



ORIGINAL ARTICLE

Clinical haemophilia

Examining patient and professional perspectives in the UK for gene therapy in haemophilia

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[Correction added on 04 May 2022, after first online publication: The copyright line was changed.]

Abstract

Introduction: With the development of gene therapy for people with haemophilia (PWH), it is important to understand how people impacted by haemophilia (PIH) and clinicians prioritise haemophilia treatment attributes to support informed treatment decisions.

Objective: To examine the treatment attribute preferences of PIH and clinical experts in the United Kingdom (UK) and to develop a profile of gene therapy characteristics fit for use in future discrete choice experiments (DCEs).

Methods: Semi-structured interviews were conducted with PIH ($n = 14$) and clinical experts ($n = 6$) who ranked pre-defined treatment attributes by importance. Framework analysis was conducted to identify key themes and treatment attributes; points were allocated based on the rankings. Synthesis of results by a multidisciplinary group informed development of a profile of gene therapy characteristics for use in future research.

Results: Key themes identified by PIH and clinical experts included patient relevant features and the importance of 'informed decision making'. The six top-ranked treatment attributes were 'effect on factor level' (79 points), 'uncertainty regarding long-term risks' (57 points), 'impact on daily life' (41 points), 'frequency of monitoring' (33 points), 'impact on ability to participate in physical activity' (29 points), and 'uncertainty regarding long-term benefits' (28 points). The final treatment characteristics were categorised as therapeutic option, treatment effectiveness, safety concerns, impact on self-management and quality of life (role limitations).

Conclusion: We identified several gene therapy characteristics important to PIH and clinicians in the UK. These characteristics will be used in a future DCE to further investigate patient preferences for gene therapy.

KEYWORDS

discrete choice experiment, haemophilia, gene therapies, preferences, qualitative research, treatment attributes

1 | INTRODUCTION

1.1 | Background

Gene therapy could be a life-changing treatment option for people with haemophilia (PWH), offering relief from disease burden as well as the practical burdens associated with currently available haemophilia treatments.¹ Acute and chronic complications of haemophilia also impact health-related quality of life (HRQoL) particularly when treatment is not effectively managed.²⁻⁴ Prophylactic treatment with replacement therapy for bleed prevention is the standard of care for haemophilia A and B. Replacement factor infusions may also be administered 'on-demand' in response to a breakthrough bleeding event or before an activity posing potential bleeding risk.⁵ Where available, subcutaneous injections of bispecific antibodies are also considered a standard of care for haemophilia A.⁶⁻⁸

Considering the lifelong nature of haemophilia and its medical management, understanding the most important treatment attributes to patients can clarify their relative value and can inform comparative assessments of existing and emerging therapeutic options, such as factor replacement, non-factor therapies and gene therapy. As such, there is growing consensus that the patient perspective should be incorporated into healthcare decision-making at both individual and national levels.⁹⁻¹² Formal evaluation of stakeholder perspectives is often comprised of preference research, where preferences are defined as 'qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions'.¹³ These qualitative methods can identify the most relevant treatment attributes, which can then be examined further in quantitative preference elicitation methods such as discrete choice experiments (DCEs).¹⁴

In haemophilia, the PAVING study recently explored the preferences of PWH in Belgium for gene therapy attributes.¹⁵ In addition, Sun et al. reported administration (frequency, route, and place) and out-of-pocket costs to be the most important gene therapy attributes in their recent DCE among patients with haemophilia A in the United States.¹⁶ Otherwise, preference research in haemophilia has focused on attributes of factor replacement therapy, such as costs, breakthrough bleeds, and impact on physical activities, among subgroups of PWH.¹⁷⁻²¹ Further understanding of people impacted with haemophilia (PIH) and clinician perspectives on relevant attributes of gene therapy can help support shared treatment decisions, health policy evaluations, and future research.

In the absence of gene therapy-specific insights, this preference study explored the importance of various treatment attributes for both gene therapy and current haemophilia therapies in the UK. Perspectives were collated from PIH and clinical experts to formulate a com-

prehensive profile of relevant treatment attributes and related considerations. The most important attributes will be used in a future DCE to further investigate patient preferences for gene therapy attributes.

2 | METHODS

We conducted semi-structured interviews with PIH and clinical experts to identify and explore preferences for haemophilia treatment attributes related to factor replacement and gene therapy. PIH were members of a patient advocacy group (The Haemophilia Society) and were either PWH or caregivers of PWH. Interviews were conducted between April and June 2020. Interview findings were synthesised with a focus group of clinical experts, industry stakeholders, and experts in patient-centred and health economics research who refined the interview data into a profile of gene therapy characteristics fit for subsequent patient preference research. The process is further described in Figure 1.

2.1 | Participant recruitment

Interview participants consisted of male adults (≥ 18 years) with haemophilia of any severity, haemophilia caregivers and haemophilia clinical experts in the UK. A minimum sample size of 20 participants was targeted; this was based on prior research upon the number of interviews to reach data saturation and a feasible number of participants we could recruit.²² Researchers contacted 31 potential participants (16 PIH and 15 clinical experts) who were identified by the patient advocacy group The Haemophilia Society from their members list and were contacted via email, 20 of whom agreed and enrolled (14 PIH and six clinical experts). Participants included 12 PWH, two caregivers of PWH and six haemophilia clinical experts with prior knowledge of gene therapy in haemophilia (two haematologists, two nurses, one psychologist and one physiotherapist). Participants provided written informed consent prior to the interviews being conducted.

2.2 | Conduct of the interviews

Researchers used an interview guide to standardise interview completion (Appendix A1). Participants were provided with a study summary prior to the interviews and PWH were asked to complete a short pre-survey about themselves. Interview materials were developed based on those used in the PAVING study¹⁵ which specified three qualitative techniques to explore preferences (open questions, a ranking exercise, and case questions), as no single technique is considered a preferred standalone method in quantitative preference research.²³

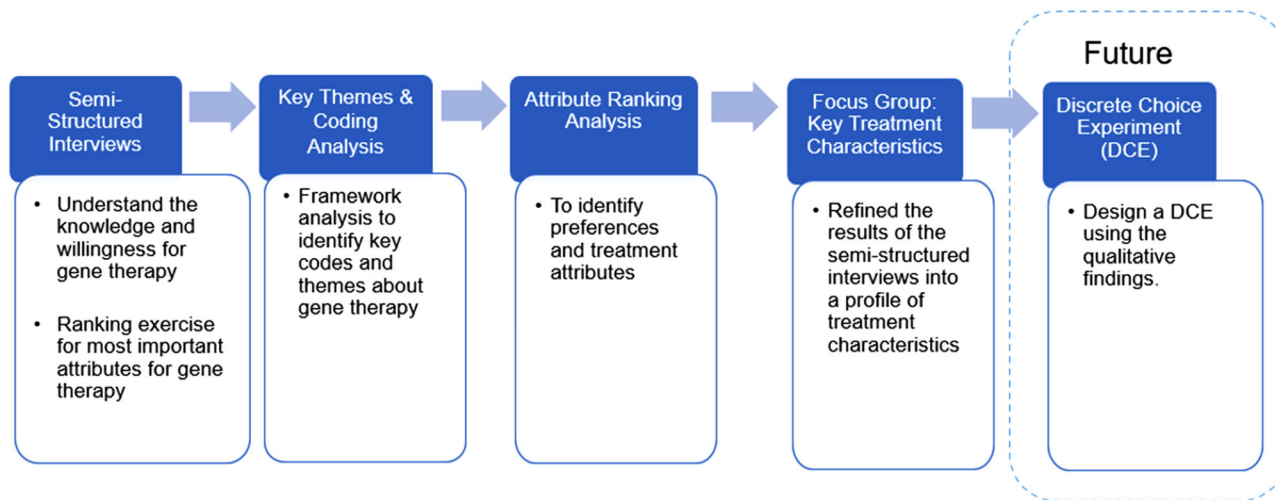


FIGURE 1 Flow Diagram of methodological steps

Participants were asked how willing they may be to receive or recommend gene therapy based on their knowledge and the information provided ('very willing', 'willing', 'neutral', or 'not willing'). Open questions were used to elicit participants' opinions and thought processes when considering haemophilia treatment attributes (Appendix A1). Researchers avoided using leading questions during the interviews. Prompts and unstructured follow-up questions were used where applicable.²⁴

Participants were then asked to spontaneously identify attributes of gene therapy that they considered to be important (Appendix A2). A list of 18 pre-defined attributes for gene therapy or factor replacement therapy was also produced based upon the PAVING study and a targeted literature review. The pre-defined attributes were broadly organised into categories relating to the nature of the treatment (mechanism of action), dosing and administration, follow-up, benefits, quality of life, and risks (Table 1). Participants then ranked the six most important gene therapy attributes from the pre-defined list and any spontaneously mentioned attributes they considered most important for themselves or their relatives/patients.

2.3 | Response analysis

A thematic framework analysis was applied to the open question responses to identify the most important overarching themes and gene therapy attributes.²⁵ Interviews were transcribed by an independent service. Researchers reviewed the transcripts prior to response coding, which was then used to identify nuances within and among participant responses. All lines of text related to the themes were coded and cross-checked by the study team (using NVivo 12 software). Any disagreements regarding code assignment were resolved via group discussion.

Analysis of participants' ranking of the six most important attributes, following the PAVING study example, assigned decremental points for each rank, from 6 points for a rank of 1 (most

TABLE 1 Pre-defined attributes used in the attribute ranking exercise based off the PAVING Study

Categories	Attributes
Nature of treatment	Mechanism of action
Administration	Route of administration
	Dose frequency
	Duration of administration
	Dosage strength
	Place of administration
	Ease of administration
Follow-up	Ease of product storage
	Frequency of monitoring
Benefits	Effect on factor level
	Effect on annual bleeding rate
	Probability that prophylaxis can be stopped after treatment
	Uncertainty regarding long-term benefits
Quality of life	Impact on daily life
	Impact on participation in physical activity
	Possibility to undergo major surgery
Risks	Probability that liver inflammation will develop
	Uncertainty regarding long-term risks

important) to 1 point for a rank of 6. This weighted point system yielded a maximum possible 120 points for a single attribute (if every participant ranked the same attribute as most important). In addition to the weighted point system, the frequency with which each attribute was identified in the top 6 attributes was also recorded (regardless of ranking within the top 6).

TABLE 2 People with haemophilia characteristics (self-reported)

Characteristics	PWH (n = 12)	
	N	%
Sex		
Females	0	0
Males	12	100
Age, years		
18–25	4	33
26–40	4	33
41–60	3	25
>60	1	8
Type of haemophilia		
A	10	83
B	2	17
Haemophilia severity		
Mild	1	8
Moderate	1	8
Severe	10	83
Current treatment regimen		
Prophylactic	8	67
On-demand	2	17
Hemlibra (emicizumab)	2	17

2.4 | Determination of the haemophilia treatment characteristic profile

Following the ranking exercise, a focus group was convened to review the top ranked attributes, consisting of two clinical experts (one haematologist and one psychologist), two industry stakeholders, two health economics researchers and one patient-centred researcher. The focus group reached consensus on five treatment characteristics; a content review of the consensus was conducted by two PWH.

3 | RESULTS

3.1 | Participant characteristics

For PWH ($n = 12$) the patient characteristics presented in Table 2 were collected. The majority of PWH were Type A (83%) compared to Type B (17%) and had severe haemophilia (83%) compared to mild (8%) and moderate (8%) haemophilia. For current treatment haemophilia treatment of PWH we saw prophylactic (67%) being the most common followed by on-demand (17%) and Hemlibra (17%). The two caregivers who completed the interviews were both female and cared for a child with haemophilia that was younger than 16.

3.2 | Knowledge about and willingness to receive gene therapy

All participants indicated awareness of gene therapy for haemophilia, and self-reported baseline knowledge (before summary information

was provided) was good or very good for approximately half of all participants (very good, 25%; good, 30%), and was otherwise deemed to be reasonable (35%), bad (5%) or very bad (5%). Participants indicated a general willingness to receive or recommend gene therapy, with responses ranging from very willing (10%) or willing (45%) to neutral (20%) and not willing (25%).

3.3 | Identification and coding of themes from interview responses

Two key themes related to considering gene therapy were identified in the participant responses to the open questions. Participants indicated that 'patient-relevant features' and 'informed decision-making' were the most important over-arching themes from the open questions, which would then help guide interpretation of the treatment attribute selections. The 'patient-relevant features' theme included codes for pros/benefits, cons/disadvantages, and long-term uncertainty of gene therapy. The 'informed decision-making' theme included codes related to accuracy, accessibility and individual applicability. Illustrative participant quotes from each of the coded themes are provided in Figure 2.

The potential pros/benefits of gene therapy were mentioned by 95% of all participants as a key factor in their decision-making. In particular, the possibilities of factor level stability, reduction of long-term damage, having a less restrictive lifestyle (e.g., travel and physical activity), and better quality of life may be highly influential in decision-making. All participants expressed concerns about potential cons/disadvantages of gene therapy, including the feasibility of gene therapy within the patient's lifestyle (65%), side effects (55%), uncertainty about long-term efficacy (45%), and development of inhibitors (30%). All were said to potentially dissuade participants from choosing gene therapy.

Concerns related to long-term uncertainty were expressed by 95% of participants, specifically citing the duration of gene therapy effectiveness (85%), long-term side effects (65%), and potential lifestyle limitations (50%). The lack of gene therapy data and uncertainty itself was cited as reasons for unwillingness to receive or recommend gene therapy.

Regarding informed decision-making, nearly all participants (90%) indicated the importance of accurate, detailed, and up-to-date information about gene therapy, as well as information about alternative options (65%). Participants believed that PWH should be fully informed about how gene therapy works and any potential side effects (75%), lifestyle changes (70%), and follow-up and monitoring requirements (35%). All participants noted that information about gene therapy should be easy for lay people to understand, emphasising the importance of having information that PWH could apply to their own circumstances.

3.4 | Treatment attributes ranking exercise

The weighted points analysis yielded a total of 417 points across the totality of the attributes in the ranking exercise; the top 10 ranked attributes are presented in Figure 3. Across all 20 interviews, 19 participants selected their top 6 treatment attributes (one participant only

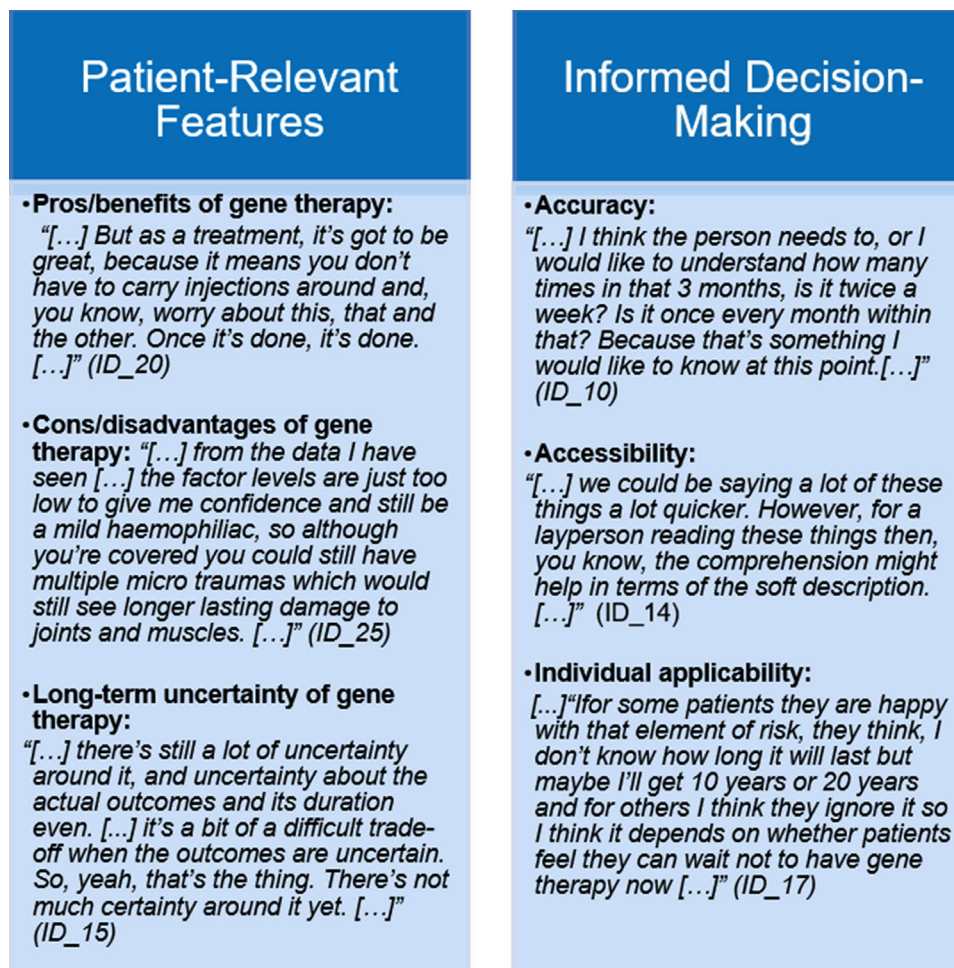


FIGURE 2 Participant quotes supporting each code included within the two key identified themes: patient-relevant features and informed decision-making

ranked their top 4 attributes). All of the top 6 ranked attributes were from the pre-defined list: 'effect on factor level' (79 points), 'uncertainty regarding long-term risks' (57 points), 'impact on daily life' (41 points), 'frequency of monitoring' (33 points), 'impact on ability to participate in physical activity' (29 points), and 'uncertainty regarding long-term benefits' (28 points). Of the spontaneously mentioned attributes, only four received any ranking within the top 6 ('life span of efficacy of gene therapy', 'level of knowledge and research on gene therapies', 'family opinions on gene therapy' and 'impact on working life').

3.5 | Focus group consensus: Gene therapy treatment characteristics profile

The final profile of five treatment characteristics, based on the focus group's distillation of the qualitative analysis findings, was:

- Therapeutic option
- Treatment effectiveness

- Safety concerns
- Hospital attendances and self-management
- Quality of life (Role limitations)

The discussions highlighted that the top ranked attribute 'effect on factor level' could be separated into two characteristics: 'Therapeutic Option' (the method of how treatment is provided, i.e., gene therapy or different frequencies and administration routes of factor infusions) and 'Treatment Effectiveness' (whether additional treatment is needed for situations involving an increased risk of bleeding, such as major or minor surgery, or traumatic or spontaneous bleeds). The characteristic 'Safety Concerns' comprised the 2nd ranked attribute ('uncertainty regarding long-term risks') and the 7th ranked attribute ('probability that liver inflammation will develop'), focusing on how safety risks differ between gene therapy and current standard of care. The 3rd ('impact on daily life') and 4th ('frequency of monitoring') ranked attributes were accounted for in the 'Hospital attendances and self-management' characteristic. The final characteristic 'Quality of life ('role limitations') was also based on the 3rd ('impact on daily life') and the 5th ('impact on participation in physical activity') ranked attributes.

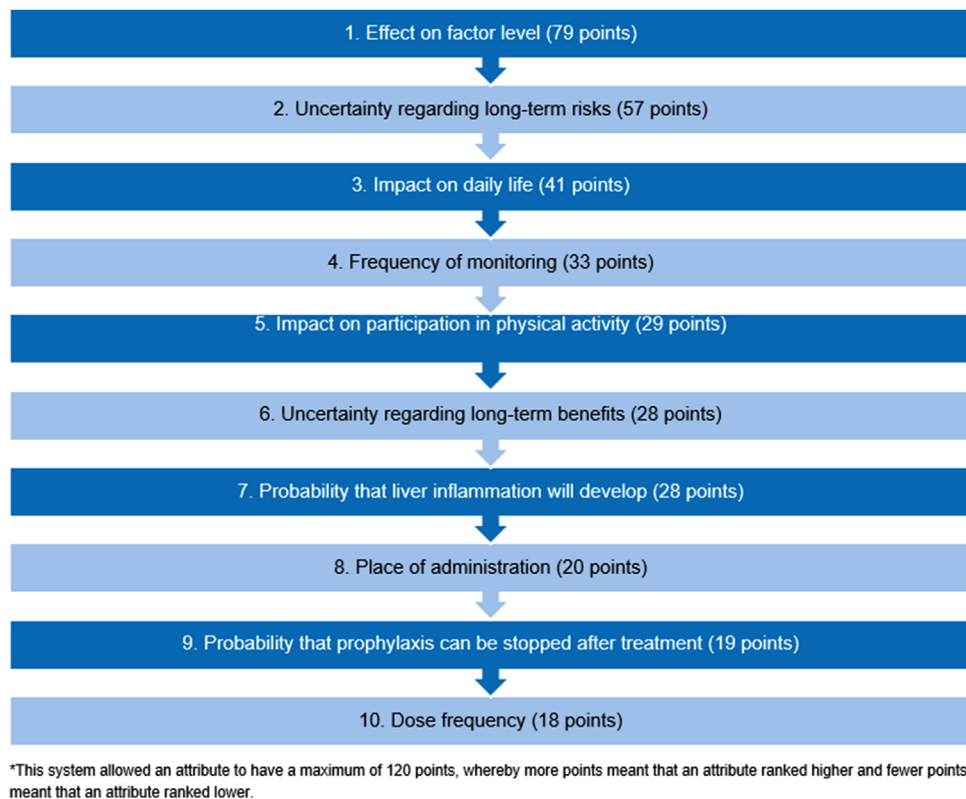


FIGURE 3 Top 10 ranked treatment attributes resulting from the ranking exercise

4 | DISCUSSION

This study examined the perspectives of PWH, their caregivers and clinicians in the UK regarding important attributes of gene therapy and existing treatment options for haemophilia. The key themes identified in the semi-structured survey were benefits, disadvantages and long-term uncertainty of gene therapy. Accuracy, accessibility and individual applicability of patient information about gene therapy was also deemed essential for truly informed decisions. The treatment attribute ranking exercise placed high importance on treatment effect on factor level, uncertainty around long-term benefits, and quality of life, particularly related to performing regular activities of life without concerns about bleeds/factor levels. Uncertainty regarding long-term risks and frequency of monitoring stood out among topics related to risks and follow-up. The focus group of experts ultimately reached consensus on five key treatment characteristics to be included in future DCE studies of patient preferences for gene therapy in haemophilia, which were derived from the participant-identified priorities, encompassing treatment choice and effectiveness, safety concerns, follow-up and self-management considerations, and quality of life.

Our findings were largely consistent with those of the PAVING study (conducted with 20 PWH in Belgium), where seven of the top 10 ranked attributes were the same between studies.¹⁵ Specifically, 'the effect of a treatment on factor level', 'uncertainty regarding long-term risks', and 'impact on daily life' were ranked in the top 5 attributes in both

studies. Unlike in this study, participants in the PAVING study ranked 'effect on annual bleeding rate' the highest (47 points), followed closely by 'effect on factor level' (43 points), perhaps due to different participant mix and greater importance given to the impact on daily life and participation in physical activities. Findings from both studies are consistent with those reported by van Balen et al. from members of the Netherlands Haemophilia Society, where participants 'expressed their concerns about the short- and long-term safety of new treatments and believed the effects of gene therapy were not yet fully understood'.²⁶ Interestingly, 'frequency of monitoring', 'impact on participation in physical activity' and 'uncertainty regarding long-term benefits' were in the top 10 in our study but not in the PAVING study. Different perspectives on monitoring may have been related to logistical differences between countries, where travel to follow-up appointments may be less of a burden for PWH in Belgium, or that the relative knowledge of gene therapy haemophilia may be more widespread in the UK versus Belgium and thus the practical impact of follow up may have been recognised more. Travel burden has been cited as a reason for reduced treatment adherence among PWH.²⁷ Differences regarding uncertainty around long-term benefits in terms of bleeding rates and factor levels may be attributable to the different participant mix in each study: the PAVING study included PWH from the general haemophilia population whereas our participants were recruited via a patient advocacy group and were a mix of PWH, caregivers and clinical experts. Carlsson et al. also reported 'participating in physical activity' as an important treatment attribute in a Swedish patient preference

study for haemophilia A treatments, as this impacts factor levels, treatment management, and quality of life.²¹

Our multidisciplinary focus group distilled the participants' perspectives into 5 core treatment characteristics, including treatment choice, effectiveness, safety, quality of life, and impact on daily life. These will be included in a future DCE to further examine preferences for haemophilia treatment on a larger scale, which may provide essential insights into how PWH will consider the potentially transformative nature of gene therapy for haemophilia.

4.1 | Strengths and limitations

Our sample consisted of a mixture of PIH and clinical experts following best practices for patient preference research in healthcare^{24,25} by including a unique multidimensional perspective. While this multi-stakeholder approach is a key strength it did not include PWH who were not affiliated with The Haemophilia Society. Inclusion of this additional group of people may have elicited additional preferences that could have supported or added to our thematic analysis. Future work should look to conduct a study specific for patients and clinical experts to assess how patient-driven attributes and clinical expert-driven attributes differ. However, our findings are consistent with recently published work in this area, reinforcing its relevance concerning gene therapy attributes.^{15,26,27}

We took several measures to standardise participants' awareness of gene therapy, but their baseline (pre-aided) knowledge was highly variable and may have influenced subsequent responses. The interview guide was based on that used in the PAVING study¹⁵ where the omission of attributes such as alcohol reduction or viral shedding may have been relevant. Little demographic data were collected during the interviews, which limited subgroup assessments and evaluation of sample heterogeneity. In future, characteristics of all participants should be collected, not just PWH. The ranking exercise is limited in the fact it uses a linear weighting which may not be truly representative of the actual weighting of one attribute to the next. Interviews were conducted by two researchers to minimise variability using the same interview materials. Both researchers had attended a seminar on gene therapy and had participated in haemophilia research.

The focus group was composed of multidisciplinary experts. However, lack of inclusion of PIH could be seen as limitation as they could have provided additional value to the discussions. The decision to not include PIH in the focus group was due to wanting a concentrated group to enable efficient discussion. Two PWH subsequently reviewed the final content and language to ensure the suitability of the conclusions of the focus group. An informal process was used to reach consensus but the final treatment characteristics selected had encompassed all of the key attributes identified by the participants. Quantitative techniques such as DCEs can provide weighting to preferences and relative importance of specific attributes and degrees of attributes.²⁸ This may yield meaningful, detailed insights into the determinants of patient preferences for different haemophilia treatments, including gene therapy.

5 | CONCLUSION

Treatment choice, effectiveness, safety, patient self-management and quality of life are important decision factors for PWH in the UK when deciding about treatment options. Further research is needed to better understand the relative importance that PWH ascribe to different haemophilia treatment attributes, particularly when considering existing or new treatment options such as gene therapy.

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CONFLICTS OF INTEREST

HCD Economics who were paid consultants to Pfizer, Inc. and Pfizer, Ltd in connection with this research and the development of this manuscript. APM and MC were employees of HCD Economics during the conduct of the study. Editorial/medical writing support was provided by Jeff Frimpter, MPH, of Integrative Life Sciences and was funded by HCD Economics. Jack Brownrigg, Jim Thomson, Ian Winburn and Ione Woollacott, employees of Pfizer Ltd. Eline van Overbeeke is an employee of Pfizer NV/SA Belgium but was an employee of the University of Leuven during the conduct of the study. Pratima Chowdary has received grant/research support from Bayer, CSL Behring, Freeline Therapeutics, Novo Nordisk, Pfizer, Sobi and Takeda (Shire); and consultancy fees from Bayer, CSL Behring, Chugai, Freeline Therapeutics, Novo Nordisk, Pfizer, Roche, Spark Therapeutics, Sanofi, Sobi and Takeda (Shire).

AUTHOR CONTRIBUTIONS

Jamie O'Hara, George Morgan, Eline van Overbeeke, and Sissel Michelsen contributed to the concept and design. Bethany Franks, George Morgan, Jim Thomson, and Ione Woollacott performed the research. George Morgan, Matthew Cawson, Bethany Franks, Jim Thomson, Ian Winburn, and Ione Woollacott analysed the data. All authors contributed to interpreting the data and writing of the paper.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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APPENDIX A1: INTERVIEW GUIDES FOR PWH, PWH CAREGIVERS, AND CLINICAL EXPERTS

INTERVIEW GUIDE FOR PEOPLE WITH HAEMOPHILIA

Interview number
Date
Location
Name interviewer
Supervisor
Starting time
Ending time

My name is *name interviewer* (and my supervisor *name supervisor* if present will also be present today). In interviews, like the one that we will conduct with you today, we want to investigate the opinion of patients on the use of a new, innovative therapy in development, namely gene therapy, for the treatment of haemophilia. This study is conducted by HCD Economics and in collaboration with the master thesis of Sissel Michelsen, the PhD of Eline van Overbeeke and the PREFER project. For this study we are working together with different organisations including the haemophilia patient organization, 'The Haemophilia Society'.

In the next hour we will discuss the following topics:

- We will talk about gene therapy, an innovative treatment that is not yet approved for use in Europe and thus not yet available for the treatment of haemophilia.
- We will first explore what you already know about gene therapy. Afterwards we will provide you with information on this topic to see if this information is understandable.
- Subsequently we will ask you about your opinion on this therapy and we will ask you why you would want to be treated with this therapy or why not.
- We will also discuss a couple of examples (cases) with you of outcomes in patients that participated in clinical trials with gene therapy and we will ask you how you would make a choice in these situations.
- In addition, we would like to know from you how you would make a choice between gene therapy and the existing therapies.

I want to thank you again for your participation in this interview. Before we start I want to clarify some aspects of the interview:

- We are looking for your opinion and wrong answers do thus not exist.
- This interview will be treated confidentially and the results will be processed in a non-identifiable way.
- The interview will take about an hour.
- You are not obliged to answer questions that you do not wish to respond to.
- You can stop the interview at any moment without having to give a reason.
- If you do not understand a question or have questions, you may always ask for more explanation.

Is the consent form completed and signed? This has to be completed and signed before the interview can start. If not: do not go further with the interview till the consent form is signed.

To allow me to process and correctly report the information gathered from this interview, I would like to audio-record this interview. This will allow me to after the interview fully transcribe the interview and to correctly process it. Can I start the audio-recording now? *If the participant does not agree to start the audio-recording and all of their questions on the recording are answered, the interview will be stopped.*

INTRODUCTION

If the introductory survey was not yet received per mail: Can I ask you to give me the survey that was sent to you in advance? When the survey was received, check if all questions are completed. IF there are still open questions: Would you mind answering the question on 'remaining question' or would you rather want to leave it open? If they want to complete it: the answer is added on the survey.

Introductory question:

- Why did you agree to participate in this study?

Gene therapy – Information part

- Have you ever heard about gene therapy?
 1. If yes, what do you already know about gene therapy?
 2. If yes, how did you receive this information?
- How would you estimate your knowledge on gene therapy to be?
 3. Very good
 4. Good
 5. Reasonable
 6. Bad
 7. Very bad

Now I will go through some information with you on the disease, current treatment options and the use of gene therapy in haemophilia. After every information section, I will ask you if the information is understandable and how I can improve the phrasing of the information to make it clearer. You might already know about some of the aspects that I will inform you about, but I still would like to receive your feedback on these information sections.

Information on haemophilia

Patients with haemophilia have an error in the gene for a certain coagulation factor, or for short referred to as factor. The error is located in the gene for coagulation factor IX in haemophilia B and the gene for coagulation factor VIII in haemophilia A. Because of this error, these patients are not able to produce the coagulation factor or they produce insufficient amounts of correct coagulation factors. Due to this insufficiency these patients bleed for a longer time compared to people with the correct gene, or bleedings can occur spontaneously in patients that produce almost no correct coagulation factor.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Information on the treatment of haemophilia

The aim of treatment in haemophilia is to supplement the body with coagulation factor to stop or prevent bleedings. Coagulation factor cannot be swallowed in pill form but has to be injected directly into a vein to reach the blood circulation. Patients can self-administer the coagulation factor when a bleeding occurs or when they know that they will participate in an activity with the risk of causing a bleeding,

this is called treatment 'on demand'. In addition, patients can also treat themselves in a 'prophylactic' manner through self-administration multiple times per week to keep the coagulation factor up to standard. For haemophilia A patients this includes two to three administrations per week and for haemophilia B patients two per week. However, the number of necessary injections per week can vary per individual. Some patients develop neutralising antibodies (inhibitors) against the administered factor, resulting in inefficacy of the treatment.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

General information on gene therapy in haemophilia

Genetic disorders are caused by an error that is present in our genetic material, in other words an error in one of our genes. This error can arise spontaneously or can be passed along by one or both parents. By means of gene therapy we try to correct the error so that the body contains the correct gene and the correct activity can take place in the body. The goal of gene therapy in haemophilia is to deliver the correct gene of the coagulation factor to the body. Hereby the correct factor will be produced in the body, and the patient no longer has to administer extra factor via injection.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

With gene therapy the correct version of the gene for the coagulation factor will be administered directly to the body. The correct gene will be packaged in 'a vector' that is responsible for delivering the gene to the liver cells, where the new gene is added next to the genetic material that is already present. It will not alter your own genetic material. For haemophilia, a modified virus is used as vector as this has a good capacity to reach the liver cells. The virus is modified in a way that it is only capable of delivering the genes to the liver cells; the virus itself is not infectious or functional. Only the casing of the virus remains as a sort of taxi.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Practical information on the treatment of haemophilia with gene therapy

Gene therapy is administered once via a vein in a hospital during 30–60 min on average. After the vector has delivered the correct gene to the liver cells, the liver cells themselves start to produce coagulation factor. After this one-time administration the patient will have to come to the hospital for check-ups regularly during a period of about 3 months to monitor the factor level. After these 3 months this becomes a yearly check-up. The treatment with gene therapy results in a factor concentration that is always on the same level. This in contrast to injections with coagulation factor that results in a high factor concentration directly after injection, but a low concentration before the next injection. This means that gene therapy will provide a stable factor level that

is high enough to protect you against bleedings, against fluctuating factor levels with the factor injections.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Side effects of gene therapy in haemophilia

In some patients a light inflammation of the liver is observed after treatment with gene therapy. This inflammation cannot cause hepatitis C and does not cause noticeable symptoms. The light inflammation will be treated with cortisone (corticosteroids) to avoid the occurrence of symptoms. In addition, 30%–50% of the population already has antibodies against the used vectors. This means that these people currently do not qualify for treatment with gene therapy as the vector will be broken down by their body. Because of the presence of these antibodies the vectors will not reach the liver cells and the gene therapy will not be effective. When patients without pre-existing antibodies participate in clinical trials, it has been determined that they always develop antibodies against the vector after administration of gene therapy, this is a normal reaction of the body. This development of antibodies does not cause noticeable symptoms and does not hinder the function of the administered gene therapy. This means that they can be treated successfully with the same vector once, but that treatment with the same vector cannot be repeated. It is unknown if it is possible to treat patients again with another type of vector for which the patient has not yet developed antibodies, if the gene therapy would not work long enough.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Results from clinical trials of gene therapy in haemophilia

This therapy is still in clinical development and is not yet approved by the European Commission. All data that we present here originate from clinical trials with severe haemophilia patients. Currently, only adult patients with severe haemophilia and without inhibitors can receive gene therapy. In these studies, we see that there is a large variability across results. Some patients no longer need factor injections after gene therapy was administered to them and experience no to almost no bleedings anymore. In contrast, other patients still need extra factor administration and experience a few bleedings per year. To date, no patients have developed inhibitors against the coagulation factor produced by the liver after administration of gene therapy. The monitoring of patients in clinical trials is now 2 years on average for haemophilia A and 8 years for haemophilia B, whereby it is uncertain for how long this therapy will result in sufficient production of coagulation factor by the liver. In other words, it is unknown whether the therapy will provide a life-long effect. In addition, it is expected that gene therapy for haemophilia will come with a one-time high cost for the government against the spread cost that is currently paid for lifelong factor administrations.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Gene therapy – Patient and parent opinion

- What is your opinion on the treatment of haemophilia with gene therapy?
- What information would you like to additionally receive on the topic of gene therapy in haemophilia?
- Would you be willing to receive treatment with gene therapy yourself/would you want your child to be treated with gene therapy? Why or why not?
- Please indicate your willingness regarding the use of gene therapy:
 1. Very willing
 2. Willing
 3. Neutral
 4. Not willing
 5. Not willing at all
- Are there any other elements that could influence your choice that we have not discussed in the information section?
- What are for you the top three elements that influence your choice? → put in the table below
- How do you perceive the fact that it is currently unknown for how long the gene therapy will be effective since there is no lifelong follow-up data yet?
- To date only patients can be treated without antibodies against the vector. Moreover, you can only be treated once with the same vector since you will develop antibodies after treatment. It is currently being investigated if it is possible to treat a second time with another vector. What is your opinion on this?
- In the table below, please indicate the six elements that you think are most important when deciding whether gene therapy is the right treatment for you/your child (using scores from 1 to 6, with '1' being the most important element).
- What elements on this list do you find not at all important when making a decision on treatment with gene therapy?

Categories	Elements	Definition	Ranking
Nature of treatment	Mechanism of action	The specific process through which a treatment produces its effect (e.g., through delivering a gene to liver cells in the case of gene therapy; or through delivering factor to the body in the case of factor replacement therapy)	
	Administration Route of administration	The path by which a treatment is administered to the body (e.g., oral, intravenous, subcutaneous)	
	Dose frequency	The number of times a treatment is administered within a specific time period (e.g., twice per week, once per year)	

(Continues)

Categories	Elements	Definition	Ranking
	Duration of administration	The amount of time needed to complete one administration (e.g., 15 min, 1 h)	
	Dosage strength	The strength of a treatment, which indicates the amount of active ingredient in each dosage (e.g., concentration of factor, concentration of vectors)	
	Place of administration	The geographical place where the treatment is administered (e.g., at home, hospital)	
	Ease of administration	The degree of ease to perform an administration	
	Ease of product storage	The degree of ease to store a treatment (e.g., the amount of storage space needed, temperature requirements)	
Follow-up	Frequency of monitoring	The number of times a patient has to visit a physician for follow-up on the effect of the treatment within a specific time period (e.g., once per month, once per year)	
Benefits	Effect on factor level	The effect on the amount of working clotting factor in the blood, delivered via factor replacement therapy or produced by the patient after gene therapy (often expressed in percentage, % of normal levels)	
	Effect on annual bleeding rate	The effect of the treatment on the number of bleeding events per year	
	Probability that prophylaxis can be stopped after treatment	The chance that use of prophylactic factor replacement therapy can be stopped after treatment (expressed in percentage, % of patients that can stop prophylaxis)	
	Uncertainty regarding long-term benefits	The degree of uncertainty that the effect of the treatment will be maintained after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	

(Continues)

Categories	Elements	Definition	Ranking
Quality of Life	Impact on daily life	The impact of the treatment on daily activities	
	Impact on participation in physical activity	The impact of the treatment on the performance of physical activity (sports)	
	Possibility to undergo major surgery	The impact of the treatment on the possibility to undergo major surgery	
Risks	Probability that liver inflammation will develop	The chance that liver inflammation develops after treatment (expressed in percentage, %, of patients that develops liver inflammation)	
	Uncertainty regarding long-term risks	The degree of uncertainty regarding the side effects that can occur after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
Spontaneously mentioned elements			

Cases

I will go through three hypothetical scenarios with you. I will ask you each time whether you prefer scenario A or scenario B.

Hypothetical scenario example 1:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 5 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a very small chance of having side effects (e.g. rashes at infusion site).	You have no treatment-related side effects.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
- 1.Why?

Hypothetical scenario examples 2:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
- 1.Why?
- 2.If they find it difficult to choose: What if you had to choose?
- If the responses on the previous two questions were the same: why did you answer in both cases gene therapy/preventive therapy?
- If the responses on the previous two questions were different: why did you give a different answer for the two cases?
- 3.Try to get in-depth information on the variability

We are going to have another look at the previously mentioned example. Besides the standard preventive therapy or gene therapy there is now also the option of long-acting coagulation factors. These lower the administration frequency to once per 3–5 days for haemophilia A patients (instead of 3 times per week) and to once per 7–14 days for haemophilia B (instead of twice per week).

Hypothetical scenario example 3:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion one time per two weeks.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
- 1.Why?

Some peoples with severe haemophilia will have other treatment options in the future, namely non-factor therapies (NFT). These NFTs act on other aspects of the coagulation of the blood and by pass in that manner factor VIII and IX. NFTs would be administered subcutaneously (not directly into the vein) and would also require less frequent administrations (once every 2–4 weeks). This administration is less invasive and easier to perform. In addition, this therapy results in a stable concentration during the full duration without administration.

Currently there is one NFT approved in Europe, namely emicizumab (Hemlibra), that can be used in haemophilia A patients with inhibitors. In the United States this therapy is also approved for haemophilia A patients without inhibitors. These treatments are currently sometimes not strong enough to prevent bleedings and therefore during active bleedings they sometimes have to be combined with coagulation factors.

- Did you understand this information?
- How does the availability of these non-factor therapies influence your willingness to use gene therapy/accept treatment with gene therapy for your child?

As a last question, knowing that you/your child can still pass along haemophilia to your/their children. When would you consider yourself/your child cured?

Finishing the interview

- We have gone through all of the questions of the interview. Did you have anything you would like to share with me that I did not yet ask you about?
- Do you have any questions for me?
- Can I contact you if I would have any follow-up questions?
- What did you think of the interview?

Thanks a lot for your participation in this interview. Do not hesitate to contact me if you would have any further questions.

INTERVIEW GUIDE FOR CAREGIVERS

Interview number
Date
Location
Name interviewer
Supervisor
Starting time
Ending time

My name is *name interviewer* (and my supervisor *name supervisor* if present will also be present today). In interviews, like the one that we will conduct with you today, we want to investigate the opinion of you as a caregiver on the use of a new, innovative therapy in development, namely gene therapy, for the treatment of haemophilia. This study is conducted by HCD Economics and in collaboration with the master thesis of Sissel Michelsen, the PhD of Eline van Overbeeke and the PREFER project. For this study we are working together with different organisations including the haemophilia patient organization, 'The Haemophilia Society'.

In the next hour we will discuss the following topics:

- We will talk about gene therapy, an innovative treatment that is not yet approved for use in Europe and thus not yet available for the treatment of haemophilia.
- We will first explore what you already know about gene therapy. Afterwards we will provide you with information on this topic to see if this information is understandable.
- Subsequently we will ask you about your opinion on this therapy and we will ask you why you would want your relative to be treated with this therapy or why not.
- We will also discuss a couple of examples (cases) with you of outcomes in patients that participated in clinical trials with gene therapy and we will ask you how you would make a choice in these situations on behalf of your relative.
- In addition, we would like to know from you how you would make a choice between gene therapy and the existing therapies.

I want to thank you again for your participation in this interview. Before we start I want to clarify some aspects of the interview:

- We are looking for your opinion and wrong answers do thus not exist.
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Is the consent form completed and signed? This has to be completed and signed before the interview can start. If not: do not go further with the interview till the consent form is signed.

To allow me to process and correctly report the information gathered from this interview, I would like to audio-record this interview. This will allow me to after the interview fully transcribe the interview and to correctly process it. Can I start the audio-recording now? *If the participant does not agree to start the audio-recording and all of their questions on the recording are answered, the interview will be stopped.*

INTRODUCTION

If the introductory survey was not yet received per mail: Can I ask you to give me the survey that was sent to you in advance? When the survey was received, check if all questions are completed. IF there are still open questions: Would you mind answering the question on 'remaining question' or would you rather want to leave it open? If they want to complete it: the answer is added on the survey.

Introductory question:

- Why did you agree to participate in this study?

Gene therapy – Information part

- Have you ever heard about gene therapy?
- If yes, what do you already know about gene therapy?
- If yes, how did you receive this information?
- How would you estimate your knowledge on gene therapy to be?
 1. Very good
 2. Good
 3. Reasonable
 4. Bad
 5. Very bad

Now I will go through some information with you on the disease, current treatment options and the use of gene therapy in haemophilia. After every information section, I will ask you if the information is understandable and how I can improve the phrasing of the information to make it clearer. You might already know about some of the aspects that I will inform you about, but I still would like to receive your feedback on these information sections.

Information on haemophilia

Patients with haemophilia have an error in the gene for a certain coagulation factor, or for short referred to as factor. The error is located in the gene for coagulation factor IX in haemophilia B and the gene for coagulation factor VIII in haemophilia A. Because of this error, these patients are not able to produce the coagulation factor or they produce insufficient amounts of correct coagulation factors. Due to this insufficiency these patients bleed for a longer time compared to people with the correct gene, or bleedings can occur spontaneously in patients that produce almost no correct coagulation factor.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Information on the treatment of haemophilia

The aim of treatment in haemophilia is to supplement the body with coagulation factor to stop or prevent bleedings. Coagulation factor cannot be swallowed in pill form but has to be injected directly into a vein to reach the blood circulation. Patients can self-administer the coagulation factor when a bleeding occurs or when they know that they will participate in an activity with the risk of causing a bleeding, this is called treatment 'on demand'. In addition, patients can also treat themselves in a 'prophylactic' manner through self-administration multiple times per week to keep the coagulation factor up to standard. For haemophilia A patients this includes two to three administrations per week and for haemophilia B patients two per week. However, the number of necessary injections per week can vary per individual. Some patients develop neutralising antibodies (inhibitors) against the administered factor, resulting in inefficacy of the treatment.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

General information on gene therapy in haemophilia

Genetic disorders are caused by an error that is present in our genetic material, in other words an error in one of our genes. This error can arise spontaneously or can be passed along by one or both parents. By means of gene therapy we try to correct the error so that the body contains the correct gene and the correct activity can take place in the body. The goal of gene therapy in haemophilia is to deliver the correct gene of the coagulation factor to the body. Hereby the correct factor will be produced in the body, and the patient no longer has to administer extra factor via injection.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

With gene therapy the correct version of the gene for the coagulation factor will be administered directly to the body. The correct gene will be packaged in 'a vector' that is responsible for delivering the gene to the liver cells, where the new gene is added next to the genetic material that is already present. It will not alter your own genetic material. For haemophilia, a modified virus is used as vector as this has a good capacity to reach the liver cells. The virus is modified in a way that it is only capable of delivering the genes to the liver cells; the virus itself is not infectious or functional. Only the casing of the virus remains as a sort of taxi.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Practical information on the treatment of haemophilia with gene therapy

Gene therapy is administered once via a vein in a hospital during 30–60 min on average. After the vector has delivered the correct gene to the liver cells, the liver cells themselves start to produce coagulation factor. After this one-time administration the patient will have to come to the hospital for check-ups regularly during a period of about 3 months to monitor the factor level. After these 3 months this becomes a yearly check-up. The treatment with gene therapy results in a factor concentration that is always on the same level. This in contrast to injections with coagulation factor that results in a high factor concentration directly after injection, but a low concentration before the next injection. This means that gene therapy will provide a stable factor level that is high enough to protect you against bleedings, against fluctuating factor levels with the factor injections.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Side effects of gene therapy in haemophilia

In some patients a light inflammation of the liver is observed after treatment with gene therapy. This inflammation cannot cause hepatitis C and does not cause noticeable symptoms. The light inflammation will be treated with cortisone (corticosteroids) to avoid the occurrence of symptoms. In addition, 30%–50% of the population already has

antibodies against the used vectors. This means that these people currently do not qualify for treatment with gene therapy as the vector will be broken down by their body. Because of the presence of these antibodies the vectors will not reach the liver cells and the gene therapy will not be effective. When patients without pre-existing antibodies participate in clinical trials, it has been determined that they always develop antibodies against the vector after administration of gene therapy, this is a normal reaction of the body. This development of antibodies does not cause noticeable symptoms and does not hinder the function of the administered gene therapy. This means that they can be treated successfully with the same vector once, but that treatment with the same vector cannot be repeated. It is unknown if it is possible to treat patients again with another type of vector for which the patient has not yet developed antibodies, if the gene therapy would not work long enough.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Results from clinical trials of gene therapy in haemophilia

This therapy is still in clinical development and is not yet approved by the European Commission. All data that we present here originate from clinical trials with severe haemophilia patients. Currently, only adult patients with severe haemophilia and without inhibitors can receive gene therapy. In these studies, we see that there is a large variability across results. Some patients no longer need factor injections after gene therapy was administered to them and experience no to almost no bleedings anymore. In contrast, other patients still need extra factor administration and experience a few bleedings per year. To date, no patients have developed inhibitors against the coagulation factor produced by the liver after administration of gene therapy. The monitoring of patients in clinical trials is now 2 years on average for haemophilia A and 8 years for haemophilia B, whereby it is uncertain for how long this therapy will result in sufficient production of coagulation factor by the liver. In other words, it is unknown whether the therapy will provide a life-long effect. In addition, it is expected that gene therapy for haemophilia will come with a one-time high cost for the government against the spread cost that is currently paid for lifelong factor administrations.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Gene therapy – Patient and parent opinion

- What is your opinion on the treatment of haemophilia with gene therapy?
- What information would you like to additionally receive on the topic of gene therapy in haemophilia?
- Would you be willing for your relative to receive treatment with gene therapy/would you want your child to be treated with gene therapy? Why or why not?

- Please indicate your willingness regarding the use of gene therapy:
 1. Very willing
 2. Willing
 3. Neutral
 4. Not willing
 5. Not willing at all
- Are there any other elements that could influence your choice that we have not discussed in the information section?
- What are for you the top three elements that influence your choice? → *put in the table below*
- How do you perceive the fact that it is currently unknown for how long the gene therapy will be effective since there is no lifelong follow-up data yet?
- To date only patients can be treated without antibodies against the vector. Moreover, you can only be treated once with the same vector since you will develop antibodies after treatment. It is currently being investigated if it is possible to treat a second time with another vector. What is your opinion on this?
- In the table below, please indicate the six elements that you think are most important when deciding whether gene therapy is the right treatment for your relative/your child (using scores from 1 to 6, with '1' being the most important element).
- What elements on this list do you find not at all important when making a decision on treatment with gene therapy?

Categories	Elements	Definition	Ranking
Nature of treatment	Mechanism of action	The specific process through which a treatment produces its effect (e.g., through delivering a gene to liver cells in the case of gene therapy; or through delivering factor to the body in the case of factor replacement therapy)	
Administration	Route of administration	The path by which a treatment is administered to the body (e.g., oral, intravenous, subcutaneous)	
	Dose frequency	The number of times a treatment is administered within a specific time period (e.g., twice per week, once per year)	
	Duration of administration	The amount of time needed to complete one administration (e.g., 15 min, 1 h)	
	Dosage strength	The strength of a treatment, which indicates the amount of active ingredient in each dosage (e.g., concentration of factor, concentration of vectors)	

(Continues)

Categories	Elements	Definition	Ranking
	Place of administration	The geographical place where the treatment is administered (e.g., at home, hospital)	
	Ease of administration	The degree of ease to perform an administration	
	Ease of product storage	The degree of ease to store a treatment (e.g., the amount of storage space needed, temperature requirements)	
Follow-up	Frequency of monitoring	The number of times a patient has to visit a physician for follow-up on the effect of the treatment within a specific time period (e.g., once per month, once per year)	
Benefits	Effect on factor level	The effect on the amount of working clotting factor in the blood, delivered via factor replacement therapy or produced by the patient after gene therapy (often expressed in percentage, % of normal levels)	
	Effect on annual bleeding rate	The effect of the treatment on the number of bleeding events per year	
	Probability that prophylaxis can be stopped after treatment	The chance that use of prophylactic factor replacement therapy can be stopped after treatment (expressed in percentage, % of patients that can stop prophylaxis)	
	Uncertainty regarding long-term benefits	The degree of uncertainty that the effect of the treatment will be maintained after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
Quality of Life	Impact on daily life	The impact of the treatment on daily activities	
	Impact on participation in physical activity	The impact of the treatment on the performance of physical activity (sports)	
	Possibility to undergo major surgery	The impact of the treatment on the possibility to undergo major surgery	

(Continues)

Categories	Elements	Definition	Ranking
Risks	Probability that liver inflammation will develop	The chance that liver inflammation develops after treatment (expressed in percentage, %, of patients that develops liver inflammation)	
	Uncertainty regarding long-term risks	The degree of uncertainty regarding the side effects that can occur after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
	Spontaneously mentioned elements		

Cases

I will go through three hypothetical scenarios with you. I will ask you each time whether you prefer scenario A or scenario B.

Hypothetical scenario example 1:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 5 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a very small chance of having side effects (e.g. rashes at infusion site).	You have no treatment-related side effects.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?

Hypothetical scenario example 2:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?
 2. *If they find it difficult to choose: What if you had to choose?*
- *If the responses on the previous two questions were the same: why did you answer in both cases gene therapy/preventive therapy?*
- *If the responses on the previous two questions were different: why did you give a different answer for the two cases?*
 3. *Try to get in-depth information on the variability*

We are going to have another look at the previously mentioned example. Besides the standard preventive therapy or gene therapy there is now also the option of long-acting coagulation factors. These lower the administration frequency to once per 3–5 days for haemophilia A patients (instead of 3 times per week) and to once per 7–14 days for haemophilia B (instead of twice per week).

Hypothetical scenario example 3:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion one time per two weeks.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?

Some peoples with severe haemophilia will have other treatment options in the future, namely non-factor therapies (NFT). These NFTs act on other aspects of the coagulation of the blood and by pass in that manner factor VIII and IX. NFTs would be administered subcutaneously (not directly into the vein) and would also require less frequent administrations (once every 2–4 weeks). This administration is less invasive and easier to perform. In addition, this therapy results in a stable concentration during the full duration without administration. Currently there is one NFT approved in Europe, namely emicizumab (Hemlibra), that can be used in haemophilia A patients with inhibitors. In the United States this therapy is also approved for haemophilia A patients without inhibitors. These treatments are currently sometimes not strong enough to prevent bleedings and therefore during active bleedings they sometimes have to be combined with coagulation factors.

- Did you understand this information?

- How does the availability of these non-factor therapies influence your willingness to use gene therapy/accept treatment with gene therapy for your child?

As a last question, knowing that your relative/your child can still pass along haemophilia to your/their children. When would you consider your relative/your child cured?

Finishing the interview

- We have gone through all of the questions of the interview. Did you have anything you would like to share with me that I did not yet ask you about?
- Do you have any questions for me?
- Can I contact you if I would have any follow-up questions?
- What did you think of the interview?

Thanks a lot for your participation in this interview. Do not hesitate to contact me if you would have any further questions.

INTERVIEW GUIDE FOR CLINICAL EXPERTS

Interview number

Date

Location

Name interviewer

Supervisor

Starting time

Ending time

My name is *name interviewer* (and my supervisor *name supervisor if present* will also be present today). In interviews, like the one that we will conduct with you today, we want to investigate the opinion of you as a clinical expert on the use of a new, innovative therapy in development, namely gene therapy, for the treatment of haemophilia. This study is conducted by HCD Economics and in collaboration with the master thesis of Sissel Michelsen, the PhD of Eline van Overbeeke and the PREFER project. For this study we are working together with different organisations including the haemophilia patient organization, 'The Haemophilia Society'.

In the next hour we will discuss the following topics:

- We will talk about gene therapy, an innovative treatment that is not yet approved for use in Europe and thus not yet available for the treatment of haemophilia.
- We will first explore what you already know about gene therapy. Afterwards we will provide you with information on this topic to see if this information is understandable.

- Subsequently we will ask you about your opinion on this therapy and we will ask you why you would want your patient to be treated with this therapy or why not.
- We will also discuss a couple of examples (cases) with you of outcomes in patients that participated in clinical trials with gene therapy and we will ask you how you would make a choice in these situations on behalf of your patient.
- In addition, we would like to know from you how you would make a choice between gene therapy and the existing therapies.

I want to thank you again for your participation in this interview. Before we start I want to clarify some aspects of the interview:

- We are looking for your opinion and wrong answers do thus not exist.
- This interview will be treated confidentially and the results will be processed in a non-identifiable way.
- The interview will take about an hour.
- You are not obliged to answer questions that you do not wish to respond to.
- You can stop the interview at any moment without having to give a reason.
- If you do not understand a question or have questions, you may always ask for more explanation.

Is the consent form completed and signed? This has to be completed and signed before the interview can start. If not: do not go further with the interview till the consent form is signed.

To allow me to process and correctly report the information gathered from this interview, I would like to audio-record this interview. This will allow me to after the interview fully transcribe the interview and to correctly process it. Can I start the audio-recording now? *If the participant does not agree to start the audio-recording and all of their questions on the recording are answered, the interview will be stopped.*

INTRODUCTION

If the introductory survey was not yet received per mail: Can I ask you to give me the survey that was sent to you in advance? When the survey was received, check if all questions are completed. IF there are still open questions: Would you mind answering the question on 'remaining question' or would you rather want to leave it open? If they want to complete it: the answer is added on the survey.

Introductory question:

- Why did you agree to participate in this study?

Gene therapy – Information part

- Have you heard much about gene therapy?
 1. If yes, what do you already know about gene therapy?
 2. If yes, how did you receive this information?
- How would you estimate your knowledge on gene therapy to be?

3. Very good
4. Good
5. Reasonable
6. Bad
7. Very bad

Now I will go through some information with you on the disease, current treatment options and the use of gene therapy in haemophilia. After every information section, I will ask you if the information is understandable and how I can improve the phrasing of the information to make it clearer. You might already know about some of the aspects that I will inform you about, but I still would like to receive your feedback on these information sections.

Information on haemophilia

Patients with haemophilia have an error in the gene for a certain coagulation factor, or for short referred to as factor. The error is located in the gene for coagulation factor IX in haemophilia B and the gene for coagulation factor VIII in haemophilia A. Because of this error, these patients are not able to produce the coagulation factor or they produce insufficient amounts of correct coagulation factors. Due to this insufficiency these patients bleed for a longer time compared to people with the correct gene, or bleedings can occur spontaneously in patients that produce almost no correct coagulation factor.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Information on the treatment of haemophilia

The aim of treatment in haemophilia is to supplement the body with coagulation factor to stop or prevent bleedings. Coagulation factor cannot be swallowed in pill form but has to be injected directly into a vein to reach the blood circulation. Patients can self-administer the coagulation factor when a bleeding occurs or when they know that they will participate in an activity with the risk of causing a bleeding, this is called treatment 'on demand'. In addition, patients can also treat themselves in a 'prophylactic' manner through self-administration multiple times per week to keep the coagulation factor up to standard. For haemophilia A patients this includes two to three administrations per week and for haemophilia B patients two per week. However, the number of necessary injections per week can vary per individual. Some patients develop neutralising antibodies (inhibitors) against the administered factor, resulting in inefficacy of the treatment.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

General information on gene therapy in haemophilia

Genetic disorders are caused by an error that is present in our genetic material, in other words an error in one of our genes. This error can arise spontaneously or can be passed along by one or both parents. By means of gene therapy we try to correct the error so that the body contains the correct gene and the correct activity can take place in the

body. The goal of gene therapy in haemophilia is to deliver the correct gene of the coagulation factor to the body. Hereby the correct factor will be produced in the body, and the patient no longer has to administer extra factor via injection.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

With gene therapy the correct version of the gene for the coagulation factor will be administered directly to the body. The correct gene will be packaged in 'a vector' that is, responsible for delivering the gene to the liver cells, where the new gene is added next to the genetic material that is already present. It will not alter your own genetic material. For haemophilia, a modified virus is used as vector as this has a good capacity to reach the liver cells. The virus is modified in a way that it is only capable of delivering the genes to the liver cells; the virus itself is not infectious or functional. Only the casing of the virus remains as a sort of taxi.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Practical information on the treatment of haemophilia with gene therapy

Gene therapy is administered once via a vein in a hospital during 30–60 min on average. After the vector has delivered the correct gene to the liver cells, the liver cells themselves start to produce coagulation factor. After this one-time administration the patient will have to come to the hospital for check-ups regularly during a period of about 3 months to monitor the factor level. After these 3 months this becomes a yearly check-up. The treatment with gene therapy results in a factor concentration that is always on the same level. This in contrast to injections with coagulation factor that results in a high factor concentration directly after injection, but a low concentration before the next injection. This means that gene therapy will provide a stable factor level that is high enough to protect you against bleedings, against fluctuating factor levels with the factor injections.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Side effects of gene therapy in haemophilia

In some patients a light inflammation of the liver is observed after treatment with gene therapy. This inflammation cannot cause hepatitis C and does not cause noticeable symptoms. The light inflammation will be treated with cortisone (corticosteroids) to avoid the occurrence of symptoms. In addition, 30%–50% of the population already has antibodies against the used vectors. This means that these people currently do not qualify for treatment with gene therapy as the vector will be broken down by their body. Because of the presence of these antibodies the vectors will not reach the liver cells and the gene therapy will not be effective. When patients without pre-existing antibodies partic-

ipate in clinical trials, it has been determined that they always develop antibodies against the vector after administration of gene therapy, this is a normal reaction of the body. This development of antibodies does not cause noticeable symptoms and does not hinder the function of the administered gene therapy. This means that they can be treated successfully with the same vector once, but that treatment with the same vector cannot be repeated. It is unknown if it is possible to treat patients again with another type of vector for which the patient has not yet developed antibodies, if the gene therapy would not work long enough.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Results from clinical trials of gene therapy in haemophilia

This therapy is still in clinical development and is not yet approved by the European Commission. All data that we present here originate from clinical trials with severe haemophilia patients. Currently, only adult patients with severe haemophilia and without inhibitors can receive gene therapy. In these studies, we see that there is a large variability across results. Some patients no longer need factor injections after gene therapy was administered to them and experience no to almost no bleedings anymore. In contrast, other patients still need extra factor administration and experience a few bleedings per year. To date, no patients have developed inhibitors against the coagulation factor produced by the liver after administration of gene therapy. The monitoring of patients in clinical trials is now 2 years on average for haemophilia A and 8 years for haemophilia B, whereby it is uncertain for how long this therapy will result in sufficient production of coagulation factor by the liver. In other words, it is unknown whether the therapy will provide a life-long effect. In addition, it is expected that gene therapy for haemophilia will come with a one-time high cost for the government against the spread cost that is currently paid for lifelong factor administrations.

- How understandable was this information to you?
 1. How can this information be formulated more clearly?

Gene therapy – patient and parent opinion

- What is your opinion on the treatment of haemophilia with gene therapy?
- What information would you like to additionally receive on the topic of gene therapy in haemophilia?
- Would you be willing for your patient to receive treatment with gene therapy? Why or why not?
- Please indicate your willingness regarding the use of gene therapy:
 1. Very willing
 2. Willing
 3. Neutral
 4. Not willing
 5. Not willing at all

- Are there any other elements that could influence your choice that we have not discussed in the information section?
- What are for you the top three elements that influence your choice? *put in the table below*
- How do you perceive the fact that it is currently unknown for how long the gene therapy will be effective since there is no lifelong follow-up data yet?
- To date only patients can be treated without antibodies against the vector. Moreover, you can only be treated once with the same vector since you will develop antibodies after treatment. It is currently being investigated if it is possible to treat a second time with another vector. What is your opinion on this?
- In the table below, please indicate the six elements that you think are most important when deciding whether gene therapy is the right treatment for your patient (using scores from 1 to 6, with '1' being the most important element).

Categories	Elements	Definition	Ranking
Nature of treatment	Mechanism of action	The specific process through which a treatment produces its effect (e.g., through delivering a gene to liver cells in the case of gene therapy; or through delivering factor to the body in the case of factor replacement therapy)	
Administration	Route of administration	The path by which a treatment is administered to the body (e.g., oral, intravenous, subcutaneous)	
	Dose frequency	The number of times a treatment is administered within a specific time period (e.g., twice per week, once per year)	
	Duration of administration	The amount of time needed to complete one administration (e.g., 15 min, 1 h)	
	Dosage strength	The strength of a treatment, which indicates the amount of active ingredient in each dosage (e.g., concentration of factor, concentration of vectors)	
	Place of administration	The geographical place where the treatment is administered (e.g. at home, hospital)	
	Ease of administration	The degree of ease to perform an administration	

(Continues)

Categories	Elements	Definition	Ranking
	Ease of product storage	The degree of ease to store a treatment (e.g., the amount of storage space needed, temperature requirements)	
Follow-up	Frequency of monitoring	The number of times a patient has to visit a physician for follow-up on the effect of the treatment within a specific time period (e.g. once per month, once per year)	
Benefits	Effect on factor level	The effect on the amount of working clotting factor in the blood, delivered via factor replacement therapy or produced by the patient after gene therapy (often expressed in percentage, %, of normal levels)	
	Effect on annual bleeding rate	The effect of the treatment on the number of bleeding events per year	
	Probability that prophylaxis can be stopped after treatment	The chance that use of prophylactic factor replacement therapy can be stopped after treatment (expressed in percentage, %, of patients that can stop prophylaxis)	
	Uncertainty regarding long-term benefits	The degree of uncertainty that the effect of the treatment will be maintained after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
Quality of Life	Impact on daily life	The impact of the treatment on daily activities	
	Impact on participation in physical activity	The impact of the treatment on the performance of physical activity (sports)	
	Possibility to undergo major surgery	The impact of the treatment on the possibility to undergo major surgery	
Risks	Probability that liver inflammation will develop	The chance that liver inflammation develops after treatment (expressed in percentage, %, of patients that develops liver inflammation)	

(Continues)

Categories	Elements	Definition	Ranking
	Uncertainty regarding long-term risks	The degree of uncertainty regarding the side effects that can occur after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
Spontaneously mentioned elements			

Cases

I will go through three hypothetical scenarios with you. I will ask you each time whether you prefer scenario A or scenario B.

Hypothetical scenario example 1:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 5 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a very small chance of having side effects (e.g. rashes at infusion site).	You have no treatment-related side effects.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?

Hypothetical scenario example 2:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion two times per week.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?

2. If they find it difficult to choose: What if you had to choose?

- If the responses on the previous two questions were the same: why did you answer in both cases gene therapy/preventive therapy?
- If the responses on the previous two questions were different: why did you give a different answer for the two cases?
 1. Try to get in-depth information on the variability

We are going to have another look at the previously mentioned example. Besides the standard preventive therapy or gene therapy there is now also the option of long-acting coagulation factors. These lower the administration frequency to once per 3–5 days for haemophilia A patients (instead of 3 times per week) and to once per 7–14 days for haemophilia B (instead of twice per week).

Hypothetical scenario example 3:

If these are the only treatments available, which one would, you choose?

Attributes	Scenario A	Scenario B
Treatment effectiveness	You have 1 haemophilia-related bleeds per year.	You have no haemophilia-related bleeds.
Treatment side effects (e.g. infusion site reactions)	You have a small chance of having side effects (e.g. rashes at infusion site).	1% Probability that liver inflammation will develop per year.
Administration time	Your treatment administration takes 10 mins per infusion.	You are not required to administer treatment.
Inhibitor development	It is very unlikely that you develop an inhibitor to factor replacement.	You will not develop an inhibitor to factor replacement.
Type of treatment	You receive factor infusion one time per two weeks.	You no longer require treatment.
Which scenario do you think is better?	<input type="checkbox"/>	<input type="checkbox"/>

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
 1. Why?

Some peoples with severe haemophilia will have other treatment options in the future, namely non-factor therapies (NFT). These NFTs act on other aspects of the coagulation of the blood and by pass in that manner factor VIII and IX. NFTs would be administered subcutaneously (not directly into the vein) and would also require less frequent administrations (once every 2–4 weeks). This administration is less invasive and easier to perform. In addition, this therapy results in a stable concentration during the full duration without administration. Currently there is one NFT approved in Europe, namely emicizumab (Hemlibra), that can be used in haemophilia A patients with inhibitors. In the United States this therapy is also approved for haemophilia A patients without inhibitors. These treatments are currently sometimes not strong enough to prevent bleedings and therefore during active bleedings they sometimes have to be combined with coagulation factors.

- Did you understand this information?
- How does the availability of these non-factor therapies influence your willingness to use gene therapy/accept treatment with gene therapy for your patient?

As a last question, knowing that your patient can still pass along haemophilia to their children. When would you consider your patient cured?

Finishing the interview

- We have gone through all of the questions of the interview. Did you have anything you would like to share with me that I did not yet ask you about?
- Do you have any questions for me?
- Can I contact you if I would have any follow-up questions?
- What did you think of the interview?

Thanks a lot for your participation in this interview. Do not hesitate to contact me if you would have any further questions.

APPENDIX A2: SPONTANEOUSLY REPORTED ATTRIBUTES INCLUDED IN THE ATTRIBUTE RANKING EXERCISE

Spontaneously mentioned attributes

Lifespan of efficacy of gene therapy

Level of knowledge and research on gene therapies

Family opinions on gene therapy

Impact on working life

Management of patient post-intervention

Viral shedding

Alcohol consumption

Additional treatments after intervention (e.g., steroids)

Underlying conditions

Patient lifestyle

Patient adherence

Costs associated with gene therapy

Certainty of risks/outcomes/duration

Emotional and identity changes