.

Am I at risk of blood clots after gene therapy?

After receiving gene therapy, your chances of developing blood clots will be like the general population's. However, if you are elderly or have certain medical conditions, the likelihood of clotting may increase. Therefore, it is important to be aware of any signs that could indicate the presence of a blood clot. These signs may include sudden chest pain, shortness of breath, sudden muscle weakness, loss of sensation and balance, feeling less alert, difficulty speaking, and swelling of one or both legs.

Practical aspects of gene therapy treatment

Where will I receive gene therapy?

NHS England has commissioned eight centres in England to give gene therapy. These eight centres will work with your local haemophilia centre to ensure you have the correct information and access to the right professionals to help you decide. It may also be available in clinical trials beyond these eight centres. You may need to travel a long distance to receive treatment. But most monitoring and follow-up will take place at your local haemophilia centre.

The current eight centres in **England** are:

- Katharine Dormandy Haemophilia and Thrombosis Centre, **Royal Free Hospital,** Royal Free London NHS Foundation Trust, London
- Haemostasis and Thrombosis Centre, **St Thomas' Hospital,** Guys and St Thomas' NHS Foundation Trust, London
- **Oxford** Haemophilia & Thrombosis Centre, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust, Oxford
- The Haemophilia Comprehensive Care Centre, **Addenbrooke's Hospital**, Cambridge University Hospitals NHS Foundation Trust
- **Bristol** Haemophilia Comprehensive Care Centre, Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Foundation Trust
- West Midlands Adult Comprehensive Care Haemophilia & Thrombosis Centre, Old Queen Elizabeth Hospital, **University Hospitals Birmingham** NHS Foundation Trust
- **Leeds** Haemophilia Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust
- **Manchester** Adult's Haemophilia Comprehensive Care Centre, Manchester Royal Infirmary, Manchester University Foundation Trust

In **Scotland**, the gene therapy hub will be at the Glasgow Adult's Haemophilia Centre (Royal Infirmary).

In **Wales**, it will be at the Cardiff Haemophilia Centre (University Hospital).

If you live in **Northern Ireland**, gene therapy will be provided at one of the gene therapy hubs in England, Wales or Scotland with your care managed from the Belfast Adult's centre at Belfast City Hsopital.

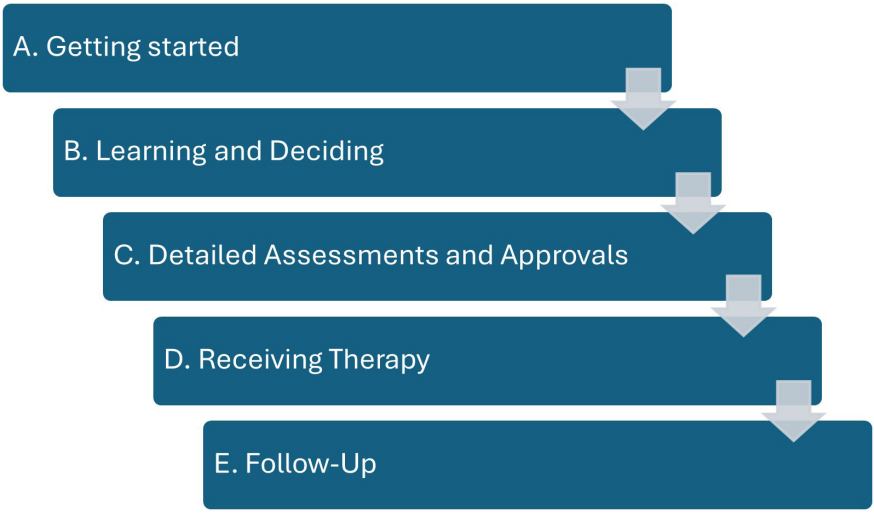
How is gene therapy given?

Gene therapy is given by an intravenous (IV) infusion from a doctor and nurse in the haemophilia centre. It is like administering a clotting factor that takes an entire day. It may be given in the day unit, or depending on how far away from the hospital, you might require admission to the hospital.

What will the journey through gene therapy treatment look like?

If you decide to undergo gene therapy, you must visit the haemophilia centre for numerous tests before and in the first few weeks after treatment. The frequency of these visits will depend on the license and regulations of the gene therapy product you receive, your overall health condition, your factor level, any side effects you may experience, and whether you require further treatment.

There are five key stages to the gene therapy journey.



A. Getting Started

First Contact: Your journey begins at your local centre, called the 'Spoke,' where the team will identify if you are potentially eligible for gene therapy.

Initial Discussions: You will speak with the team to discuss your interests and learn how the treatment might benefit you.
Referral: If gene therapy seems right for you, you will be referred to a specialised centre, known as the 'Hub,' for further evaluation.

B. Learning and Deciding

Information Session: The team will provide comprehensive information about gene therapy at the Hub or through a virtual appointment in collaboration with your home centre.

Understanding the Process: The team will discuss the step-by-step process, so you know what to expect at each stage.
Resources and Consent: Your centre will provide additional resources for your learning and obtain your consent to proceed with preliminary screening for anti-AAV antibodies, which are important for the next steps.

C. Detailed Assessments and Approvals

Testing for Eligibility: The team will take samples to test for anti-AAV antibodies and review your medical and liver health at the Hub or Spoke.

Team Review: A regional multidisciplinary team (MDT) will review your medical information to confirm your eligibility for gene therapy.

Preparation: If eligible, your centre will conduct baseline investigations and refer you to a psychologist to help with the journey and to ensure you are fully prepared.

Final Consent: You will be asked for your written consent for the actual gene therapy infusion and for your data to be included in the national registry.

D. Receiving Therapy

Infusion Day: The gene therapy infusion takes place at the Hub, adhering to strict national regulations.

Monitoring: The team carefully monitors you during the infusion for any reactions and to ensure your safety.
Aftercare: Once the infusion is complete, the team plans your

discharge and handover back to your local Spoke centre.

E. Follow-Up

Short-term checks: Soon after treatment, your centre will arrange for you to have blood tests between one to three times a week to check whether the gene therapy is working and to look for any side effects. The blood tests will also check whether your liver enzymes are healthy. If your liver is inflamed, you may be prescribed a course of steroid therapy, and you will need to have regular blood tests until it returns to normal. You may be referred to a liver specialist (hepatologist) during this time. The team shares the results of your follow-up with the Hub.

Long-term health tracking: The long-term effect of gene therapy is an important question, and participants must be followed up on a long-term basis. In the first few years, this may require visits to your haemophilia centre every 3-6 months for testing, followed by twice-yearly follow-up for the rest of your life. If you have agreed, your data will be submitted to the national registry.

What preparation is required before the day of the infusion?

When the day of your infusion arrives, it's essential to consider the practical details carefully. Take some time to confirm the exact date and time of your infusion and the location of the designated treatment centre. You may need to arrive a few hours before your infusion, so check beforehand.

Once you have confirmed all the essential details, planning your transportation to and from the centre in advance is crucial. Considering the distance between your home and the centre and expected traffic conditions would be best. It is advised that you don't drive on the day of your infusion, so you'll need someone else to drive you home if you're taking your car.

Apart from transportation, it's also important to consider what you might need to bring to the centre. This may include any

medications, snacks, or other items that will make you feel more comfortable during the infusion. You may also want to bring a book or other forms of entertainment to help pass the time.

What would a typical infusion day look like if I decided to go ahead?

This is an example of how an infusion day may go. Keep in mind that timings may vary.

1. Arrive early in the morning.
2. The nursing team will meet you and carry out some initial observations and checksThe pharmacist will prepare your infusion after the nursing team checks you.
3. A nurse will insert a cannula into a vein in your arm.
4. A nurse will connect the infusion bag to the cannula.
5. You will be closely monitored during the infusion and for some time after
6. You can go home early in the evening after the infusion.

During your infusion, you might experience some mild side effects that can be treated easily. If you feel any discomfort, please inform your nurse immediately. They can slow down your infusion or pause it for a while to alleviate the side effects. Your comfort and safety are their top priority.

Do I need to stay overnight in the hospital?

Typically, you can return home on the same day after your treatment. However, if the designated haemophilia centre is far away, you might need to arrive the night before your infusion. Additionally, you may need to stay overnight after your infusion so your haemophilia centre team can monitor your condition. Please let the team know before the day of infusion if you are likely to need to stay overnight before and/or after the treatment.

About the Haemophilia Society (THS)

We are the only UK-wide charity and free membership organisation for everyone affected by a genetic bleeding disorder.

We aim to empower people affected by bleeding disorders to live life to the fullest. We offer support, including events and local groups, the latest news and in-depth information resources, and campaigning and advocacy to demand the best possible care, safe and effective treatment, and equitable access for everyone.

The Haemophilia Society has over 5,500 members, including families living with a bleeding disorder and healthcare professionals.

The charity's supporters help fundraise the costs vitally needed to offer membership—and services such as events and printed publications entirely free to all members.

What we do:

Support each other
We understand each other. We offer advice and support from personal experience. Our growing community is there for each other because we're in it together.

Raise awareness
We rally together because every little thing we do makes a difference and gives hope to you living with a bleeding disorder.

Make a lasting difference
We influence and advocate for what matters to our community, such as health and social care policy, access to treatment, and much more.

To find out more or to become a member for free, visit our website at haemophilia.org.uk or call 020 7939 0780.

Notes

Notes

This booklet is intended for a UK audience and has been developed in consultation with healthcare professionals. It is meant to enhance medical advice, not to replace it. Please seek medical advice first from your haemophilia centre.

We want to express our sincere gratitude to the following individuals for their invaluable contributions to this information booklet:

- **Pratima Chowdary**, Professor of Haemophilia and Haemostasis, University College London; Centre Director, Katharine Dormandy Comprehensive Care Haemophilia Centre, Royal Free London NHS Foundation Trust
- **Gillian Lowe**, Consultant Haematologist, University Hospitals Birmingham NHS Foundation Trust Haemophilia Comprehensive Care Centre, Queen Elizabeth Hospital, Birmingham
- **Debra Pollard**, Advanced Nurse Practitioner, Haemophilia Centre & Thrombosis Unit, Royal Free London NHS Foundation Trust
- **John Spoors**, Programme Director for Commercial, Managed Access and Medicines Policy, The National Institute for Health and Care Excellence (NICE)

Their expertise and dedication have been instrumental in ensuring we provide current, unbiased and accurate information.

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Registered charity no. 288260 (Scotland SC039732)
Company limited by guarantee reg. no. 1763614
Members of the European Haemophilia Consortium and the World Federation of Hemophilia

Review date 2026