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Patient perspectives regarding gene therapy in haemophilia: Interviews from the PAVING study

Eline van Overbeeke[1] | Sissel Michelsen[1] | Brett Hauber[2] | Kathelijne Peerlinck[3] | Cedric Hermans[4] | Catherine Lambert[4] | Michel Goldman[5] | Steven Simoens[1] | Isabelle Huys[1]

[1]Clinical Pharmacology and Pharmacotherapy, University of Leuven, Leuven, Belgium

[2]Health Preference Assessment, RTI Health Solutions, Research Triangle Park, NC, USA

[3]Haemophilia Center, UZ Leuven, Leuven, Belgium

[4]Haemophilia Clinic, St-Luc University Hospital, Brussels, Belgium

[5]Institute for Interdisciplinary Innovation in healthcare, Université libre de Bruxelles, Brussels, Belgium

Correspondence
Eline van Overbeeke, Clinical Pharmacology and Pharmacotherapy, University of Leuven, Herestraat 49 Box 521, 3000 Leuven, Belgium.
Email: Eline.vanoverbeeke@kuleuven.be

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Abstract

Introduction: Exploring patient perceptions regarding gene therapies may provide insights about their acceptability to patients.

Objective: To investigate opinions of people with haemophilia (PWH) regarding gene therapies. Moreover, this study aimed to identify patient-relevant attributes (treatment features) that influence PWH's treatment choices.

Methods: Semi-structured individual interviews were conducted with Belgian PWH, types A and B. A predefined interview guide included information sections and open, attribute ranking and case questions. Qualitative data were organized using NVivo 12 and analysed following framework analysis. Sum totals of scores obtained in the ranking exercise were calculated per attribute.

Results: In total, 20 PWH participated in the interviews. Most participants demonstrated a positive attitude towards gene therapy and were very willing (40%; n = 8) or willing (35%; n = 7) to receive this treatment. The following five attributes were identified as most important to PWH in making their choice: annual bleeding rate, factor level, uncertainty of long-term risks, impact on daily life, and probability that prophylaxis can be stopped. While participants were concerned about the uncertainty regarding long-term safety, most participants were less concerned about uncertainty regarding long-term efficacy.

Conclusions: This qualitative study showed that most PWH have a positive attitude towards gene therapy and that besides efficacy, safety and the related uncertainties, also impact on daily life is important to patients. The identified patient-relevant attributes may be used by regulators, health technology assessment bodies and payers in their evaluation of gene therapies for haemophilia. Moreover, they may inform clinical trial design, pay-for-performance schemes and real-world evidence studies.

KEYWORDS
advanced therapy, attitudes, gene therapies, haemophilia, interviews, opinion, preference

1 | INTRODUCTION

Gene therapies are novel treatments that have the potential to generate permanent benefits for patients. For many rare diseases, gene therapies are in development and are increasingly obtaining marketing authorization. However, at the time that market access is sought often uncertainties regarding long-term efficacy and safety of these therapies remain; reducing the perceived value of these high-cost treatments.[1–4]

For haemophilia A and B, gene therapies are in late stages of development, but have not yet gained market authorization. These gene therapies come with the promise of a cure for haemophilia where one infusion could possibly replace lifelong administration of other high-cost treatment options. Current standard of care of severe haemophilia consists of regular invasive intravenous administrations of factor replacement therapy (FRT) that result in fluctuations of achieved factor levels that make people with haemophilia (PWH) more prone to bleeds and joint damage, and may result in development of inhibitors (neutralizing antibodies against exogenous clotting factors) in some PWH.[5–8]

Previous studies investigating attitudes of PWH towards treatment modalities have focused on FRT, blood transfusion, or treatments no longer under development.[9,10] Attitudes of PWH towards their current therapy and gene therapy have, to date, only been reported through FDA public patient meetings.[11] and a study of van Balen et al.[12] on patient perspectives regarding multiple novel haemophilia treatments. As gene therapies come with a novel mode of action and uncertainties, gaining a better understanding of patient perceptions regarding these therapies may provide insights about their acceptability to PWH.

This qualitative research aimed to investigate the opinions and concerns of PWH regarding gene therapies. We investigated comprehensibility of information about gene therapies, information needs, willingness to use, and attitudes towards uncertainties. Moreover, this research formed the qualitative phase of the Patient preferences to Assess Value IN Gene therapies (PAVING) study that aims to investigate trade-offs that adult Belgian PWH make when asked to choose between a standard of care and gene therapy. In preparation of the quantitative phase (survey), this research therefore also aimed to identify patient-relevant attributes (treatment features).

2 | METHODS

Interviews and focus group discussions can be used for in-depth exploration of the patient perspective regarding treatments.[13,14] As there was no interest in group dynamics, the choice was made to conduct semi-structured individual interviews. These interviews were conducted with haemophilia patients from January till June 2019. An advisory board of haematologists, health technology assessment (HTA) and payer decision-making experts, industry market access experts, rare disease experts, patient education experts and patient representatives was consulted during study design. Details on the methods and results of the interviews were reported according to the guidelines of Hollin et al.[15] and the consolidated criteria for reporting qualitative research (COREQ) checklist was completed (Appendix S1 I) [16].

2.1 | Interview guide development

A predefined interview guide was designed for use in the interviews (Appendix S1 II). Prior to any questions, participants received information regarding the disease, standard of care and gene therapy. Comprehensibility to participants and additional information needs were assessed during the interviews. The content of the information sections and the rest of the interview guide were informed by a systematic literature review that resulted in the identification of 13 clinical trial publications and 19 patient preference studies/public meetings (Appendix S1 III). Moreover, information sections covered aspects highlighted in the work of Miesbach et al,[17] including but not limited to uncertainty in long-term safety and efficacy, eligibility criteria, variability in achieved outcomes, and current absence of major safety issues. The information sections were followed by open questions to investigate participants' attitudes towards gene therapy and reasons to refrain from or accept gene therapy.

To date, there is no single guideline stating how attributes should be identified for subsequent quantitative preference research.[18] Our interview guide combined three techniques: 1) open questions to detect new attributes not identified during literature review (bottom-up) and to question participants about the importance of attributes identified in literature (top-down), 2) ranking exercises and 3) case questions.[18–21] Bottom-up attributes were identified by asking participants about the top three elements that would influence their choice between standard of care and gene therapy before showing any top-down identified attributes. Literature from the systematic literature review informed the identification of 22 top-down attributes. Consultation with the advisory board resulted in the exclusion of four top-down attributes relating to cost and manufacturing. In the end, 18 top-down attributes were included in the ranking exercise. Participants ranked their top six attributes among the top-down and bottom-up identified attributes. Case questions were then asked to confirm the importance of attributes in making choices between gene therapy and other treatment profiles (standard prophylactic FRT, long-acting FRT or non-factor replacement therapy; NFT).

The content of the interview guide was validated by three haematologists and piloted with two patient representatives. The interview guide was established in Dutch and translated into English and French by a certified translator; translations were checked by one of the researchers (EvO).

2.2 | Participant recruitment

Participants were recruited through purposive sampling to reach heterogeneity in age, type of haemophilia (A/B) and disease severity

(moderate/severe). Recruiting parties included the Belgian national haemophilia patient organization (AHVH), and haematologists from Belgian haemophilia reference centres (UZ Leuven and Cliniques Universitaires Saint-Luc-UCLouvain). Participants were included if they were 18 years or older, suffered from haemophilia A or B and lived in Belgium.

2.3 | Conduct of interviews

Semi-structured interviews were executed in person and in the native language of the participant (Dutch or French). After informed consent was given, a short demographics and health literacy[20] questionnaire was completed (Appendix S1 IV). The interview guide was used to present information and ask predetermined questions. However, open discussion was also held to explore opinions in-depth. Interviews were audio-recorded and transcribed verbatim. All transcripts were produced in the original language and non-English quotes were only translated into English upon inclusion in the manuscript.

2.4 | Analysis

Demographic, clinical and health literacy information, as well as answers to closed, ranking and case questions, were reported using descriptive statistics. Results from the ranking exercise were transformed: for each participant, a score between 1 and 6 was assigned to each of the attributes in their top six, with 6 points being assigned to the most important attribute. Sum totals of the scores were calculated per attribute to generate a list of the ten attributes most important to PWH.

Data from answers to open questions were organized using NVivo 12 and analysed following framework analysis, a type of thematic analysis[22] (Appendix S1 V). Framework analysis was chosen as it allows for a structured analysis of qualitative data by themes.[22] Analysis started with familiarization through the conduct, transcription and reading of interviews. Themes of the interview guide informed the creation of deductive codes. The first 4 transcripts were independently coded by two researchers (EvO and SM) and then compared. Based on observed patterns, inductive codes were created. The inductive and deductive codes together formed a 'coding tree' (Appendix S1 VI). The coding tree was uploaded in NVivo and applied to all transcripts, where sections of transcripts relating to a particular theme were classified under the respective code. All data were summarized into a framework matrix. The data of the interviews were interpreted, summarized per code, and some quotes of individual interviewees were added for clarification. Data saturation, meaning that no new topics, opinions or views were gathered in following interviews, was assessed through a saturation table and documented codebook development according to Kerr et al.[14,23] (Appendix S1 VII).

3 | RESULTS

3.1 | Participant characteristics

First contact was established with 32 PWH of which 20 participated in interviews. Data saturation was reached after inclusion of the first 11 participants (Appendix S1 VII). Most participants were older than 40 years of age (75%) and lived in Flanders (65%) (Table 1). Most had severe haemophilia (80%), had moderate (45%) to severe (45%) joint damage and were on a prophylactic treatment regimen (75%). All participants were either satisfied or very satisfied with their current treatment. Health literacy was adequate in all participants. Participants that had already discussed treatment with gene therapy with their physician (65%) reached a decision to not receive gene therapy, to receive gene therapy in a clinical trial or no decision was reached.

There was variability in baseline knowledge about gene therapy. While all participants had already heard of gene therapy before the interview, they had very good (5%), good (30%), reasonable (50%) bad (10%) or very bad (5%) self-reported baseline knowledge about gene therapy. Most participants knew that a virus-based vector is used to provide a gene to the liver that will allow the liver to produce coagulation factor. Most participants received information about gene therapy through their haematologist (60%), Internet/media (50%) and local patient organization (30%).

3.2 | Information about the disease, standard of care and gene therapy

Participants found all provided information about haemophilia, standard of care and gene therapy comprehensible. Additional information about the following topics was requested by multiple participants: inhibitors against FRT, durability and magnitude of achieved factor level, number of years evidence has been gathered, number of PWH treated, the concept of viral vectors, the difference between inhibitors and antibodies against the vector, (long-term) side effects, development of light inflammation of the liver, duration and side effects of treatment with corticosteroids, follow-up and restrictions after gene therapy administration, alternative treatment if benefits are not maintained in the long-term (re-administration of gene therapy or re-use of FRT), as well as cost and reimbursement. Moreover, several participants suggested using examples and illustrations to visualize difficult concepts and ensure comprehension by other PWH.

3.3 | Willingness to use gene therapy

Most participants (65%) had a positive attitude towards gene therapy, were surprised by this medical advancement and thought it would greatly impact many PWH lives. Some participants thought

TABLE 1 Participant characteristics (self-reported).

Characteristics	Patients (n = 20) n	%
Sex		
Females	1	5
Males	19	95
Age, years		
18-25	4	20
26-40	1	5
41-60	10	50
>60	5	25
Residence		
Flanders	13	65
Wallonia	6	30
Brussels	1	5
Type of haemophilia		
A	17	85
B	3	15
Age of onset		
0-1 year	13	65
2-5 years	4	20
>5 years	2	10
Disease severity		
Mild	1	5
Moderate	3	15
Severe	16	80
Treatment regimen		
On-demand	5	25
Prophylactic	15	75
Treatment satisfaction		
Very satisfied	12	60
Satisfied	8	40
Bleeding frequency		
1-2/week	3	15
2-3/month	1	5
1/month	5	25
4/year	1	5
1-2/year	7	35
<1/year	3	15
Severity of joint damage		
No damage	1	5
Mild	1	5
Moderate	9	45
Severe	9	45
Health literacy		
Adequate health literacy	20	100
Inadequate health literacy	0	0

the most benefit could be gained in younger PWH as gene therapy could protect them against joint damage and could have a positive effect on their personal and professional lives. Some participants said that gene therapy is still novel and that more evidence is needed regarding efficacy and safety. Others mentioned that it could lead to societal savings and could be a solution for third world countries. When participants were asked if they would be willing to receive treatment with gene therapy, 40% (n = 8) of participants was 'very willing', 35% (n = 7) was 'willing', 10% (n = 2) was 'neutral' and 15% (n = 3) was 'not willing'. Reasons for using gene therapy were as follows: stable factor level resulting in less risk and number of bleeds, no need for injections, less practical requirements and possibility of travelling, age (more benefit for young PWH and older ones that have lost self-administration autonomy), and societal cost savings as one administration of gene therapy could potentially replace recurrent administration of current high-cost FRT. Especially, the number of bleeds seemed to be of substantial importance to participants as *'it are the bleeds that cause the consequences of your hemophilia'* (PA_7). Reasons to refrain from using gene therapy included: satisfaction with current therapy and PWH *'don't want to take an unnecessary risk'* (PA_19), uncertainty regarding long-term safety of gene therapy, loss of haemophilia identity and advantages (invalidity allowance and protection against cardiovascular disease) that was perceived as *"scary"* (PA_18), intense initial follow-up, old age and the potential high cost of gene therapy. Most participants found the light liver inflammation provoked by gene therapy administration not to be disturbing if temporary and treatable with corticosteroids, while two others were concerned about the inflammation due to past liver problems (hepatitis C infection). Participants willing to use gene therapy were on average older (54y) and had more severe joint damage (moderate to severe) than participants that would refrain from it (23.5y; mild to moderate joint damage).

3.4 | Perception of uncertainties related to gene therapies

Many participants (n = 8) found it *'logic'* (PA_4) that gene therapy comes with uncertainty regarding long-term outcomes as it is a novel therapy. Nevertheless, uncertainty regarding long-term safety of gene therapy was a concern to many participants. In contrast, uncertainty regarding long-term efficacy was less perceived as an issue by participants as they would already appreciate short periods of efficacy to have a break from FRT administrations and knew they could fall back on FRT if necessary. Five participants required a minimum efficacy duration, from 1 year, to 2, 5 and 20 years. Five other participants expressed some concern regarding the uncertainty in long-term efficacy. Three participants mentioned that variability in achieved factor level between PWH treated with gene therapy was an important aspect influencing their decision-making, while others considered small increases in factor level (e.g. 5%) already to be beneficial.

When it was mentioned that a second administration of gene therapy (in case efficacy is not maintained) is currently not possible due to development of antibodies, most participants responded in a neutral manner and did not perceive this as a problem and would switch back to the FRT if necessary. However, three participants found this to be a risk and wondered whether it would be better to wait until better vectors are developed.

3.5 | Attribute ranking

From the bottom-up identified attributes, the attributes mentioned by multiple participants included treatment administration (chance of stopping, mode and frequency; 50%), impact of practical requirements on daily life and travel (40%), bleeding rate (30%), uncertainties (30%), cost (20%) and factor level (variability and stability; 20%). The ranking exercise with top-down and bottom-up identified attributes revealed that the five attributes most important to PWH are as follows: annual bleeding rate (ABR), factor level, uncertainty of long-term risks, impact on daily life and probability that prophylaxis can be stopped (Table 2). A participant mentioned that while ABR and factor level are both important, they are related and that annual bleeding rate as a clinical result is more important; *'The two are linked. It is the consequence of the treatment that is most important' (PA_13)*. Attributes found unimportant by PWH mostly included attributes related to administration (e.g. dosage, duration, place, ease, and route of administration; n = 13) and follow-up/monitoring (n = 7).

TABLE 2 Top 10 attributes important to patients.

Rank	Attribute	Score*
1	Effect on annual bleeding rate	47
2	Factor level	43
3	Uncertainty long-term risks	39
4	Impact on daily life	39
5	Probability that prophylaxis can be stopped	32
6	Possibility of underdoing major surgery	26
7	Route of administration	21
8	Probability of liver inflammation	21
9	Mechanism of action	20
10	Dose frequency	17

*n = 18; maximum score is 108 (6 points x 18 interviewees) per attribute.

3.6 | Attributes in cases

Hypothetical cases were presented to participants comparing gene therapy to standard prophylactic FRT, long-acting FRT or NFT. Attributes that were mentioned across cases by multiple participants include annual bleeding rate, factor level, chance of stopping prophylaxis, risk of light liver inflammation (not feared by most), risk of inhibitor development, uncertainty regarding side effects and impact on daily life and travel (Appendix S1 VIII).

4 | DISCUSSION

Through interviews with PWH, we were able to gain insights into their willingness to receive gene therapy as well as attributes that influence their choice. Most participants demonstrated a positive attitude towards gene therapy and were very willing or willing to receive treatment with gene therapy. Participants perceived the benefits of gene therapy to be the greatest for younger PWH. However, our study showed that younger PWH may be more reluctant towards gene therapy. This might be a result of current treatment satisfaction with limited joint damage, as also mentioned during the FDA patient meeting [11].

Five attributes most important to PWH were identified in the ranking exercise: ABR, factor level, uncertainty of long-term risks, impact on daily life, and probability that prophylaxis can be stopped. These attributes were also mentioned in response to the open and case questions. In the study of van Balen et al. [12] similar factors were identified: 'Ease of use of the medication' (including probability that prophylaxis can be stopped), 'Equally good or better bleed prevention' (ABR) and 'Fear of the unknown' (uncertainty of long-term risks). The importance of the factor 'Do not want to be a guinea pig/research subject' as identified by van Balen et al. [12] was not confirmed in the current study; this difference may be explained by the dissimilar focus of the two studies as the current study focused on use of gene therapy outside the clinical trial setting and the study of van Balen et al.[12] focused on willingness to participate in research and covered multiple novel treatments. Other attributes frequently mentioned in interviews of the current study were variability in achieved factor level, uncertainty in long-term efficacy and development of light inflammation. However, most participants perceived these uncertainties and risks to be manageable. Many of the concerns reported in the current study were also highlighted in the recent paper of Pierce et al,[24] including eligibility, variability in achieve factor level, durability of expression, quality of life, redosing and impact of liver inflammation. Concerns regarding long-term safety and efficacy of gene therapy were also mentioned by PWH in the FDA patient meeting.[11] Overall, efficacy (including uncertainties), safety (including uncertainties) and quality of life appear to form the pillars of therapeutic value of gene therapy to PWH (Figure 1). Besides therapeutic value, this study showed that PWH also want to limit the burden on society caused by societal costs of their current therapy and gene therapy; confirming similar results of van Balen et al.[12] However, opposite beliefs were identified on the cost-saving potential of gene therapy.

Results of this study confirm the importance of certain outcomes included in the coreHEM core outcomes set for gene therapy in haemophilia identified through a multi-stakeholder project by Iorio et al,[25] namely bleeding rate, factor level and duration of efficacy.

However, the importance of chronic pain, healthcare resource use after gene therapy administration and mental health were not confirmed. While pain and mental health may be important to PWH, the researchers believe that participants in the current study may have perceived prioritized attributes to be proxies for these non-prioritized attributes. Other differences may be explained by the difference in consulted stakeholders and the difference in decision context; the coreHEM initiative aimed to identify outcomes for gene therapy unrelated to any other treatment while the current study investigates how PWH make choices between gene therapy and standard of care.

4.1 | Strengths and limitations

While qualitative research allows for the exploration of thoughts and opinions and cannot ensure objectivity, validity of the study was ensured through validation of the interview guide by clinical experts and patient representatives, pilot interviews and assessment of data saturation. While identification of attributes was carried out via a systematic search, measures taken in haemophilia gene therapy clinical trials that may impact lifestyle (e.g. reduction of alcohol consumption and use of contraception to prevent sexual transmission of the vector) were not included in the list of top-down identified attributes as at the time of the study it was uncertain if these measures should also be taken when gene therapy is administered outside clinical trials once the therapy is approved. Results of this qualitative research were transparently reported according to the guidelines of Hollin et al[15] and the COREQ checklist.[16] Moreover, triangulation of patient-relevant attributes was achieved by employing three approaches to identify these: open, ranking and case questions.

Participants were recruited via the national patient organization and two hospitals. The study had a high response rate (62.5%). While the researchers aimed to include a heterogeneous sample of PWH (in terms of severity, residence and other demographics, and prior knowledge), it is uncertain if interest in gene therapy may have resulted in sampling bias. Health literacy was adequate in all participants, but substantial variability was observed in baseline knowledge about gene therapy. The researchers aimed to correct this variability by educating participants about gene therapy. However, differences in baseline knowledge may still have influenced responses.

To ensure information on gene therapy was objectively presented to participants and to minimize the variability between interviews, only two researchers (EvO and SM) conducted the interviews and they were both trained on the topic. SM conducted the interviews with Dutch-speaking participants and EvO the interviews with French-speaking participants. EvO supervised the conduct of the first three interviews by SM to ensure interviews were performed in the same manner by the two interviewers in the two languages. Both interviewers were trained on the topic of gene therapy in haemophilia by attending seminars given on the topic by experts in the field, conducting the literature review that informed the interview guide, and discussing the content of the interview guide with three haematologists and two patient representatives. Furthermore, the clinical information provided to participants in interviews was predefined in the interview guide and validated by three haematologists, and the interviewers did not deviate from this script.

While a large amount of often new information was provided to PWH, the interviewers made sure to go through the information and questions at the pace comfortable for the participant to prevent participants from feeling overwhelmed. Moreover, after every information section participants were asked whether they understood the information and all participants found these sections comprehensible. It could be possible that some bias in responses to these comprehension questions occurred as participants may not have wanted to admit that they did not understand the information. However, many participants asked additional questions about the information provided; showing that they felt comfortable expressing their additional information needs.

This research was performed with a small sample, in which PWH type B and PWH between 26 and 40 years old were underrepresented. Therefore, the results are likely not representative of the entire Belgian haemophilia population. However, a quantitative preference study (survey) will be designed based on the findings of the interviews reported in this paper to obtain more representative results in a larger sample of PWH. For this quantitative study, we aim to include a sample representative of the gene therapy target population. Results from this quantitative phase may provide more insights regarding the relative importance of attributes, acceptance of gene therapy to the full population, and influence of patient characteristics on acceptance; such as age and joint damage as preliminary identified in the current study.

4.2 | Implications and future use

This qualitative study identified attributes important to PWH which may be used by regulators, HTA bodies and payers in their evaluation of gene therapy for haemophilia.[26–29] The identified attributes represent patient-relevant outcomes and needs of PWH which may inform HTA in the identification of gene therapy clinical trials reaching patient-relevant endpoints and studies investigating quality of life. The patient-relevant outcomes identified in the current study may also be included in pay-for-performance schemes of managed-entry agreements. Additionally, the concerns of PWH about uncertainty of long-term safety and efficacy may inform future real-world evidence studies.

5 | CONCLUSIONS

Most PWH have a positive attitude towards gene therapy. Their willingness to receive gene therapy is predominantly motivated by the promise of a reduction in bleeds, high and stable factor level,

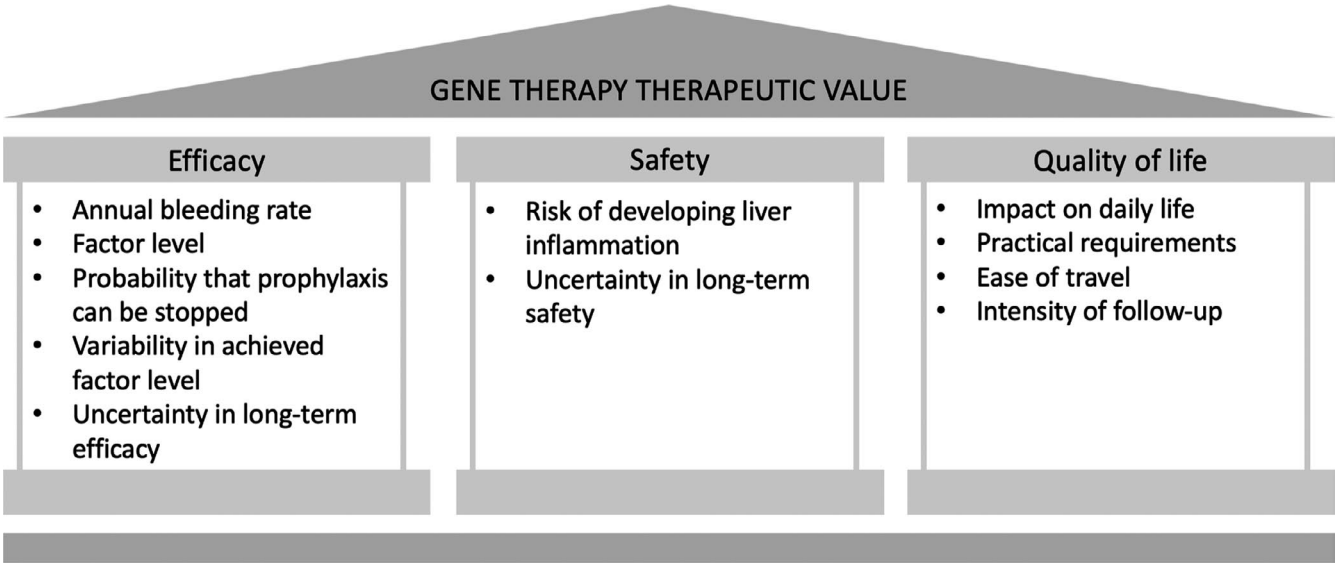

FIGURE 1 Pillars of gene therapy therapeutic value to patients.

potential impact on daily life and chance of stopping prophylactic FRT. However, PWH also recognize the uncertainties that gene therapies come with and are more concerned about uncertainty regarding long-term safety than long-term efficacy. Regulators, HTA bodies and payers can use the patient-relevant attributes identified in this study to support gene therapy evaluations in haemophilia.

ETHICS STATEMENT

All interviewees provided written informed consent prior to starting the interview. Ethical approval was obtained from the Medical Ethics Committee of UZ KU Leuven/Research in Belgium (S62670).

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

EvO, SM, BH, KP, CH, CL, MG, SS and IH were involved in the design of the study. EvO and SM designed study materials, held interviews with patients and analysed results. BH, KP, CH, CL, MG, SS and IH participated in meetings and reviewed study materials. EvO produced the first draft of the manuscript, which was subsequently revised and finalized with all authors. All authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. Participants did not provide consent for the sharing of interview transcripts with parties other than the researchers.

ORCID

Eline van Overbeeke https://orcid.org/0000-0003-0073-9350
Cedric Hermans https://orcid.org/0000-0001-5429-8437
Catherine Lambert https://orcid.org/0000-0003-2222-0357

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Appendix S1

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