Patient perspectives regarding gene therapy in hemophilia: interviews from the PAVING study

van Overbeeke E, Michelsen S, Hauber B, Peerlinck K, Hermans C, Lambert C, Goldman M, Simoens S, Huys I

Table of Contents

Supporting information I The COREQ checklist ................................................................. 2
Supporting information II Interview guide ........................................................................... 5
Supporting information III Systematic literature review ...................................................... 12
Supporting information IV Patient characteristics survey .................................................. 16
Supporting information V Procedure for the analysis of interviews: Framework Method Analysis .................................................................................................................. 19
Supporting information X Final code book for the analysis of interviews ......................... 24
Supporting information VII Saturation table and codebook development .......................... 28
Supporting information VIII Results from case comparisons ......................................... 29
References .................................................................................................................................. 31
Supporting information I The COREQ checklist
Consolidated Criteria for Reporting Qualitative Studies (COREQ): 32-item Checklist

| No. | Item                                                                 | Response                                                                                                                                                                                                 |
|-----|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     | **Domain 1: Research team and reflexivity**                           |                                                                                                                                                                                                         |
|     | **Personal Characteristics**                                         |                                                                                                                                                                                                         |
| 1.  | Which author/s conducted the interview or focus group?              | EvO and SM                                                                                                                                                                                              |
| 2.  | What were the researcher’s credentials?                              | EvO and SM hold a MSc in biomedical sciences.                                                                                                                                                           |
| 3.  | What was their occupation at the time of the study?                 | EvO is completing her PhD in patient preference research at the KU Leuven and as part of the IMI PREFER project. SM started her PhD in market access of gene therapies.                                         |
| 4.  | Was the researcher male or female?                                  | Both researchers are female.                                                                                                                                                                            |
| 5.  | What experience or training did the researcher have?                | EvO had previous experience and training in completing qualitative interviews and has trained SM via preparatory meetings and supervision during the first interviews.                                |
|     | **Relationship with participants**                                   |                                                                                                                                                                                                         |
| 6.  | Was a relationship established prior to study commencement?         | No, study participants were only contacted through e-mail beforehand to agree on a place and time for the interview.                                                                                |
| 7.  | What did the participants know about the researcher?                | The participants were informed on the goal of the research and the future use of the data.                                                                                                                |
| 8.  | What characteristics were reported about the interviewer/facilitator? | The researchers’ background and the fact that the study was part of the masters’ thesis of SM, the PhD of EvO and studies of PREFER.                                                                 |
|     | **Domain 2: Study design**                                          |                                                                                                                                                                                                         |
| 9.  | What methodological orientation was stated to underpin the study?   | Qualitative research evaluated through framework method content analysis.                                                                                                                                    |
| 10. | How were participants selected?                                     | Via purposive sampling.                                                                                                                                                                                   |
| 11. | How were participants approached?                                   | Via the information services of the Belgian hemophilia patient association and physicians.                                                                                                                |
| 12. | How many participants were in the study?                            | 20 participants were interviewed during the study.                                                                                                                                                        |
| 13. | How many people refused to participate or dropped out? Reasons?     | First contact was established with 32 patients of which 12 patients did not respond to further e-mailing. Reasons are unknown.                                                                            |
| 14. | Where was the data collected?                                       | At the home of the participants or at another neutral location of choice by the participant (e.g. the university campus).                                                                            |
| 15. | Was anyone else present besides the participants and researchers?  | No, only the participant and one or both researchers were present.                                                                                                                                     |
| 16. | What are the important characteristics of the sample?              | See table 1: patient characteristics                                                                                                                                                                    |
|   | Data collection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17.| **Were questions, prompts, guides provided by the authors? Was it pilot tested?** Yes, a full interview guide was prepared. This guide was validated through input from physicians and patient representatives and was pilot tested in 2 interviews.                                                                                                                                                                                                                                                                                                                                                     |
| 18.| **Were repeat interviews carried out? If yes, how many?** No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 19.| **Did the research use audio or visual recording to collect the data?** Audio recording was used to collect the data.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 20.| **Were field notes made during and/or after the interview or focus group?** All audio recordings were fully transcribed and field notes were taken.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 21.| **What was the duration of the interviews or focus group?** The total duration of interviews was around 1 hour. The recording that were made from the interview only started from the first question (self-reported knowledge on gene therapy). The durations of the recordings per interview were:  
  - Interview 1: 30 min  
  - Interview 2: 35 min  
  - Interview 3: 48 min  
  - Interview 4: 38 min  
  - Interview 5: 25 min  
  - Interview 6: 35 min  
  - Interview 7: 1 hour and 6 min  
  - Interview 8: 30 min  
  - Interview 9: 40 min  
  - Interview 10: 47 min  
  - Interview 11: 38 min  
  - Interview 12: 43 min  
  - Interview 13: 1 hour and 4 minutes  
  - Interview 14: 1 hour and 8 minutes  
  - Interview 15: 52 min  
  - Interview 16: 1 hour and 3 minutes  
  - Interview 17: 1 hour and 2 minutes  
  - Interview 18: 1 hour  
  - Interview 19: 51 min  
  - Interview 20: 45 min  

  Of note:  
  1. Ranking exercise was not recorded  
  2. Piloting interview and the participant had already read the information section on beforehand  
Person was very direct and short in answering the questions but satisfactorily detailed answers were obtained for all questions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 22.| **Was data saturation discussed?** Yes. Furthermore, saturation was assessed using a saturation table and documented codebook development.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 23.| **Were transcripts returned to participants for comment and/or correction?** No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |


### Domain 3: analysis and findings

#### Data analysis

|   | Question                                      | Answer                                                                 |
|---|-----------------------------------------------|------------------------------------------------------------------------|
| 24 | How many data coders coded the data?          | The first 4 transcripts were independently coded by SM and EvO. The remaining transcripts were coded by SM and EvO, after agreement of SM and EvO on the coding tree. |
| 25 | Did authors provide a description of the coding tree? | Yes, a codebook was developed including a definition of the code, the inclusion and exclusion criteria and an example per code. |
| 26 | Were themes identified in advance or derived from the data? | Both deductive and inductive codes were used. |
| 27 | What software, if applicable, was used to manage the data? | Nvivo 12 was used to manage the data. |
| 28 | Did participants provide feedback on the findings? | No. |

#### Reporting

|   | Question                                      | Answer                                                                 |
|---|-----------------------------------------------|------------------------------------------------------------------------|
| 29 | Were participant quotations presented to illustrate the themes/ findings? Was each quotation identified? | Yes, quotes are followed by the participant code. |
| 30 | Was there consistency between the data presented and the findings? | Yes. |
| 31 | Were major themes clearly presented in the findings? | Yes, all major reasons to use or refrain from gene therapy have been discussed. |
| 32 | Is there a description of diverse cases or discussion of minor themes? | Yes, attention was given to statements mentioned by individual participants |
Supporting information II Interview guide

KU LEUVEN

PATIENT PREFERENCES

Haemophilia interview guide

| 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 in the context of 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 AHVH.

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?
  - 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?
  - Very good
  - Good
  - Reasonable
  - Bad
  - 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?
  - 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?
  - 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?
  - 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?
  - 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 minutes 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?
  - 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?
  - 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?
  - 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:
    - Very willing
    - Willing
    - Neutral
    - Not willing
    - 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).

| 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 minutes, 1 hour)                                                                                                                        |         |
|                          | 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) |         |
| 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) |         |

- What elements on this list do you find not at all important when making a decision on treatment with gene therapy?
I will go through two examples with you from a publicly published clinical trial with haemophilia B patients. I will ask you each time whether in that case you would prefer gene therapy or the preventive therapy:

Example 1: a patient of 35 years old with severe haemophilia B and physical complaints in 4 joints. The patient can choose between the two following treatments:

| Preventive therapy | Gene therapy |
|--------------------|--------------|
| Administration: one to two times per week factor IX administration via the vein (on average 61 infusions per year) | Administration: one-time administration of the vector with the correct IX gene. This correct gene is added next to the genetic material in the liver cells. |
| Effect: strongly fluctuating factor concentrations in the blood with 12 yearly bleedings. | Effect: a stable factor concentration is achieved of 45% of normal factor levels. There are no bleedings anymore and there is no longer a need for preventive treatment. |
| Possible side effects: | Possible side effects: |
| - The development of neutralising antibodies (inhibitors) against the administered factor resulting in inefficacy of the treatment | - Light inflammation of the liver, treated with corticosteroids |

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

Example 2: a patient of 35 years old with severe haemophilia B and physical complaints in 4 joints. The patient can choose between the two following treatments:

| Preventive therapy | Gene therapy |
|--------------------|--------------|
| Administration: one to two times per week factor IX administration via the vein (on average 61 infusions per year) | Administration: one-time administration of the vector with the correct IX gene. This correct gene is added next to the genetic material in the liver cells. |
| Effect: strongly fluctuating factor concentrations in the blood with 12 yearly bleedings. | Effect: a stable factor concentration is achieved of 25% of normal factor levels. The patient has 4 bleedings per year and requires 10 factor infusions per year. |
| Possible side effects: | Possible side effects: |
| - The development of neutralising antibodies (inhibitors) against the administered factor resulting in inefficacy of the treatment | - Light inflammation of the liver, treated with corticosteroids |

- Did you understand this example?
- Would you in this case prefer the gene therapy or the preventive therapy?
  - Why?
  - 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?
  - Try to get in-depth information on the variability
We are going to have another look at the previously mentioned example: a patient of 35 years old with severe haemophilia B and physical complaints in 4 joints. 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 three times per week) and to once per 7-14 days for haemophilia B (instead of twice per week).

| Long-acting coagulation factors | Gene therapy |
|---------------------------------|--------------|
| Administration: Once every 14 days factor IX administration via the vein (3 times per month). | Administration: one-time administration of the vector with the correct IX gene. This correct gene is added next to the genetic material in the liver cells. |
| Effect: strongly fluctuating factor concentrations in the blood with 3 yearly bleedings. | Effect: a stable factor concentration is achieved of 36% of normal factor levels. There are no bleedings anymore and there is no longer a need for preventive treatment. |
| Possible side effects: - The development of neutralising antibodies (inhibitors) against the administered factor resulting in inefficacy of the treatment | Possible side effects: Light inflammation of the liver, treated with corticosteroids |

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

The same patient of 35 years old 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 emicisumab (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.
Supporting information III Systematic literature review

The content of the interview guide was informed by a systematic literature review of AAV-based gene therapy clinical trials in haemophilia and previous initiatives investigating patient preferences and patients’ needs in hemophilia. Gene therapy clinical trials in hemophilia were identified through a search strategy (8th of December 2018) designed for PubMed (search terms “gene therapy” AND “hemophilia”; filters “Clinical Trial” and “Human”), screening of the worldwide clinical trial gene therapy database (1), clinicaltrials.gov we and the review of Batty and Pasi (2). Following exclusion of five publications (gene therapy clinical trials published before 2005 or describing a non-intravenous application), 13 clinical trial publications (Table III.I) and 19 patient preference studies/public meetings (Table III.II) were included.

| Table III.I | Gene therapy clinical trials in haemophilia |
|---|---|
| Vector (sponsor) | Date initiated | Status | Number of patients included | Doses (vg/kg) | Mean outcome (factor level; % of normal) | Phase | Trial number (results reference) |
| **Haemophilia B (Factor IX)** | | | | | | | |
| scAAV2/8-LP1-hFIXco (UCL and SJCRH) | 2009 | Closed | 2 6 | 2x10^{11} 6x10^{11} 2x10^{12} | 1.8 (1.4-2.2) 2.5 (2.2-2.9) 5.1 (1.4-7.2) | Phase I/II | (3, 4) NCT00979238 |
| SPK-9001 (Spark Therapeutics) | 2009 | Closed | 10 | 5x10^{11} | 33.7 (14-81) | Phase I/II | (5, 6) NCT00979238 |
| Fidancogene elaparvovec (SPK-9001; Pfizer) | 2018 | Open | NR | NR | NR | Phase III | NCT03587116 (lead-in study) US-1742 |
| AMT-060 (UniQure) | 2015 | Closed | 5 5 | 5x10^{12} 2x10^{13} | 4.4 (1.3-6.8) 6.9 (3.1-12.7) | Phase I/II | (7, 8) NCT02396342 EudraCT#2013-00579-42 |
| AMT-061 (UniQure) | 2018 | Open | NR | 2x10^{13} | NR | Phase III | NCT03569891 |
| FLT180a (Freeline Therapeutics) | 2018 | Open | NR | 4.5x10^{11} | NR | Phase I/II | NCT03641703 (9) |
| SB-FIX (Sangamo) | 2016 | Open | NR | NR | NR | Phase I/II | NCT02695160 |
| AskBio009 (Shire) | 2012 | Closed | NR | NR | NR | Phase I/II | NCT01687608 |
| DTX201 (Bayer) | 2018 | Open | NR | NR | NR | Phase I/II | NCT03588299 |
| Coagulin-B (Avigen) | 1999 | Closed | 3 | 2x10^{11} | >1 | Phase I | (10) |
| The Children’s Hospital of Philadelphia | 2006 | Closed | 7 | 2x10^{12} | NR | Phase I/II | (11) |
| The Children’s Hospital of Philadelphia | 2006 | Closed | 8 | 2x10^{11} 1.8x10^{12} | <1 | Phase I | (12) |
| Fudan University | 1993 | Closed | 2 | NR | 220 ng/ml | Phase I | (13) |
| **Haemophilia A (Factor VIII)** | | | | | | | |
| Valoctocogene roxaparvovec (BMN-270; BioMarin) | 2015 | Closed | 6 7 | 4x10^{13} 6x10^{13} | 51 (48-54) 86 (65-107) | Phase I/II | (14-16) |
| Valoctocogene roxaparvovec (BMN-270; BioMarin) | 2018-2017 | Open | NR | 4x10^{13} 6x10^{13} | NR | Phase III | NCT03392974 NCT03370913 US-1676 US-1691 |
| SPK-8011 (Spark Therapeutics) | 2016 | Open | 2 3 7 | 5x10^{11} 1x10^{12} 2x10^{12} | 13 15 30 (16-49) | Phase I/II | NCT03003533 (17) |
| SB-525 (Sangamo) | 2017 | Open | NR | NR | NR | Phase I/II | NCT03061201 |
| SHP654 (Shire) | 2017 | Open | NR | NR | NR | Phase I/II | NCT03370172 |
| GO-8 (UCL) | 2016 | Open | NR | 6x10^{11} 2x10^{12} | NR | Phase I | NCT03001830 (18) |
| hFVIII(V) (Chiron, Emeryville, CA) | 2003 | Closed | 13 | 2.8x10^{7} - 8.8x10^{8} TU/kg | >1 | Phase I | (19) |
| Non-viral (Transkaryotic Therapies) | 2001 | Closed | 6 | NR | <0.8 | Phase I | (20) |
| Study                      | Year | Aim                                                                 | Method               | Treatments                   | Outcomes                                                                                                                                 |
|---------------------------|------|----------------------------------------------------------------------|----------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| FDA workshop (21)         | 2016 | To hear experience with bleeding disorders and their treatment       | Public meeting       | Current + future options     | The ideal treatment would be a cure, through gene therapy or a transplant, with no accompanying side effects and no need for continuing maintenance of therapy. Patients want safe, effective, potent, inexpensive, very long acting, and easy to administer products. Patients are willing to take part in a trial only for “better option – a curative gene therapy or a treatment with a longer half-life.” |
| FDA workshop (21)         | 2018 | To understand patient/caregiver concerns, perceived risks and benefits, and expectations of gene therapy | Public meeting       | Gene therapy                 | Accurate information on gene therapy if important. Patient/caregiver’s interest in new therapy is partly dependent on the success of their current treatment modality; uncertainty relating to benefits and risks influences acceptance. Benefit: no further infusions, ability to be more active, prevention of additional pain and joint deterioration. Frequency of safety monitoring was not seen as a high priority. Some patients/ caregivers would be satisfied with Factor IX levels of 5-10% while others indicated they hope for levels of 40% or more. Some patients/ caregivers would be satisfied with a duration of elevated Factor levels for 5 years, while others indicated they hope for a duration of more than 10 years. |
| Tael et al. (22)          | 2014 | To develop a brief, clinically relevant tool to measure ease of use and patients’ preference for haemophilia treatment | 40-item questionnaire | Factor replacement therapy   | The study resulted in the setup of a 14-item questionnaire - the HaemoPREF (tested in Bonanad et al. (23))                                      |
| Bonanad et al. (23)       | 2017 | Patient perception of Haemophilia A treatment                        | HaemoPREF            | Factor replacement therapy   | Important attributes: dosing frequency, ease of use, risk (viral infections and inhibitor development), and impact on daily life.          |
| Chaugule et al. (24)      | 2015 | Preferences and willingness to pay (WTP)                             | Discrete choice experiment | On-demand and long-acting factor replacement therapy | Out-of-pocket treatment costs, side effects, and treatment effectiveness and dosing frequency were found to be statistically significant in the model |
| Study                         | Year | Aim                                                                 | Method                  | Treatments             | Outcomes                                                                                                                                 |
|-------------------------------|------|----------------------------------------------------------------------|-------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Brown et al. (25)             | 2011 | Identify treatment attributes that patients/caregivers consider most important | Discrete choice experiment | Factor replacement therapy | The three most important attributes: time required to stop bleeding, possibility that the level of inhibitor may rise and risk of contracting a virus from the product |
| Steen Carlsson et al. (26)    | 2017 | Valuation of treatment attributes                                     | Time Trade-Off          | Factor replacement therapy | Important attributes: Participation in physical activity, duration of injection interval; frequency of bleeds                                 |
| Furlan et al. (27)            | 2015 | To identify the relative importance of frequency of administration, efficacy, and other treatment characteristics | Conjoint analysis       | Factor replacement therapy | Important attributes: administration, efficacy, and manufacturer                                                                       |
| Mantovani et al. (28)         | 2005 | To identify treatment preferences                                     | Discrete Choice Experiment | Factor replacement therapy | Important attribute: Distribution from home or community pharmacist instead of hospital                                                |
| Mohamed et al. (29)           | 2011 | To quantify patient and parent preferences                            | Conjoint analysis       | Factor replacement therapy | Attributes in decreasing order of importance: Risk of viral infection, developing inhibitor risk, dosage strengths, percent of bleeds stopped, shortage history, preparation volume. |
| Scalone et al. (30)           | 2009 | To evaluate preferences towards characteristics of coagulation factor concentrates for haemophilia inhibitors patients | Discrete Choice Experiment | Factor replacement therapy | Important attribute: Allowment to undergo major surgery                                                                              |
| DiBenedetti et al. (31)       | 2014 | To assess preferences with FVIII product storage and stability        | Survey                  | Factor replacement therapy | Important attribute: Ease of product storage (longer storage on room temperature)                                                      |
| Costea et al. (32)            | 2009 | Explore patient perspectives                                         | Survey                  | Genetically modified autologous adult stem cells | Acceptable symptom free time interval would be 1 month till 1 year. Short term and long term safety is important. |
| Lock et al. (33)              | 2016 | To evaluate barriers and facilitators for individualized pharmacokinetic (PK)-guided dosing | Discrete Choice Experiment | Factor replacement therapy | If bleeding was consequently reduced, more frequent infusions were acceptable. However, daily dosing remained an important barrier for all involved. 'Reduction of costs for society' was a facilitator for implementation in all groups. |
| Cimino et al. (34)            | 2014 | To identify preferences for different administration systems          | Survey                  | Factor replacement therapy | Ease of use: the device scenario requiring the least equipment and reconstitution steps (the DCS) received the highest preference rating |
| Study       | Year | Aim                                                                 | Method                        | Treatments                        | Outcomes                                                                                                                                                                                                 |
|------------|------|----------------------------------------------------------------------|-------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Musso et al. (36) | 2010 | To identify preferences for different administration systems       | Survey                        | Factor replacement therapy        | The ease of use, perceived safety from needlesticks, and the speed of reconstitution were identified as main advantages by the majority of patients.                                                                 |
| Moia et al. (37) | 2013 | To elicit patient preferences, and estimate their willingness to pay for the different treatment options | Discrete Choice Experiment    | Across treatments                 | Important attributes: route and number of medication administrations, frequency of monitoring, risk of some minor bleeding, and out-of-pocket treatment cost.                                                      |
| Wasserman et al. (38) | 2005 | To develop a disease-specific utility instrument that measures patient preferences for various health states unique to hemophilia | Visual analog scale (VAS) and standard gamble (SG) | Health states                     | Adult participants took more risk than paediatric. SG yielded higher preference scores than the VAS for the majority of health states.                                                                 |
| Barlow et al. (39) | 2007 | Burden of disease                                                    | Semi-structured interviews    | Blood transfusions                | Majore impact of infected transfusions on QoL + prefer treatment by specialist over GP                                                                                                                  |
Haemophilia patient short survey

Please fill out the information below. We would like to collect your answers on the questions below to learn more about you. The answers of all participants on these questions will be summarized as group characteristics in reports and publications on these interviews. All information provided by you will be anonymized during the analysis, meaning the results of this study will never be linked to your name and identity. If any question is not clear to you, please leave them open.

Age: _______________

Sex:
☐ Male
☐ Female
☐ Other
☐ I prefer not to answer

Where do you live?
☐ Flanders
☐ Wallonia
☐ Brussels
☐ Other: _______________

Type of haemophilia:
☐ Haemophilia A
☐ Haemophilia B

Year of diagnosis: ____________

Severity of haemophilia:
☐ Mild
☐ Moderate
☐ Severe

What is your factor level without treatment?
☐ Lower than 1%
☐ Between 1% and 5%
☐ Between 5% and 40%
What treatment are you on now? You do not have to specify the exact product.

☐ Prophylaxis (preventive treatment)
☐ Episodic (treatments when a bleeding occurs)
☐ Intensive treatment because of presence of inhibitors
☐ Other: _____________________________________________

How many bleedings do you have on average?

☐ 1-2 times per week
☐ 2-3 times per months
☐ 1 time per month
☐ 1 time per two months (6 times per year)
☐ 1 time per three months (4 times per year)
☐ 1-2 times per year
☐ Never/less than 1 time per year

How many of these bleedings do you treat? __________________

Do you already have joint damage?

☐ Yes
☐ No

If yes, in what joints does this damage occur? (You may indicate multiple options)

☐ Right ankle
☐ Left ankle
☐ Right elbow
☐ Left elbow
☐ Right knee
☐ Left knee
☐ Other: _____________________________________________

If yes, how do you classify the severity of the damage?

☐ Mild
☐ Moderate
☐ Severe

Are you currently having inhibitors against the treatment?

☐ Yes
☐ No

How satisfied are you with the treatment?

☐ Very satisfied
☐ Satisfied
☐ Neutral
☐ Unsatisfied
☐ Very unsatisfied
What would you like to improve in the treatment?

Have you already discussed your treatment with gene therapy with a physician?
- [ ] Yes
- [ ] No

If yes, what was the decision that you made (with the physician)?
- [ ] To receive gene therapy in a clinical trial
- [ ] To receive gene therapy outside of a clinical trial
- [ ] To not receive gene therapy

Please shortly explain why this decision was taken

How often do you have someone (like a family member, friend, hospital/clinic worker, or caregiver) help you read hospital materials?
- [ ] Always
- [ ] Often
- [ ] Sometimes
- [ ] Occasionally
- [ ] Never

How often do you have problems learning about your medical condition because of difficulty understanding written information?
- [ ] Always
- [ ] Often
- [ ] Sometimes
- [ ] Occasionally
- [ ] Never

How confident are you filling out medical forms by yourself?
- [ ] Extremely
- [ ] Quite a bit
- [ ]Somewhat
- [ ] A little bit
- [ ] Not at all

Thank you for completing this short survey. You can send the completed survey via e-mail to Eline van Overbeeke (elie.vanoverbeeke@kuleuven.be) or you can take it with you and hand it over at the start of the interview. The interviewer will discuss your answers on this form with you and information can be supplemented if necessary.
Supporting information V Procedure for the analysis of interviews: Framework Method Analysis

Stage 1: Transcription

- All interviews were transcribed by the person who conducted the interview (Dutch interviews) or a professional transcription company (French interviews).
- All interviews will be transcribed in their native language. Quotes will be translated in English, if necessary.

Stage 2: Familiarization with the interview

- The persons analyzing all interviews are the same persons conducting the interview. The first 4 interviews will be analyzed by both SM and EvO. EvO will also be present during the first 4 interviews of SM.
- The persons analyzing all interviews are the same persons conducting the interview. The first 4 interviews will be analyzed by both SM and EvO. EvO will also be present during the first 4 interviews of SM.
- For both researchers, the transcripts will be used for familiarization. If the analyzer has difficulty in understanding the transcript, the analyzer will re-listen the audio file. If the analyzer still does not understand a certain part of the transcript after re-listening the audio-file, he/she will ask the interviewer who conducted the interview for clarification about that part.
- Each transcript will be read and re-read, and the audio-recorded interviews will be listened to if necessary to become familiar with the whole data set.
- The margins of the transcripts will be used to write down analytical notes, thoughts or impressions (e.g., when interviewees expressed exceptionally strong or contrasting views to other interviewees). No feedback will be given towards interviewees about these notes.
Stage 3: Coding

**General explanation and important considerations, see: Gale et al. BMC Medical Research Methodology 2013, 13:117**

After familiarization, the researcher carefully reads the transcript line by line, applying a paraphrase or label (a ‘code’) that describes what he has interpreted in the passage as important. In more inductive studies, at this stage ‘open coding’ takes place, i.e. coding anything that might be relevant from as many different perspectives as possible. Codes could refer to substantive things (e.g. particular behaviours, incidents or structures), values (e.g. those that inform or underpin certain statements, such as a belief in evidence-based medicine or in patient choice), emotions (e.g. sorrow, frustration, love) and more impressionistic/methodological elements (e.g. interviewee found something difficult to explain, interviewee became emotional, interviewer felt uncomfortable). In purely deductive studies, the codes may have been pre-defined (e.g. by an existing theory, or specific areas of interest to the project) so this stage may not be strictly necessary and you could just move straight onto indexing (stage 5: assigning text to codes), although it is generally helpful even if you are taking a broadly deductive approach to do some open coding on at least a few of the transcripts to ensure important aspects of the data are not missed. Coding aims to classify all of the data so that it can be compared systematically with other parts of the data set. At least two researchers (or at least one from each discipline or speciality in a multi-disciplinary research team) should independently code the first few transcripts, if feasible. Patients, public involvement representatives or clinicians can also be productively involved at this stage, because they can offer alternative viewpoints thus ensuring that one particular perspective does not dominate. It is vital in inductive coding to look out for the unexpected and not just to code in a literal, descriptive way so the involvement of people from different perspectives can aid greatly in this. As well as getting a holistic impression of what was said, coding line-by-line can often alert the researcher to consider that which may ordinarily remain invisible because it is not clearly expressed or does not ‘fit’ with the rest of the account. In this way the developing analysis is challenged; to reconcile and explain anomalies in the data can make the analysis stronger. Coding can also be done digitally using CAQDAS, which is a useful way to keep track automatically of new codes. However, some researchers prefer to do the early stages of coding with a paper and pen, and only start to use CAQDAS once they reach Stage 5 (see below).

- We will take a combined approach to analysis: themes will be both inductive from the accounts (experiences and views) of research participants and deductive from specific pre-defined sets of interests to the project and thus the research questions and questions in the interview guide. We will use the following pre-defined coding list and hierarchy (coding tree):
  - Information needs
  - Reasons to use gene therapy
  - Reasons for refraining from gene therapy
  - Feelings associated with side effects and uncertainties of gene therapy
  - Comparison of gene therapy with other treatment modalities

- To ensure important aspects of the data will not be missed, SM and EvO will also independently do open-coding on the first available 4 transcripts to check if all relevant themes are covered with the predefined coding tree. The 4 transcripts will be printed out and coded independently: meaning that each researcher will check if all themes are covered and if not, new codes will be assigned.

- Gale et al. argue that in this stage, it is valuable to involve other stakeholders to give alternative viewpoints, e.g. clinicians. In our case however, we found it sufficient and more pragmatic that coding was independently done by two researchers, without actively involving the stakeholders themselves. The reason for this is that involving other stakeholders might slow down the coding stage considerably, as well as lead to discussions as other stakeholders may not agree with opinions of patients.

- The following example format will be used for open-coding. Coding labels (these could be the ones from the pre-existing coding tree or new ones) will be noted left from the transcript. Notes and ideas will be noted on the right side of the transcript:
Stage 4: Developing a working analytical framework

General explanation and important considerations, see: Gale et al. BMC Medical Research Methodology 2013, 13:117

After coding the first few transcripts, all researchers involved should meet to compare the labels they have applied and agree on a set of codes to apply to all subsequent transcripts. Codes can be grouped together into categories (using a tree diagram if helpful), which are then clearly defined. This forms a working analytical framework. It is likely that several iterations of the analytical framework will be required before no additional codes emerge. It is always worth having an ‘other’ code under each category to avoid ignoring data that does not fit; the analytical framework is never ‘final’ until the last transcript has been coded.

- After SM and EvO have each coded the same 4 transcripts, we will meet to discuss the labels we have assigned to each passage. We will discuss each coded section of each of the 4 transcripts in terms of why we have coded it and why we perceived it as meaningful to answer the research questions. After discussion, we will agree on a set of codes, each with a brief definition. This will form the initial analytical framework. The initial analytical framework will have an ‘other’ code underneath each category where data that does not fit will be placed in.
- Following consensus reached by both SM and EvO, SM will code all further Dutch transcripts and EvO the French transcripts using the established the analytical framework. If new codes arise, these will be discussed resulting in the process of refining, applying, and refining the analytical framework until no new codes are generated.
- The final framework will consist of codes and categories, each with a brief explanatory description of their meaning, the inclusion and exclusion criteria of the code and an example as proposed by MacQueen and colleagues (MacQueen et al. Cultural Anthropology Methods 10(2):31-36.)
Stage 5: Applying the analytical framework

We will use NVivo for this stage: the final analytical framework (coding tree) will be uploaded in NVivo. SM and EvO will systematically go through each transcript and highlight passages of text, selecting and attaching an appropriate code from the final analytical framework (coding).

Stage 6: Charting the data into the framework matrix

After coding all transcripts, we will use NVivo 12 to generate the matrix from the coded text. Afterwards, the matrix will be exported to excel to generate an overview of all results. Each row will represent a participant with his/hers assigned pseudonym and each column will represent a code of the final analytical framework. A subdivision will be made between themes and subthemes by the following numeric order: 1, 2, 3 for main themes and 1.1, 1.2, 2.1, 2.2, ... for subthemes. In excel, a new row will be added underneath all codes where a short summary, and first interpretation, of all participants' views from that code will be noted. All codes and all participants will be charted into a single matrix due to the limited amount of participants and codes and to maintain a clear overview.

Example of how a matrix might look like:

| 1. Information needs | 2. Reasons to use gene therapy | 3. Reasons to refrain from gene therapy | ...
|---------------------|-------------------------------|----------------------------------------|------|
| Participant 1       |                               |                                        |      |
| Participant 2       |                               |                                        |      |
| Participant 3       |                               |                                        |      |
| ...                 |                               |                                        |      |
| Summary             |                               |                                        |      |
Stage 7: Interpreting the data

EVO and SM will interpret the data by reviewing the matrix and making connections within and between participant and categories. This process will be influenced by the research questions and by new codes generated inductively from the data. During the interpretation stage, we will try to go beyond descriptions of individual cases.

General explanation and important considerations, see: Gale et al. BMC Medical Research Methodology 2013, 13:117
It is useful throughout the research to have a separate note book or computer file to note down impressions, ideas and early interpretations of the data. It may be worth breaking off at any stage to explore an interesting idea, concept or potential theme by writing an analytic memo to then discuss with other members of the research team, including lay and clinical members. Gradually, characteristics of and differences between the data are identified, perhaps generating typologies, interrogating theoretical concepts (either prior concepts or ones emerging from the data) or mapping connections between categories to explore relationships and/or causality. If the data are rich enough, the findings generated through this process can go beyond description of particular cases to explanation of, for example, reasons for the emergence of a phenomena, predicting how an organisation or other social actor is likely to instigate or respond to a situation, or identifying areas that are not functioning well within an organisation or system. It is worth noting that this stage often takes longer than anticipated and that any project plan should ensure that sufficient time is allocated to meetings and individual researcher time to conduct interpretation and writing up of findings.
**Supporting information X** Final code book for the analysis of interviews

| CODE | DESCRIPTION | INCLUSION CRITERIA | EXCLUSION CRITERIA | EXAMPLES |
|------|-------------|--------------------|--------------------|----------|
| **Information needs** | | | | |
| Awareness | The participant has already or not yet heard of gene therapy before the interview | The participant states if he/she had already heard from gene therapy before the interview or not. | When the participant states to have heard of gene therapy due to interview participation. | "Have you ever heard of gene therapy? Yes." |
| Previous info on gene therapy | All previous knowledge on gene therapy | Explanation of gene therapy mode of action in own words or expressing knowledge of gene therapy studies, side effects, administration, etc. | The source of that information or additional information the participant would like to acquire. | "That they use a virus that has been weakened and modulated to go to the liver because they have built in a gene in the virus. That virus will give the gene to the liver which will activate the factor 8 or 9 level. The body will make factor 8 on its own." |
| Source | The source of the previous knowledge on gene therapy. | The places, events or persons where the participant gained information on gene therapy such the treating physician, etc. | The difficulty of finding this information or the content of the information received from the source. | "Mainly via congresses and symposia. "Via professor Peerlinck" |
| **Disease comprehension** | Expression of (in)comprehension of haemophilia disease information | The participant states that he/she does/does not understand the given information on haemophilia or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | "Did you understand the information? Yes. Could the information be worded more clearly? I think it is good as it is." |
| Treatment comprehension | Expression of (in)comprehension of current haemophilia treatment information | The participant states that he/she does/does not understand the given information on the current treatment of haemophilia or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | "Did you understand the information? Yes. Could the information be worded more clearly? I thought it was very clearly and simply explained." |
| GT general comprehension | Expression of (in)comprehension of general gene therapy information | The participant states that he/she does/does not understand the given general information on gene therapy or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | "Did you understand the information? Yes. Could the information be worded more clearly? It might be not bad to show a scheme to the patient during the explanation. There are a lot of scientific words and for laymen this is what more complicated. It is also quite a lot, it is all correct but quite a lot so explaining it schematically would not be bad." |
| GT practical comprehension | Expression of (in)comprehension of practical gene therapy administration information | The participant states that he/she does/does not understand the given information practical aspects of gene therapy or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | "Did you understand the information? Yes. Could the information be worded more clearly? I think it is worded very good, clear with the scheme." |
| **GT risk comprehension** | Expression of (in)comprehension of information on risks and side effects of gene therapy | The participant states that he/she does/does not understand the given information on the risks of gene therapy or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | "Did you understand the information? Yes. Could the information be worded more clearly? Not for me." |
| GT benefit comprehension | Expression of (in)comprehension of information on the benefits of gene therapy | The participant states that he/she does/does not understand the given information on the benefits of gene therapy or questions raised by the participant regarding the given information. | Questions asked regarding information not discussed in the information part. | “Did you understand the information? Yes. Could the information be worded more clearly? I think it is complete, it is really easy to follow. So it is very understandable.” |
| Additional info | Expression of the need for additional information on gene therapy | The participant asks questions regarding gene therapy topics not yet discussed in the information sections. The participant expresses that he/she would like to know more on certain aspects of gene therapy such as long-term data or that he/she does not know where to find adequate information regarding gene therapy. | Expressions regarding their feelings on the uncertainties of the benefits and/or risks of gene therapy. | “Up until now, everything is very clear but it is just that we don’t know what the future will bring. Is it lifelong yes or no, is it after a few years that it reduces completely, can it be readministered yes or no. That is the big question, how long does your factor level stay high?” |
| Use of gene therapy | General opinion on gene therapy | The opinion of the participant on gene therapy related to the whole haemophilia population which is broader than the person’s own willingness to use. | The participant states their personal willingness to use gene therapy. | “It are actually the youngsters, of 18-25 years that can benefit the most of gene therapy.” |
| GT opinion | Personal willingness to use gene therapy | Expression of the participant of wanting to use gene therapy or not. | Expression of willingness to use gene therapy not related to the participant themselves such as choosing gene therapy in the cases and the reasons behind the participants’ willingness. | “Me, personally, I am completely open for gene therapy.” “At this moment, I am not jumping at the opportunity to use gene therapy.” |
| GT willingness | Reasons to use gene therapy | The participant lists reason why he/she would want to use gene therapy him/herself. | The reasons the participant chose for gene therapy in the cases. | “Also, on one side clinical because then I am more certain, that I won’t have bleeds – or also at an event, that I am better protected at that moment. For practical reasons, you don’t have to take medication with you, you don’t need to inject yourself three times per week.” “I am used to injecting myself two to three times per week via prophylaxes and I already do this for so many years in my life with the same product from the beginning, so I also have built up trust on that aspect. And the treatment as I am following it now, is perfect for me. It is well adapted to my life and I trust this. I also know when I have to inject myself and I would find it very weird if I had to change all this all of sudden.” |
| GT use | Reasons to refrain from gene therapy | The participant lists reason why he/she would not want to use gene therapy him/herself. | The reasons the participant chose for gene therapy in the cases. | “It is just waiting but it already positive that we do not have to inject for a few years. Just wait and see.” |
| GT refrain | Feelings towards possibility of a second administration of gene therapy | The participant states how he/she feels about the fact that there is uncertainty on a second administration of gene therapy. | Expression of feelings regarding uncertain long-term benefit from gene therapy or of feelings regarding long-term risks. | “We as haemophilia patients, a lot of us have had liver cirrhosis for a time due to the blood. So yes, it is already a bit affected and this on top of it. That is one of the maybe small worries.” |
| Second | Feelings towards the possibility of liver inflammation after gene therapy | The participant states how he/she feels about a possible liver inflammation after gene therapy or raises concerns regarding this inflammation. | The discussion of the liver in terms of administration of the gene or vector to the body. | “Lot of us have already had liver cirrhosis.” |
| Uncertainties                                                                 | Comprehension 1                                                                 | Choice 1                                                                 | Cases                                                                 |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| Feelings towards uncertainties due to shortage of lifelong data on gene therapy | The participant states he/she does or does not understand the information given in case 1. | Statement of understanding information in other parts of the interview. | “Did you understand this example? Yes.”                              |
| **Top 3 elements influencing gene therapy used, spontaneously mentioned by participant** | The three elements the participant states when asked to give their top 3 of the elements that influence their choice to use gene therapy or not. | All reasons to use gene therapy not related to case 1. The comparison of the answers stated in case 1 versus case 2. | “I would go for gene therapy. For the same reasons, I already stated, you don’t have to inject anymore and everything that goes with it and better protection.” |
| **New elements**                                                            | The participant states that other elements not discussed in the information section are of importance for his/her decision to use gene therapy or not. | All other reasons to use or refrain from gene therapy regarding to aspects discussed in the information parts. | “Here it is more difficult because he is only on 25% and thus to say it is very good, very protective. I would start to doubt now. Shall I stay on prophylaxis, yes or no?” |
| **Cases**                                                                    | The choice the participant made in case 1 together with the reasons he/she made this choice. | All reasons to use gene therapy not related to case 2. The comparison of the answers stated in case 1 versus case 2. | “Why did you give the same answer on the two previous questions? Still the bleeds. Because that is important in your life, if you don’t have bleeds, zero bleeds on a yearly basis, yes then, pf?” |
| **Comprehension 1**                                                         | Expression of (in)comprehension of information in case 1                        | The choice the participant made in case 2 together with the reasons he/she made this choice. | “I still chose gene therapy, as long as you have yearly bleeds, they affect your body. They cause arthritis in the joints in the long-term, they affect your body, your life, your daily life.” |
| **Choice 1**                                                                 | The comparison of the choice made in case 1 versus case 2                      | The explanation of the participant why he/she made the same choice in case 1 and 2 or why he/she made a different choice in case 1 or 2. | “Also for me a big issue, is that the long-term effects are not yet known. And I don’t really have a lot of confidence in this, I would prefer to wait and see how it evolves.” |
| **Comprehension 2**                                                         | Expression of (in)comprehension of information in case 2                        | Expression of feelings regarding the variation in results achieved by gene therapy due to long-term uncertainty not related to case 1 or 2. | “Also for me a big issue, is that the long-term effects are not yet known. And I don’t really have a lot of confidence in this, I would prefer to wait and see how it evolves.” |
| **Choice 2**                                                                 | The choice the participant made in case 2 together with the reasons he/she made this choice. | All reasons to use gene therapy not related to case 3. Statement of understanding information in other parts of the interview. | “Also for me a big issue, is that the long-term effects are not yet known. And I don’t really have a lot of confidence in this, I would prefer to wait and see how it evolves.” |
| **Choice 1 vs. 2**                                                          | Expression of (in)comprehension of information in case 3                        | The choice the participant made in case 3 together with the reasons he/she made this choice. | “Also for me a big issue, is that the long-term effects are not yet known. And I don’t really have a lot of confidence in this, I would prefer to wait and see how it evolves.” |

"Also for me a big issue, is that the long-term effects are not yet known. And I don’t really have a lot of confidence in this, I would prefer to wait and see how it evolves."

"Never again injecting, that is 1. Then, always de medication, the prescription et cetera, the pharmacy, also this all falls away. On the physical domain, the joints are protected more so that no bleeds start. The damage will be much less in the future."

"Because of which you can have a freer live and for vacation and stuff. Now this is always a hassle to take everything with you."

"Did you understand this example? Yes."
| Category           | Description                                                                 | Example                                                                                                           | Example                                                                                           |
|--------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Comprehension      | Expression of (in)comprehension of information regarding non-factor therapies (NFTs) | The participant states he/she she does or does not understand the information given regarding NFTs. | Statement of understanding information in other parts of the interview. "Did you understand this example? Yes." |
| Additional info    | Expression for the need for additional information on NFTs                  | Questions raised by the participant regarding NFTs or the participant states he/she cannot make a choice due to insufficient in-depth knowledge on NFTs. | Other statements or questions regarding the need of additional info not related to NFTs. "Are there already more results known from Hemlibra?" |
| NFT vs GT          | The choice for NFT or gene therapy together with the reasons for this choice. | The statement of the participant if the presence of NFTs influences their willingness to use gene therapy, together with the reasons he/she made this choice. | All reasons to use gene therapy not related to NFTs. "I would still chose gene therapy. Because it is more stable on the long-term and because there would be more control. Here you still have to inject frequently even it is once per week or once per month. What certainty would be for the patient with gene therapy is that the level will be more stable and here you still have some fluctuations." |
| Other              | Perception of the possibility of a cure in haemophilia                      | The participant states he/she she would ever perceive to be cured or not and the reasons why.                      | All other statements regarding perceived changes in the participants’ life after gene therapy. "For me, yes. Because I would not have bleeds anymore. Still with the notion that I can pass it on but personally because I would not have symptoms anymore." |
| Opinion on interview | General opinion on the interview of the participant                        | The general opinion and feedback of the participant about the conducted interview.                                 | The statements of the participant regarding formulation of the given information. "Good. I wouldn’t know how you can do it differently." |
Supporting information VII Saturation table and codebook development

### Saturation table

| CODE                        | INTERVIEW |
|-----------------------------|-----------|
|                             | 1 2 3 4 5 6 7 8 9 10 11 12 |

**Information needs**

|                      |     |
|----------------------|-----|
| Awareness            | X   |
| Previous info        | X   |
| Source               | X   |
| Disease comprehension| X   |
| Treatment comprehension| X   |
| GT general comprehension| X   |
| GT practical comprehension| X   |
| GT risk comprehension | X   |
| GT benefit comprehension| X   |
| Additional info      | X   |

**Use of gene therapy**

|                      |     |
|----------------------|-----|
| GT opinion           | X   |
| GT willingness       | X   |
| GT use               | X   |
| GT refrain           | X   |
| New elements         | X   |
| Second               | X   |
| Liver                | X   |
| Uncertainties        | X   |
| Top 3                |     |

**Cases**

|                      |     |
|----------------------|-----|
| Comprehension 1      | X   |
| Choice 1             | X   |
| Comprehension 2      | X   |
| Choice 2             | X   |
| 1 vs 2               | X   |
| Comprehension 3      | X   |
| Choice 3             | X   |
| Comprehension NFT    | X   |
| Additional info NFT  | X   |
| NFT vs GT            | X   |

**Other**

|                      |     |
|----------------------|-----|
| Perception of cure   | X   |
| Opinion on interview | X   |

X indicates the interview in which the code was first applied

### Codebook development

| Change made to the codebook                             | Based on transcript | Date - Time       |
|---------------------------------------------------------|---------------------|-------------------|
| First draft of the codebook                             | 1 – 2 – 6 – 7       | 27/03/2019 – 17:00|
| Inclusion criteria “additional info” adapted            | 3                   | 1/04/2019 – 10:13  |
| “Liver” code added                                      | 5                   | 1/04/2019 – 14:34  |
| “New elements” code added                              | 11                  | 3/04/2019 – 13:17  |
Supporting information VIII  Results from case comparisons

The tables below indicate the choices per case per participant (Table VIII.I), as well as what attributes were mentioned by participants as reasons for their choice (Table VIII.II).

| Table VIII.I Participants' choices per case |
|-------------------------------------------|
| **Case 1** (standard PFRT) | **Case 2** (standard PFRT) | **Case 3** (Long-acting PFRT) | **Case 4** (NFT) |
| HP1  | Gene therapy | Undecided | Gene therapy | Gene therapy |
| HP2  | Gene therapy | Preventive therapy | EHL | NFT |
| HP3  | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP4  | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP5  | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP6  | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP7  | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP8  | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP9  | Gene therapy | Preventive therapy | Gene therapy | NFT |
| HP10 | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP11 | Gene therapy | Preventive therapy | Gene therapy | Gene therapy |
| HP12 | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP13 | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP14 | Gene therapy | Gene therapy | Gene therapy | Gene therapy |
| HP15 | ? Recording | ? Recording | Gene therapy | Gene therapy |
| HP16 | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP17 | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP18 | Gene therapy | Gene therapy | EHL | NFT |
| HP19 | Gene therapy | Gene therapy | Gene therapy | Indecisive |
| HP20 | Gene therapy | Gene therapy | Gene therapy | Gene therapy |

Abbreviations: NFT, non-factor replacement therapy; PFRT, prophylactic factor replacement therapy
|                              | Case 1 (standard PFRT) | Case 2 (standard PFRT) | Case 3 (Long-acting PFRT) | Case 4 (NFT) |
|------------------------------|------------------------|------------------------|---------------------------|--------------|
| Annual bleeding rate<sup>a</sup> | 11                     | 12                     | 12                        | 3            |
| Factor level<sup>b</sup>     | 9                      | 9                      | 8                         | 5            |
| Chance to stop prophylaxis <sup>b</sup> | 6                      | 5                      | 7                         | 14<sup>i</sup> |
| Light liver inflammation     | 6<sup>g</sup>          | 1                      | 2<sup>h</sup>             |              |
| Inhibitors<sup>d</sup>       | 2                      | 3                      | 1                         |              |
| Uncertainty regarding side effects<sup>e</sup> | 2                      | 2                      | 3                         | 4            |
| Impact on daily QoL/travel <sup>f</sup> | 1                      | 1                      | 5                         | 2            |
| Loss of genetic error        | 1                      | 1                      | 1                         |              |
| Possibility to add factor level if necessary | 1                      | 1                      | 1                         | 1            |
| Societal cost                | 1                      | 1                      | 1                         | 3            |
| Risk on cardiovascular disease |                        |                        |                           | 1            |

<sup>a</sup> And the impact of bleeds on joint damage that causes pain

<sup>b</sup> Magnitude (cure but also going from severe to moderate or mild hemophilia) and impact of stable vs fluctuating factor on protection against bleeds and possibility to undergo surgery

<sup>c</sup> No longer a need for injections, reduction of number of injections, or reduction of invasiveness (intravenous vs. subcutaneous)

<sup>d</sup> The risk of developing inhibitors with factor replacement therapy was found to be more severe than the risk of developing light liver inflammation as this is treatable with corticosteroids

<sup>e</sup> Caused by limited time that the medicine is studied and the perception of level of surrealism/novelty of a therapy

<sup>f</sup> Including practical and time restrictions caused by factor replacement therapy

<sup>g</sup> 5 participants were not afraid of the risk of light liver inflammation and 1 was afraid due to previous history with hepatitis C

<sup>h</sup> 1 participant was not afraid of the risk of light liver inflammation and 1 was afraid

<sup>i</sup> Some preferred intravenous injections and some preferred subcutaneous
References

1. Gene Therapy Clinical Trials Worldwide database [Internet]. Journal of Gene Medicine. 2018 [cited 2018 Dec 8]. Available from: http://www.abedia.com/wiley/search_results.php?TrialCountry=&CategoryMain=Monogenic-diseases&Vector=&GeneTypes=&Phase=Phase+III&Status=Open&FinalApprYear=&Submit=%A0%A0Search%A0%A0.

2. Batty P, Pasi KJ. Gene therapy trials for haemophilia: a step closer to a cure? Expert Review of Precision Medicine and Drug Development. 2019:1-4.

3. Nathwani AC, Tuddenham EGD, Rangarajan S, Rolases C, McIntosh J, Linch DC, et al. Adenovirus-Associated Virus Vector-Mediated Gene Transfer in Hemophilia B. The New England Journal of Medicine. 2011;365(25):2357-65.

4. Nathwani AC, Reiss UM, Tuddenham EGD, Rolases C, Chowdary P, McIntosh J, et al. Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B. New England Journal of Medicine. 2014;371(21):1994-2004.

5. George LA, Sullivan SK, Giemmasz A, Rasko JEJ, Samelson-Jones BJ, Ducore J, et al. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. New England Journal of Medicine. 2017;377(22):2215-27.

6. Sullivan SK, Giemmasz A, Samelson-Jones BJ, Ducore JM, Teitel JM, Cuker A, et al. Investigational SPK-9001: Adeno-associated virus-mediated gene transfer for hemophilia B - persistent, stable factor IX activity at one year independent of downstream purification method. Haemophilia. 2018;24:209-18.

7. Miesbach W, Meijer K, Coppens M, Kampmann P, Klamroth R, Schutgens R, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. Blood. 2018;131(9):1022-32.

8. Leebeek F, Meijer K, Coppens M, Kampmann P, Klamroth, Schutgens R, et al. Reduction in annualized bleeding and factor IX consumption up to 2.5 years in adults with severe or moderate/severe haemophilia B treated with AMT-006 (AAV5-hFIX) gene therapy. Blood. 2018;132(2):595-606.

9. Chowdary P, Shapiro S, Davidoff AM, Reiss U, Alade R, Brooks G, et al. A Single Intravenous Infusion of FLT180a Results in Factor IX Activity Levels of More Than 40% and Has the Potential to Provide a Functional Cure for Patients with Haemophilia B. ASH Annual Meeting2018.

10. Fabb SA, Dickson JG. Technology evaluation: AAV factor IX gene therapy, Avigen Inc. Curr Opin Mol Ther. 2000;2(5):601-6.

11. Manno CS, Pierce GF, Arruda VR, Glader B, Ragni M, Rasko JJ, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med. 2006;12(3):342-7.

12. Ji, H, Pierce GF, Ozelo MC, de Paula EV, Vargas JA, Smith P, et al. Evidence of multiyear factor IX expression by AAV-mediated gene transfer to skeletal muscle in an individual with severe hemophilia B. Mol Ther. 2006;14(3):452-5.

13. Lu DR, Zhou JM, Zheng B, Qiu XF, Xue JL, Wang JM, et al. Stage I clinical trial of gene therapy for hemophilia B. Sci China B. 1993;36(11):1342-51.

14. Rangarajan S, Walsh L, Lester W, Perry D, Madan B, Laffan M, et al. AAV5–Factor VIII Gene Transfer in Severe Hemophilia A. New England Journal of Medicine. 2017:NEJMoa1708483-NEJMoa.

15. Pasi KJ, Rangarajan S, Kim B, Lester W, Perry D, Madan B, et al. Achievement of normal circulating factor VIII activity following Bmn 270 AAV5-FVIII gene transfer: interim, long-term efficacy and safety results from a phase 1/2 study in patients with severe hemophilia A. Blood. 2017;130(603).

16. Rangarajan S, Kim B, Lester W, Symington E, Madan B, Laffan M, et al. Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvecovec (BMN 270): Long-term efficacy and safety results in patients with severe hemophilia A. Haemophilia. 2018;24(6-65).

17. High KA, George LA, Eyster E, Sullivan SK, Ragni MV, Croteau SE, et al. A Phase 1/2 Trial of Investigational Spk-8011 in Hemophilia a Demonstrates Durable Expression and Reduction in Bleeds. ASH Annual Meeting2018.

18. Nathwani AC, Tuddenham EGD, Chowdary P, McIntosh J, Lee D, Rosales C, et al. GO-8: Preliminary Results of a Phase I/II Dose Escalation Trial of Gene Therapy for Haemophilia a Using a Novel Human Factor VIII Variant. ASH Annual Meeting2018.

19. Powell JS, Ragni MV, White GC, 2nd, Lusher JM, Hillman-Wiseman C, Moon TE, et al. Phase 1 trial of FVIII gene transfer for severe hemophilia A using a retroviral construct administered by peripheral intravenous infusion. Blood. 2003;102(6):2038-45.

20. Roth DA, Tawa NE, Jr., O’Brien JM, Treco DA, Selden RF. Nonviral transfer of the gene encoding coagulation factor VIII in patients with severe hemophilia A. N Engl J Med. 2001;344(23):1735-42.
21. U.S. Food and Drug Administration. Gene Therapy as a Treatment Modality for Hemophilia. [cited 2019 Feb 12]. Available from: https://www.fda.gov/downloads/ForPatients/PatientEngagement/UCM628022.pdf.

22. Teal S, Brohan E, Hettema Y, Humphrey L, Willgoss T, Hudgens S, et al. Development and psychometric evaluation of a novel tool for assessing patient perception and preference for haemophilia treatment (HaemoPREF). Haemophilia. 2014;20(5):666-73.

23. Bonanad S, Schulz M, Gordo A, Spurden D, Cicchetti M, Cappelleri JC, et al. HaemoPREF: Further evaluation of patient perception and preference for treatment in a real world setting. Haemophilia. 2017;23(6):884-93.

24. Chaugule SS, Hay JW, Young G. Understanding patient preferences and willingness to pay for hemophilia therapies. Patient Prefer Adherence. 2015;9:1623-30.

25. Brown TM, Pashos CL, Joshi AV, Lee WC. The perspective of patients with haemophilia with inhibitors and their care givers: preferences for treatment characteristics. Haemophilia. 2011;17(3):476-82.

26. Steen Carlsson K, Andersson E, Berntorp E. Preference-based valuation of treatment attributes in haemophilia A using web survey. Haemophilia. 2017;23(6):894-903.

27. Furlan R, Krishnan S, Vietri J. Patient and parent preferences for characteristics of prophylactic treatment in hemophilia. Patient Prefer Adherence. 2015;9:1687-94.

28. Mantovani LG, Monzini MS, Mannucci PM, Scalone L, Villa M, Gringeri A, et al. Differences between patients', physicians' and pharmacists' preferences for treatment products in haemophilia: a discrete choice experiment. Haemophilia. 2005;11(6):589-97.

29. Mohamed AF, Epstein JD, Li-McLeod JM. Patient and parent preferences for haemophilia A treatments. Haemophilia. 2011;17(2):209-14.

30. Scalone L, Mantovani LG, Borghetti F, Von Mackensen S, Gringeri A. Patients', physicians', and pharmacists' preferences towards coagulation factor concentrates to treat haemophilia with inhibitors: results from the COHIBA Study. Haemophilia. 2009;15(2):473-86.

31. DiBenedetti DB, Coles TM, Sharma T, Pericleous L, Kulkarni R. Assessing patients' and caregivers' perspectives on stability of factor VIII products for haemophilia A: a web-based study in the United States and Canada. Haemophilia. 2014;20(4):e296-303.

32. Costea I, Isasi R, Knoppers BM, Lillicrap D. Haemophilia gene therapy: the patients' perspective. Haemophilia. 2009;15(5):1159-61.

33. Lock J, de Bekker-Grob EW, Urhan G, Peters M, Meijer K, Brons P, et al. Facilitating the implementation of pharmacokinetic-guided dosing of prophylaxis in haemophilia care by discrete choice experiment. Haemophilia. 2016;22(1):e1-e10.

34. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basle G, Gross F, Yvon E, Nusbaum P, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science. 2000;288(5466):669-72.

35. Michelsen S, van Overbeeke E, Huys I. Review on gene therapy in hemophilia. To be published. 2018.

36. Musso R, Santoro R, Coppola A, Marcucci M, Sottilotta G, Targhetta R, et al. Patient preference for needleless factor VIII reconstitution device: the Italian experience. Int J Gen Med. 2010;3:203-8.

37. Moia M, Mantovani LG, Carpenedo M, Scalone L, Monzini MS, Cesana G, et al. Patient preferences and willingness to pay for different options of anticoagulant therapy. Intern Emerg Med. 2013;8(3):237-43.

38. Wasserman J, Aday LA, Begley CE, Ahn C, Lairson DR. Measuring health state preferences for hemophilia: development of a disease-specific utility instrument. Haemophilia. 2005;11(1):49-57.

39. Barlow JH, Stapley J, Ellard DR. Living with haemophilia and von Willebrand's: a descriptive qualitative study. Patient Educ Couns. 2007;68(3):235-42.