

BMJ Open Exploration of the impact of gene therapy on the lives of people with haemophilia and their families: a protocol for the mixed-methods exigency study

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ABSTRACT

Introduction Gene therapy has the potential to change the life experience of people with haemophilia and their families. A growing number of studies have examined the experience for those who have had gene therapy. A few studies have examined the process with other gene therapy among a wider cross-section of the haemophilia community.

Exigency is a nested group of studies investigating the experience and understanding of the haemophilia community to identify what place gene therapy is likely to have in haemophilia care.

Five groups have been identified: those who have already undergone gene therapy, those who do not want it, those who wanted to have it but withdrew or were withdrawn before dosing, those who have not yet been offered it and parents of children with haemophilia.

Methods A qualitative, mixed-methods process will identify what each group understands about gene therapy and what it might mean for the haemophilia community in the future.

Analysis All of the transcripts will be analysed by the lead and coinvestigator using a grounded theory approach. The texts will be coded into themes for further analysis. The data will be summarised and synthesised, and the views expressed will be represented descriptively.

Ethics and dissemination Written consent will be required, and participants will be anonymised. All elements of the study will be reviewed by UK statutory bodies. The study findings will be submitted for publication in peer-reviewed journals, and at haemophilia conferences and symposia.

The study results will also be disseminated directly to study participants. Each participant will receive a copy of any publication and a summary report at the end of the study.

Trial registration number NCT04723680

INTRODUCTION

Haemophilia A and B are rare congenital disorders caused by an inherited genetic defect of the X chromosome, resulting in a deficiency in factor VIII or IX production in haemophilia A and B, respectively. Factor

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ First large-scale study of the lived experience of individuals who have gone through gene therapy.
- ⇒ First study in the world to look at the lived experience of family members of individuals who have undergone gene therapy.
- ⇒ First study in the world to examine why people with haemophilia might not want gene therapy.
- ⇒ This study is being carried out in a high-income country with good access to intensive treatment, therefore, the concerns and issues expressed may differ from those in low-income and middle-income countries.

VIII and IX play pivotal roles in the coagulation cascade, facilitating the formation of a blood clot to help stop bleeding. Haemophilia results in impaired clot formation and can lead to uncontrolled and often spontaneous bleeding. It affects approximately one in every 5000 males.¹ Different types of severity are recognised²:

- Severe—factor activity is less than 1%.
- Moderate—factor activity is 1%–5%
- Mild—factor activity is 6%–40%.

In its severe form, haemophilia results in recurrent joint and muscle bleeds that predispose to arthropathy, muscle contracture and disability. Treatment of affected individuals in the UK involves prophylactic replacement of the missing factor, which decreases spontaneous bleeding events and resultant joint damage.³ Although replacement therapy has improved life expectancy and quality, limitations include high costs and the frequency of infusions. Prophylaxis requires frequent intravenous infusions, which can be as often as daily but are usually 2–3 times per week.

Recent years have witnessed the development of gene therapy for the treatment of haemophilia. Most gene therapies now

undergoing clinical trials rely on a viral vector to achieve transduction of liver cells so that they produce the replacement gene. The majority of vectors are derived from adeno-associated viruses (AAV). Initial infusions of an AAV vector expressing a human factor IX transgene resulted in therapeutic but low factor IX plasma levels and clinical improvement for up to 7 years in 10 men with severe haemophilia B.^{4 5} However, following the introduction of gene therapy with the Padua variant of the factor IX gene, near normal levels of factor expression have been seen in more recent cohorts.⁶ Infusion of an AAV5 vector encoding a B-domain-deleted human factor VIII gene was associated with sustained normalisation of factor VIII activity level over a period of 1 year in six of seven participants who received a high dose, with stabilisation of haemostasis and a profound reduction in factor VIII use in all seven participants.⁷

With many more gene therapy trials in development, and with the possibility of regulatory approval in the near future, gene therapy may become a standard-of-care treatment.^{8 9}

However, a number of challenges remain including, the presence of pre-existing AAV antibodies, the need for immunosuppression to avoid hepatotoxicity, the lack of data as to variability and durability and concerns about genomic integration and malignancy.^{10–13}

Furthermore, gene therapy is unlikely to be available to those under the age of 18 years for some time.

Rationale for the study

In potentially offering a 'cure' for haemophilia, expectations within the haemophilia community are high. Many patients have voiced optimism on haemophilia-specific social media forums and websites for a treatment that is likely to have a significant impact on all areas of an individual's life, including mobility and pain, and to result in freedom from infusions.

Quality-of-life (QoL) measurement tools have been integrated into all current gene therapy studies to assess the benefits of the treatment to the patients. Existing QoL tools have many limitations and may not offer adequate insight into outcomes that are relevant to those who undergo gene therapy.¹⁴ A number of the individuals involved in these studies have anecdotally expressed a degree of psychological distress as a result of a perceived change of identity (personal communication within the UK haemophilia nurse community). This phenomenon has been seen in other treatment areas including, Parkinson's disease and epilepsy,^{15 16} but has not yet been described in haemophilia care.

Gene therapy represents a substantial shift in the entire life experience of living with haemophilia. As such, there is a need to look beyond the quantitative data collected in clinical trials and to assess and understand the real impact of gene therapy on the everyday lives of patients and their families. This data is best captured using qualitative research techniques. As yet, no group involved in gene

therapy studies has sought to undertake in-depth qualitative research into the lived impact of this treatment.

Patient populations are rarely homogeneous in how they react. For some people with haemophilia (PwH) and their families, gene therapy is likely to hold little interest; for others (perhaps those with blood-borne infection or anti-factor inhibitors, or those with non-severe haemophilia) it may not currently be a realistic treatment option. Furthermore, it seems that around one third of the population with haemophilia will not be eligible for gene therapy due to the presence of pre-existing viral vector antibodies.⁹ Being screened for a potentially life-changing therapy only to find that it is not available is likely to result in significant disappointment, for which healthcare professionals will need to offer support. It may affect current treatment-taking behaviours and is also likely impact the lives of close family members (partners/parents/carers/children/siblings).

METHODS AND ANALYSIS

This is a prospective, observational, multiple cohort, qualitative research study to be conducted among diverse groups within the haemophilia community whose lives may be impacted by gene therapy.

Most experienced practitioners familiar with haemophilia have preconceived ideas and theories that may potentially bias data capture. To help overcome this, grounded theory methodology is incorporated into the study design. Grounded theory involves gathering rich data using a variety of methods, including interviews, ethnography and textual analysis to identify themes. Data are coded and the themes analysed; research questions can be reshaped as themes evolve and new concepts are identified; and finally, theories are developed about the data that has emerged.¹⁷ This approach has been used extensively in research with children and families¹⁸ and within haemophilia.¹⁹ In this study, it will allow PwH and their families to tell their own life stories through narrative accounts that represent a true sharing of experiences valued by the tellers, listeners and gatherers,²⁰ and will therefore offer insight into how PwH and their families cope with haemophilia.

The study will form part of a PhD by published works undertaken by the lead researcher and supervised by KK.

Primary aims

- To gather a deep and thorough understanding about the real impact of gene therapy on the everyday lives of PwH and their families.

Secondary endpoints

- To understand the motivation of PwH for taking part in gene therapy studies, both at an early stage and when the procedure is known to be safe and efficacious.
- To understand the expectations of gene therapy among PwH, and whether these have been met.

- ▶ To understand how gene therapy impacts the lives of PwH and their families with regard to levels of factor expression and the postgene therapy monitoring regimen.
- ▶ To understand the impact on PwH of being told they are ineligible for gene therapy, and how this affects their subsequent approaches to treatment.
- ▶ To understand why some PwH are not interested in gene therapy, and whether it will be possible to overcome these barriers in the future.
- ▶ To understand the considerations that may influence uptake in the future among PwH who are interested in gene therapy but have not been offered a trial.
- ▶ To understand the concerns of PwH who are undecided as to whether to have gene therapy, and whether the burden of initial follow-up is a factor at the present time.

Data gathering

Data gathering will be undertaken through a combination of focus groups and interview-based assessment, in each case using grounded theory methodology. In some interviews, 'dyads' comprising a patient and a close family member will be interviewed to identify both patient and family/carer perspectives. In all cases, each participant will be interviewed once only.

Focus group discussion will be guided by the lead researcher. The focus groups will use a grounded theory approach to explore a variety of issues relating to gene therapy and its impact on the participants' everyday experience of living with haemophilia, and to generate and test ideas where appropriate.

In-depth qualitative interviews can be conducted with both members of the dyad together, though the interviews can be conducted separately at the request of the participants. Initial subject interviews will follow a guide developed by the research team (see online supplemental interview guide). Each interview will be conducted by the lead researcher with a coinvestigator in attendance.

The semistructured nature of both the interviews and the focus groups have been specifically chosen as they allow researchers to understand complex and sensitive topics. They also allow the discussion to be directed by the participant rather than the researcher and therefore allow for a bottom-up approach, one that focuses on the concerns of the individual participants^{21 22}

All focus groups and individual interviews will be recorded digitally so that the researcher can pay full attention to the subject.²³ After each of the focus groups and interviews, the sound files will be transcribed verbatim.

Study population

The study population will comprise people over the age of 16, who fall into the following categories:

Inclusion criteria

- ▶ PwH A or B who consented to and have undergone gene therapy in the early dose-finding studies.

- ▶ PwH A or B who consented to a gene therapy trial but who withdrew from, were withdrawn from, or were ineligible for the study.
- ▶ PwH A or B who are definitely not interested in gene therapy.
- ▶ PwH A or B who are interested in but have not been offered gene therapy.
- ▶ Parents of children (<18years) with haemophilia.
- ▶ Those who have given written consent to be in the study.

Exclusion criteria

- ▶ Anyone with a bleeding condition other than severe haemophilia A or haemophilia B.
 - ▶ Non-English speakers.
 - ▶ Those who do not consent to be in the study.
- We hope to recruit up to 105 participants to the study in total, to include:
- ▶ Approximately 65 men with haemophilia.
 - ▶ Approximately 40 family members (spouse/partner/parent/carer/sibling of the person with haemophilia) to form patient/family member dyads.

Data analysis and sample size calculation

This is a qualitative study using established qualitative research methodologies. Statistical evaluation is therefore not appropriate.

Immediately following each focus group or interview, the researcher and coresearcher will record any thoughts, reflections or observations that arose during the interview. These will be analysed as part of the framework analysis described below.²⁴

All of the transcripts will be analysed by the lead and coinvestigator using a grounded theory approach. The texts will be read and reread, then coded into themes for further analysis using a transformational framework, identifying themes or concepts, summarising and synthesising the data, and using descriptive analysis to represent the views expressed.²⁵ A table of themes will then be produced, characterising recurring ideas and thoughts captured in the focus groups and interviews. These will form the basis for further analysis. Individual direct quotes may be used; this will be outlined in the information sheet(s) and consent.

Inferential testing will be used to describe how outcomes differ between groups. Correlation between groups may be achievable with explanatory factors (eg, age, treatment regimen, bleeds, joint health).

Recruitment screening and study procedures

Once ethical approval has been received, PwH A or B who have undergone gene therapy and PwH A or B who withdrew from were withdrawn from or who were ineligible for gene therapy will be recruited through six participant identification centre (PIC) sites (ie, sites that were responsible for either referring patients to dosing sites or were the primary dosing sites for the gene therapy).

The PIC sites are:

- ▶ Royal Free London National Health Service (NHS) Foundation Trust.
- ▶ Guy's and St Thomas' NHS Foundation Trust.
- ▶ University Hospital Southampton NHS Foundation Trust.
- ▶ Hammersmith Hospital, London—Imperial College Healthcare NHS Trust.
- ▶ Royal London Hospital—Barts Health NHS Trust.
- ▶ Addenbrooke's Hospital—Cambridge University Hospitals NHS Foundation Trust.

Once identified, potential participants will be given information about the study by their clinical team and will be invited to participate. If they agree to participate, they will be contacted by the research team from the Oxford Haemophilia and Thrombosis Centre at the Oxford University Hospitals NHS Foundation Trust (the lead site) to organise a mutually convenient time for their study interview/focus group. These may be undertaken at hospital, in their home or other mutually convenient site, either face to face or via videoconference.

The study will also be advertised on social media platforms to recruit those PwH A or B who have thought about gene therapy but are not interested, those who are interested in gene therapy but have not been offered gene therapy, and those who do not know about gene therapy, including parents of children where gene therapy is not yet a treatment option (see online supplemental social media plan).

Study visits

For all participants, there will be a single study visit at which all study data will be collected. This is summarised in the panel below. Each participant and/or dyad will participate once only either in a focus group or a face-to-face interview, either in person or via videoconference.

The participant and dyad interviews can be carried out as a pair or individually, according to the preference of the interviewees.

Study sequence

Subject to patient availability, data-gathering activities will be conducted in two phases.

The first phase will involve four focus groups lasting 1–2 hours with individuals from two subgroups:

- ▶ PwH who did not want to be part of gene therapy trials.
- ▶ Parents of children with haemophilia.

Each focus group will be composed of up to five individuals and will be conducted either face-to-face or via a videoconferencing platform.

The second phase will involve approximately 65 in-depth qualitative individual interviews, each lasting around 1 hour, conducted with PwH/family member dyads from three subgroups:

- ▶ PwH who have undergone gene therapy.
- ▶ PwH who were withdrawn from or withdrew themselves after initial consent to gene therapy.

- ▶ PwH who have not been offered gene therapy at this point.

In all cases, each participating PwH and family member (if one is available) will be interviewed once only, either face-to-face or via videoconferencing platform.

Patient and public involvement statement

This protocol has been written with the assistance of a patient representative (Luke Pembroke) and has been reviewed by two patient representatives. Both reports are available for review.

LIMITATIONS

This is a UK-based study in a self-selecting sample of individuals who have ready access to prophylaxis and report high satisfaction rates with their treatment. As such the results may have limited applicability beyond that cultural milieu. The sample size, though small represents the largest and broadest sample studied thus far and will be the first to include family members as participants. The study will, therefore, at the very least, establish a baseline that can be further elaborated on as gene therapy becomes more widely available. It will also be important to follow-up these early adopters of gene therapy to see what their experiences are as they age and as the therapy matures.

ETHICS AND DISSEMINATION

There is minimal risk to participants or researchers from this study. Participants will be invited to either one focus group or one interview to discuss their hopes, fears, expectations and the realities of gene therapy.

In the event that any patient or family member becomes distressed by this, they will be referred (with consent) to the psychology services affiliated with the haemophilia centres from which they have been recruited.

Informed consent

Study participants will be required to consent to be in the study; their consent can be withdrawn at any stage and will not have any impact on their haemophilia care. Consent will be reaffirmed before the focus groups and interviews take place.

Anonymity/confidentiality

The use of focus groups and interviews raises issues of confidentiality, especially when direct quotes and/or the circumstances of quotes may be used in reports and publications. It is therefore imperative that individuals are anonymised. This will be achieved by the individual reports and quotes using study numbers which are known only to the research team.

Ethical approval

The study will be registered with the research and development office at Oxford University Hospitals NHS

Foundation Trust. It will also be registered on the National Institute for Health Research (NIHR) portfolio.

Ethical approval for the focus groups and patient/family member dyad interviews will be sought from the Health Research Authority (HRA) using the standard IRAS application forms.

Reward for participants

Participants who agree to attend focus groups or interviews will be given a gift voucher for their participation, up to a maximum of £100 per household, along with reimbursement of any travel costs if incurred.

In both cases, details of these will be included in the participant information sheet(s).

Data protection

Participants in the Exigency study will be anonymised and will be known by study number only and managed in line with the European Union General Data Protection Regulation (successor to the UK Data Protection Act 1998).

- ▶ All audiorecordings will be transcribed verbatim by a professional transcriptionist unknown to the study participants. The transcriptionist will have signed a confidentiality agreement.
- ▶ All data (paper records and audiorecordings) will be kept in locked cupboards by Haemnet for the duration of the study.
- ▶ Recordings will be deleted once the study has been analysed.
- ▶ Paper records, including transcripts of interviews, will be kept for 10 years after the study, after which they will be shredded.
- ▶ Any data on computers will be password protected in line with NHS data protection procedures.

Dissemination

Abstracts will be submitted to national and international haemophilia conferences, including the European Association for Haemophilia and Allied Disorders Congress, the Haemophilia Nurses Association Conference and the World Federation of Haemophilia Congress.

The study findings will also be submitted for publication in peer-reviewed journals serving medical/nursing/allied health professionals who work with PwH.

The study results will be disseminated directly to study participants. Each participant will receive a copy of the publication relevant to their particular arm of the study and a final summary report at the end of the study. Results will also be shared on social media and through the UK Haemophilia Society and European Haemophilia Consortium websites, and through member newsletters.

All investigators will contribute to study publications and will be named as coauthors. Authorship will be confirmed in line with journal publication guidance, including International Committee of Medical Journal Editors recommendations.

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Contributors SF was the originator of the project concept and primary writer of the protocol and interview schedule. He was also the primary investigator. LP was involved in the design of the interview schedule as a patient advocate and helped plan the social media campaign. MH was involved in the design of the protocol. KK was involved in the design of the protocol and interview schedule. She was also a coinvestigator on the study and was the PhD supervisor of SF.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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REFERENCES

- 1 Srivastava A, Brewer AK, Mauser-Bunschoten EP. Treatment guidelines Working group on behalf of the world Federation of haemophilia. guidelines for the management of haemophilia. *Haemophilia* 2013;19:e1–47. doi:10.1111/j.1365-2516.2012.02909.x
- 2 Makris M, Oldenburg J, Mauser-Bunschoten EP. For the Subcommittee on factor VIII, factor IX and rare bleeding disorders. The definition, diagnosis and management of mild hemophilia A: communication from the SSC of the ISTH. *J Thromb Haemost* 2018;16:2530–3. doi:10.1111/jth.14315
- 3 Richards M, Williams M, Chalmers E, et al. A United Kingdom haemophilia centre doctors' organization guideline Approved by the British Committee for standards in haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia a. *Br J Haematol* 2010;149:498–507.
- 4 Nathwani AC, Tuddenham EGD, Rangarajan S, et al. Adenovirus-Associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med* 2011;365:2357–65.
- 5 Nathwani AC, Reiss UM, Tuddenham EGD, et al. Long-Term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med* 2014;371:1994–2004.
- 6 Perin GQ, Herzog RW, Markusic DM. Update of clinical gene therapy for haemophilia. *Blood* 2018;33:407–14. doi:10.1182/blood-2018-07-820720
- 7 Rangarajan S, Walsh L, Lester W, et al. AAV5-Factor VIII gene transfer in severe hemophilia a. *N Engl J Med* 2017;377:2519–30.
- 8 Brown K, Green G. The haemophilia drug market. *Nat Rev Drug Discov* 2018;17:541–2.
- 9 Pierce GF, Iorio A. Past, present and future of haemophilia gene therapy: from vectors and transgenes to known and unknown outcomes. *Haemophilia* 2018;24 Suppl 6:60–7.

- 10 Stanford S, Pink R, Creagh D, *et al.* Adenovirus-Associated antibodies in UK cohort of hemophilia patients: a seroprevalence study of the presence of adenovirus-associated virus vector-serotypes AAV5 and AAV8 neutralizing activity and antibodies in patients with hemophilia a. *Res Pract Thromb Haemost* 2019;3:261–7.
- 11 Batty P, Lillicrap D. Advances and challenges for hemophilia gene therapy. *Hum Mol Genet* 2019;28:R95–101.
- 12 Makris M. Gene therapy 1·0 in haemophilia: effective and safe, but with many uncertainties. *Lancet Haematol* 2020;7:e186–8.
- 13 Pierce GF. Gene therapy for hemophilia: Anticipating the unexpected. *Blood Adv* 2020;4:3788.
- 14 Iorio A, Skinner MW, Clearfield E, *et al.* Core outcome set for gene therapy in haemophilia: results of the coreHEM multistakeholder project. *Haemophilia* 2018;24:e167–72.
- 15 Gilbert F. The burden of normality: from 'chronically ill' to 'symptom free'. New ethical challenges for deep brain stimulation postoperative treatment. *J Med Ethics* 2012;38:408–12.
- 16 Wilson S, Bladin P, Saling M. The "burden of normality": concepts of adjustment after surgery for seizures. *J Neurol Neurosurg Psychiatry* 2001;70:649–56.
- 17 Charmaz K. *Constructing Grounded theory*. 2nd ed. London: SAGE Publications, 2014.
- 18 Neill SJ. Grounded theory sampling: 'whole' family research. *Journal of Research in Nursing* 2007;12:435–43.
- 19 Khair K, Pollard D, Harrison C, *et al.* How patients view extended half-life products: impressions from real-world experience (the hope study). *Haemophilia* 2019;25:814–20.
- 20 Hardy S, Gregory S, Ramjeet J. An exploration of intent for narrative methods of inquiry. *Nurse Res* 2009;16:7–19.
- 21 Roulston K, Choi M. The SAGE handbook of qualitative data. In: Flick U, ed. *Qualitative interview*. London: Sage Publishers Ltd, 2018: 233–49.
- 22 Corbin J, Morse JM. The unstructured interactive interview: issues of reciprocity and risks when dealing with sensitive topics. *Qualitative Inquiry* 2003;9:335–54.
- 23 Balen R, Holroyd C, Mountain G, *et al.* Giving children a voice: methodological and practical implications of research involving children. *Paediatr Nurs* 2000;12:24–9.
- 24 Ritchie J, Spencer L, O'Connor W. Carrying out qualitative analysis. In: Ritchie J, Lewis J, eds. *Qualitative Research Practice: A Guide for Social Science Students and Researchers*. London: SAGE Publications, 2003.
- 25 Spencer L, Ritchie J, O'Connor. Analysis: practices, principles and processes. In: Ritchie J, Lewis J, eds. *Qualitative Research Practice: A Guide for Social Science Students and Researchers*. London: SAGE Publications, 2003.

Supplementary Information 1. Interview Guide

Part 1. People with haemophilia who underwent gene therapy	
<p>Thank you for agreeing to take part in this project about how people feel about having undergone or considered undergoing gene therapy. Everything you tell us in this interview will be treated with complete confidence – your identity will never be revealed.</p> <p>We know that people who have undergone gene therapy show better quality of life on questionnaires, but we want to know more about how gene therapy impacts on your day-to-day life.</p> <p>Are you OK to proceed and are you happy that we record the interview?</p>	
Questions	Prompts
Can you begin by telling me how old you are and a little bit about what hobbies you have?	
Can you tell me about your haemophilia – when were you diagnosed? What treatment you were on before consenting to take part in the gene therapy study?	
Can you recall how many bleeds you had in an average year before consenting to take part in the gene therapy study?	
How are your joints? Do you have any joints that bleed more than others? How did you manage those before and has that changed now?	
Have you ever had an operation in hospital? What was it for?	
Now I'd like to talk about your reasons for choosing to take part in the gene therapy study and what influenced your decision.	<ul style="list-style-type: none"> • When and how did you first hear about gene therapy? • Who instigated the idea of gene therapy – was it you or your clinicians? • Can you tell me about the tests you had to go through to take part in the study?

	<ul style="list-style-type: none"> • Did you feel that you were given enough time and information to make your mind up about taking part? • How long did the process take? • Did you feel fully informed throughout this time? • What were you thinking during this time? • What did you feel when you finally found out you were eligible to undergo the gene therapy?
Can you tell me about the actual therapy and what you went through as part of the therapy?	<ul style="list-style-type: none"> • Did you find any of the procedures embarrassing? • Did you find the frequency of visits difficult? • Did you find any of the post therapy requirements difficult?
<p>Now that you have had the treatment can you describe to me the impact that it has had on your life</p> <ul style="list-style-type: none"> • Imagine a scale of 1 to 6, where 1 is no impact and 6 is the highest impact. How much of an impact on your life does your treatment represent? <p>o Now vs before</p>	<ul style="list-style-type: none"> • How active are you on a day-to-day basis? Do you do any sports? • How have you adjusted to not having to treat yourself in the way you used to? • What has surprised you most since you had the gene therapy • What is it like to no longer have to treat yourself with prophylactic factor? Who taught you to do prophylaxis? What was it like?
What impact has having gene therapy had on you and your family?	<ul style="list-style-type: none"> • Has anything surprised you about the impact gene therapy has had on your life? • Have there been any negative impacts? • How worried are you about an injury? • Have you had any bleeds since having undergone gene therapy? • If yes, where were they? When did they happen? Do you know what caused them? What action did you take? How would you treat now vs. past? How did you feel about this bleed?

	<ul style="list-style-type: none"> • If no, then how does the prospect of a bleed make you feel?
<p>What about pain? Do you have any pain now?</p> <ul style="list-style-type: none"> • Imagine a scale of 1 to 6, where 1 is very little pain and 6 is the worst pain. How bad is that pain? 	<ul style="list-style-type: none"> • How has it been over the past month (do you get pain every day, is it joint related, is it haemophilia related?) • What did you usually do in the past when you experience pain related to your haemophilia? – is it different now? • How does arthritic pain differ from the pain of a bleed (if applicable)? • Is the pain different now?
What impact has gene therapy had on your time?	
What are your hopes/expectations for gene therapy? What are your goals for the next 6 months? Do you have any concerns about it?	
Have you heard about any other treatments that might be available in the future?	
If the gene therapy stopped working, how would you feel about having to go back to your previous treatment?	
What advice would you give to others considering having gene therapy?	
Is there anything else you would like to say or ask of me?	
Part 2. Family participants of individuals who have undergone gene therapy	
<p>Thank you for agreeing to take part in this project about how people feel about having undergone or considered undergoing gene therapy. Everything you tell us in this interview will be treated with complete confidence – your identity will never be revealed.</p> <p>We know that people who have undergone gene therapy show better quality of life on questionnaires, but we want to know more about how gene therapy impacts on their day-to-day life.</p>	

Are you happy to proceed and are you happy that we record the interview?	
Can you begin by telling me how old you are and a little bit about what activities you and your partner/spouse/child/sibling enjoy doing together?	
How long have you known your partner/spouse?	
How long have you known that your partner/spouse/child/sibling has haemophilia?	
Did you have any idea what haemophilia was before this?	
How different was the reality of your partner's/spouse's/child's/sibling's haemophilia from what you thought it might be?	
I'd like to go on now to ask a little bit about your partner/spouse/child/sibling and how their haemophilia has affected both him and your family:	<ul style="list-style-type: none"> • What treatment was your partner/spouse/child/sibling on before he took part in the gene therapy study? • Can you recall how many bleeds your partner/spouse/child/sibling would normally have in an average year? • When your partner/spouse/child/sibling had a bleed, how did he manage them?
What difference has the gene therapy made to you partner/spouse/child/sibling?	<ul style="list-style-type: none"> • How long has it been since your partner/spouse/child/sibling underwent the gene therapy? • Has your partner/spouse/child/sibling had any bleeds since he has had the gene therapy? • Does he react to the bleeds he has now in a way different now than he did before having the gene therapy treatment?
How do you think the therapy has impacted on you as a family/carer?	

Can you give me examples of what impact this has made?	
Do you have any worries for the future?	
If the gene therapy stopped working, how would you feel about your partner/spouse/child/sibling having to go back to his previous treatment?	
What advice would you give to others considering having gene therapy?	
Is there anything else you would like to say or ask of me?	

Supplementary Information 2. Social media recruitment plan

Social media will play a key part in driving awareness and supplementing recruitment to the Exigency project.


Haemnet will post to a variety of social media platforms including:


- Twitter
- Instagram
- Facebook
- LinkedIn
- YouTube

Social media posts will provide a link to a dedicated Exigency website page hosted on the Haemnet site: www.haemnet.com/exigency/
This site is currently password protected until the study receives REC and HRA approvals.

This webpage will contain key information about the project, as well as details of how to get in touch with the research team if interested, along with a downloadable link to the Patient Information Sheet.

Examples of all of the advertisements and a screen-print of the Web page can be found below.

Platform(s)	Content For People with Haemophilia who definitely do not want to have gene therapy
Facebook, LinkedIn, Instagram and Twitter	 An advertisement for the Exigency project. It features a light blue background with a large, stylized DNA double helix at the bottom. The text is in a teal, sans-serif font. It asks if the viewer is a man with haemophilia living in England who has decided that gene therapy is definitely not for them, and invites them to a focus group. A call to action button points to the website www.haemnet.com/exigency. Icons include a map of England, a group of people, and a DNA helix. Logos for haemnet and Exigency are at the bottom.

Platform(s)	Content For People with Haemophilia who have not been offered gene therapy
Facebook, LinkedIn, Instagram and Twitter	 <p>The advertisement features a white background with a blue border. At the top left is an orange outline of the United Kingdom. At the top center is an orange icon of three people with speech bubbles. At the top right is an orange DNA double helix. The text in the center reads: "Are you a man with haemophilia living in England? Are you interested in gene therapy but have not been offered participation in a clinical trial by your haemophilia team? We'd like to hear your views and invite you to take part in a focus group". Below this is an orange button with the text "To find out more, head to: www.haemnet.com/exigency". At the bottom is a blue banner with a white DNA double helix and the Exigency logo. The haemnet logo is in the bottom left corner.</p>

Platforms	Content for people with haemophilia who consented to have gene therapy but were withdrawn by the study
Facebook, LinkedIn, Instagram and Twitter	 <p>The advertisement features a blue background with a white DNA double helix. The Exigency logo is at the top center. The text in the center reads: "Are you a man with haemophilia living in England who was screened for gene therapy only to be told you were not eligible? We'd like to hear your story". Below this is an orange button with the text "To get involved and find out more go to www.haemnet.com/exigency". The haemnet logo is in the bottom right corner.</p>

Platforms	Content for people with haemophilia who have undergone gene therapy
Facebook, LinkedIn, Instagram and Twitter	 <p>The poster features a blue background with a faint DNA double helix. At the top center is the 'Exigency' logo, which consists of a stylized orange and green figure. Below the logo, the text reads: 'Are you a man with haemophilia living in England who has had gene therapy?' followed by 'We'd like to hear your story'. At the bottom, an orange box contains the text: 'To get involved and find out more go to www.haemnet.com/exigency'. The 'haemnet' logo is in the bottom right corner.</p>

Platforms	Content for people with haemophilia who consented to have gene therapy but chose not to take part
Facebook, LinkedIn, Instagram and Twitter	 <p>The poster features a blue background with a faint DNA double helix. At the top center is the 'Exigency' logo, which consists of a stylized orange and green figure. Below the logo, the text reads: 'Are you a man with haemophilia living in England who successfully screened for gene therapy but decided not to take part?' followed by 'We'd like to hear your story'. At the bottom, an orange box contains the text: 'To get involved and find out more go to www.haemnet.com/exigency'. The 'haemnet' logo is in the bottom right corner.</p>

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