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who have already undergone gene therapy, those who do not want it, those who wanted to have it but withdrew or were withdrawn before dosing, those who have not yet been offered it and parents of children with haemophilia.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

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.

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 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 recognised[2]:

- 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 families[18] 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 (<18 years) 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 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 Word 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.

Twitter Simon Fletcher @abookclubof1

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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Competing interests SF unrestricted educational grants: Roche Chugai and uniQure Biopharma BV Speaker/consultancy fees: Novo Nordisk, Bayer and Roche/Chugai. Luke Pembroke Employee of Haemnet Speaker/consultancy fees: Novo Nordisk, Bayer Biomarin, Sobi, and Roche/Chugai. Michael Holland Employee of Haemnet. KK unrestricted educational grants: CSL Behring, Roche Chugai, Sobi, Pfizer, uniQure Biopharma BV Speake/consultancy fees: Bayer, CSL Behring, Novo Nordisk, Roche/Chugai, Sobi, Takeda, Pfizer, uniQure.

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.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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