The lived experience of haemophilia and impact of gene therapy on the haemophilia patient community and their families: The Exigency Programme.

Candidate
Simon Fletcher
MA, BA (Hons), Dip N, RGN

Research Assistant
University of Oxford

Research Supervisors

Prof. Eila Watson
Professor in Supportive Cancer Care, and Deputy Director, Oxford Institute of Applied Health Research (OxInAHR).
Faculty of Health and Life Sciences

Dr Kate Khair
Associate Professor: London South Bank University
Director of Research: Haemnet

Submitted: August 2025

Submitted in partial fulfilment of the requirements of Oxford Brookes University for the degree of Doctor of Philosophy on the basis of published works.

Abstract

Gene therapy has the potential to change the lives of people with haemophilia, offering, if not a complete cure, then a significant reduction in treatment burden and an improvement in overall quality of life. Little is known, however, about the lived experiences of those who have undergone gene therapy or the impact on the haemophilia community and their families. The Exigency programme is the first comprehensive study to examine these psychosocial aspects.

The nine papers presented here as evidence for this PhD by Published Work are the results of a five-year mixed methods study programme examining the experiences of 69 participants across five distinct cohorts: those who had undergone gene therapy, those who do not want it, those who had withdrawn or were withdrawn from trials, those who have not yet been offered therapy, and parents of children with haemophilia. Data were collected through interviews, focus groups, and surveys. Three main themes were identified.

Safety and efficacy concerns dominated many of the discussions across all the cohorts, especially regarding the side effects of immunosuppressive medication and treatment durability. **Identity** also emerged as a key factor, with some considering their haemophilia an essential part of their sense of self, leading to complex responses to the idea of a "cure." **Expectations** varied widely; some saw gene therapy as transformative, while others felt it increased rather than reduced their treatment burden. The programme, therefore, highlights significant unmet psychosocial needs that have not been previously recognised or addressed.

All papers have been published in specialised journals and have directly influenced clinical practice guidelines, highlighting the need for wide-ranging psychosocial support throughout the gene therapy journey. The research also demonstrates that the impact of gene therapy extends beyond just clinical outcomes, affecting individual and family identity, relationships and quality of life.

Plain Language Summary

Gene Therapy for Haemophilia: What We Learned

What is haemophilia?

Haemophilia is a condition in which a person's blood doesn't clot properly. It mainly affects boys and men, but girls and women can have it too. People with haemophilia can bleed inside their knee, elbow and ankle joints as well as into their muscles. This bleeding can cause pain and make it hard to move.

How do people treat it now?

Most people with haemophilia need regular injections of a medicine to help their blood clot. Some people need these injections every week.

What is gene therapy?

Gene therapy is a new kind of treatment. Instead of getting regular injections, people with haemophilia would only need one treatment. This treatment would then help their body clot like everyone else's.

What did we do?

Between 2020 and 2024, we spoke to 69 people from all over the United Kingdom. We spoke to:

- Parents of children with haemophilia
- Men who did not want to have gene therapy
- People with haemophilia who wanted to have gene therapy
- People who had already had gene therapy
- People who were going to get gene therapy but couldn't in the end
- Partners of people with haemophilia

What did we find out?

Problem 1: Side effects

People who get gene therapy sometimes need to take other medicines to make sure it work. These medicines can cause problems like:

- Trouble sleeping
- Gaining weight
- Feeling moody or sad

During COVID-19 epidemic (2020), some people worried because these medicines can make it easier to get sick.

People were also worried about problems that might happen years later, problems that we might not know about yet.

Problem 2: Who am I?

Some people said that having haemophilia is part of who they are, like their hair colour or where they're from. It has shaped their whole life. But most of them still wanted gene therapy, even though haemophilia is part of their identity.

Women and girls with haemophilia felt like doctors didn't understand them as well. They thought this meant they weren't getting the same treatment options as boys and men.

Problem 3: What people hoped for vs. what happened

Some people who had gene therapy felt really free and happy, that they didn't have to worry about bleeding as much. But other people were disappointed. They had to go to the hospital a lot for check-ups and blood tests. This felt like even more work than before.

Some people were told they could have gene therapy but were later told that they couldn't have it after all. This made them very upset. They had imagined life without bleeding and without the need to have injections, and then that dream was taken away.

Why does this matter?

Gene therapy isn't just a medicine – it can change someone's whole life and their family's life too. People who can't have the treatment need help and support just like people who can have it.

Gene therapy gives people hope for a better life. But to make it work well, people need:

- Doctors who explain things clearly
- Someone to talk to about their feelings with
- Understanding that getting rid of a condition you've had your whole life is a big change.

Acknowledgements

I would like to thank the following people for their support during all phases of this PhD process.

My supervisors, Professor Eila Watson and Dr Kate Khair, thank you for your advice and support during the production of this PhD synthesis. I would also like to thank all my co-authors, Kathryn Jenner, Mike Holland, Steve Chapman, Lisa Steadman, Luke Pembroke and Dr Kate Khair.

Thank you also to my colleagues at Haemnet, the Oxford University Hospitals NHS Foundation Trust, and the University of Oxford, including Dr Nicola Curry, and Dr Elizabeth Ormondroyd.

To all the participants in the Exigency study: This PhD is about your experiences, stories, and journeys. I have walked alongside you for a short while and I am honoured to be able to share your stories here.

I would also like to thank uniQure Biopharma B.V. for the educational grant they awarded to undertake the Exigency programme.

I would also like to acknowledge the support of the Horizons Research Group, including Greta Mulders and Linda Myrin Westesson. Your steadfast encouragement throughout the whole of my studies has been incalculable.

Most of all, I want to thank my wife, Claire. She has shared this PhD journey with me every day, providing unwavering support through the highs and the lows.

Cover Image

Image created by author.

Excerpt of poem taken from John Donne's Meditation XVII (1624)

AI Statement

Both Grammarly and Microsoft's editor tool have been used during the writing of the papers and this synthesis.

An online assessment tool (https://www.webfx.com/tools/read-able/) was used to gauge the educational level of the plain language summary (Fleisch-Kinkade Level = 7[1]).

[1] Kincaid, Fishburne, Rogers and Chissom, (1975).

Table of Contents

List of Figures

List of Tables

Glossary of Terms and Abbreviations

AAV – Adeno-Associated Virus

ABR – Annualised Bleeding Rate

AUB – Abnormal Uterine Bleeding.
This is a new non-gendered nomenclature for any condition that causes uterine bleeding that is not within the normal parameters of regularity, frequency, volume, or duration. It is both non-gendered and recognises that abnormal bleeding is not always linked to menstruation.

CRT – Coagulation Replacement Therapy

FIX – Factor IX

FVIII – Factor VII

GT – Grounded Theory

ITI – Immune Tolerance Therapy

iu/dl – International units per Decilitre

Pathogenic Gene Variant – a change in the DNA sequence of a gene that can result in an individual developing a genetic disorder or disease. In haemophilia, these variants are either missense mutations (changes in a single nucleotide that alter the function or structure of a protein), nonsense mutations (changes in the DNA that cause a protein to terminate or end its translation earlier than expected), inversions (a change in the structure of the DNA caused when a segment of DBA breaks off and reattaches to the same chromosome in reverse order, altering the genes function or expression) or deletions (a change in the structure of the DNA caused by the loss of a single nucleotide or an entire chromosome during DNA replication).

PROM – Patient Reported Outcome Measure

PwH – Person/People with Haemophilia

PwHI – Person/people with Haemophilia and Inhibitor

QoL – Quality of Life

List of Papers[2]

i. Khair, K., Steadman, L., Chaplin, S., Holland, M., Jenner, K. and Fletcher, S. (2020) Parental perspectives on gene therapy for children with haemophilia: The Exigency study. Haemophilia.27(1):120-128. https://doi.org10.1111/hae.14188.

ii. Fletcher, S., Jenner, K., Holland, M., Chaplin, S. and Khair, K. (2021). An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. Haemophilia. 27:11-15. https://doi.org/10.1111/hae.14378.

iii. Fletcher, S. (2021) Seeing the bigger picture: Qualitative research in the Zoom® age. J Haem Pract. 8(1): 141-144. https://doi.org/10.2478/jhp-2021-0019.

iv. Fletcher, S., Jenner, K., Pembroke, L., Holland, M. and Khair, K. (2022). The experiences of people with haemophilia, and their families, of gene therapy in a clinical trial setting: Regaining Control, the Exigency Study. Orphanet Journal of Rare Diseases. 17:155 https://doi.org/10.1186/s13023-022-02256-2.

v. Fletcher, S. (2022) "I didn't know women could have Haemophilia": A Qualitative Case Report. J Haem Pract. 9(1):85-95. https://doi.org/10.2478/jhp-2022-0011.

vi. Fletcher, S, Pembroke, L., Holland, M. and Khair, K. (2022). An 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. BMJ Open 12:e060351. http://doi.org/10.1136/bmjopen-2021-060351.

vii. Fletcher, S., Jenner, K., Holland, M. and Khair, K. (2023). Expectation and Loss when Gene Therapy for Haemophilia is Not an Option: An Exigency Sub-study. Haemophilia. 1-8. https://doi.org/10.1111/hae.14774.

viii. Fletcher, S., Jenner, K. and Khair, K. (2023). Shared decision-making for gene therapy in haemophilia care. J Haem Pract. 2023;10(1) https://doi.org?10.2478/jhp-2023-0009.

ix. Fletcher, S., Jenner, K., Holland, M. and Khair K (2024). Barriers to gene therapy, understanding the concerns people with haemophilia have: an exigency sub-study. Orphanet J Rare Dis 19, 59. https://doi.org/10.1186/s13023-024-03068-2.

[2] References to the papers used in evidence in this synthesis will be referred to using the roman numerals noted above

Chapter One: Introduction

Since the 1960s, the care and treatment of people with haemophilia (PwH) has greatly improved (High, 2014). This has resulted in a significant reduction in the number of bleeds experienced by PwH and an improvement in mortality (Manco-Johnson, 2003; Mejia-Carvajal, Czapek and Valentino, 2006). Over the past 20 years, haemophilia, because of its monogenic nature – a disorder caused by a single genetic variation – has been regarded as a template disease and proof of concept for gene therapy (Pasi, 1996). Consequently, numerous gene therapy clinical trials have been conducted (Nathwani et al., 2011; Nathwani et al., 2014; Rangarajan et al., 2017), and in 2024, gene therapy was licensed in Europe and the US for treating both haemophilia A and haemophilia B (Chowdary et al., 2024; Donnelly, 2024). Only one gene therapies (for haemophilia B) has been approved and is available in the UK (Iacobucci, 2024).

In 2018, the haemophilia centre in Oxford, where I worked, began exploring the possibility of becoming a referral and follow-up care centre for two haemophilia gene therapy studies: one for haemophilia A and the other for haemophilia B. As part of this process, the centre started discussing gene therapy with PwH they provided care for.

None of those approached fully understood what gene therapy might involve or what they might be asked to do if they were to undergo it, but all saw it as a potential cure for their haemophilia. Three expressed immediate interest in receiving gene therapy if it were offered. One was a little more hesitant, stating he would "*need to know more about it*" before making a decision (unreferenced conversation between patient and author, 2018). However, two said they would not want gene therapy. One stated he believed his current treatment was sufficient, "*I only have to treat myself once a week and I don't bleed"* (unreferenced conversations between patient and author, 2018). The other, however, remarked, "*although it would be beneficial not to worry about bleeding, I wouldn't want gene therapy*. *I am who I am because of my haemophilia"* (unreferenced conversations between patient and author, 2018).

Shortly after these conversations, the centre began referring potential participants to a gene therapy research centre in London for treatment. In 2019, one gene therapy recipient experienced a sudden and sustained increase in his factor levels, to the point that he could stop his usual prophylaxis. During a follow-up visit to the centre, he expressed difficulty

adapting to his new reality, or rather, the perceived absence of his previous condition. He explained that throughout his life, he had understood what he could and could not do in relation to his condition. If he was about to engage in an activity that might be risky or potentially lead to a bleed, he knew he should treat himself beforehand. Now, however, he was uncertain about what actions to take. He remarked, "*I don't know who I am anymore; for my whole life, I've been "NAME" with haemophilia, now I don't have haemophilia, and I don't know what that means."* (unreferenced conversations between patient and author; 2019)

As a team, we were surprised by this reaction, and I began to question whether I truly understood what having haemophilia means for the individual and what the implications of gene therapy are for PwH. Consequently, I decided to conduct research in this area.

The Exigency programme was implemented during a period of rapid change in gene therapy regulation. When recruitment started in July 2020, gene therapy was only available through clinical trials. By the end of the study, regulatory approval was near but had not yet been granted in the UK. This timing proved advantageous, as it allowed the collection of experiences during the final phases of clinical development when anticipation of licensing was high but uncertainty still existed. The programme, therefore, provides insights into the clinical trial experience and the community's expectations as gene therapy moved from an experimental treatment towards a licensed therapy.

Aim

The primary aim of the Exigency programme has been to examine the lived experiences of PwH and the impact of gene therapy on the UK haemophilia patient community and their families, and to understand what educational and psychological support might be needed to enable them to decide whether gene therapy is a treatment option they might pursue.

Specific Study Aims

- To understand what parents of children with haemophilia know about gene therapy and explore the information and support they feel they need in order to prepare their children to decide about gene therapy in the future (paper i).
- To understand the lived experiences of PwH and their families (papers i, ii, iv, v, vii and ix).
- To understand the lived experiences of those PwH who do not want gene therapy as a treatment option (paper ii).

- To understand the lived experiences of people who have undergone gene therapy and the impact the treatment has had on them and on their family (paper iv).
- To understand the impact of withdrawal from gene therapy on the ongoing attitude of individuals to their haemophilia care and the impact it has on their family (paper vii).
- To understand the lived experience of a woman with haemophilia and highlight the treatment inequalities that exist within this marginalised subgroup (paper v).
- To understand the barriers and concerns that people with haemophilia have in accessing gene therapy and explore what impact this might have for them and their family (papers viii and ix).

The Exigency programme began recruiting in July 2020 and completed recruitment in December 2023. The first paper was published in October 2020, and the final paper, paper ix, was published in February 2024

Positionality

I qualified as a nurse in 1991 and have worked across various fields, including rheumatology, respiratory medicine, and haemophilia care. I have always been interested in the impacts of chronic conditions and the experiences of those living with them. More recently, I have been working with disease conditions where gene therapy could be a treatment option, including bleeding disorders and cardiomyopathy.

I was born with talipes equinovarus in my left foot and have undergone multiple surgeries throughout my life, including an ankle fusion. This surgery corrects the ankle's position but can lead to mobility issues and is a procedure that some PwH undergo to both prevent bleeding into an arthritic joint and as a pain relief strategy. My condition disrupted my schooling, and I was prevented from participating in many sporting activities. I also feel that, despite the difficulties I have faced over the years because of my foot, I am proud of my achievements, and in many ways, the challenges I have encountered have shaped who I am. I feel, therefore, that I have some understanding of the impact a congenital condition can have on an individual's life.

However, I am also aware that while there may be similarities between my own experiences and those of some of the participants in the Exigency programme, there are significant differences. These differences include the pain experienced by many PwH and the restrictions placed on their lives by both the condition and the treatment they have to endure.

Throughout the whole study process, I have been conscious of maintaining a strict separation between my own experiences and feelings and those described by the participants.

Between 2017 and 2025, I have published 25 peer-reviewed articles and one book chapter. I have undertaken qualitative research and published in other bleeding disorders including Glanzmann Thrombasthenia (Khair et al., 2024a; Khair et al., 2024b), Factor VII deficiency (Fletcher, Khair and Holland, 2024) and von Willebrand Disease (Khair et al., 2025a; Khair et al., 2025b).

I am currently involved in the patient preference arm of a qualitative study with the University of Oxford on gene therapy for people with cardiomyopathy (CUREHEART). This explores the lived experience of people with cardiomyopathy and what they want from new treatments, including gene therapy

The nine papers presented here as evidence for a PhD by published works come out of the Exigency programme.

Further positional reflections can be found in the paper Living, Caring, Learning – The power of qualitative research in bleeding disorders care (Fletcher, 2024a).

Chapter Two: Background

Haemophilia

Haemophilia is a rare X-linked genetic disorder that primarily affects males. It is characterised by a quantitative reduction in the production of the clotting proteins factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B. Affecting all ethnicities equally (Badou, 2000), it has a prevalence rate of 1 in 3333 males worldwide, with haemophilia A occurring at a rate of 17.1 cases per 100,000 males and haemophilia B at 3.8 cases per 100,000 males (Iorio *et al.*, 2019). In the UK, in the year 2019-2020 (when the Exigency programme began), there were 8616 people registered with haemophilia A and 1914 with haemophilia B (United Kingdom Haemophilia Centre Doctors' Organisation, 2020).[3]

Both haemophilia A and B are classified into three main subtypes: mild (factor levels >5 iu/dl and <50 iu/dl), moderate (factor levels >1 iu/dl and <5 iu/dl), and severe (factor levels <1 iu/dl). Normal factor levels range from 50 iu/dl to 150 iu/dl (Blanchette et al., 2014; Srivastava et al., 2020). Bleeding can occur due to injury or spontaneously. The risk of bleeding, particularly spontaneous bleeding, increases with the severity of the condition: those with factor levels of <1 iu/dl experience bleeding more frequently than those with moderate or mild disease. These bleeds, particularly into major joints (knees, hips, and ankles) and muscles, can result in severe joint arthropathy, muscle contractures, disability, and chronic pain (Curtis et al., 2015; Manco-Johnson et al., 2007).

In two-thirds of presentations, boys are born into families with a known history of haemophilia and are therefore diagnosed at or shortly after birth. In one-third of cases, however, there is no family history, and their condition is believed to be due to a *de novo* mutation. In this case, depending upon the severity of the condition (as outlined above), diagnosis occurs later, usually following investigations into unexplained and persistent bruising. Diagnosis in milder presentations, however, might not occur until an individual faces a significant haemostatic challenge, such as surgery or dental extractions. This means that while most PwH are diagnosed by 36 months of age some might be delayed until adulthood, especially where there is no prior family history of haemophilia (Mendoza *et al.*, 2025)

[3] These figures include all those registered in the UK including those female carriers with low FVIII and FIX levels, women with either FVIII or FIX deficiencies.

While haemophilia is an X-linked condition that typically affects only men, women who carry a pathogenic gene variant can also present with low factor levels. This may occur if they inherit a pathogenic variant on both X chromosomes, one from each parent. It can also happen when a non-pathogenic variant is disproportionately inactivated due to X chromosome inactivation (Shoukat *et al.*, 2020). X chromosome inactivation is a process that occurs in all female mammals, in which one of the two paired X chromosomes is randomly inactivated to ensure that only one copy is active in a given cell. Occasionally, in women with a pathogenic genetic variant on one X chromosome, this process may disproportionately inactivate the non-pathogenic variant, meaning that the individual may express features of the pathogenic variant that has not been deactivated.

Haemophilia Treatment

Since the 1970s, the treatment of affected individuals has involved coagulation replacement therapy (CRT) the intravenous administration of the missing coagulation factor either on demand (after a bleeding episode) or prophylactically to maintain factor levels greater than 3-5 iu/dl and therefore prevent bleeding episodes. (Richards et al., 2010; Srivastava et al., 2020; Carcao et al., 2020). CRT, particularly factor prophylaxis, has resulted in a significant reduction in comorbidity and an improved overall quality of life (QoL) for PwH (Nilsson, Blomback and Ahlberg, 1970; van Creveld, 1969; Manco-Johnson et al., 2007). There is, however, a significant burden associated with the treatment, including concerns about and management of breakthrough bleeding, the frequent trips to treatment centres, and the impact on both work and schooling (Farrugia *et al.*, 2013). The high cost of treatment is also seen as a major burden both individually and to the healthcare economy in low and middle-income countries (Li *et al.*, 2021).

Recent advancements in haemophilia treatments have included the introduction of extended half-life factor products, which have reduced the average number of infusions to one per week (Oldenburg et al., 2017a; Young, Liesner and Sidonio, 2019; Pipe et al., 2019; Chhabra et al., 2020). However, this benefit has not extended to individuals with haemophilia A or B who have developed inhibitory antibodies to CRT.

Thirty percent of PwH A and approximately three percent of PwH B, treated with CRT develop alloantibodies (or inhibitors) to treatment (Gouw, van der Bom and van der Berg, 2007; Blatny and Mathew, 2011; van der Bom, 2011) rendering the treatment ineffective. It is possible to suppress inhibitors with immune tolerance induction therapy (ITI), allowing for the

reintroduction of CRT prophylaxis. ITI requires the infusion of large doses of factor, often twice daily, meaning that individuals need either good venous access (which can be problematic in young children) or a central venous access device. Up to 30 percent of PwH A and inhibitors and up to 70 percent of PwH B and inhibitors, however, never tolerise (Kempton and Meeks, 2014; Ljung et al., 2018; Astermark et al., 2021). Bypassing agents, either Factor Eight Inhibitor Bypassing Agent (FEIBA) or activated factor VII (FVIIa), are used to manage breakthrough bleeds during ITI (Hay and DiMichele, 2012) and may be used prophylactically in those with persistent inhibitors (Perry et al., 2010; Ewing, Escuriola-Ettingshausen and Kreuz, 2015). These agents, however, have short half-lives (4-7 hours and 2-3 hours, respectively) and are less protective than standard CRT prophylaxis. Both ITI and the use of bypassing agents in PwH and inhibitors are burdensome due to the frequency and volume of infusion, and time needed for preparation and administration (Mannucci, 2020).

Further advances, have led to the development of medications which prevent bleeding by either mimicking the action of FVIII, binding FVII to FX, normalising the intrinsic clotting pathway (Shima, 2017; Persson et al., 2023), or downregulating negative feedback loops within the clotting pathways (Pipe et al., 2020; Mast and Ruf, 2022). Unlike FVIII, these molecules are not neutralised by any existing FVIII inhibitors and can be given subcutaneously either weekly, bi-weekly or monthly, decreasing treatment burden and reducing the ABR (Oldenburg et al., 2017; Wada, Matsumoto and Katayama, 2017).

While both extended half-life and mimetic products have enhanced the QoL of PwH (van Balen *et al.*, 2020), they still fall significantly short of providing a cure for haemophilia (Iorio et al., 2019; Peyvandi and Garagiola, 2019).

No review of haemophilia treatment, regardless of how brief, can overlook the infected blood scandal. Between 1970 and 1991, an estimated 27,000 men were infected with Hepatitis C and 100 with HIV through their CRT (Mitchell, 2017; Gourd, 2024); many were co-infected. Approximately 3,000 men and their partners are believed to have died as a direct consequence in the UK (The Hepatitis C Trust, 2024). Consequently, many of the surviving men and the families of those who died continue to live with the trauma of the disaster and remain deeply distrustful of medical care and the pharmaceutical industry (Orsini, 2002; Keshavjee, Weiser and Kleinman, 2001; (Wherry, Berragan and Jennings, 2023). As a result,

some remain cautious about new treatments and may be slow to embrace any that are developed.

Haemophilia's Impact on the Family

Despite recent developments and improvements in treatment haemophilia can impose significant emotional strain on families. This is particularly so for parental caregivers who frequently experience increased anxiety and stress as they manage the uncertainties of their children's healthcare needs and treatment (Wiedebusch et al., 2008; Gringeri and Von Mackensen, 2008; Khair et al., 2014). Parents often report feelings of guilt, fear, and helplessness as they worry about uncontrolled bleeding episodes and the potential for long-term complications.

There are also considerable financial implications for many families, both through direct costs, when treatment is not provided by the state, and the indirect costs of missed work while caring for their children during hospital visits for routine or emergency care (Price et al., 2015; Myrin Westesson et al., 2018). These ongoing burdens can affect family dynamics, sometimes leading to conflict or feelings of isolation, as parents adapt to managing their children's condition.

While these burdens are known and understood there is a paucity of literature on the impact of having a spouse or partner with haemophilia

Gene Therapy for Haemophilia

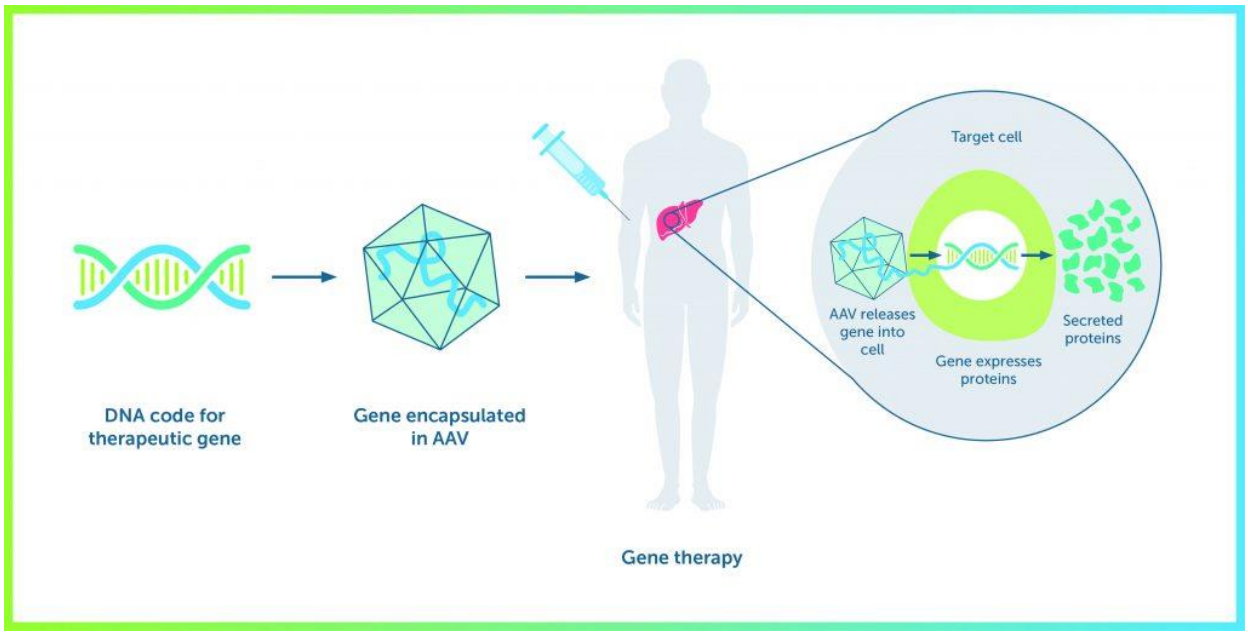
Until recently, treatment for haemophilia was focused on bleed prevention and management, the possibility of a cure being unachievable (Iorio et al., 2019; Peyvandi and Garagiola, 2019). However, with the development of a number of gene therapy platforms for haemophilia A and B, a potential functional cure (one that can change the phenotypical presentation rather than correct the underlying chromosomal defect) became a real possibility (Skinner *et al.*, 2004).

There are a number of different technologies for gene therapy including allelic-specific silencing (Castanotto and Rossi, 2009; Jiang et al., 2013), signalling pathway modulation (Bezzerides et al., 2020; Kieserman et al., 2019), gene editing (Patsali, Kleanthous and Lederer, 2010; Lieber, 2010; Richardson et al., 2016) and gene replacement. The latter has become the dominant technology for haemophilia gene therapy (Nathwani et al., 2011; Rangarajan et al., 2017). Utilising an adeno-associated virus (AAV) as a delivery vehicle (vector), gene replacement therapy for haemophilia inserts a gene of interest (either a FVIII

gene or a FIX gene) into the nucleus of hepatocytes where it produces the relevant clotting factor (Nathwani et al., 2011; Nathwani et al., 2014; Perrin, Herzog and Markusic, 2019; Rangarajan et al., 2017). (See Figure 1, page 17).

The vector, which has been modified to prevent it from replicating, is then excreted over a period of days to weeks, though in some cases capsid proteins have been seen up to a year after infusion (Zhao et al., 2005; Favaro et al., 2009). Early studies demonstrated that there was a good response to gene replacement technology and many study participants saw increases in their factor levels of between 50 and 150 iu/dl for PwH A (Pasi *et al.*, 2020) and 20 and 50 iu/dl for PwH B (Nathwani et al., 2014).

Figure 1. Diagrammatic Representation of Gene Replacement Therapy.



(Haemnet, 2019)

Clinical trials of gene therapy for haemophilia A and B show that it has the potential to offer affected individuals a clinically significant and sustained increase in intrinsic factor expression, which would reduce bleeding risk (Machin and Ragni, 2018; High and Roncarolo, 2019; Pierce et al., 2020). While gene therapy holds out hope for lifelong freedom from CRT, it is, however, neither suitable nor available for all PwH.

At the time that the Exigency programme was conceived and began recruiting (July 2020) gene therapy was only available within clinical trials programmes. Access was, therefore limited to those with severe haemophilia A or with haemophilia B with a factor level ≤2iu/dl who were willing to participate in a Phase 3 study. Of this potential cohort, however, up to half may also be ineligible due to the presence or history of the previously discussed factor-neutralising antibodies (inhibitors) and/or antibodies to the viral vectors currently used to package and deliver the FVIII or FIX genes (Stanford et al., 2019; Batty and Lillicrap, 2019).

Challenges

While gene therapy offers significant potential to improve QoL by reducing bleeds and treatment burden, a number of challenges need to be acknowledged.

The first challenge is that the viral vector is known to cause transaminitis in participants, which is associated with a corresponding loss in factor expression (Lheriteau, Davidoff, and Nathwani, 2015). This effect is thought to be dose-dependent; the greater the viral load infused, the more likely the occurrence of transaminitis. Many protocols, have aimed to address the issue by introducing immunosuppressive strategies, either prophylactically or reactively. In many cases this has been successful, though the use of immunosuppressive treatments, and in particular corticosteroids is not without risk. Side effects include insomnia, weight gain, altered mood, increased risk of infection and adrenal suppression, and in some cases, steroid induced diabetes and psychosis (Joint Formulary Committee, 2025a).

A second challenge is that of durability and the apparent decline in factor expression observed in both gene therapies for haemophilia A and B. However, the rate of decline is less pronounced in haemophilia B (Pasi et al., 2020; Nathwani et al., 2014). Nonetheless, annualised bleeding rates (ABR) and factor consumption rates remain significantly lower than pre-treatment levels. Indications suggest that this rate of decline may be beginning to plateau or, at the very least, slow down. However, it is still too early to ascertain whether this is indeed the case.

A third challenge, linked to the concern about durability of treatment is the immune response which has been seen in all cases following treatment. This response leads to the development of AAV capsid antibodies, which prevent repeat dosing and mean that gene therapy is a once-in-lifetime treatment option (Hasbrouck and High, 2008; Batty and Lillicrap, 2019).

Gene Therapy for Children with Haemophilia

Gene therapy for haemophilia is currently an option exclusively for individuals over the age of 18 due to insufficient data regarding its safety, efficacy, and duration of effects in children. The rapid growth of the liver observed until approximately 12-13 years has raised concerns, as this may result in the loss of expression seen in some adults following gene therapy. Consequently, several research groups are exploring technologies that might enable liver-specific gene therapy in children (Milani *et al.*, 2019). The risk-benefit balance for gene therapy in children with haemophilia also differs significantly from that of adults with haemophilia or even children with other long-term, life-limiting genetic conditions (Thrasher and Williams, 2017; Hacein-Bey Abina et al., 2015). As such, the decision-making processes are markedly distinct, with parents bearing the responsibility for the decisions taken rather than the individual child themselves (Landrum Peay *et al.*, 2019). However, there is limited information regarding parents' understanding of gene therapy in haemophilia or their attitudes towards its potential as a treatment for their children. Thus, it is crucial moving forward to listen to and consider the views and wishes of both parents and children regarding whether gene therapy is something they would wish to pursue (Dimichele, Miller, and Fins, 2003).

Chapter Three: Literature Review

At the time the Exigency programme began (1st June 2020), gene therapy was not licensed and was only available to those who had participated in Phase 1 or the ongoing Phase 2/3 clinical trials. In this chapter, therefore, I provide an overview of the literature available prior to the finalisation of the Exigency protocol (April 30th 2020).

As this programme used a Grounded Theory approach (see Chapter Four: Methodology), a full literature review was not undertaken prior to data collection as I did not wish to impose any existing theories or knowledge gained from my own personal experience in bleeding disorders care between 2012 and 2020 and prejudice subject data (Glasser and Strauss, 1967; Corbin and Strauss, 2008). Charmaz (2014), however, suggests that it is not completely possible or even desirable to separate the researcher's pre-existing knowledge from drawing on pre-existing knowledge or literature. I therefore felt that I should seek to understand, if not the specifics of the existing literature, at least the extent to which patient and family experiences of gene therapy had been studied. A scoping review was therefore performed (Urquhart, 2012; Birks and Mills, 2015). Details of all search terms used, databases searched, and articles returned can be found in Appendix 1.

As noted above, the concept of gene therapy is not new (Mukherjee, 2017), but the reality of its potential as a treatment for haemophilia is more recent (Nathwani et al., 2011; Rangarajan et al., 2017; George et al., 2017). As such, although the concept and scientific underpinning have been discussed (Nathwani et al., 2014; Batty and Lillicrap, 2019), the experiences of those for whom the treatment has been developed and their families have been poorly described and are less well understood.

Four articles were discovered during this process, two pieces of grey literature and two qualitative interview studies (see Table 1. Identified Literature, page 23).

Each article was assessed using type-specific assessment tools from the Julia Briggs Institute. The two articles written by Zhang (2018) and Konduros (2019) were assessed using the narrative assessment tool (McArthur *et al.*, 2015). Lockwood, Munn and Porritt, (2015) was used to assess the papers by van Balen et al. (2020) and Miesbach and Klamroth (2020a). Copies of the appraisal score for each paper can be found in Appendix 2.

Table 1. Identified Literature

Authors	Title	Publication	Citation details and DOI	Jaonna Briggs Institute Assessment
Peer-reviewed papers				
Miesbach W, Klamroth R.	The Patient Experience of Gene Therapy for Hemophilia: Qualitative Interviews with Trial Patients	Patient Preference and Adherence	2020;14:767-770 https://doi.org/10.2147/PPA.S239810	Qualitative Assessment. 7/10
van Balen EC, Wesselo, ML, Baker, BL, Westerman MJ, Coppens M, Smit C Driessens MHE, Leebeek FWG, van der Bom JG, Gouw SC.	Patient Perspectives on Novel Treatments in Haemophilia: A Qualitative Study	The Patient: Patient-Centered Outcomes Research	2020;13(2):201-210 https://doi.org/10.1007/s40271-019-00395-6	Qualitative Assessment. 7/10
Non peer-reviewed papers				
Konduros J.	Patient Testimonial: My Experience on a Gene Therapy Trial	Transfusion and Apheresis Science: Official Journal of the World Apheresis Association: Official Journal of the European Society for Haemapheresis	2019;58(5):601 https://doi.org/10.1016/j.transci.2019.08.011	Narrative Assessment. 3/6
Zhang S.	The patients who don't want to be cured: A hemophiliac says his genetic disorder is part of his identity, and therapies like CRISPR threaten to erase it	The Atlantic	(2018) August 29 https://www.theatlantic.com/science/archive/2018/08/hemophilia-gene-therapy-cure-identity/540987/	Narrative Assessment. 2/6

The paper by Miesbach and Klamroth (2020a) is a qualitative study involving three PwH who had undergone gene therapy at the haemophilia treatment centres where the authors were centre directors. In their paper, they reported that the participants felt they had a better QoL after gene therapy.

One, however, stated that he had found the transition from someone needing regular prophylaxis to not needing any at all difficult. He understood on one level that he now had higher factor levels and should be protected from bleeds, but he still found it challenging to accept that any pain he had was unrelated to bleeds and, therefore, did not require treatment. Their paper did not report any of the participants' experiences with the gene therapy process itself.

There was, however, one significant issue with the paper: the fact that both authors were lead clinicians in the gene therapy studies in which the participants took part. Consequently, both authors knew one or more interviewees before their participation in the qualitative interview study. Although the authors attempted to mitigate this by involving independent researchers to facilitate and analyse the interviews, the interviewees may still have been reluctant to openly voice concerns, knowing that the same team overseeing their ongoing gene therapy trial also conducted the research.

The paper by van Balen et al. (2020) is a qualitative study designed to explore the factors influencing treatment decisions of patients and parents of boys with moderate to severe haemophilia in the Netherlands. The authors interviewed 16 participants and were particularly interested in identifying factors which may be involved in switching treatments. Although the study did not specifically focus on gene therapy, it was discussed.

The authors reported that many participants recognised that novel treatments can improve QoL, reducing bleeding and current treatment burden. However, they found that many respondents were unwilling to consider new treatments because they did not perceive their current treatment regimen as burdensome enough to outweigh their concerns about the new therapy. These concerns included short and long-term risks and, in the case of gene therapy, the variability of effect that had been seen in some trials. There were, however, some limitations with this paper, including limited geographical scope and the potential for sampling bias.

The first six participants were recruited through the Netherlands Haemophilia Society. This may have resulted in participants who were better informed and more interested in discussing treatment. However, many of the participants had a limited scope of knowledge; they knew far more about gene therapy and extended half-life products but less about other treatment options, including bypassing agents and non-factor replacement treatments. The authors acknowledged each of these limitations. To address these issues and increase diversity, the researchers recruited an additional eight participants through a regional specialist haemophilia outpatient clinic.

The hesitancy found towards novel treatments contrasts sharply with individual patient experiences documented elsewhere. Konduros (2019) shares his experiences with gene therapy and describes the feeling of finally leaving his haemophilia behind to live a bleed-free life as “magical”, though he characterises the procedure as anticlimactic.

Jeff Johnson, a PwH, questioned the concept of gene therapy for haemophilia in an interview with Sarah Zhang (2018). In the interview, Johnson talks about living with haemophilia and how, rather than being something to be removed, it is an essential concept in his understanding of self. He, therefore, felt uncomfortable with the idea of gene therapy and having a part of his identity taken away.

Because of the paucity of research returned an expanded literature search was undertaken in 2019, including the terms ‘cure’ and ‘liver transplant’. These terms were added because a number of PwH who were infected with Hepatitis C in the 1970s and 1980s developed liver failure and required solid organ transplants (Wilde et al., 2002; Togashi et al., 2016). Following the transplant surgery, as the liver is a primary site of factor production, these men’s factor levels increased and they no longer required CRT. They were deemed to have been cured of their haemophilia.

The term ‘chronic illness’ was also included in the expanded search but did not return any relevant papers. However, it did return several studies on gene therapy applications for haemoglobinopathies, including beta thalassaemia (Biffi, 2018) and sickle cell disease (Mapara *et al.*, 2019), as well as cystic fibrosis (Moss et al., 2007; Alton et al., 2015). Nonetheless, all these papers were excluded because they were either phase 1 proof of concept studies or Phase 2 dose-finding studies and, as such, did not report any QoL or lived experience data.

The search also returned several papers on the lived experience of other chronic illness-modifying treatments, including surgery for Parkinson's disease (Gilbert, 2012), epilepsy (Wilson, Bladin and Saling, 2007; O'Brien et al., 2020), and obsessive-compulsive disorders (Bosanac *et al.*, 2018), as well as solid organ transplantation for cystic fibrosis (Vermeulen et al., 2004; Smith et al., 2020). While these papers were not directly relevant to haemophilia, they did demonstrate that people with chronic and lifelong conditions had difficulty adapting to the increased freedom and decreased reliance on others following new therapies. They also highlighted the problem of hypervigilance in terms of symptoms previously associated with their condition or masked by it. These papers further indicated that the families of these individuals had difficulty adjusting to the changes that might occur regarding previous role functions or even missed aspects of their pre-treatment condition that they had shared together. Whether similar difficulties could be observed post-gene therapy for haemophilia was unknown and has therefore been the focus of this PhD programme.

Chapter Four: Methodology

This chapter outlines the methodological approaches underpinning the Exigency programme, and highlight the methods used. A more detailed discussion of the methods can be found in the published protocol (paper vi). The chapter will begin by establishing the research's theoretical foundations of the research and explaining the concept of lived experience.

Theoretical Standpoints

The overall perspective of this synthesis is based in human science rather than the empiricism of natural science. As such it emphasises the subjective lived experiences of people with haemophilia and their families.

Lived Experience

While many antecedents of our understanding of the term “lived experience” can be traced back to the 15th and 16th centuries, specifically the work of Gale (1628–1678), Lock (1632–1704), and Hume (1711–1776), it was not until the 19th and 20th centuries that the term itself was more thoroughly described in the writings of Dilthey (1883–1911), Husserl (1859–1938), and Heidegger (1889–1986) (Lindseth and Norberg, 2004).

Dilthey was interested not only in how human beings understood the world in which they lived but also in how they saw themselves within that world. To understand this latter element, he felt that the scientific method, which aimed to understand cause and effect, was too reductive. He argued that human science, the study of how beings see themselves and their place in the world, should seek to understand the relationship of the parts to the whole. He emphasised the concept of “*Lebenszusammenhang*”, or life context, as a primary object of any inquiry (Owensby, 1987; Smith et al., 2009b).

This concept was subsequently taken up and adapted by Husserl. Influenced by both Dilthey’s concept and Heidegger’s concept of being-in-the-world (*In-der-Welt-Sein*), Husserl introduced the concept of the lifeworld (*lebenswelt*), the belief that the world in which all individuals live, experience, think, learn, feel, and act, is the foundation upon which they make assumptions and choices. (Moran, 2012; Berndtsson et al., 2007). Though the lifeworld is a largely unconscious understanding of the world in which individuals live, it can be both personal and shared.

From these philosophical foundations, the term "lived experience" has emerged as a key concept in qualitative research, with its usage increasing significantly over the past 50 years

(Google Books, 2025). Despite the growing prominence of the term, there appears to be little commonality in how it is defined, utilised or even written. In a review of 36 papers published between 2017 and 2023, Jones (2024) found that the term “lived experience” was never comprehensively defined. It appears to have been used as a heuristic shortcut to signify the qualitative nature of the studies and to confer authority on the participants.

Therefore, this synthesis will seek to define lived experience as a process of highlighting the experiences, choices, and direct knowledge of individuals who have lived through a particular situation, occurrence, or series of events. This experience is peculiar to them but affords valuable insight beyond the individual.

Grounded Theory

Traditionally, the concept of lived experience has been most closely associated with phenomenological approaches that seek to describe the meaning of an experience related to a specific phenomenon of interest (Starks and Trinidad, 2007; Stewart and Mickunas, 1990). This link partly arises from its origins, which, as described above, can be traced back to the work of the early phenomenological philosophers.

I did not believe that the examination of gene therapy for haemophilia would easily align with a strict phenomenological approach, which emphasises understanding and describing individuals' subjective experiences while distilling these experiences to their universal core (Creswell and Porth, 2018; Smith, Flowers and Larkin, 2009). Rather than examining gene therapy through a single experience, such as those who have received it, the Exigency programme aimed to understand the knowledge, experiences, and impacts of gene therapy on various members of the haemophilia community. This includes individuals who have undergone gene therapy, those who do not want it, those who might want it, and those who cannot have it, along with their families. While there may be similarities among these diverse groups, I did not believe it would be possible to identify a single, clear essence. I felt I needed an approach that could explore the structures and interactions among the different members of the haemophilia community more fully. I also wished to employ a methodology that could generate its own theory rather than impose a pre-existing philosophical framework or theory onto the data. Grounded Theory (GT) was, therefore, chosen as the methodology.

GT was originally developed in 1967 by Barney Glaser and Anselm Strauss (Glaser and Strauss, 1967). Using a flexible, iterative process of data collection, analysis, and coding, it aims to identify patterns and emergent themes within the gathered data (Birks and Mills,

2015). Emphasising the significance of complete objectivity, Glaser and Strauss (1967) argued that through constant comparative analysis, where any data generated is compared with itself and with any codes and themes developed, researchers could maintain a degree of detachment from the data.

The methodology also introduced crucial procedures such as theoretical sampling, where data collection is directed by concepts emerging from the analysis, and memo writing, which captures the researcher's analytical thinking throughout the process (Glaser and Strauss, 1967). Furthermore, any theory that may emerge should emerge from the data itself rather than being influenced by the researcher's pre-existing knowledge, experience, or beliefs (Glaser and Strauss, 1967; Rieger, 2018; Flick, 2018).

Following a prominent methodological split between Glaser and Strauss in the early 1990s there have been two major modifications to their original model. The first, by Juliet Corbin and Anselm Strauss, introduced greater structure by incorporating a more predefined three-step coding approach along with a defined coding paradigm, which focused on the conditions, context, actions/interactions and consequences (Corbin and Strauss, 1996; Corbin and Strauss, 2008). Corbin and Strauss, (2015) also moved away from the strict objectivism of the "Glaserian" model by acknowledging the preconceptions and prior knowledge that researchers bring to their analysis and, therefore, the interpretive nature of the research process.

Like Corbin and Strauss (2008), Kathy Charmaz (2014) rejected the idea of any essential objectivity in research, emphasising the role of the researcher in the process. However, she took this further, positioning her approach within a constructivist paradigm in contrast to the positivist underpinnings of earlier versions. She proposed that meaning is co-created rather than simply discovered or interpreted. For Charmaz (2016), it is essential to examine the context, assumptions, perceptions, and beliefs of the researcher, acknowledging how this impacts the research and shapes their understanding of the data. Charmaz, however, rejected the prescriptive nature of the analysis proposed by Corbin and Strauss. Like Glaser and Strauss (1967) and, latterly, Glaser (2008), she felt that the rigidity of Strauss and Corbin's framework risked forcing the data to fit a preconceived framework. She emphasised an approach closer to that of Glaser, one in which themes emerged from the data. To ensure this, she proposed that coding should be less abstract and should adhere to the meaning as defined by the data.

This emphasis on emergent themes and flexible analysis makes GT a research methodology that facilitates the identification and description of the wide spectrum of life with haemophilia from the perspectives of patients and their families. This methodology enables comprehensive data collection across a broad age range and allows for in-depth analysis, permitting research questions to be reshaped as evolving themes and new concepts emerge.

Today, GT has evolved into multiple contemporary applications across various disciplines, with researchers often adapting and combining elements from different versions to specific research contexts and questions.

Programme Design

This was a mixed-methods research programme across multiple cohorts, focusing on five specific groups within the UK haemophilia community whose lives have been or may be impacted by gene therapy. It utilised surveys (paper i), focus groups (papers i and ii), dyad pair interviews (papers vi, vii and ix), and individual interviews (papers ii, iv, vii and ix). While there are inherent differences between the methodologies, none were regarded as better or worse. They were employed in each case because they were believed to be the most effective way to access the data needed to meet the aims of the study programme.

Descriptive analysis was employed to convey the views expressed (Doyle et al., 2019). In each study, a table of themes characterised recurring ideas and thoughts captured in the focus groups and interviews, which served as the foundation for further analysis.

Data Gathering

Five key patient groups were identified:

1. People with haemophilia who had had gene therapy
2. People with haemophilia who had not yet been offered gene therapy
3. Parents of children with haemophilia
4. People with haemophilia who do not want gene therapy
5. People with haemophilia who withdrew or were withdrawn from a gene therapy study

The diverse nature of the research questions meant that a number of different data collection approaches were required. The survey in paper i (see Appendix 3) was essential for capturing quantitative baseline data about parental knowledge before exploring it further qualitatively. Focus groups were used for papers i and ii, to explore shared concerns and allow participants

to build upon each other's responses and experiences. Individual interviews were employed for papers ii, iv, vii, and ix when exploring sensitive personal experiences might be uncomfortable to share in a group setting. The interviews were conducted either individually or as a 'dyad pair' when a close family member was available and willing to take part (papers ii, iv, vii and ix). Although each dyad pair had the opportunity to participate in interviews separately, none chose to do so. Dyad interviews were used when family dynamics were central to the research question, recognising that gene therapy impacts extend beyond the individual PwH.

Initial subject interviews followed a guide developed by myself in consultation with a patient representative and one of the PhD supervisors (Dr Kate Khair) (see Appendix 4). All individual and dyad pair interviews, along with focus groups, were conducted either by myself or, in the case of paper i, by myself and a patient representative. In all instances, each participant was interviewed only once.

My initial intention was to interview all participants in person. However, early in 2020, this changed due to the nationwide lockdown imposed as a result of the COVID-19 pandemic. Consequently, to conduct the interviews and protect interviewees, particularly those undergoing immunosuppressive high-dose steroid therapy mandated by the gene therapy protocols, I felt that a videoconferencing tool would be essential to facilitate the interviews.

Despite the existence of various video conferencing tools, such as Skype® and Microsoft Teams®, Zoom® was ultimately selected. I felt that, as the market leader at that time, its simplicity and the widespread familiarity many had with it made it the obvious choice (Evans, 2020; Karl et al., 2022). Checks were made to ensure that the platform provided the necessary levels of security and privacy, including the option for participants to turn off their cameras, a secure invitation system, and the use of a waiting room to prevent uninvited entrants. Zoom® was also the preferred because participants were not required to download a separate application to participate in the interview. The convenience of recording, downloading, and saving combined digital/audio files and separate audio files also played a significant role in its selection. These changes, along with the precautions implemented, were submitted to the Research Ethics Committee as a protocol amendment, and approval was granted. Further discussion regarding the use and relevance of Zoom® in qualitative research can be found in paper iii.

Recruitment

Participants were recruited through a combination of direct referrals from NHS participant identification centres (two in London and one in Southeast England), or word of mouth and social media advertising on UK haemophilia charity websites, Facebook and Twitter feeds.

Analysis

The Exigency programme employed a constructivist GT approach to data analysis, following the constructivist methodology of Charmaz (2014 and 2016).

All interviews were analysed using a modified version of Clarke and Braun's thematic analysis, a bottom-up inductive methodology (Clarke and Braun, 2017). The methodology was modified as the primary analysis was conducted concurrently with the data collection. Emergent concepts were used to inform and refine subsequent data collection and theme generation. Throughout the analysis, an in vivo coding strategy, where codes and themes are created based on the exact words, terms or phrases used by the interviewees, was employed (Given, 2008). This was done so that the analysis would remain grounded in the experiences of the participants rather than my own or those imputed from existing literature. This also made the comparison of themes between cohorts, and the identification of patterns and variations easier.

Field notes recorded immediately after each interview provide extra context for interpretation, capturing nonverbal cues, emotional responses, and initial analytical insights that might not be evident in transcripts alone. A reflexive journal and the writing of analytical memos were also key to the analytical process, capturing the ongoing rationale for decisions made. These field notes and memos were not formally coded and have only been used, alongside the video and audio recordings, to provide added context to the analysis (Arthur et al., 2014; Phillippi and Lauderdale, 2017). A random selection of the interviews was reviewed and re-coded independently by one of the PhD supervisors (Dr Kate Khair). These findings were then compared and discussed to ensure that intra- and inter-cohort coding remained consistent throughout the lifetime of the programme.

Ethics

All participants in the Exigency programme were provided with a Participant Information Sheet (PIS) detailing the reasons for the study, the voluntary nature of participation, and their right to withdraw from the study at any time. Before participating in the programme and the

interview, all participants were asked to sign a written consent form remotely (using AdobeSign®). Verbal consent was also obtained prior to the commencement of the interview to ensure ongoing consent and willingness to be recorded.

All aspects of the programme were reviewed by the Southeast Scotland Research Ethics Committee (02). Both Health Research Agency and REC approvals were issued in 2020. The study was registered on the ClinicalTrials.gov website [NCT04723680] and published in BMJ Open (Fletcher et al., 2022).

Patient and Public Involvement (PPI)

The Exigency Protocol was developed with input from a patient representative (a PwH) who was also involved in designing the interview schedule. Two additional patient representatives reviewed the protocol before it was submitted to the REC: the first, a carrier of haemophilia A with an affected son, and the second, a partner of a PwH.

All interviewees were sent a copy of the papers in which their data were published and were offered the opportunity to discuss the findings if they wished.

Equality, diversity and Inclusion (EDI)

Gender

Since haemophilia is X-linked, it has historically been viewed as a condition specific to males. Women have been thought of only as carriers of the disorder, despite some cases where their factor levels are identical to those of men with a formal diagnosis of severe haemophilia. Such cases, however, are extremely rare. When the Exigency programme was launched, the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) reported only three women registered in the UK, two with haemophilia A and one with haemophilia B (United Kingdom Haemophilia Centre Doctors' Organisation, 2020). There were, however, 735 women with FVIII levels <40 iu/dl and 319 women with FIX levels <40iu/dl.

Ethnicity

As haemophilia is known to affect all ethnicities equally (Badou, 2000), neither the UKHCDO nor the World Federation of Hemophilia collects ethnicity data. No formal EDI inclusion criteria were, therefore, outlined for the Exigency study programme, although four non-white and one mixed race participants were recruited (see Table 2 below).

Finance

The Exigency programme was funded through an unrestricted investigator-initiated research grant from unQure Biopharm BV, a biotechnology company with multiple gene therapy platforms for conditions including Fabry disease, Huntington's disease, and haemophilia B. No publication restrictions or editorial control were requested by the company.

These methodological approaches enabled a comprehensive exploration of the diverse haemophilia community, with the findings synthesised in Chapter 5.

Chapter Five: Synthesis

Demographics

Sixty-nine people were interviewed in total in the Exigency programme.

Table 2. Participant Demographics

Participants with Haemophilia		
Age Range	<20	1
	21-30	19
	31-40	10
	41-50	6
	51-60	5
	61-70	4
	>71	1
Mean Age		37yrs
Type	Haemophilia A	36
	Haemophilia B	10
Severity	Severe	46
	Moderate	0
	Mild	0
Sex	Male	45
	Female	1
Ethnicity	Asian	2
	Black	1
	Chinese	0
	Mixed	0
	White	43
	Other	0
Family Members with Low Factor Levels		
Type	FVIII	3
	FIX	0
Relationship to Person with Haemophilia	Parent	3
	Partner	0
	Wife	0
Ethnicity	Asian	0
	Black	1
	Chinese	0
	Mixed	0
	White	2
	Other	0
Family Members Without Haemophilia		
Sex	Male	0
	Female	20

Relationship to Person with Haemophilia	Parent	8
	Partner	1
	Wife	1
Ethnicity	Asian	1
	Black	0
	Chinese	0
	Mixed	1
	White	17
	Other	1

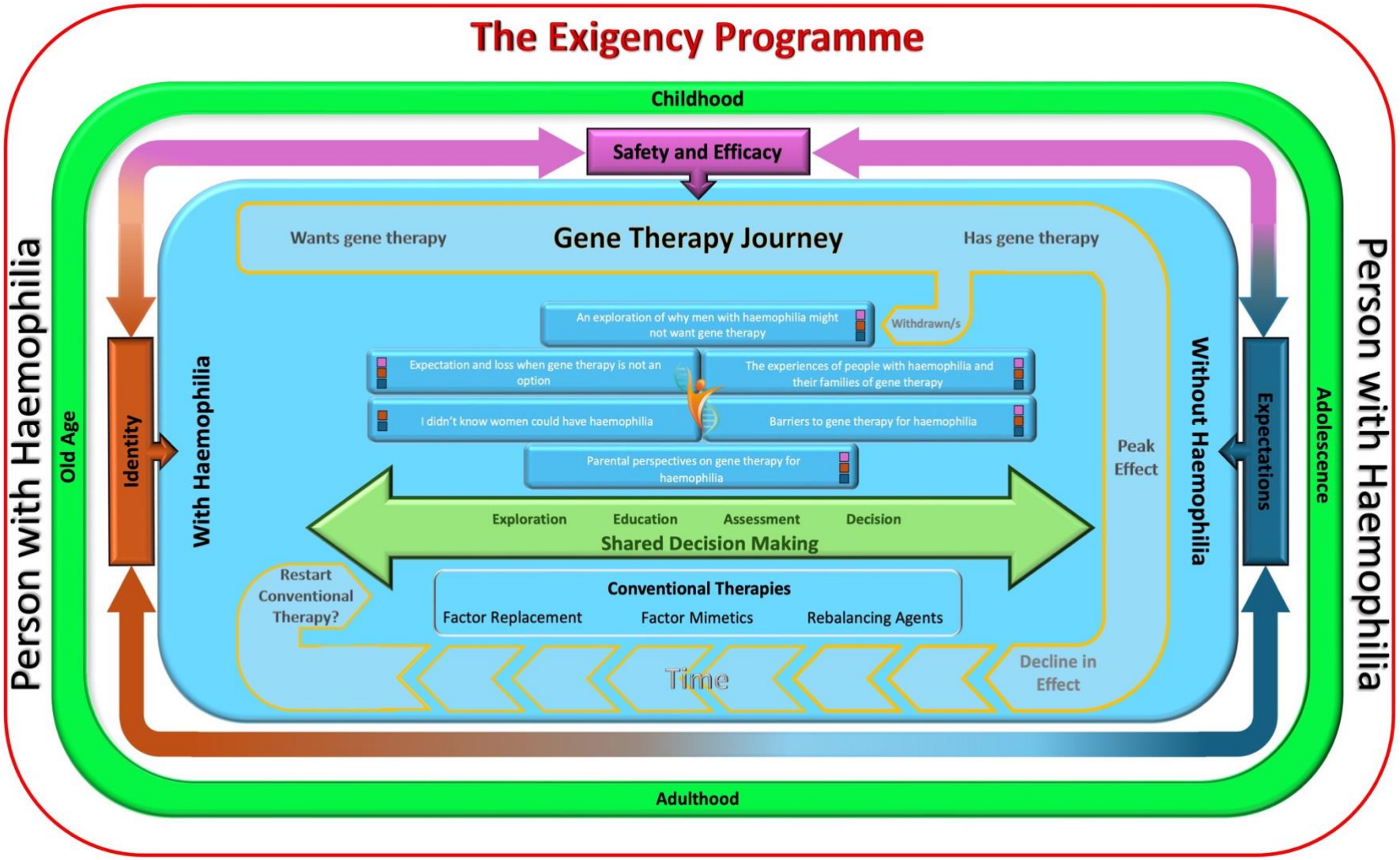
The results for the individual subgroups (papers i, ii, iv, v, vii, and ix) were published between October 2020 and February 2024. All the papers were published in open-access, peer-reviewed journals to increase their reach and availability to both the academic and patient communities (see Appendix 6 for copies of all the papers).

Integration of individual papers.

The nine papers in this synthesis are interconnected parts of a comprehensive exploration. Papers i and ii, therefore seek to establish an initial understanding of the perspectives of the community, while papers iv and vii explore the range of experiences from successful treatment to withdrawal. Paper v highlights gender-specific challenges, while papers viii and ix examine barriers to access. Paper vi discusses the methodological framework, and paper iii examines methodological innovations required by the pandemic. This progression allowed for an iterative refinement, with each paper informing subsequent data collection and analysis.

The results from these papers have been combined and mapped through a process of comparative analysis to develop a framework. It was developed iteratively: initial themes, *safety, efficacy*, *identity* and *expectations* were identified from the coding for papers i, ii and iv. These themes were further refined in paper vii where the complexity of expectations and the previously unrecognised impact of treatment withdrawal were identified. Paper ix confirmed and validated the universality of these themes across all the cohorts. The framework (see Figure 2, page 37) illustrates the interaction between the individual's understanding of their condition and what it might be to live without it. It highlights the decision-making processes involved in choosing a therapy, whether conventional or gene therapy, and shows how the gene therapy journey might fit or even disrupt an individual's understanding of their condition.

Figure 2. A Lived Experience Model of Haemophilia and Gene Therapy



The framework, however, has not been developed further into a full theory, which is often the primary endpoint of GT (Glaser and Strauss 1965), as, at this time, gene therapy remains a new treatment option, and the outcomes seen so far come from individuals who have undergone gene therapy as part of a clinical trial. The tight inclusion criteria for these trials mean those who have undergone gene therapy may differ from those PwH who are not willing to take part in a clinical trial. As more PwH undergo gene therapy, the picture reported here may change. Therefore, it is not possible currently to elaborate on the data further. The framework though has been used to structure the commentaries below.

Key Themes

Safety and Efficacy

For many interviewees across all cohorts, concerns regarding the safety and efficacy of gene therapy were a primary concern. This was particularly pressing for those participants who did not want gene therapy (paper ii) and for the parents of children with haemophilia (paper i). However, it was also discussed by participants in the other cohorts (papers v and ix) and by those who had lived through the infected blood scandal and were slightly more cautious about adopting any new treatment. There was a feeling that, having previously been harmed by a treatment that was meant to be safe and improve their QoL, there was an unwillingness to accept any new treatment until they had seen further evidence that it was genuinely safe.[4] Even those who had no direct experience of the scandal, who felt that it had little relevance to their condition, expressed concerns about the technology's safety, particularly regarding the need for immunosuppression to prevent the possible loss of treatment effect caused by transaminitis.

The potentially toxic side effects of immunosuppressive medications, particularly corticosteroids, are well recognised (Joint Formulary Committee, 2025b). As a result, the duration of use is often deliberately limited to the smallest effective dose for the shortest period. Many participants in paper iv, however, reported that despite reporting side effects,

[4] It is important to note that throughout the lifetime of the Exigency programme, the Infected Blood Inquiry was hearing evidence (Infected Blood Inquiry, 2025) so for many the events and effects of the scandal were fresh in their minds.

including weight gain, insomnia, mood swings, hyperglycaemia, and mania, they often had to endure multiple courses of high dose immunosuppression for extended periods of time.

While many of the participants understood the need for immunosuppression, many found the side effects difficult to manage because they felt they had not been adequately prepared for them. Reduced immunity to infections caused by immunosuppressant therapy was a particular concern for participants during the COVID-19 pandemic of 2020 and 2021.

The variability in treatment effect (the levels of factor expressed following gene therapy) and duration (the length of time the therapy was anticipated to last) was also a significant concern for many participants.

In terms of the duration of effect, many participants in papers ii, iv vii and ix were aware that, in the case of gene therapy for haemophilia A, its effects seemed to diminish year on year. Consequently, they understood that the effects of gene therapy would not last for the rest of their lives. Many also recognised that, given the nature of the technology, they would only be able to have the treatment once, and if/when their factor expression did diminish, they would return to their pre-therapy factor levels and would need to restart their previous prophylactic regimens.

Identity

The concept of identity was a significant aspect for many of the interviewees across various cohorts, particularly those interviewed for paper ii, who were reluctant to pursue gene therapy. This hesitance is linked not only to concerns about the therapy itself but also to their sense of identity. Several interviewees felt that their understanding of who they were as individuals was intrinsically connected to their condition. They felt that their haemophilia was an essential part of their identity, something they would prefer not to lose, and therefore, did not want to have gene therapy. However, others in paper ix, who also viewed their condition as a significant aspect of their identity, did not think that undergoing gene therapy would make them any less a person with haemophilia.

Linked to this concept of identity is the notion of “the burden of normality”. First proposed by Wilson, Bladin and Saling (2007), who suggest that there are psychological, emotional, and social challenges associated with the experience of transitioning from a known identity state to an unknown one. This burden has also been noted in family relationships when changes in the needs and abilities of an individual with a condition potentially change the role function or previously accepted dynamic within the family (Gilbert, 2012).

The concept of identity was also explored in paper v. This paper highlighted the difficulty that some women have in having their identity as a PwH recognised and therefore of being able to access the same treatment as men, including gene therapy. The debate about the designation of women as potential symptomatic carriers has been an issue for many years and has meant that many women have been unable to access the care and treatment they require, despite recognition that women can be more significantly impacted by a bleeding disorder than men (Weyand and James, 2021; Khair et al., 2024; Khair et al., 2024).

Expectations

All participants in the study programme spoke about their expectations of gene therapy in haemophilia. Those who did not wish to pursue gene therapy (paper ii) or were ineligible (papers i, v and vii) nonetheless felt that gene therapy represented a positive advancement in the care offered to the community, as it would mean, in the future, there would be a generation of PwH who could lead a bleed-free life and would therefore, be free from the associated comorbidities of their condition.

Some noted, however, that instead of helping them live free from the burden of their condition, they felt that it would, in the short term, increase the burden of their condition (papers ii and ix). Indeed, those participants who underwent gene therapy found the increased frequency of their visits to their treatment centres to monitor treatment particularly onerous (paper iv) and felt that they were often asked to attend visits more frequently than indicated at the start of the process. There was a sense that the goalposts were being moved and that they had not been fully informed of all that might be required of them. Many of them, however, felt that despite this, it had been worth it and that in some cases, they had been cured of their haemophilia.

Others, however, have not seen gene therapy as a cure. They have seen that their factor levels have decreased over time and realise that they will eventually return to their baseline levels. Some have suggested that rather than being a cure, gene therapy is something akin to a long-acting treatment; one that they may only be able to have once in their lives, but still one that will last for many years.

The discussion in the literature about gene therapy has focused on those individuals who can and have undergone gene therapy. Less attention has been paid to those who cannot, whether due to choice or ineligibility. The implications of having had the possibility of a life-changing treatment withdrawn have not been considered. Paper vii is therefore the first paper

to actively research this important subgroup. Like paper iv, this paper found that there are diverse reasons for choosing to have gene therapy, including a desire to reduce the burden of treatment, freedom from bleeds, and therefore pain relief, as well as an altruistic desire to help prevent PwH in the future suffering as they felt they had and were. Whatever their reason, however, the loss of that potential for change and improvement in their lives had a profound and sometimes self-destructive effect, which in turn affected their families. The paper, therefore, went on to suggest that this group needed as much and, in some cases, more psychological support than those who were undergoing gene therapy.

To help implement these findings in clinical practice, decision-making, and policy development, Figure 3 presents a schematic of how the three core themes impact different stakeholder groups over time.

Figure 3. Practice, Decision-making and Policy Schematic

Stakeholder		Safety & Efficacy	Identity	Expectations
PEOPLE WITH HAEMOPHILIA	Immediate (0-12 months)	• Transaminitis response • Immunosuppression • Side effects • Infection risk concerns	• Initial identity disruption • Loss of routine/control	• Reality vs promise gap • Treatment burden • Uncertainty about expression
	Long-term (>12 months)	• Durability concerns • Variable expression • Re-treatment impossibility	• "Burden of normality" • Community belonging questions • Reconstructed self-concept	• Adjustment to new normal • Managing decline if occurs • Living with uncertainty
FAMILIES	Immediate (0-12 months)	• Supporting through side effects • Care burden shifts	• Role confusion • Changed care dynamics • "Helper" identity loss	• Supporting partner's disappointment • Own expectations unmet • Navigating hope/fear
	Long-term (>12 months)	• Monitoring for complications • Managing health anxiety	• Relationship rebalancing • New family dynamics • Redefined partnerships	• Adjusting life plans • Supporting if treatment fails
HEALTHCARE TEAMS	Immediate (0-12 months)	• Managing immunosuppression protocols • Addressing unexpected responses	• Recognizing identity crisis • Providing psychological support	• Managing unrealistic hopes • Communicating uncertainties • Supporting excluded patients
	Long-term (>12 months)	• Monitoring durability • Managing treatment failures	• Long-term psychological care • Identity counselling skills	• Realistic goal-setting • Ongoing education needs
HEALTHCARE SYSTEM	Immediate (0-12 months)	• Infrastructure for delivery • Safety monitoring systems	• Psychological support services • Training requirements	• Cost-benefit decisions • Access criteria • Public communication
	Long-term (>12 months)	• Outcome tracking • Registry maintenance	• Community support programs • Identity-aware care models	• Sustainable funding • Equity of access

Chapter Six: Discussion

The primary objective of my research was to investigate the lived experiences of individuals with haemophilia and to understand the impact of gene therapy on the UK haemophilia patient community and their families. In this discussion, I examine the impact of the Exigency programme's findings on both the current discourse and the ongoing development of patient-focused processes and education around haemophilia gene therapy, as well as the strengths and limitations of the programme.

Throughout this discussion, it is necessary to acknowledge my clinical experience in haemophilia care before commencing the Exigency programme. This experience will inevitably have influenced my interpretation of participants' experiences in some ways. Indeed, having witnessed the evolution of treatment options firsthand, including the introduction of extended half-life products and factor mimetics, I brought existing assumptions about treatment burden and patient expectations to this research. However, the grounded theory approach I employed, with its emphasis on participant-driven themes and constant comparative analysis, enabled me to both challenge and refine these preconceptions. Where relevant, I reflect on those moments where the participant narratives either confirmed or contradicted my clinical expectations.

Prior to the publication of paper iv, side effect monitoring had largely been limited to those related to gene therapy itself, including thromboembolic events, infusion-related reactions and AAV-induced transaminitis (Rangarajan et al., 2017; George et al., 2017). If immunosuppression was mentioned, it was largely an acknowledgement that it had been administered and that it had rescued factor expression if transaminitis had occurred. There was minimal discussion of the side effects of the immunosuppression nor the duration of treatment. Following the publication of the paper and the associated presentation of the results at the International Society of Thrombosis and Haemostasis congress in 2022, there has been an increase in the number of studies reporting immunosuppressant-related adverse events as well as the length of time that immunosuppressant therapy has been required (Ozelo et al., 2022; Leavitt, Kavakli, et al., 2024).

There have also been multiple attempts to mitigate the side effect burden of immunosuppression, particularly the use of high-dose corticosteroids, by adding other agents such as Tacrolimus, Mycophenolate, or Sirolimus (Chowdary et al., 2022; Roy et al., 2025). It is hoped that introducing these other agents will enable a reduction in both corticosteroid

dosage and treatment duration. Despite this, although the median duration of immunosuppressive therapy in haemophilia B gene therapy has decreased to 78 days, the duration of therapy for haemophilia A gene therapy remains unchanged at 230 days (Ozelo and Yamaguti-Hayakawa, 2022; Miesbach et al., 2022). Concerns about these side effects continue to be a significant worry (Thornburg, Simmons and von Drygalski, 2023).

As noted previously, prophylaxis for haemophilia has focused on maintaining factor levels above 3-5 iu/dl to prevent bleeding. As such the monitoring of factor levels has become an element of shared understanding of treatment effectiveness between PwH and healthcare professionals and a primary indicator of treatment efficacy. It was therefore almost inevitable that this shared understanding carried over into any conversations PwH and healthcare professionals had about the outcomes of gene therapy. Many participants, therefore, began to fixate on their factor levels and became concerned when they saw their factor levels begin to decline. Indeed, a number of participants in paper iv stated that there were times when they felt that they and their clinical teams were concentrating too fixedly on levels.

This has been recognised by many researchers and there is now a tendency in recent papers to reframe the discussion, de-emphasising absolute factor values and possible decline in effect over time, focusing instead on the number of bleeds experienced since treatment and the potential number of years an individual might expect to remain bleed-free or off prophylactic treatment (Symington et al., 2024; Leavitt et al., 2024).

Paper ii, has also been cited in the American College of Genetics and Genomics guidance paper on genetic therapies (Peña *et al.*, 2023) and in the UKHCDO Guidance for the implementation of gene therapy in the UK (Chowdary *et al.*, 2024). Both documents emphasise the need for psychological support for PwH undergoing gene therapy and experiencing the side effects of immunosuppressives.

The UKHCDO guidance (Chowdary *et al.*, 2024) has also cited and accepted the recommendations of paper i, which state that discussions regarding gene therapy and eligibility should ideally begin before any formal decision-making commences. The recommendations of paper vii, which advocate for providing support to individuals who are ineligible for gene therapy, were also referenced, although not directly cited. These recommendations have since been cited by Bala and Thornburg (2025), who support extending psychological assistance to those who are ineligible for or withdraw from gene

therapy, as the expectations they may have set for themselves and their families could now be unachievable.

While the integration of psychological support for the care of people undergoing GT has been widely advocated, its provision has often been poor. In the UK, in particular, the haemophilia centre peer review processes in 2020 and 2024 highlighted the patchy provision of psychological support in many centres (West Midlands Quality Review Service, 2020) (*UKHCDO Haemophilia Peer Review Audit Reports 2024 – UKHCDO*, 2024). Greater support and training are therefore required to enable existing multidisciplinary teams to provide care that integrates psychological principles and clearly outlines referral pathways, specifying when, where, and how to refer individuals for specialist care if needed (Main and George, 2011; Dekker *et al.*, 2023).

The debate on ineligibility has, however, focused less on the support of those who cannot have gene therapy and more on improving the technology to reduce the number of people who are excluded (Yamaguti-Hayakawa and Ozelo, 2023; Herzog, Kaczmarek and High, 2025). While this is in many ways laudable, it does little in the short term to support those individuals and their families who are not currently eligible.

Previous literature has explored how being diagnosed with a life-threatening or chronic condition can impact an individual's sense of identity and their ability to control both their lives and their condition. Karnilowicz (2011), Charmaz (1983) and (1991) and Bury (1991) in particular, discuss the often disruptive and transformative nature of diagnosis, which King et al. (2003) have described as frequently epiphanic. While these changes can sometimes be beneficial, they are more commonly seen as negative and involve a loss of self. There is also a similar change that can occur after a condition has been cured, as an individual's self-image attempts to return to its pre-illness state. More often than not, however, it involves a reinterpretation of their previous self-image and their illness experiences.

While it is evident that there are clear similarities between the impact of sudden illness on self-image and the development of self-image in individuals with lifelong illnesses, there are also notable differences. The first of these is the absence of an epiphanic experience. Individuals with lifelong conditions grow up aware of their condition, and their self-image, rather than being altered by the illness, develops alongside it. Therefore, there is no distinct before-and-after experience; self-image and sense of identity are linked to their

understanding of their condition and, in some cases, their membership of a specific group, such as PwH.

The concept that haemophilia could be an important element of a person's identity initially surprised me. My nurse training and own subsequent experience had led me to believe that haemophilia was a treatable condition rather than a marker of identity. My conversations with patients in 2018-2019, prior to beginning the Exigency programme, however, hinted that this belief might not be wholly correct. Despite that, I did not think that it would be a widely shared belief, even though my own experience living with talipes equinovarus resonated with the concept of condition-as-identity. The systematic analysis of participant narratives across the multiple cohorts, however, forced me to recognise that identity is a fundamental dimension of both the haemophilia and gene therapy experiences, and as such would require attention and support.

The Exigency programme contributes to chronic illness theory by identifying unique aspects of 'curative' interventions for lifelong conditions. While Charmaz (1983), Bury (1991) and Helgeson and Novak (2002) have explored illness centrality and identity disruption in illness, much of the focus has been on the negative aspects of illness on QoL, psychological wellbeing and condition control. The Exigency programme has, however, found that while there are negative impacts to a diagnosis of haemophilia, for some men there have been positive impacts, including a sense of being part of a community of people with haemophilia and pride in the way they have been able to transcend the difficulties and burdens of their haemophilia.

The programme has also shown that there are parallel challenges when an illness identity is removed, and when individuals find themselves in some way not the person they believed they were or thought they might be. Similarly, the concept of 'burden of normality' (Wilson, Bladin and Saling, 2007) is expanded here to show how families, not just individuals, experience this phenomenon. The programme also challenges traditional medical models that focus solely on clinical outcomes, demonstrating the need for psychosocial support frameworks in gene therapy implementation. As more curative treatments develop, it will be important to consider and research the effects of identity development and possible loss thereof.

Since the publication of papers ii and iv, the concept of cure has been further explored by Baas et al. (2023) and (2024). They report that the modest increase in factor expression

offered by current haemophilia A gene therapies and its decline over time, did not provide improvements in QoL PwH were seeking. There was, however, a greater satisfaction with gene therapy for haemophilia B, as it seems to offer greater longevity, although again, the increment in factor levels did not bring many into a normal range. Baas et al. (2024) wondered whether it is truly possible for gene therapy to be considered a cure, and felt that, in some situations, standard treatments might actually be preferable.

Some positive changes following gene therapy have been highlighted by others, including Miesbach and Klamroth (2020), Thornburg (2022), and Fletcher et al. (2022). Krumb and Hermans (2021) have also suggested that gene therapy may help individuals live with a haemophilia-free mind, reducing both the physical and psychological burden of the disease in a way that corresponds with the burdens felt by those with moderate and mild haemophilia. However, this assumes that individuals with moderate and mild haemophilia – who bleed less frequently and therefore have a reduced treatment burden – also experience a decreased psychological burden compared to those with severe haemophilia. This may not necessarily be the case; there is recognition that, although the nature and impact may differ, it is no less significant for those with less severe forms of haemophilia (Chai-Adisaksopha et al., 2021; Castaman et al., 2023).

It is also important to understand what the physical sequelae of severe haemophilia such as haemophilic arthropathy, chronic pain, mobility issues, or blood-borne viral infections, may mean for those with severe haemophilia who have undergone gene therapy. These sequelae may not always be alleviated by gene therapy; as such, some will continue to bear burdens beyond those experienced by individuals with moderate or mild haemophilia (Fletcher *et al.*, 2021). Consequently, they may never truly be able to live with a haemophilia-free life (Fletcher et al., 2022; Fletcher et al., 2022; Baas et al., 2023).

Further research is necessary to better understand the physical and psychological effects of having moderate or mild haemophilia, as well as in those who have undergone gene therapy to explore the impact of any shift from severe to less severe haemophilia (Peng et al., 2023; Miesbach et al., 2024).

While a number of the study participants were aware of gene therapy and what was involved, there were many who did not feel that they understood enough about it. The parents of children with haemophilia in paper i and the woman in paper v in particular felt that, since neither they nor their children were currently able to have gene therapy, they were not being

provided with any information about what may be involved or whether they or their children might be able to have gene therapy at some point in the future. A number of the men interviewed for paper ix also expressed concern over the lack of information, which they viewed as a significant barrier in deciding whether gene therapy would be a suitable treatment option for them.

This need to ensure that all PwH have access to the information they require to make a decision about whether gene therapy is a suitable option has been highlighted in all of the individual Exigency papers (papers i, ii, iv, v, and vii). These points have also been synthesised in a single paper on shared decision making (paper vii), emphasising the importance of understanding the preferences, values, and biases of those individuals who might want gene therapy; providing them with jargon free, tailored information about the potential benefits and risks of gene therapy; and enabling them to make the decision that is right for them in their own time.

For many years, women and girls affected with haemophilia have also struggled to gain recognition for the problems they routinely face, including abnormal uterine bleeding, which has been dismissed, ignored or passed off as normal by both the individuals concerned and the medical community (Clancy, 2023). The case study included here (paper v) highlights many of these issues. It has, however, received little academic attention since its publication, though it has been cited by Fletcher (2024b) in reference to the care of another minority group within bleeding disorders care, trans men.

Although a complete model cannot yet be developed, the current framework (Figure 2, page 37) provides a foundation for future theoretical advances. The three-theme structure (safety and efficacy, identity, and expectations), I believe, has shown internal reliability and may also be reliable across other 'curative' genetic therapies. Future research should explore this framework in conditions such as sickle cell disease and beta-thalassaemia gene therapies and potentially develop it into a comprehensive theory of the lived experience of genetic medicine.

Impact

A number of papers examining gene therapy for other disease indications, including Friedrichs Ataxia (Lieschke *et al.*, 2023), lysosomal storage disorders (Eskes *et al.*, 2022), Rett syndrome (Ramsey *et al.*, 2024), and Sickle Cell Disease (Dovern *et al.*, 2025), have also cited papers from the Exigency programme, including papers i, ii and iv.

The insights revealed in the papers have also led to multiple invitations to address specialist professional and patient groups, where ongoing developments around haemophilia gene therapy remain a primary concern.

In February 2024 I was invited to speak at the European Association for Haemophilia and Allied Diseases (EAHAD) psychosocial committee's interdisciplinary roundtable on multidisciplinary approaches to caring for individuals during gene therapy (Teela *et al.*, 2025). Following the roundtable, the committee published a framework for the care of individuals undergoing gene therapy which also recognised the need to integrate and support the extended families of those individuals undergoing gene therapy (Haverman *et al.*, 2025).

The publication of the papers ii and iv also led to invitations to speak at a number of patient organisations, including the American National Bleeding Disorders Foundation (2022), the World Federation of Hemophilia (2022), the European Haemophilia Foundation (2024) and the Irish Haemophilia Society (2024)

I have also been invited, along with other stakeholders within the haemophilia community, to work on a number of ongoing gene therapy plain language summaries highlighting the technology as well as the post-therapy health-related quality of life improvements (Lowe et al., 2023; Madan et al., 2025).

Paper viii has subsequently been translated into German and published as a chapter in a book (Fletcher *et al.*, 2024). Bringing together papers from researchers working in haemophilia gene therapy, the book discusses the current knowledge and potential for the therapy and highlights the importance of collaborative and interdisciplinary care (Miesbach, 2024).

Strengths and Limitations

One of the main strengths of the Exigency programme as a whole has been the voice it has given to the haemophilia community, not just to those who have haemophilia but also to their family members, including spouses and partners. As highlighted previously, the impact of haemophilia and its treatment on the wider family beyond those with direct caregiving responsibilities is poorly understood. In 2021, I published one of the first papers to explore the impact of factor mimetics on PwH and their families, and in particular their effect on their spouses and partners (Fletcher et al., 2021). Exigency has continued this exploration and

has shown how haemophilia and gene therapy can affect the psychosocial wellbeing of the whole family: spouses, partners, caregivers, and children.

Another strength of the Exigency programme is that participants who underwent gene therapy were interviewed at different time points in the process. Some were interviewed within the first six to twelve months following treatment, while others were interviewed, in some cases, up to five years after their treatment. In this way, it was possible to see if there were experiences common to all participants at all time periods, how they were interpreted and even reinterpreted over time.

Another important element of the programme that needs to be acknowledged is that of insider status (Gardner, 1998; Borbasi et al., 2005). I feel that my position as a nurse in the haemophilia care community may have helped to facilitate and encourage participants to share their stories, trusting that I would understand their experiences. However, this same insider status posed potential limitations as participants may have adapted their stories to align with what they thought I would want to hear. Conversely, some might have been more critical than they intended, thinking I would already have heard about the positives from other participants. The grounded theory approach, with its emphasis on participant language as well as the independent verification of coding by my supervisor, helped mitigate these risks, but I need to acknowledge that my professional background may have influenced the analysis in some way.

A further strength, and validation of the paper's findings, particularly in relation to the cohort of men who had undergone gene therapy was the fact that I was able to recruit 50% of the men in the UK who had undergone gene therapy at the time. Similarly, although only one woman with haemophilia was interviewed as part of the Exigency programme, she was one of only three women in the UK who had a confirmed definition of severe haemophilia.

Funding for the Exigency programme was awarded through a competitive process by uniQure Biopharm and came with no demands or requests for publication restrictions or editorial control. I see this as a real strength of the programme, because although the company, due to their involvement in gene therapy for haemophilia, would have been eager to see it portrayed positively, they were willing to allow the publication of all data resulting from the study, whether positive or negative in relation to gene therapy. They recognised the value of the programme's aim to understand the lived experiences of people with haemophilia, both in considering and undergoing gene therapy.

One limitation of the Exigency programme is its limited international scope. The study took place in a high-income country (UK) where access to multiple treatment modalities is readily available. This might mean that the results seen here might not be generalisable beyond that cultural and social or economic setting.

Though not a limitation of the Exigency programme specifically, the issue of generalisability in qualitative research is a frequently raised and contentious problem (Stake, 1978; Carminati, 2018). This concern, however, I believe results from a misunderstanding of the nature of qualitative research in general and GT in particular. As noted in chapter four, grounded theory, through its use of constant comparison, aims to identify shared experiences rather than those that are unique to an individual (Glaser and Strauss, 1967; Charmaz, 2014). In this way, it is possible to generalise beyond the immediate context or cultural setting (Firestone, 1993). The reflexivity inherent in the methodology also helps the researcher recognise their own beliefs and experiences, and how they can influence data interpretation and theme development, and so reduce bias, improving internal validity (Mruck and Mey, 2012).

I recognise, therefore, that complete objectivity is neither possible nor wholly desirable and that the value of this research programme lies not in eliminating my personal or professional perspective, but in making it explicit and allowing it to be scrutinised alongside the participants' voices. Ultimately, this research represents not a view from nowhere, but a considered synthesis of participant expertise, clinical knowledge, and theoretical analysis. Nevertheless, it remains important to conduct further qualitative studies to determine whether the findings in this synthesis remain valid over time or whether, as technology advances and the therapy becomes a standard treatment modality, participants' perceptions change.

Chapter Seven: Conclusions and Recommendations for Further Research

The Exigency programme was the first comprehensive exploration of the lived experience of gene therapy for haemophilia, examining how the therapy affects not only individuals who have undergone the treatment, but also those who decline it, those who cannot access it, or those who may not be eligible. More than this, though, it sought to investigate the broader impact on the families of these groups; an area that had received little previous attention.

The research has identified three key contributions to the field: the identification of previously unrecognised psychosocial support needs throughout the entire gene therapy journey, the demonstration that the impact of the treatment extends beyond the individual PwH to the family, and that withdrawal or ineligibility for gene therapy creates a distinct psychological challenge that requires dedicated support.

In particular, the programme demonstrated that some participants had a strong self-identity as a PwH and did not want to lose that identity in any way. Conversely, many did not feel this, stating that even if they were no longer to have haemophilia, and did not need to treat themselves prophylactically or suffer the risk of severe bleeding episodes, they would still consider themselves to be a part of the haemophilia community.

More information should be made available to those interested in gene therapy, and this information should be provided as early as possible. This would better enable PwH to determine whether gene therapy is an option for them and what steps to take to achieve the best outcome.

At the beginning of this synthesis, I quoted from Meditation XVII by John Donne (1624), which famously begins with the line, 'No man is an island, entire of itself'. Donne's meditation explores how humanity is connected and argues that an individual's experiences both diminish and enrich us all, because we are all part of a whole. Through this metaphor, I aimed to show that although gene therapy might primarily impact the individual receiving it, its effects extend far beyond the individual. The treatment's consequences - whether positive, negative, or uncertain - impact the entire family. Therefore, it is essential that psychological support be available not only for the individual undergoing gene therapy, but also for their family members who share their journey. As demonstrated throughout this synthesis, many partners of people with haemophilia struggled to provide or access effective support. They often felt

helpless, uncertain what to say or do when treatments failed to meet expectations or when they learned that gene therapy would never be an option for their loved ones.

Recommendations for Future Research

Inasmuch as any programme of research seeks to answer questions, it also seeks to ask them, and the Exigency programme is no different. In highlighting the need to increase the psychosocial support for people with haemophilia and their families undergoing gene therapy, it raises a number of issues that need further study. This is a particular imperative given the licensing of gene therapy technologies in the United States, Europe and the United Kingdom since the publication of the Exigency papers.

As a first recommendation, there is a need for a deeper understanding of how a diagnosis of haemophilia affects an individual's sense of identity. This is particularly important for women who experience the symptoms of haemophilia, but are unable, because of a lack of recognition and the paucity of research in women, to access many of the treatments available to men with the condition.

Secondly, while extensive research has been conducted on the lived experiences of people with severe haemophilia, there is less understanding of those with moderate and mild haemophilia. As the aim of gene therapy is to transform individuals with severe haemophilia into those with moderate or mild forms, it is essential to gain a clearer understanding of what it is to live with non-severe haemophilia and what similarities and differences exist between these two groups.

Thirdly, it is important that, as technology evolves, as it undoubtedly will, there are ongoing discussions with those undergoing gene therapy to determine whether their experience aligns with or differs from that of others who were previously treated.

Fourthly, the three-theme framework developed through the Exigency programme should be tested and validated across other curative genetic therapies to evaluate its wider applicability and theoretical robustness, ultimately supporting more effective psychosocial support strategies in genetic medicine.

Fifthly, it would be helpful to undertake a similar programme of study in low and middle-income countries to determine whether the findings, particularly those related to the concept of identity reported here, are similar or if significant differences exist.

Finally, it would be insightful to follow some of the participants in these studies in five and ten years to see if their experiences of their treatment and their haemophilia have remained the same or changed.

References

Alton, E.W.F.W., Armstrong, D.K., Ashby, D., Bayfield, K.J., Bilton, D., Bloomfield, E. V., Boyd, A.C., Brand, J., Buchan, R., Calcedo, R., Carvelli, P., Chan, M., Cheng, S.H., Collie, D.D.S., Cunningham, S., Davidson, H.E., Davies, G., Davies, J.C., Davies, L.A., Dewar, M.H., Doherty, A., Donovan, J., Dwyer, N.S., Elgmati, H.I., Featherstone, R.F., Gavino, J., Gea-Sorli, S., Geddes, D.M., Gibson, J.S.R., Gill, D.R., Greening, A.P., Griesenbach, U., Hansell, D.M., Harman, K., Higgins, T.E., Hodges, S.L., Hyde, S.C., Hyndman, L., Innes, J.A., Jacob, J., Jones, N., Keogh, B.F., Limberis, M.P., Lloyd-Evans, P., Maclean, A.W., Manvell, M.C., McCormick, D., McGovern, M., McLachlan, G., Meng, C., Montero, M.A., Milligan, H., Moyce, L.J., Murray, G.D., Nicholson, A.G., Osadolor, T., Parra-Leiton, J., Porteous, D.J., Pringle, I.A., Punch, E.K., Pytel, K.M., Quittner, A.L., Rivellini, G., Saunders, C.J., Scheule, R.K., Sheard, S., Simmonds, N.J., Smith, K., Smith, S.N., Soussi, N., Soussi, S., Spearing, E.J., Stevenson, B.J., Sumner-Jones, S.G., Turkkila, M., Ureta, R.P., Waller, M.D., Wasowicz, M.Y., Wilson, J.M. and Wolstenholme-Hogg, P. (2015) 'Repeated nebulisation of non-viral CFTR gene therapy in patients with cystic fibrosis: A randomised, double-blind, placebo-controlled, phase 2b trial', *The Lancet Respiratory Medicine*, 3(9), pp. 684–691. Available at: https://doi.org/10.1016/S2213-2600(15)00245-3.

Arthur, S., Mitchel, M., Lewis, J. and McNaughton Nicholls, C. (2014) 'Designing Fieldwork', in J. Richie, J. Lewis, C. McNaughton Nicholls, and R. Ormston (eds.) *Qualitative Research Practice: A Guide for Social Science Students and Researchers.* . 2nd ed. London: SAGE, pp. 147–176.

Astermark, J., Holstein, K., Abajas, Y.L., Kearney, S., Croteau, S.E., Liesner, R., Funding, E., Kempton, C.L., Acharya, S., Lethagen, S., LeBeau, P., Bowen, J., Berntorp, E. and Shapiro, A.D. (2021) 'The B-Natural study—The outcome of immune tolerance induction therapy in patients with severe haemophilia B', *Haemophilia*, 27(5), pp. 802–813. Available at: https://doi.org/10.1111/hae.14357.

Baas, L., Meijer, K., Bredenoord, A.L. and van der Graaf, R. (2024) 'What is a cure through gene therapy? An analysis and evaluation of the use of "cure"', *Medicine, Health Care and Philosophy* [Preprint]. Available at: https://doi.org/10.1007/S11019-024-10223-W.

Baas, L., Meijer, K., Driessens, M., Bredenoord, A.L., van der Graaf, R., Cnossen, M.H. and Reitsma, S.H. (2023) 'Ethical aspects of hemophilia gene therapy: a qualitative interview study with stakeholders', *Research and Practice in Thrombosis and Haemostasis*, 7(7), p. 102237. Available at: https://doi.org/10.1016/j.rpth.2023.102237.

Badou, W.F. (2000) *Genetics for Haematologists: The molecular genetic basis of haematological disorders*. London: ReMEDICA.

Bala, N.S. and Thornburg, C.D. (2025) 'Gene Therapy in Hemophilia A: Achievements, Challenges, and Perspectives', *Seminars in Thrombosis and Hemostasis*, 51(01), pp. 028–040. Available at: https://doi.org/10.1055/s-0044-1785483.

van Balen, E.C., Wesselo, M.L., Baker, B.L., Westerman, M.J., Coppens, M., Smit, C., Driessens, M.H.E., Leebeek, F.W.G., van der Bom, J.G. and Gouw, S.C. (2020) 'Patient

Perspectives on Novel Treatments in Haemophilia: A Qualitative Study', *The Patient - Patient-Centered Outcomes Research*, 13(2), pp. 201–210. Available at: https://doi.org/10.1007/s40271-019-00395-6.

Batty, P. and Lillicrap, D. (2019) 'Advances and challenges for hemophilia gene therapy', *Human Molecular Genetics*. Oxford University Press, pp. R95–R101. Available at: https://doi.org/10.1093/hmg/ddz157.

Berndtsson, I., Claesson, S., Friberg, F. and Öhlén, J. (2007) 'Issues about thinking phenomenologically while doing phenomenology', *Journal of Phenomenological Psychology*, 38(2), pp. 256–277. Available at: https://doi.org/10.1163/156916207X234293.

Bezzerides, V.J., Prondzynski, M., Carrier, L. and Pu, W.T. (2020) 'Gene therapy for inherited arrhythmias', *Cardiovasc Res*, 116, pp. 1635–1650.

Biffi, A. (2018) 'Gene Therapy as a Curative Option for β-Thalassemia', *New England Journal of Medicine*, 378(16), pp. 1551–1552. Available at: https://doi.org/10.1056/nejme1802169.

Birks, M. and Mills, J. (2015) *Grounded theory: A practical guide (2nd ed.). Los Angeles, CA: Sage*, *Nursing Science Quarterly*. London: SAGE Publications.

Blanchette, V.S., Key, N.S., Ljung, L.R., Manco-Johnson, M.J., van den Berg, H.M. and Srivastava, A. (2014) 'Definitions in hemophilia: communication from the SSC of the ISTH', *Journal of thrombosis and haemostasis : JTH*, 12(11), pp. 1935–1939. Available at: https://doi.org/10.1111/JTH.12672.

Blatny, J. and Mathew, P. (2011) 'Immune tolerance induction programs', in E.C. Rodriguez-Merchan and L. Valentino (eds.) *Current and Future Issues in Hemophilia Care*. Oxford: Wiley-Blackwell, pp. 91–96.

van der Bom, J.G. (2011) 'Epidemiology of Inhibitors', *Current and Future Issues in Hemophilia Care*, pp. 60–67. Available at: https://doi.org/10.1002/9781119979401.CH13.

Borbasi S. Jackson D. and Wilkes L. (2005) Fieldwork in Nursing Research: Positionality, Practicalities and Predicaments. *Journal of Advanced Nursing*, 51(5), 493–501.

Bosanac, P., Hamilton, B.E., Lucak, J. and Castle, D. (2018) 'Identity challenges and "burden of normality" after DBS for severe OCD: A narrative case study', *BMC Psychiatry*, 18(1), pp. 1–7. Available at: https://doi.org/10.1186/S12888-018-1771-2/PEER-REVIEW.

Bury, M. (1991) 'The sociology of chronic illness: a review of research and prospects', *Sociology of Health & Illness*, 13(4), pp. 451–468. Available at: https://doi.org/10.1111/J.1467-9566.1991.TB00522.X.

Carcao, M., van den Berg, H.M., Gouider, E., Khair, K., Baarslag, M.A., Bagley, L., de Paula Careta, F., Ljung, R.C.R., Ragni, M.V., Santagostino, E., Pierce, G.F., Srivastava, A. (2020) Prophylaxis in Haemophilia. In Srivastava, A, Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S.W., Carcao, M., Mahlangu, J., Ragni, M. V., Windyga, J., Llinás,

A., Goddard, N.J., Mohan, R., Poonnoose, P.M., Feldman, B.M., Lewis, S.Z., van den Berg, H.M. and Pierce, G.F. (eds). WFH Guidelines for the Management of Hemophilia, 3rd edition', *Haemophilia*, 26(S6), pp. 81-95. Available at: https://doi.org/10.1111/hae.14046.

Carminati, L. (2018) 'Generalizability in Qualitative Research: A Tale of Two Traditions', *Qualitative Health Research*, 28(13), pp. 2094–2101. Available at: https://doi.org/10.1177/1049732318788379.

Castaman, G., Peyvandi, F., De Cristofaro, R., Pollio, B. and Di Minno, D.M.N. (2023) 'Mild and Moderate Hemophilia A: Neglected Conditions, Still with Unmet Needs', *Journal of Clinical Medicine*, 12(4), p. 1368. Available at: https://doi.org/10.3390/JCM12041368.

Castanotto, D. and Rossi, J.J. (2009) 'The promises and pitfalls of RNA-interference based therapeutics', *Nature*, 457(7228), pp. 426–433.

Chai-Adisaksopha, C., Noone, D., Curtis, R., Frick, N., Nichol, M.B., Germini, F., O'Mahony, B., Page, D., Stonebraker, J.S., Skinner, M.W. and Iorio, A. (2021) 'Non-severe haemophilia: Is it benign? – Insights from the PROBE study', *Haemophilia*, 27(S1), pp. 17–24. Available at: https://doi.org/10.1111/HAE.14105,.

Charmaz, K. (1983) 'Loss of self: a fundamental form of suffering in the chronically ill', *Sociology of Health and Illness*, 5(2), pp. 168–195.

Charmaz, K. (2014) *Constructing Grounded Theory*. 4th ed. London: SAGE.

Charmaz, K. (2016) 'Qualitative Interviewing and Grounded Theory Analysis', *Handbook of Interview Research*, pp. 675–694. Available at: https://doi.org/10.4135/9781412973588.N39.

Chhabra, E.S., Liu, T., Kulman, J., Patarroyo-White, S., Yang, B., Lu, Q., Drager, D., Moore, N., Liu, J., Holthaus, A.M., Sommer, J.M., Ismail, A., Rabinovich, D., Liu, Zhan, van der Flier, A., Goodman, A., Furcht, C., Tie, M., Carlage, T., Mauldin, R., Dobrowsky, T.M., Liu, Zhiqian, Mercury, O., Zhu, L., Mei, B., Schellenberger, V., Jiang, H., Pierce, G.F., Salas, J. and Peters, R. (2020) 'BIVV001, a new class of factor VIII replacement for hemophilia A that is independent of von Willebrand factor in primates and mice', *Blood*, 135(17), pp. 1484–1496. Available at: https://doi.org/10.1182/BLOOD.2019001292,.

Chowdary, P., Duran, B., Batty, P., Lowe, G., Jones, A., Pollard, D., Boyce, S., Motwani, J., Amirloo, B., Musgrave, K., Hopper, D., Classey, S., Whitaker, S., Dunn, N., Bowyer, A. and Shapiro, S. (2024) 'UKHCDO gene therapy taskforce: Guidance for implementation of haemophilia gene therapy into routine clinical practice for adults', *Haemophilia*, 31(1). Available at: https://doi.org/10.1111/HAE.15125,.

Chowdary, P., Shapiro, S., Makris, M., Evans, G., Boyce, S., Talks, K., Dolan, G., Reiss, U., Phillips, M., Riddell, A., Peralta, M.R., Quaye, M., Patch, D.W., Tuddenham, E., Dane, A., Watissée, M., Long, A. and Nathwani, A. (2022) 'Phase 1–2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B', *New England Journal of Medicine*, 387(3), pp. 237–247. Available at: https://doi.org/10.1056/NEJMOA2119913.

Clancy, K. (2023) *Period: The Real Story of Menstruation*. Princeton: Princeton University Press.

Clarke, V. and Braun, V. (2017) 'Thematic analysis', *Journal of Positive Psychology*, 12(3), pp. 297–298. Available at: https://doi.org/10.1080/17439760.2016.1262613.

Cooke, A., Smith, D. and Booth, A. (2012) 'Beyond PICO: the SPIDER tool for qualitative evidence synthesis', *Qualitative health research*, 22(10), pp. 1435–1443. Available at: https://doi.org/10.1177/1049732312452938.

Corbin, J. and Strauss, A. (1996) 'Analytic ordering for theoretical purposes', *Qualitative Inquiry*, 2(2), pp. 139–150. Available at: https://doi.org/10.1177/107780049600200201.

Corbin, J. and Strauss, A. (2008) *Basics of Qualitative Research (3rd ed.): Techniques and Procedures for Developing Grounded Theory*. 3rd ed, *Basics of Qualitative Research (3rd ed.): Techniques and Procedures for Developing Grounded Theory*. 3rd ed. 2455 Teller Road, Thousand Oaks California 91320 United States : SAGE Publications, Inc. Available at: https://doi.org/10.4135/9781452230153.

Corbin, J. and Strauss, A. (2015) *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. 4th ed. London: SAGE.

Creswell, J.W. and Porth, C.N. (2018) *Qualitative Inquiry and Research Design: Choosing Among Five Approaches* . 4th ed. London: SAGE.

van Creveld, S. (1969) 'Prophylaxis of Joint Hemorrhages in Hemophilia', *Acta Haematologica*, 41(4), pp. 206–214. Available at: https://doi.org/10.1159/000208852.

Curtis, R., Baker, J., Riske, B. and others (2015) 'Young adults with hemophilia in the U. S.: demographics, comorbidities, and health status', *Am J Hematol*, 90(Suppl 2), pp. S11-6.

Dekker, J., Sears, S.F., Asenlöf, P. and Berry, K. (2023) "Psychologically informed health care," *Translational behavioral medicine*, 13(5), pp. 289–296. Available at: https://doi.org/10.1093/TBM/IBAC105.

Dimichele, D., Miller, F.G. and Fins, J.J. (2003) 'Gene therapy ethics and haemophilia: an inevitable therapeutic future?', *Haemophilia*, 9, pp. 145–152.

Donnelly, L. (2024) *NHS £2.6m blood infusion transforms life for haemophilia B sufferers*. Available at: https://www.telegraph.co.uk/news/2024/06/27/nhs-26m-blood-transfusion-transforms-life-for-haemophilia/?ICID=continue_without_subscribing_reg_first (Accessed: 7 June 2025).

Doyle L, McCabe C, Keogh B, Brady A, McCann M. (2019) An overview of the qualitative descriptive design within nursing research. J Res Nurs. 2020 Aug;25(5):443-455. https://doi.prg/10.1177/1744987119880234.

Dovern, E., Nijland, S.J.A.M., Braamse, A.M.J., van Muilekom, M.M., Suijk, E.M.J., Hoogendoorn, G.M., van Tuijn, C.F.J., DeBaun, M.R., Biemond, B.J., Haverman, L. and

Nur, E. (2025) ‘Changes in the quality of life of adults with sickle cell disease following allogeneic stem cell transplantation: A mixed-methods, prospective cohort study’, *HemaSphere*, 9(3), p. e70100. Available at: https://doi.org/10.1002/HEM3.70100;PAGEGROUP:STRING:PUBLICATION.

Eskes, E.C.B., Beishuizen, C.R.L., Corazolla, E.M., van Middelaar, T., Brands, M.M.M.G., Dekker, H., van de Mheen, E., Langeveld, M., Hollak, C.E.M. and Sjouke, B. (2022) ‘Patients’ view on gene therapy development for lysosomal storage disorders: a qualitative study’, *Orphanet Journal of Rare Diseases*, 17(1). Available at: https://doi.org/10.1186/S13023-022-02543-Y.

Evans, B. (2020) *The Zoom Revolution: 10 Eye-Popping Stats from Tech’s New Superstar - Cloud Wars*, *Cloud Wars*. Available at: https://cloudwars.com/news/the-zoom-revolution-10-eye-popping-stats-from-techs-new-superstar/ (Accessed: 22 February 2025).

Ewing, N., Escuriola-Ettingshausen, C. and Kreuz, W. (2015) ‘Prophylaxis with FEIBA in paediatric patients with haemophilia A and inhibitors’, *Haemophilia*, 21(3), pp. 358–364. Available at: https://doi.org/10.1111/hae.12602.

Farrugia, A., Cassar, J., Kimber, M.C., Bansal, M., Fischer, K., Auserswald, G. and others (2013) ‘Treatment for life for severe hemophilia A-A cost-utility model for prophylaxis vs. on-demand treatment’, *Haemophilia*, 19, pp. e228-38.

Favaro, P., Downey, H.D., Shangzhen Zhou, J., Fraser Wright, J., Hauck, B., Mingozzi, F., High, K.A. and Arruda, V.R. (2009) ‘Host and vector-dependent effects on the risk of germline transmission of AAV vectors’, *Molecular therapy : the journal of the American Society of Gene Therapy*, 17(6), pp. 1022–1030. Available at: https://doi.org/10.1038/MT.2009.56.

Fineout-Overholt, E. and Johnston, L. (2005) ‘Teaching EBP: Asking searchable, answerable clinical questions’, *Worldviews on Evidence-Based Nursing*, 2(3), pp. 157–160. Available at: https://doi.org/10.1111/J.1741-6787.2005.00032.X.

Firestone, W.A. (1993) ‘Alternative Arguments for Generalizing From Data as Applied to Qualitative Research’, *Educational Researcher*, 22(4), pp. 16–23. Available at: https://doi.org/10.3102/0013189X022004016.

Fletcher, S. (2024a) ‘Living, Caring, Learning – The power of qualitative research in bleeding disorders care: One voice, from soloist to choir’, *The Journal of Haemophilia Practice*, 11(1), pp. 78–81. Available at: https://doi.org/10.2478/JHP-2024-0012.

Fletcher, S. (2024b) ‘(Mis)Gendering bleeding disorders care: A qualitative case study of a trans person with a bleeding disorder’, *The Journal of Haemophilia Practice*, 11(1), pp. 84–91. Available at: https://doi.org/10.2478/JHP-2024-0015.

Fletcher, S., Jenner, K., Holland, M. and Khair, K. (2021) ‘The lived experience of a novel disruptive therapy in a group of men and boys with haemophilia A with inhibitors: Emi

& Me', *Health Expectations*, 25(1), pp. 443–454. Available at: https://doi.org/10.1111/hex.13404.

Fletcher, S., Jenner, K., Holland, M. and Khair, K. (2024) 'Die Rolle Von Shared Decision Making', in W. Miesbach (ed.) *Gene Therapy Concepts in the Treatment of Hemophilia*. Bremen: Uni-Med, pp. 71–74.

Fletcher, S., Jenner, K., Pembroke, L., Holland, M. and Khair, K. (2022) 'The experiences of people with haemophilia and their families of gene therapy in a clinical trial setting: regaining control, the Exigency study', *Orphanet Journal of Rare Diseases*, 17(1). Available at: https://doi.org/10.1186/s13023-022-02256-2.

Fletcher, S., Khair, K. and Holland, M. (2024) 'Interim results from the lived experience of people with FVII deficiency study', in *World Federation of Haemophilia Congress*. Montreal.

Fletcher, S., Pembroke, L., Holland, M. and Khair, K. (2022) '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', *BMJ Open*, 12, p. 60351. Available at: https://doi.org/10.1136/bmjopen-2021-060351.

Flick, U. (2018) *Doing Grounded Theory*. London: SAGE.

Gardner G. (1996) The nurse researcher: an added dimension to qualitative research methodology. *Nursing Inquiry*, 3(1), 153–158.

George, L.A., Sullivan, S.K., Giermasz, A., Rasko, J.E.J., Samelson-Jones, B.J., Ducore, J., Cuker, A., Sullivan, L.M., Majumdar, S., Teitel, J., McGuinn, C.E., Ragni, M. V., Luk, A.Y., Hui, D., Wright, J.F., Chen, Y., Liu, Y., Wachtel, K., Winters, A., Tiefenbacher, S., Arruda, V.R., van der Loo, J.C.M., Zelenaia, O., Takefman, D., Carr, M.E., Couto, L.B., Anguela, X.M. and High, K.A. (2017) 'Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant', *The New England journal of medicine*, 377(23), p. 2215. Available at: https://doi.org/10.1056/NEJMOA1708538.

Gilbert, F. (2012) 'The burden of normality: from "chronically ill" to "symptom free". New ethical challenges for deep brain stimulation postoperative treatment', *Journal of medical ethics*, 38(7), pp. 408–412. Available at: https://doi.org/10.1136/MEDETHICS-2011-100044.

Given, L. (2008) *The SAGE Encyclopedia of Qualitative Research Methods*, *The SAGE Encyclopedia of Qualitative Research Methods*. 2455 Teller Road, Thousand Oaks California 91320 United States : SAGE Publications, Inc. Available at: https://doi.org/10.4135/9781412963909.

Glaser, B. (2008) *Doing quantitative Grounded Theory*. Mill Valley: Sociology Press.

Glaser, B. and Strauss, A. (1967) *The Discovery of Grounded Theory: Strategies for qualitative research*. New York: Aldine Publishing Company.

Glaser, B.A. and Strauss, A.L. (1965) *Awareness of Dying* . Chicago: Aldine.

Google Books (2025) *Google Ngram Viewer: lived experience*. Available at: https://books.google.com/ngrams/graph?content=lived+experience&year_start=1950&year_end=2022&corpus=en&smoothing=0&case_insensitive=true (Accessed: 17 February 2025).

Gourd, E. (2024) 'Infected blood scandal linked to more than 3000 deaths', *The Lancet Haematology*, 11(7), pp. e481–e482. Available at: https://doi.org/10.1016/S2352-3026(24)00182-0.

Gouw, S.C., van der Bom, J.G. and van der Berg, H.M. (2007) 'Treatment-related risk factors of inhibitor development in previously untreated patients with haemophilia: The CANAL cohort study', *Blood*, 109, pp. 4648–4654. Available at: https://doi.org/10.1182/blood-2006-11-056291.

Gringeri, A. and Von Mackensen, S. (2008) 'Quality of life in haemophilia', *Haemophilia*, 14(SUPPL. 3), pp. 19–25. Available at: https://doi.org/10.1111/J.1365-2516.2008.01709.X.

Hacein-Bey Abina, S., Gaspar, H.B., Blondeau, J. and others (2015) 'Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome', *JAMA*, 313(15), pp. 1550–1563. Available at: https://doi.org/10.1001/jama.2015.3253.

Haemnet (2019) *Where is Gene Therapy? - haemnet.com*. Available at: https://www.haemnet.com/blog/where-is-gene-therapy/ (Accessed: 30 March 2025).

Hasbrouck, N.C. and High, K.A. (2008) 'AAV-mediated gene transfer for the treatment of hemophilia B: problems and prospects', *Gene Therapy 2008 15:11*, 15(11), pp. 870–875. Available at: https://doi.org/10.1038/gt.2008.71.

Haverman, L., Teela, L., O'Brien, G., Bučková, P., Golan, G., Rooney, G., Bartels, K., Torres-Ortuño, A. and Burgess, C. (2025) 'Psychosocial Care During Novel Therapies in Haemophilia: A Psychological Framework', *Haemophilia* [Preprint]. Available at: https://doi.org/10.1111/HAE.70008.

Hay, C.R.M. and DiMichele, D.M. (2012) 'The principal results of the International Immune Tolerance Study: a randomized dose comparison', *Blood*, 119, pp. 1335–1344. Available at: https://doi.org/10.1182/blood-2011-08-369132.

Helgeson, V.S. and Novak, S.A. (2007) "Illness Centrality and Well-Being Among Male and Female Early Adolescents with Diabetes," *Journal of Pediatric Psychology*, 32(3), pp. 260–272. Available at: https://doi.org/10.1093/JPEPSY/JSL018.

Herzog, R.W., Kaczmarek, R. and High, K.A. (2025) 'Gene therapy for hemophilia – From basic science to first approvals of "one-and-done" therapies', *Molecular Therapy*, 33(5), pp. 2015–2034. Available at: https://doi.org/10.1016/J.YMTHE.2025.03.043.

High, K.A. and Roncarolo, M.G. (2019) 'Gene Therapy', *N Engl J Med*, 381(5), pp. 455–464. Available at: https://doi.org/10.1056/NEJMra1706910.

Iacobucci, G. (2024) ‘NICE recommends new gene therapy for adults with haemophilia B’, *BMJ*, 385, p. q1440. Available at: https://doi.org/10.1136/BMJ.Q1440.

Iorio, A., Stonebraker, J.S., Chambost, H. and others (2019) ‘Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using national registries’, *Ann Intern Med*, 171, pp. 540–546.

Jiang, J., Wakimoto, H., Seidman, J.G. and Seidman, C.E. (2013) ‘Allele-specific silencing of mutant Myh6 transcripts in mice suppresses hypertrophic cardiomyopathy’, *Science*, 342(6154), pp. 111–114.

Joint Formulary Committee (2025a) *Corticosteroids, general use | Treatment summaries | BNF | NICE*. Available at: https://bnf.nice.org.uk/treatment-summaries/corticosteroids-general-use/ (Accessed: 17 June 2025).

Joint Formulary Committee (2025b) *Prednisolone | Drugs | BNF | NICE*. Available at: https://bnf.nice.org.uk/drugs/prednisolone/#side-effects (Accessed: 30 March 2025).

Jones, P. (2024) ‘Engaging With Lived Experience: Towards a Sociological Biography of a Sociological Category’, *Sociological Research Online* [Preprint]. Available at: https://doi.org/10.1177/13607804241254285.

Karl, K.A., Peluchette, J. V. and Aghakhani, N. (2022) ‘Virtual Work Meetings During the COVID-19 Pandemic: The Good, Bad, and Ugly’, *Small Group Research*, 53(3), p. 343. Available at: https://doi.org/10.1177/10464964211015286.

Karnilowicz, W. (2011) ‘Identity and psychological ownership in chronic illness and disease state’, *European Journal of Cancer Care*, 20(2), pp. 276–282. Available at: https://doi.org/10.1111/J.1365-2354.2010.01220.X.

Kempton, C.L. and Meeks, S.L. (2014) ‘Toward optimal therapy for inhibitors in hemophilia’, *Blood*, 124(23), pp. 3365–3372. Available at: https://doi.org/10.1182/BLOOD-2014-05-577643.

Keshavjee, S., Weiser, S. and Kleinman, A. (2001) ‘Medicine betrayed: hemophilia patients and HIV in the US’, *Social Science & Medicine*, 53(8), pp. 1081–1094. Available at: https://doi.org/10.1016/S0277-9536(00)00403-2.

Khair, K., Fletcher, S., Boyton, M. and Holland, M. (2024) ‘Bleeding and quality of life in people with Glanzmann thrombasthenia—insights from the Glanzmann’s 360 study’, *Research and Practice in Thrombosis and Haemostasis*, 8(7). Available at: https://doi.org/10.1016/J.RPTH.2024.102586.

Khair, K., Fletcher, S., Boyton, M. and Holland, M. (2025a) ‘Living with von Willebrand Disease: Final report from the VWD360 Study’, in *International Society for Thrombosis and Haemostasis*. Washington.

Khair, K., Fletcher, S., Boyton, M. and Holland, M. (2025b) ‘Prospective Observational Analysis of Bleeding in People with vWD: The VWD360 Study’, in *International Society of Thrombosis and Haemostasis Congress*. Washington.

Khair, K., Fletcher, S., Jenner, K. and Holland, M. (2024) ‘One day at a time: Life with Glanzmann thrombasthenia – Qualitative results from the GT 360 study’, *Haemophilia* [Preprint]. Available at: https://doi.org/10.1111/HAE.15126.

Khair, K., Phillott, A., Loran, C., Pollard, D., Forrester, C., Alavian, S. and Hook, S. (2014) ‘HaemophiliaLIVE: an ethnographic study on the impact of haemophilia on daily life’, *The Journal of Haemophilia Practice*, 1(3), pp. 14–20. Available at: https://doi.org/10.17225/jhp.00030.

Kieserman, J.M., Myers, V.D., Dubey, P., Cheung, J.Y. and Feldman, A.M. (2019) ‘Current Landscape of Heart Failure Gene Therapy’, *J Am Heart Assoc*, 8.

Kincaid, J.P.; Fishburne, R.P.; Rogers, R.L.; Chissom, B.S. (1975). Derivation of new readability formulas (automated readability index, fog count, and flesch reading ease formula) for Navy enlisted personnel (PDF) (Report). Naval Air Station Memphis: Chief of Naval Technical Training. Research Branch Report 8–75. Retrieved October 15, 2024.

King, G., Cathers, T., Brown, E., Specht, J.A., Willoughby, C., Polgar, J.M., MacKinnon, E., Smith, L.K. and Havens, L. (2003) ‘Turning Points and Protective Processes in the Lives of People With Chronic Disabilities’, *Qualitative Health Research*, 13(2), pp. 184–206. Available at: https://doi.org/10.1177/1049732302239598.

Konduros, J. (2019) ‘Patient Testimonial: My Experience on a Gene Therapy Trial’, *Transfusion and Apheresis Science*. Elsevier Ltd, p. 601. Available at: https://doi.org/10.1016/j.transci.2019.08.011.

Krumb, E. and Hermans, C. (2021) ‘Living with a “hemophilia-free mind” – The new ambition of hemophilia care?’, *Research and Practice in Thrombosis and Haemostasis*, 5(5). Available at: https://doi.org/10.1002/rth2.12567.

Landrum Peay, H., Fischer, R., Tzeng, J.P. and others (2019) ‘Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: A qualitative preference study of patients and parents’, *PLoS One*, 2019, p. 14. Available at: https://doi.org/10.1371/journal.pone.0213649.

Leavitt, A.D., Kavakli, K., Frenzel, L., Antmen, A.B., Ozelo, M., Matino, D., Alzahrani, H., Konkle, B.A., Pipe, S.W., Teitel, J.M., Tseng, L.-J., Fang, A.F., Ganne, F., Dirusso, G., Rupon, J., Klaus, P., Healy, J., Agathon, D., Biondo, F. and Plonski, F. (2024) ‘Efficacy and Safety of Giroctocogene Fitelparvovec in Adults with Moderately Severe to Severe Hemophilia A: Primary Analysis Results from the Phase 3 AFFINE Gene Therapy Trial’, *Blood*, 144(Supplement 1), pp. 1053–1053. Available at: https://doi.org/10.1182/BLOOD-2024-208486.

Leavitt, A.D., Mahlangu, J., Raheja, P., Symington, E., Quon, D. V., Giermasz, A., López Fernández, M.F., Kenet, G., Lowe, G., Key, N.S., Millar, C.M., Pipe, S.W., Madan, B., Chou, S.C., Klamroth, R., Mason, J., Chambost, H., Peyvandi, F., Majerus, E., Pepperell, D., Rivat, C., Yu, H., Robinson, T.M. and Ozelo, M.C. (2024) 'Efficacy, safety, and quality of life 4 years after valoctocogene roxaparvovec gene transfer for severe hemophilia A in the phase 3 GENEr8-1 trial', *Research and practice in thrombosis and haemostasis*, 8(8). Available at: https://doi.org/10.1016/J.RPTH.2024.102615.

Lheriteau, E., Davidoff, A.M. and Nathwani, A.C. (2015) 'Haemophilia gene therapy: Progress and challenges', *Blood Reviews*, 29(5), pp. 321–328. Available at: https://doi.org/10.1016/J.BLRE.2015.03.002.

Li, N., Sawyer, E.K., Maruszczyk, K., Guzauskas, G., Slomka, M.T., Burke, T., Martin, A.P., O'Hara, J., Stevenson, M. and Recht, M. (2021) 'Adult lifetime cost of hemophilia B management in the US: payer and societal perspectives from a decision analytic model', *Journal of Medical Economics*, 24(1), pp. 363–372. Available at: https://doi.org/10.1080/13696998.2021.1891088.

Lieber, M.R. (2010) 'The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway', *Annu Rev Biochem*, 79, pp. 181–211.

Lieschke, K., Scott, V., Delatycki, M.B., Lewis, S., Munsie, M., Tanner, C. and Corben, L.A. (2023) 'How Great a Risk Do You Take? A Qualitative Study Exploring Attitudes of Individuals with Friedreich Ataxia Toward Gene Therapy', *Human Gene Therapy*, 34(19–20), pp. 1041–1048. Available at: https://doi.org/10.1089/HUM.2023.088;ISSUE:ISSUE:10.1089/HUM.2023.34.ISSUE-19-20;PAGE:STRING:ARTICLE/CHAPTER.

Lindseth, A. and Norberg, A. (2004) 'A phenomenological hermeneutical method for researching lived experience', *Scandinavian Journal of Caring Sciences*, 18(2), pp. 145–153. Available at: https://doi.org/10.1111/j.1471-6712.2004.00258.x.

Ljung, R., Auerswald, G., Benson, G., Dolan, G., Duffy, A., Hermans, C., Jiménez-Yuste, V., Lambert, T., Morfini, M., Zupančić-Šalek, S. and Santagostino, E. (2018) 'Inhibitors in haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients', *European Journal of Haematology*, 102(2), p. 111. Available at: https://doi.org/10.1111/EJH.13193.

Lockwood, C., Munn, Z. and Porritt, K. (2015) 'Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation', *International journal of evidence-based healthcare*, 13(3), pp. 179–187. Available at: https://doi.org/10.1097/XEB.0000000000000062.

Lowe, G., Fletcher, S., James Lynch, P., Mahlangu, J., Ozelo, M.C., Pembroke, L., Pipe, S.W., Yamaguti-Hayakawa, G.G., York, D., Robinson, T.M., Yu, H. and Valentino, L.A. (2023) 'Plain language summary of the GENEr8-1 clinical trial of valoctocogene roxaparvovec gene therapy for hemophilia A', *Future Rare Diseases*, 3(4). Available at:

https://doi.org/10.2217/FRD-2023-0007;WEBSITE:WEBSITE:TFOPB;PAGEGROUP:STRING:PUBLICATION.

Machin, N. and Ragni, M. V (2018) 'Measuring success in hemophilia gene therapy using a factor level & outcomes yardstick', *Expert Rev Hematol*, 11(2), pp. 83–86. Available at: https://doi.org/10.1080/17474086.2018.1423961.

Madan, B., Ozelo, M.C., Kenet, G., Chou, S.-C., Pipe, S.W., Leavitt, A.D., Careta, F.P., Lynch, P.J., Fletcher, S., Goshen, D., Ruiz, A., Dashiell-Aje, E., Kordsachia, C., Rivat, C. and Mahlangu, J. (2025) 'Health-related quality-of-life outcomes 4 years after treatment with valoctocogene roxaparvovec', *Hämostaseologie*, 45(S 01), p. T-07-36. Available at: https://doi.org/10.1055/S-0044-1801640.

Main, C.J. and George, S.Z. (2011) "Psychologically informed practice for management of low back pain: Future directions in practice and research," *Physical Therapy*, 91(5), pp. 820–824. Available at: https://doi.org/10.2522/PTJ.20110060.

Manco-Johnson, M.J. (2003) 'Update on treatment regimens: Prophylaxis versus on-demand therapy', *Seminars in Hematology*, 40(3 SUPPL. 3), pp. 3–9. Available at: https://doi.org/10.1016/S0037-1963(03)80732-1.

Manco-Johnson, M.J., Abshire, T.C., Shapiro, A.D., Riske, B., Hacker, M.R., Kilcoyne, R., Ingram, J.D., Manco-Johnson, M.L., Funk, S., Jacobson, L., Valentino, L.A., Hoots, W.K., Buchanan, G.R., DiMichele, D., Recht, M., Brown, D., Leissinger, C., Bleak, S., Cohen, A., Mathew, P., Matsunaga, A., Medeiros, D., Nugent, D., Thomas, G.A., Thompson, A.A., McRedmond, K., Soucie, J.M., Austin, H. and Evatt, B.L. (2007) 'Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia', *New England Journal of Medicine*, 357(6), pp. 535–544. Available at: https://doi.org/10.1056/NEJMoa067659.

Mannucci, P.M. (2020) 'Hemophilia therapy: The future has begun', *Haematologica*. Ferrata Storti Foundation, pp. 545–553. Available at: https://doi.org/10.3324/haematol.2019.232132.

Mapara, M.Y., Tisdale, J.F., Kanter, J., Kwiatkowski, J.L., Krishnamurti, L., Schmidt, M., Miller, A.L., Pierciey, F.J., Shi, W., Ribeil, J.-A., Asmal, M., Thompson, A.A. and Walters, M.C. (2019) 'Lentiglobin Gene Therapy in Patients with Sickle Cell Disease: Updated Interim Results from Hgb-206', *Biology of Blood and Marrow Transplantation*, 25(3), pp. S64–S65. Available at: https://doi.org/10.1016/j.bbmt.2018.12.147.

Mast, A.E. and Ruf, W. (2022) 'Regulation of coagulation by tissue factor pathway inhibitor: Implications for hemophilia therapy', *Journal of Thrombosis and Haemostasis*, 20(6), pp. 1290–1300. Available at: https://doi.org/10.1111/JTH.15697.

McArthur, A., Klugárová, J., Yan, H. and Florescu, S. (2015) 'Innovations in the systematic review of text and opinion', *International journal of evidence-based healthcare*, 13(3), pp. 188–195. Available at: https://doi.org/10.1097/XEB.0000000000000060.

Mejia-Carvajal, C., Czapek, E.E. and Valentino, L.A. (2006) ‘Life expectancy in hemophilia outcome’, *Journal of Thrombosis and Haemostasis*, 4(3), pp. 507–509. Available at: https://doi.org/10.1111/J.1538-7836.2006.01776.X.

Mendoza, A., Rivas, I., Hidalgo, O.B., Cid, A.R., Olivieri, M., Ranta, S., Labarque, V., Andersson, N.G., de Kovel, M. and Álvarez-Román, M.T. (2025) ‘Impact of Family History of Haemophilia on Diagnosis, Management and Outcomes in Severe Haemophilia’, *Haemophilia*, 31(4), pp. 679–686. Available at: https://doi.org/10.1111/HAE.70018;PAGEGROUP:STRING:PUBLICATION.

Methley, A.M., Campbell, S., Chew-Graham, C., McNally, R. and Cheraghi-Sohi, S. (2014) ‘PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews’, *BMC Health Services Research*, 14(1), pp. 1–10. Available at: https://doi.org/10.1186/S12913-014-0579-0/TABLES/7.

Miesbach, W. and Klamroth, R. (2020a) ‘ The Patient Experience of Gene Therapy for Hemophilia: Qualitative Interviews with Trial Patients ’, *Patient Preference and Adherence*, Volume 14, pp. 767–770. Available at: https://doi.org/10.2147/PPA.S239810.

Miesbach, W. and Klamroth, R. (2020b) ‘The patient experience of gene therapy for hemophilia: Qualitative interviews with trial patients’, *Patient Preference and Adherence*, 14, pp. 767–770. Available at: https://doi.org/10.2147/PPA.S239810.

Miesbach, W., Klamroth, R., Oldenburg, J. and Tiede, A. (2022) ‘Gene Therapy for Hemophilia—Opportunities and Risks’, *Deutsches Ärzteblatt International*, 119(51–52), p. 887. Available at: https://doi.org/10.3238/ARZTEBL.M2022.0353.

Miesbach, W., Mulders, G., Breederveld, D., Pinachyan, K., Le Quellec, S. and Pabinger, I. (2024) ‘A 360-degree perspective on adeno-associated virus (AAV)-based gene therapy for haemophilia: Insights from the physician, the nurse and the patient’, *Orphanet Journal of Rare Diseases*, 19(1). Available at: https://doi.org/10.1186/S13023-024-03181-2.

Milani, M., Annoni, A., Moalli, F., Liu, T., Cesana, D., Calabria, A., Bartolaccini, S., Biffi, M., Russo, F., Visigalli, I., Raimondi, A., Patarroyo-White, S., Drager, D., Cristofori, P., Ayuso, E., Montini, E., Peters, R., Iannacone, M., Cantore, A. and Naldini, L. (2019) ‘Phagocytosis-shielded lentiviral vectors improve liver gene therapy in nonhuman primates’, *Science Translational Medicine*, 11(493), p. 7325. Available at: https://doi.org/10.1126/SCITRANSLMED.AAV7325/SUPPL_FILE/AAV7325_SM.PDF.

Mitchell, F. (2017) ‘Tainted blood: four decades of scandal’, *The Lancet Haematology*, 4(6), p. e256. Available at: https://doi.org/10.1016/S2352-3026(17)30083-2.

Moran, D. (2012) ‘Husserl’s Crisis of the European Sciences and Transcendental Phenomenology: An Introduction’, *Husserl’s Crisis of the European Sciences and Transcendental Phenomenology: An Introduction*, pp. 1–323. Available at: https://doi.org/10.1017/CBO9781139025935.

Moss, R.B., Milla, C., Colombo, J., Accurso, F., Zeitlin, P.L., Clancy, J.P., Spencer, L.T., Pilewski, J., Waltz, D.A., Dorkin, H.L., Ferkol, T., Plan, M., Ramsey, B., Carter, B.J., Martin, D.B. and Heald, A.E. (2007) 'Repeated aerosolized AAV-CFTR for treatment of cystic fibrosis: a randomized placebo-controlled phase 2B trial', *Human gene therapy*, 18(8), pp. 726–732. Available at: https://doi.org/10.1089/HUM.2007.022.

Mruck, K. and Mey, G. (2012) 'Grounded theory and reflexivity', in A. Bryant and K. Charmaz (eds.) *The SAGE handbook of grounded theory*. Paperback Edition. London: SAGE, pp. 515–538.

Mukherjee, Siddhartha. (2017) *The gene : an intimate history*. London: Vintage.

Myrin Westesson, L., Wallengren, C., Baghaei, F. and Sparud-Lundin, C. (2018) 'Reaching Independence Through Forced Learning: Learning Processes and Illness Management in Parents of Children Affected by Hemophilia', *Qualitative Health Research*, 28(14), pp. 2142–2154. Available at: https://doi.org/10.1177/1049732318789631.

Nathwani, Amit C., Reiss, U.M., Tuddenham, E.G.D., Rosales, C., Chowdary, P., McIntosh, J., Della Peruta, M., Lheriteau, E., Patel, N., Raj, D., Riddell, A., Pie, J., Rangarajan, S., Bevan, D., Recht, M., Shen, Y.-M., Halka, K.G., Basner-Tschakarjan, E., Mingozzi, F., High, K.A., Allay, J., Kay, M.A., Ng, C.Y.C., Zhou, J., Cancio, M., Morton, C.L., Gray, J.T., Srivastava, D., Nienhuis, A.W. and Davidoff, A.M. (2014) 'Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B', *New England Journal of Medicine*, 371(21), pp. 1994–2004. Available at: https://doi.org/10.1056/NEJMOA1407309.

Nathwani, Amit C., Tuddenham, Edward G.D., Rangarajan, Savita, Rosales, C., McIntosh, J., Linch, D.C., Chowdary, P., Riddell, A., Pie, A.J., Harrington, C., O'Beirne, J., Smith, K., Pasi, J., Glader, B., Rustagi, P., Ng, C.Y.C., Kay, M.A., Zhou, J., Spence, Y., Morton, C.L., Allay, J., Coleman, J., Sleep, S., Cunningham, J.M., Srivastava, D., Basner-Tschakarjan, E., Mingozzi, F., High, K.A., Gray, J.T., Reiss, U.M., Nienhuis, A.W. and Davidoff, A.M. (2011) 'Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B', *New England Journal of Medicine*, 365(25), pp. 2357–2365. Available at: https://doi.org/10.1056/NEJMoa1108046.

Nilsson, I.M., Blomback, M. and Ahlberg, A. (1970) 'Our experience in Sweden with prophylaxis on haemophilia', *Bibl Haematol.*, 34, pp. 111–124.

O'Brien, T.J., Borghs, S., He, Q., Schulz, A.L., Yates, S. and Biton, V. (2020) 'Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: An up to 11-year, open-label, follow-up trial', *Epilepsia*, 61(4), pp. 636–646. Available at: https://doi.org/10.1111/EPI.16484.

Oldenburg, J., Mahlangu, J.N., Kim, B., Schmitt, C., Callaghan, M.U., Young, G., Santagostino, E., Kruse-Jarres, R., Negrier, C., Kessler, C., Valente, N., Asikanius, E., Levy, G.G., Windyga, J. and Shima, M. (2017) 'Emicizumab Prophylaxis in Hemophilia A with Inhibitors', *New England Journal of Medicine*, 377(9), pp. 809–818. Available at: https://doi.org/10.1056/nejmoa1703068.

Orsini, M. (2002) ‘The Politics of Naming, Blaming and Claiming: HIV, Hepatitis C and the Emergence of Blood Activism in Canada’, *Canadian Journal of Political Science*, 35(3), pp. 475–498. Available at: https://doi.org/10.1017/S0008423902778323.

Owensby, J. (1987) ‘Dilthey’s Conception of the Life-Nexus’, *Journal of the History of Philosophy*, 25(4), pp. 557–572. Available at: https://doi.org/10.1353/HPH.1987.0062.

Ozelo, M.C., Mahlangu, J., Pasi, K.J., Giermasz, A., Leavitt, A.D., Laffan, M., Symington, E., Quon, D. V., Wang, J.-D., Peerlinck, K., Pipe, S.W., Madan, B., Key, N.S., Pierce, G.F., O’Mahony, B., Kaczmarek, R., Henshaw, J., Lawal, A., Jayaram, K., Huang, M., Yang, X., Wong, W.Y. and Kim, B. (2022) ‘Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A’, *New England Journal of Medicine*, 386(11), pp. 1013–1025. Available at: https://doi.org/10.1056/NEJMOA2113708/SUPPL_FILE/NEJMOA2113708_DATA-SHARING.PDF.

Ozelo, M.C. and Yamaguti-Hayakawa, G.G. (2022) ‘Impact of novel hemophilia therapies around the world’, *Research and Practice in Thrombosis and Haemostasis*, 6(3). Available at: https://doi.org/10.1002/RTH2.12695.

Pasi, K.J., Rangarajan, S., Mitchell, N., Lester, W., Symington, E., Madan, B., Laffan, M., Russell, C.B., Li, M., Pierce, G.F. and Wong, W.Y. (2020) ‘Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A’, *New England Journal of Medicine*, 382(1), pp. 29–40. Available at: https://doi.org/10.1056/nejmoa1908490.

Patsali, P., Kleanthous, M. and Lederer, C.W. (2010) ‘Disruptive technology: CRISPR/Cas-based tools and approaches’, *Mol Diagn Ther*, 2019(23), pp. 187–200.

Peña, L.D.M., Burrage, L.C., Enns, G.M., Esplin, E.D., Harding, C., Mendell, J.R., Niu, Z. (Neal), Scharfe, C., Yu, T. and Koeberl, D.D. (2023) ‘Contributions from medical geneticists in clinical trials of genetic therapies: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)’, *Genetics in Medicine*, 0(0), p. 100831. Available at: https://doi.org/10.1016/J.GIM.2023.100831.

Peng, Z., Zhu, X., Wang, C., Zhou, M., Xu, X. and Chen, Y. (2023) ‘Depression and anxiety among hemophilia patients enrolled in clinical trials: a multi-center cohort study’, *ANNALS OF HEMATOLOGY*, 102(7), pp. 1927–1937. Available at: https://doi.org/10.1007/s00277-023-05277-4.

Perrin, G.Q., Herzog, R.W. and Markusic, D.M. (2019) ‘Review Series NEW THERAPEUTICS FOR INHERITED AND ACQUIRED BLEEDING CONDITIONS Update on clinical gene therapy for hemophilia’. Available at: http://ashpublications.org/blood/article-pdf/133/5/407/1552132/blood820720.pdf (Accessed: 27 January 2025).

Perry, D., Berntorp, E., Tait, C. and others (2010) ‘FEIBA prophylaxis in haemophilia patients: a clinical update and treatment recommendations’, *Haemophilia*, 16(1), pp. 80–89. Available at: https://doi.org/10.1111/j.1365-2516.2009.02104.x.

Persson, P., Amstrup, A.B., Coester, H.V., Matytsina, I. and Bas, S. (2023) ‘Mim8, a novel factor VIIIa mimetic bispecific antibody, shows favorable safety and pharmacokinetics in healthy adults’, *Research and Practice in Thrombosis and Haemostasis*, 7(6), p. 102181. Available at: https://doi.org/10.1016/J.RPTH.2023.102181.

Peyvandi, F. and Garagiola, I. (2019) ‘Clinical advances in gene therapy updates on clinical trials of gene therapy in haemophilia’, *Haemophilia*, 25(5), pp. 738–746. Available at: https://doi.org/10.1111/hae.13816.

Phillippi, J. and Lauderdale, J. (2017) ‘A Guide to Field Notes for Qualitative Research: Context and Conversation’, *https://doi.org/10.1177/1049732317697102*, 28(3), pp. 381–388. Available at: https://doi.org/10.1177/1049732317697102.

Pierce, G.F., Pasi, K.J., Coffin, D., Kaczmarek, R., Lillicrap, D., Mahlangu, J., Rottellini, D., Sannié, T., Srivastava, A., VandenDriessche, T., Weill, A., Almeida, A.J., Baumann, A., Brooker, M., Durante, L., Naccache, M. and Robinson, F. (2020) ‘Towards a global multidisciplinary consensus framework on haemophilia gene therapy: Report of the 2nd World Federation of Haemophilia Gene Therapy Round Table’, *Haemophilia*, 26(3), pp. 443–449. Available at: https://doi.org/10.1111/hae.13971.

Pipe, S., Shima, M., Lehle, M., Shapiro, A., Chebon, S., Fukutake, K., Key, N., Portron, A., Schmitt, C., Podolak-Dawidziak, M., Bienz, N., Hermans, C., Campinha-Bacote, A., Kiialainen, A., Peerlinck, K., Levy, G. and Jimenez-Yuste, V. (2019) ‘Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study’, *The Lancet Haematology*, 6(6). Available at: https://doi.org/10.1016/S2352-3026(19)30054-7.

Pipe, S.W., Pasi, J., Lissitchkov, T., Ragni, M. V., Négrier, C., Yu, Q., Poloskey, S., Mei, B. and Andersson, S.R. (2020) ‘Long-Term Durability, Safety and Efficacy of Fitusiran Prophylaxis in People with Hemophilia a or B, with or without Inhibitors - Results from the Phase II Study’, *Blood*, 136(Supplement 1), pp. 3–4. Available at: https://doi.org/10.1182/BLOOD-2020-136501.

Price, V.E., Hawes, S.A., Bouchard, A., Vaughan, A., Jarock, C. and Kuhle, S. (2015) ‘Unmeasured costs of haemophilia: The economic burden on families with children with haemophilia’, *Haemophilia*, 21(4), pp. e294–e299. Available at: https://doi.org/10.1111/HAE.12715,.

Ramsey, K., LaFleur, M., Robinson, K., Borgstrom, M., Ryan, A., Narayanan, V. and Schaibley, V. (2024) ‘Family and caregiver perspectives on gene therapy for Rett syndrome’, *Rare*, 2, p. 100045. Available at: https://doi.org/10.1016/J.RARE.2024.100045.

Rangarajan, S., Walsh, L., Lester, W., Perry, D., Madan, B., Laffan, M., Yu, H., Vettermann, C., Pierce, G.F., Wong, W.Y. and Pasi, K.J. (2017) ‘AAV5–Factor VIII Gene Transfer in Severe Hemophilia A’, *New England Journal of Medicine*, 377(26), pp. 2519–2530. Available at: https://doi.org/10.1056/nejmoa1708483.

Richards, M., Williams, M., Chalmers, E., Liesner, R., Collins, P., Vidler, V. and Hanley, J. (2010) ‘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’, *British Journal of Haematology*, 149(4), pp. 498–507. Available at: https://doi.org/10.1111/J.1365-2141.2010.08139.X/PDF.

Richardson, C.D., Ray, G.J., DeWitt, M.A., Curie, G.L. and Corn, J.E. (2016) ‘Enhancing homology-directed genome editing by catalytically active and inactive CRISPR-Cas9 using asymmetric donor DNA’, *Nat Biotechnol*, 34, pp. 339–344.

Richardson, W. S., Wilson, M. C., Nishikawa, J. and Hayward, R.S. (1995) ‘The well-built clinical question: a key to evidence-based decisions’, *ACP Journal Club*. Edited by W. Scott Richardson, Mark C. Wilson, Jim Nishikawa, and R.S.A. Hayward, 123(3), p. A12. Available at: https://doi.org/10.7326/ACPJC-1995-123-3-A12.

Rieger, K.L. (2018) ‘Discriminating among grounded theory approaches’, *Nursing Inquiry*, 26(1), p. e12261. Available at: https://doi.org/10.1111/NIN.12261.

Roy, A., Bansal, S., Kulkarni, A. and Reddy, K.R. (2025) ‘Hepatic Manifestations Following Gene Therapy’, *Gastro Hep Advances*, 4(8), p. 100681. Available at: https://doi.org/10.1016/J.GASTHA.2025.100681.

Shima, M. (2017) ‘Emicizumab prophylaxis overcomes factor VIII inhibitors in Hemophilia A’, *Journal of Pediatrics*, 190, pp. 287–290. Available at: https://doi.org/10.1016/j.jpeds.2017.08.053.

Shoukat, H.M.H., Ghulam Ghous, G., Tarar, Z.I., Shoukat, M.M. and Ajma, N. (2020) ‘Skewed inactivation of X chromosome: a cause of hemophilia manifestation in carrier females’, *Cureus*, 12(10), p. e11216. Available at: https://doi.org/10.7759/cureus.11216.

Skinner, M.W., Lillicrap, D.P., McMillan, J., Castro Ozelo, M. and Pierce, G.F. (2004) ‘What is a cure and how do we get there?’, *Haemophilia, Supplement*, 10(4), pp. 115–118. Available at: https://doi.org/10.1111/J.1365-2516.2004.00999.X.

Smith, J.A., Flowers, P. and Larkin, M. (2009) *Interpretive Phenomenological Analysis: Theory, Methods and Research*. First. London: Sage.

Smith, P.J., Dunitz, J.M., Lucy, A., Hempstead, S.E., Tallarico, E., Faro, A., Pilewski, J.M. and Ramos, K.J. (2020) ‘Incorporating patient and caregiver feedback into lung transplant referral guidelines for individuals with cystic fibrosis-Preliminary findings from a novel paradigm’, *Clinical transplantation*, 34(10). Available at: https://doi.org/10.1111/CTR.14038.

Srivastava, A., Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S.W. and al., et (2020) ‘WFH Guidelines for the management of hemophilia, 3rd edition’, *Haemophilia*, 26, pp. 1–158.

Srivastava, Alok, Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S.W., Carcao, M., Mahlangu, J., Ragni, M. V., Windyga, J., Llinás, A., Goddard, N.J., Mohan, R.,

Poonnoose, P.M., Feldman, B.M., Lewis, S.Z., van den Berg, H.M. and Pierce, G.F. (2020) 'WFH Guidelines for the Management of Hemophilia, 3rd edition', *Haemophilia*, 26(S6), pp. 1–158. Available at: https://doi.org/10.1111/hae.14046.

Stake, Robert. (1978) 'The Case Study Method in Social Inquiry', *Educational Researcher*, 7(2), pp. 5–8. Available at: https://doi.org/10.3102/0013189X007002005.

Stanford, S., Pink, R., Creagh ChB, D.M., Clark MBBS, A., Lowe, G.B., BChir, M., Curry, N.B., Pasi ChB, J.M., Perry, D., ChB, M., French, D., Fong, S., Hayes, G., Chandrakumaran, K.M. and Rangarajan MBBS, S. (2019) '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*, 3, pp. 261–267. Available at: https://doi.org/10.1002/rth2.12177.

Starks, H. and Trinidad, S.B. (2007) 'Choose Your Method: A Comparison of Phenomenology, Discourse Analysis, and Grounded Theory', *http://dx.doi.org/10.1177/1049732307307031*, 17(10), pp. 1372–1380. Available at: https://doi.org/10.1177/1049732307307031.

Stewart, D. and Mickunas, A. (1990) *Exploring Phenomenology: A Guide to the Field & Its Literature: Amazon.co.uk: Stewart, David, Mickunas, Algis: 9780821409626: Books*. 1st ed. Ohio University Press. Available at: https://www.amazon.co.uk/Exploring-Phenomenology-Guide-Field-Literature/dp/082140962X (Accessed: 22 February 2025).

Symington, E., Rangarajan, S., Lester, W., Madan, B., Pierce, G.F., Raheja, P., Robinson, T.M., Osmond, D., Russell, C.B., Vettermann, C., Agarwal, S.K., Li, M., Wong, W.Y. and Laffan, M. (2024) 'Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment', *Haemophilia*, 30(2), pp. 320–330. Available at: https://doi.org/10.1111/HAE.14936;PAGE:STRING:ARTICLE/CHAPTER.

Teela, L., O'Brien, G., Bučková, P., Golan, G., Rooney, G., Bartels, K., Torres-Ortuño, A., Burgess, C. and Haverman, L. (2025) 'Recommendations for Psychosocial Support during Gene Therapy: Results From an EAHAD Interdisciplinary Roundtable', *Haemophilia*, 31(3), pp. 578–581. Available at: https://doi.org/10.1111/hae.70005.

The Hepatitis C Trust (2024) *The Infected Blood Inquiry*. Available at: https://www.hepctrust.org.uk/find-support/infected-blood-and-blood-products/infected-blood-inquiry/ (Accessed: 30 March 2025).

Thornburg, C.D. (2022) 'Prepare the Way for Hemophilia A Gene Therapy.', *The New England journal of medicine*, 386(11), pp. 1081–1082. Available at: https://doi.org/10.1056/NEJMe2200878.

Thornburg, C.D., Simmons, D.H. and von Drygalski, A. (2023) 'Evaluating Gene Therapy as a Potential Paradigm Shift in Treating Severe Hemophilia', *BioDrugs*, 37(5), pp. 595–606. Available at: https://doi.org/10.1007/S40259-023-00615-4/TABLES/4.

Thrasher, A.J. and Williams, D.A. (2017) ‘Evolving Gene Therapy in Primary immunodeficiency’, *Mol Ther*, 25(5), pp. 1132–1141. Available at: https://doi.org/10.1016/j.ymthe.2017.03.018.

Togashi, J., Akamatsu, N., Tanaka, T., Sugawara, Y., Tsukada, K., Kaneko, J., Arita, J., Sakamoto, Y., Hasegawa, K. and Kokudo, N. (2016) ‘Living donor liver transplantation for hemophilia with special reference to the management of perioperative clotting factor replacement’, *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*, 22(3), pp. 366–370. Available at: https://doi.org/10.1002/LT.24341.

UKHCDO Haemophilia Peer Review Audit Reports 2024 – UKHCDO (no date). Available at: https://www.ukhcdo.org/about-us/peer-review-ukhcdo-haemophilia-peer-review-audit-reports-2024/ (Accessed: 17 October 2025).

United Kingdom Haemophilia Centre Doctors’ Organisation (2020) *UKHCDO Annual Report:2020*. Manchester.

Urquhart, C. (2012) ‘The Evolving Nature of Grounded Theory Method: The Case of the Information Systems Discipline’, in A. Bryant and C. Charmaz (eds.) *The SAGE Handbook of Grounded Theory*. London: SAGE Publications Ltd, pp. 339–359. Available at: https://doi.org/10.4135/9781848607941.N16.

Vermeulen, K.M., Van Der Bij, W., Erasmus, M.E., Duiverman, E.J., Koëter, G.H. and TenVergert, E.M. (2004) ‘Improved quality of life after lung transplantation in individuals with cystic fibrosis’, *Pediatric pulmonology*, 37(5), pp. 419–426. Available at: https://doi.org/10.1002/PPUL.20009.

Wada, H., Matsumoto, T. and Katayama, N. (2017) ‘Emicizumab Prophylaxis in Hemophilia A with Inhibitors.’, *The New England journal of medicine*, 377(22), pp. 2193–4. Available at: https://doi.org/10.1056/NEJMc1712683.

West Midlands Quality Review Service (2020) *Inherited and Acquired Haemophilia and other Bleeding Disorders Peer Review Programme: Overview Report*. Available at: https://haemophilia.org.uk/wp-content/uploads/pdf/IABD-Overview-Report-2020-V1-20200514.pdf (Accessed: 17 October 2025).

Weyand, A.C. and James, P.D. (2021) ‘Sexism in the management of bleeding disorders’, *Research and Practice in Thrombosis and Haemostasis*, 5(1), pp. 51–54. Available at: https://doi.org/10.1002/RTH2.12468.

Wherry, S.-A., Berragan, L. and Jennings, R. (2023) ‘The impact of the Contaminated Blood Scandal on the next generation: the state of the evidence’, *The Journal of Haemophilia Practice*, 10(1), pp. 20–27. Available at: https://doi.org/10.2478/JHP-2023-0003.

Wiedebusch, S., Pollmann, H., Siegmund, B. and Muthny, F.A. (2008) ‘Quality of life, psychosocial strains and coping in parents of children with haemophilia’, *Haemophilia*, 14(5), pp. 1014–1022. Available at: https://doi.org/10.1111/J.1365-2516.2008.01803.X.

Wilde, J., Teixeira, P., Bramhall, S.R., Gunson, B., Mutimer, D. and Mirza, D.F. (2002) ‘Liver transplantation in haemophilia’, *British Journal of Haematology*, 117, pp. 952–956.

Wilson, S.J., Bladin, P.F. and Saling, M.M. (2007) ‘The burden of normality: A framework for rehabilitation after epilepsy surgery’, *Epilepsia*, 48(SUPPL. 9), pp. 13–16. Available at: https://doi.org/10.1111/J.1528-1167.2007.01393.X.

Yamaguti-Hayakawa, G.G. and Ozelo, M.C. (2023) ‘Gene therapy for hemophilia: looking beyond factor expression’, *Experimental Biology and Medicine*, 247(24), p. 2223. Available at: https://doi.org/10.1177/15353702221147565.

Young, G., Liesner, R. and Sidonio, C.T. (2019) ‘A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors’, *Blood*, 134(24), pp. 2127–2138.

Zhang, S. (2018) ‘The Patients Who Don’t Want to Be Cured’, *The Atlantic*, 29 August. Available at: https://www.theatlantic.com/science/archive/2018/08/hemophilia-gene-therapy-cure- identity/540987/ (Accessed: 19 January 2020).

Zhao, W., Zhong, L., Wu, J., Chen, L., Qing, K., Weigek-Kelley, K.A., Larsen, S.H., Srivastava, A., Wu, Z., Duan, H., Jude Samulski, R., Hsieh, M.-Y., Khazi, F.R., Schlachterman, A., Liu, Y.-L. and High, K.A. (2005) ‘13. Persistence of AAV Capsid in Transduced Cells’, *Molecular Therapy*, 11, pp. S5–S6. Available at: https://doi.org/10.1016/j.ymthe.2005.06.016.

Appendix 1. Literature Search Strategy

Search Terms

The PICo framework devised by Richardson et al. (1995) and revised by Lockwood, Munn and Porritt (2015) was used to define my Population, the phenomenon of Interest, and Context (see Table 1).

Table 3. PICo Terms	
Population	- Any person with haemophilia (either haemophilia A or haemophilia B), irrespective of severity or comorbidity - Family members of people with haemophilia - Health care professionals
Phenomenon of Interest	- Gene therapy for haemophilia
Context	- Lived Experience / Experience

I used the framework of Lockwood, Munn and Porritt (2015) as opposed to that proposed by (Richardson *et al.*, 1995) because I felt, like Fineout-Overholt and Johnston (2005), some of the assumptions and terms used in the original framework, including intervention and comparison, were unhelpful in a qualitative context. Other frameworks including SPICE (Sample, Population, Intervention, Control, Evaluation) and SPIDER (Sample, Phenomena of Interest, Design, Evaluation, Research) (Cooke, Smith and Booth, 2012) were considered, but the PICo framework (Methley *et al.*, 2014), remains the most used and was the most appropriate for this research programme.

The search used both haemophilia and hemophilia, as the latter is the more internationally recognised spelling. The Boolean operators AND and OR, as well as truncation, were employed to arrive at the final search query.

Table 4. PICo Search Strategy		
Population	Phenomenon of Interest	Context
Haemophilia Hemophilia Famili* Nurs* “Healthcare Professiona*” “Multidisciplinary Team”	“Gene therapy”	“Lived Experience*” Experience*

Databases

The following databases were searched

Table 5. Databases Accessed	
Database	Number of Hits
APA PsychInfo	65
CINHAL	
Medline	
Web of Science	43

The search returned 108 papers. 37 were immediately removed as duplicates, and the remaining 71 were hand-searched for any relevant papers not returned in the database searches. Three more papers were found this way. All 71 papers were then screened according to the inclusion and exclusion criteria. (see tables 4 and 5 and figure 1) and four papers were identified two pieces of grey literature and two peer-reviewed papers (table 6).

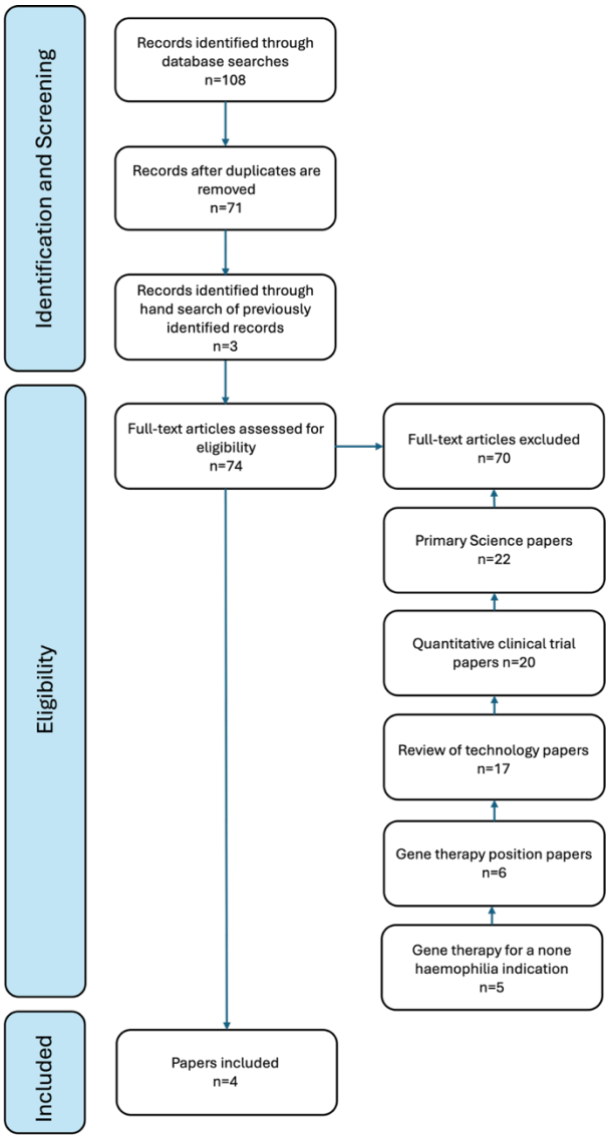
Table 6. Literature Review Inclusion and Exclusion Criteria	
Inclusion Criteria	- Papers published between January 2000 and July 2020 - Qualitative, phenomenological, mixed methods or narrative papers - Papers published in English
Exclusion Criteria	- Quantitative research

Quantitative papers were excluded because all were known to be focused on quantitative measures, factor levels, annualised bleeding rates, and factor usage. While PROM data had been collected during the clinical trials, they were linked to secondary outcome measures and were largely unpublished.

A further expanded literature search was undertaken to include the terms ‘cure’, ‘liver transplant’ and ‘chronic illness’, see table 8.

Table 7. Expanded Search Terms		
Population	**Phenomenon of Interest**	**Context**
Chronic Illne*	**“Liver Transplant”** **Cure**	**“Lived Experience*”** **Experienc***

Figure 4: Prisma Diagram (Jan 2000 to July 2020)



Appendix 2. Joanna Briggs Institute Assessment Forms

JBI Critical Appraisal Checklist for Textual Evidence: Narrative

Reviewer **Simon Fletcher** Date **January 2025**

Author **Zhang, S** Year **2018** Record Number

	Yes	No	Unclear	Not applicable
1. Is the generator of the narrative a credible or appropriate source?	✓	☐	☐	☐
2. Is the relationship between the text and its context explained? (where, when, who with, how)	✓	☐	☐	☐
3. Does the narrative present the events using a logical sequence so the reader or listener can understand how it unfolds?	☐	☐	☐	✓
4. Do you, as reader or listener of the narrative, arrive at similar conclusions to those drawn by the narrator?	☐	☐	☐	✓
5. Do the conclusions flow from the narrative account?	☐	☐	☐	✓
6. Do you consider this account to be a narrative?	☐	✓	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

This narrative is being included as, although it is grey in nature and scores only 2 out of 6 on the checklist and fails to meet the criteria for a narrative account it is the only account an individuals explicit refusal to consider gene therapy because of the connection between his identity and his haemophilia.

JBI Critical Appraisal Checklist for Textual Evidence: Narrative

Reviewer **Simon Fletcher** Date **January 2025**

Author **Konduros, J** Year **2019** Record Number

	Yes	No	Unclear	Not applicable
7. Is the generator of the narrative a credible or appropriate source?	✓	☐	☐	☐
8. Is the relationship between the text and its context explained? (where, when, who with, how)	✓	☐	☐	☐
9. Does the narrative present the events using a logical sequence so the reader or listener can understand how it unfolds?	☐	✓	☐	☐
10. Do you, as reader or listener of the narrative, arrive at similar conclusions to those drawn by the narrator?	☐	☐	☐	✓
11. Do the conclusions flow from the narrative account?	☐	☐	☐	✓
12. Do you consider this account to be a narrative?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

This narrative is being included as, although it is grey in nature and scores only 3 out of 6 on the checklist it is the only account of an individual's gene therapy journey

JBI Critical Appraisal Checklist for Qualitative Research

Reviewer **Simon Fletcher** Date **Jan 2025**

Author **van Balen et al.** Year **2020** Record Number

		Yes	No	Unclear	Not applicable
1.	Is there congruity between the stated philosophical perspective and the research methodology?	☐	✓	☐	☐
2.	Is there congruity between the research methodology and the research question or objectives?	✓	☐	☐	☐
3.	Is there congruity between the research methodology and the methods used to collect data?	✓	☐	☐	☐
4.	Is there congruity between the research methodology and the representation and analysis of data?	✓	☐	☐	☐
5.	Is there congruity between the research methodology and the interpretation of results?	✓	☐	☐	☐
6.	Is there a statement locating the researcher culturally or theoretically?	☐	✓	☐	☐
7.	Is the influence of the researcher on the research, and vice- versa, addressed?	☐	✓	☐	☐
8.	Are participants, and their voices, adequately represented?	✓	☐	☐	☐
9.	Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	✓	☐	☐	☐
10.	Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

No additional comments

JBI Critical Appraisal Checklist for Qualitative Research

Reviewer **Simon Fletcher** Date **Jan 2025**

Author **Meisbach W and Klamroth R Year 2020** Record Number

	Yes	No	Unclear	Not applicable
11. Is there congruity between the stated philosophical perspective and the research methodology?	☐	✓	☐	☐
12. Is there congruity between the research methodology and the research question or objectives?	✓	☐	☐	☐
13. Is there congruity between the research methodology and the methods used to collect data?	✓	☐	☐	☐
14. Is there congruity between the research methodology and the representation and analysis of data?	✓	☐	☐	☐
15. Is there congruity between the research methodology and the interpretation of results?	✓	☐	☐	☐
16. Is there a statement locating the researcher culturally or theoretically?	☐	✓	☐	☐
17. Is the influence of the researcher on the research, and vice- versa, addressed?	☐	✓	☐	☐
18. Are participants, and their voices, adequately represented?	✓	☐	☐	☐
19. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	✓	☐	☐	☐
20. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	✓	☐	☐	☐

Overall appraisal: Include ✓ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

No additional comments

Appendix 3. Parental Project (Paper I) Questionnaire

Exigency

An exploration of the impact of gene therapy on the lives of people with haemophilia and their families

Parents Project Questionnaire

Thank you for showing interest in the Exigency study. This is an interview-based study that will capture parents' views of gene therapy for haemophilia.
We are only seeking your views and thoughts about gene therapy; this is NOT currently a treatment option for those under 18 years of age. Participating in this study will NOT result in early access for your child/children to any gene therapy studies.
If you have questions about gene therapy please contact the study team (research@haemnet.com) or your child's haemophilia treatment team.

Please complete the following questions.

ABOUT YOU AND YOUR FAMILY

Which of these best describes the area in which you live

- ❑ North East England
- ❑ North West England
- ❑ Wales
- ❑ South East England
- ❑ South West England
- ❑ Scotland
- ❑ Midlands
- ❑ Northern Ireland
- ❑ London
- ❑ Other (please specify)

……

Are you the mum or dad of children with haemophilia?

- ❑ Mum
- ❑ Dad

Was there haemophilia in your family before you had children?

- ❑ No
- ❑ Yes

If yes was this your child's

- ❑ Uncle
- ❑ Cousin
- ❑ Grandfather
- ❑ Other (please specify)

……

How many children do you have?

- ❑ One
- ❑ Two
- ❑ Three
- ❑ Four
- ❑ More

(please specify) ……

How many have haemophilia?

- ❑ One
- ❑ Two
- ❑ Three
- ❑ Four
- ❑ More
- ❑ (please specify) ……

How old is child 1 with haemophilia?

- ❑ 1-4 years
- ❑ 5-8 years
- ❑ 8-12 years
- ❑ 12-16 years
- ❑ >16 years

Does he have

- ❑ Haemophilia A
- ❑ Haemophilia B

Is his haemophilia

❑ Severe ❑ Moderate ❑ Mild

Has he ever had an inhibitor

❑ No ❑ Yes

If yes was does he have an inhibitor now

❑ Yes ❑ No

Does Child 1 have treatment for their haemophilia

❑ Prophylaxis ❑ On-demand

❑ Which treatment (please specify)

…….

❑ Advate ❑ Adynovi ❑ Alprolix ❑ Benefix ❑ Elocta

❑ FEIBA ❑ Hemlibra ❑ Idelvion ❑ NovoSeven ❑ NovoEight

❑ Octanate ❑ Nuwiq ❑ ReFacto ❑ Refixia ❑ Other (please specify)

…….

[REPEAT FOR CHILD 2, 3 AS NEEDED]

ABOUT GENE THERAPY

We'd like to get a feel for how you feel about the future possibility of gene therapy for your child's haemophilia? Please answer yes or no to each of the following statements

I have heard of gene therapy

❑ No ❑ Yes (if yes, please specify:

❑ On social media ❑ Through patient groups ❑ At my haemophilia centre

I have heard about gene therapy but haven't really considered or researched it

❑ No ❑ Yes

I think I have a good understanding of gene therapy

❑ No ❑ Yes

I have thought a lot about gene therapy for my child

❑ No ❑ Yes

I have thought a lot about gene therapy but would never consider it for my child

❑ No ❑ Yes

I have had a conversation with our clinical team about gene therapy for my child

❑ No ❑ Yes

We have discussed gene therapy within the family

❑ No ❑ Yes

My child has asked me if he could have gene therapy

❑ No ❑ Yes

Do you know anyone with haemophilia who has had gene therapy?

❑ No ❑ Yes

If yes are they related to you?

❑ No ❑ Yes

If yes are they your child's

❑ Uncle ❑ Cousin ❑ Grandfather

❑ Other (please specify)

……

Did you know gene therapy MIGHT be available in the UK, outside of trials, for ADULTS later this year?

❑ No ❑ Yes

Do you know why gene therapy is NOT available for children with haemophilia?

❑ No ❑ Yes

If yes, why do you think this is?

……

Please tick up to 5 words/phrases from this list that gene therapy makes you think of

❑ Scary	❑ Interesting	❑ Cure	❑ Fearful	❑ Life-changing
❑ Dangerous	❑ Amazing	❑ No way	❑ Loss-of-community	❑ Worrying
❑ I want it	❑ Risky	❑ Wrong	❑ Never	❑ Extreme
❑ Radical	❑ Optimistic	❑ Pessimistic	❑ Revolutionary	❑ Encouraging
❑ Positive	❑ Life-saving	❑ Expensive	❑ Hopeful	❑ Exciting
❑ Safety	❑ Not-yet	❑ Scary	❑ Independence	❑ Freedom
❑ Beneficial	❑ Important	❑ Cautious	❑ What does it mean?	❑ I don't understand

❑ Other (please specify)

……

THANK YOU FOR COMPLETING THE SURVEY

Would you like to be entered into our prize draw? If so please leave your email address here

……

Would you would be willing to be part of a Zoom focus group meeting to discuss your views further?

Each meeting should last no more than 90 minutes and we would offer you £100 for your participation. There will be a few other parents / carers joining the same discussion. You will be required to join by audio and video link. The session will be recorded for later analysis.

Are you happy to take part in this research?

If you wish to take part, please leave your name and email address

…….

We are looking for a mix of people with different experiences to take part in this research as we need to make sure we capture a range of viewpoints from across the country. If you fit the criteria we are looking for, we will be in touch to tell you the dates we have available for the meetings.

GDPR alert: Your personal details will ONLY be used for the purposes of this research. If you would like to take part in further Haemnet research studies, you can join our mailing list at https://subscribe.haemnet.com/mailinglist

Target date for first group is evening 26 May, then again on 28 and possibly Saturday

Appendix 4. Exigency Interview Schedule

Exigency

An exploration of the impact of gene therapy on the lives of people with haemophilia and their families

Interview Guide

Q1 Interview guide – PWH who underwent gene therapy

- 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.
- 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. Are you OK to proceed?

I'd like to start by asking a few questions about you:

  - 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 were you 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? Did 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.***

Prompts

  - 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?
  - 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?***

Prompts

  - 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?

- ***Now that you have had the treatment can you describe to me the impact that it has had on your life***
    - 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?
        - Now vs before

Prompts

- 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 them? What was it like?

- ***What impact has having gene therapy had on you and your family?***

Prompts

- 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?
- If no then how does the prospect of a bleed make you feel?

- ***What about pain? Do you have any pain now?***
    - Imagine a scale of 1 to 6, where 1 is very little pain and 6 is the worst pain. How bad is that pain?

Prompts

- 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?***

Q2 Interview guide – PWH who did not undergo gene therapy

- 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.
- 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. Are you OK to proceed?

I'd like to start by asking a few questions about you:

- 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 were you 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? Did 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.***

Prompts

- 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?
- 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?
- Did you decide that you did not want to go on to have the gene therapy or were you withdrawn from the study before having the gene therapy?
- What did you feel when you finally found out you were ineligible to undergo the gene therapy?
- Who told you you were ineligible?

- ***What impact has not being able to have gene therapy had on you and your family?***

The future:

- ***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?***

- ***What advice would you give to others considering having gene therapy?***

- ***Is there anything else you would like to say or ask of me?***

Q3 Interview guide – family participants of individuals who have undergone gene therapy

- 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.
- 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. Are you happy to proceed?

- ***I'd like to start by asking a few questions about you:***
  - Can you begin by telling me how old you are and a little bit about what activities you and your partner/spouse/father/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/father'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:***

Prompts

  - 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 has a bleed how did he manage them.

- ***What difference has the gene therapy made to you partner/spouse/child/sibling?***

Prompts

  - 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?***

Q4 Interview guide – family participants of individuals who have not undergone gene therapy

- 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.
- 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. Are you happy to proceed?

- ***I'd like to start by asking a few questions about you:***
  - Can you begin by telling me how old you are and a little bit about what activities you and your partner/spouse/father/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:***
  - What treatment was your partner/spouse/child/sibling currently taking?
  - Can you recall how many bleeds your partner/spouse/child/sibling would normally have in an average year?
  - When your partner/spouse/child/sibling has a bleed how did he manage them.

- ***When your partner/spouse/child/sibling knew he wasn't going to have gene therapy what was his reaction***

- ***When you found out that your partner/spouse/child/sibling was not going to have gene therapy how did that make you feel?***

- ***Can you give me examples of what impact not having had gene therapy has made to your family?***

- ***What are your hopes/expectations for gene therapy? What are your goals for the next 6 months? Do you have any concerns about it?***

- ***Do you have any worries for the future?***

- ***Have you heard about any other treatments that might be available in the future?***

- ***What advice would you give to others considering having gene therapy?***

- ***Is there anything else you would like to say or ask of me?***

Appendix 5. Co-Author Statements[5]

[5] One co-author (Steve Chaplin) was unable to sign the declaration as he is retired and no longer contactable.

Haemnet
74 Glenwood Road
London
N15 3JR

Dear Oxford Brookes University Submissions Department

We confirm that in the case of the multi-authored papers offered in evidence for a PhD by published works, the following reflect the proportion of the work undertaken by all the authors.

The Exigency Programme

The programme was conceived and designed by Simon Fletcher.

The Protocol was written by Simon Fletcher and reviewed by Kate Khair, Michael Holland and Luke Pembroke.

The Interview schedules and focus groups were designed by Simon Fletcher, Kate Khair and Luke Pembroke.

The Papers

Paper 1

Khair K, Steadman L, Chaplin S, Holland M, Jenner K, **Fletcher S** Parental perspectives on gene therapy for children with haemophilia: The Exigency study. *Haemophilia*.2021;27(1):120-128. https://doi.org/10.1111/hae.14188.

Author	Contribution	Percentage Contribution
Khair K	Focus group design, data coding check, and completion of final manuscript.	30%
Steadman L	Facilitation of focus groups, review & amendment of manuscript	10%
Chaplin S	Review and approval of final manuscript	5%
Holland M	Review and approval of final manuscript	5%
Jenner K	Transcription of focus group and review and approval of final manuscript	15%
Fletcher S	Focus group design, data coding & interpretation, first draft of the manuscript and review & approval of final manuscript	35%

Paper 2

Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. *Haemophilia*. 2021;27:11-15. https://doi.org/10.1111/hae.14378.

Author	Contribution	Percentage Contribution
Fletcher S	Facilitation of interviews, data coding & interpretation, and production manuscript	65%
Jenner K	Transcription of interviews and review and approval of final manuscript	10%
Holland M	Review and approval of final manuscript	5%
Chaplin S	Review and approval of final manuscript	5%
Khair K	Interview design, data coding check, and review and approval of final manuscript	15%

Paper 3

Fletcher S. Seeing the bigger picture: Qualitative research in the Zoom® age. *J Haem Pract* 2021; 8(1): 141-144. https://doi.org/10.2478/jhp-2021-0019.

Author	Contribution	Percentage Contribution
Fletcher S	Conception and production of manuscript	100%

Paper 4

Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experiences of people with haemophilia, and their families, of gene therapy in a clinical trial setting: Regaining Control, the Exigency Study. *Orphanet Journal of Rare Diseases. 2022;17:155* https://doi.org/10.1186/s13023-022-02256-2.

Author	Contribution	Percentage Contribution
Fletcher S	Facilitation of interviews, data coding & interpretation, and production manuscript	65%
Jenner K	Transcription of interviews and review and approval of final manuscript	10%
Pembroke L	Review and approval of final manuscript	5%
Holland M	Review and approval of final manuscript	5%
Khair K	Interview design, data coding check, and review and approval of final manuscript	15%

Paper 5

Fletcher S. "I didn't know women could have haemophilia": A qualitative case study. *J Haem Pract* 2022;9(1):85-95. *https://doi.org/10.2478/jhp-2022-0011*.

Author	Contribution	Percentage Contribution
Fletcher S	Publication concept, interview design, interview and data analysis and production of manuscript.	100%

Paper 6

Fletcher S, Pembroke L, Holland, M and Khair K. An 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. *BMJ Open* 2022;12:e060351. http://doi.org/10.1136/bmjopen-2021-060351

Author	Contribution	Percentage Contribution
Fletcher S	Study Concept, protocol design and manuscript production	70%
Pembroke L	Protocol review and review & approval of final manuscript	10%
Holland M	Protocol review and review & approval of final manuscript	10%
Khair K	Protocol review, interview guide design and review & approval of final manuscript	10%

Paper 7

Fletcher S, Jenner K, Holland, M and Khair K. Expectation and Loss when Gene Therapy for Haemophilia is Not an Option: An Exigency Sub-study. *Haemophilia*. 2023;1-8. https://doi.org/10.1111/hae.14774

Author	Contribution	Percentage Contribution
Fletcher S	Facilitation of interviews, data coding & interpretation, and Manuscript production	70%

Jenner K	Transcription of interviews and review and approval of final manuscript	10%
Holland M	Review and approval of final manuscript	5%
Khair K	Interview guide design, data coding check, and review and approval of final manuscript	15%

Paper 8

Fletcher S, Jenner K and Khair K. Shared decision-making for gene therapy in haemophilia care. J Haem Pract. 2023;10(1) https://doi.org?10.2478/jhp-2023-0009

Author	Contribution	Percentage Contribution
Fletcher S	Concept and Manuscript production	70%
Jenner K	Review and approval of final manuscript	15%
Khair K	Review and approval of final manuscript	15%

Paper 9

Fletcher S. Jenner K, Holland M, Khair K. Unlocking the Potential of Gene Therapy for People with Haemophilia: An Exigency Sub-study

Author	Contribution	Percentage Contribution
Fletcher S	Facilitation of interviews, data coding & interpretation, and Manuscript production	70%
Jenner K	Transcription of interviews and review and approval of final manuscript	10%
Holland M	Review and approval of final manuscript	5%
Khair K	Data coding check, and review and approval of final manuscript	15%

Kate Khair: Kate Khair Kate Khair (Jan 9, 2024 11:26 GMT) ..... Date: 09/01/2024

Mike Holland: ..... Date: 26/01/2024

Luke Pembroke: ..... Date: 01/02/2024

Kathryn Jenner: Kathryn Jenner Kathryn Jenner (Jan 9, 2024 12:11 GMT) Date: 09/01/2024

Lisa Steadman: Lisa Steadman Lisa Steadman (Feb 1, 2024 8:55 GMT) Date: 01/02/2024

Appendix 6. Copies of papers included in the body of the synthesis [6]

[6] Reprints of papers 1, 2 and 7 with permission from Wiley under the Creative Commons Attribution-NonCommercial 4.0 International licence (CC BY-NC 4.0) [https://creativecommons.org/licenses/by-nc/4.0] Other papers are reprinted under the same open access terms as when originally published.

Received: 7 August 2020 | Revised: 15 October 2020 | Accepted: 15 October 2020

DOI: 10.1111/hae.14188

Haemophilia WILEY

ORIGINAL ARTICLE

Parental perspectives on gene therapy for children with haemophilia: The Exigency study

Kate Khair[1] | Lisa Steadman[1] | Steve Chaplin[1] | Michael Holland[1] | Kathryn Jenner[1] | Simon Fletcher[2]

[1]Haemnet, London, UK

[2]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Correspondence
Kate Khair, Haemnet, London, UK.
Email: Kate@haemnet.com

Abstract

Introduction: Gene therapy is used in life-limiting conditions of childhood. While not a current therapeutic option for children with haemophilia, it may be considered in the future especially for those where access to treatment is limited.

Aim: To assess the attitudes and opinions of parents of children with haemophilia about gene therapy as a potential future treatment, by understanding their awareness about gene therapy and what they need to know now and in the future; gauging levels of interest in gene therapy for their children; and exploring perceived current motivations and barriers.

Methods: A mixed methods study with an online questionnaire and in-depth qualitative interviews in focus groups which were analysed using thematic analysis.

Results: One hundred and fifty-eight participants commenced the online survey; 63 were fully completed (39%). 60 had heard of gene therapy but few (17/60 [28.3%]) felt they had a good understanding. 38/60 (63.3%) respondents did not know that gene therapy is not available for children. However, most held positive views: 53/60 (88.3%) saying they would consider it for their child. In the interviews, participants (N = 10, all mothers) discussed their awareness and understanding of gene therapy and opinions about it for children, including how this should be communicated to the child and parents.

Conclusion: A coherent, community-wide strategy for communicating information and news about gene therapy should now be provided for children and families living with haemophilia. This should come primarily from trusted haemophilia nursing teams, who can give tailored, age-appropriate, factual advice.

KEYWORDS
child, decision-making, gene therapy, Haemophilia, informed consent, parents

1 | INTRODUCTION

Results from clinical trials of gene therapy in adults with severe haemophilia suggest that a long-lasting, clinically significant increase in clotting factor activity is feasible.[1] Gene therapy is not currently being evaluated in children with haemophilia (CwH) due to lack of information about long-term safety and uncertainty about the duration of effect. However, few would disagree that this option should be considered for the future and for those where access to treatment is currently limited.

Gene therapy for childhood life-limiting diseases is not a new concept[2] and is being used as a treatment option for children with

TABLE 1 Overview of questions asked in the online survey

Demographic data of parent	Where they live
	Mother or father of affected child?
	Past history of haemophilia?—if yes what relationship to child/children
	Number of affected child/children
Information about child/children with haemophilia	Age of affected child/children
	Type and severity of haemophilia
	Treatment regimen
	Inhibitor—yes/no, past/current
About gene therapy	Have they heard of it?
	Where did they hear about it from?
	Rating of understanding about gene therapy overall
	Rating of knowledge of gene therapy for children
	Personal knowledge of someone who has had gene therapy? (if yes—are they related?)
	Child/children have asked about gene therapy?
	Knowledge of regulatory status of gene therapy.
Word-cloud development	Write down up to five words/phrases that spring to mind when you think of gene therapy

life-threatening disorders.[3,4,5,6,7] The decision-making process for children (aged <18 years) is different to that for adults, because parents are required to undertake complex decision-making about the potential risks and benefits of gene therapy.[8,9,10]

As haemophilia can be effectively managed by replacement therapy, the balance of risk and benefit of gene therapy for children is different to other long-term conditions. There is little information about parental understanding of gene therapy in haemophilia, or about their attitudes to its potential as a treatment for their children. In 2003, DiMichele et al called for public debate, including the "voices of parents of young children and children themselves" about gene therapy in haemophilia.[11] The Exigency study is a comprehensive qualitative exploration of the impact of gene therapy on the haemophilia community. The study includes an element that assesses the attitudes and opinions of parents of CwH, with the aim of determining levels of awareness and understanding about why children cannot currently have gene therapy; what parents need to know about gene therapy now and in the future; gauging levels of interest in gene therapy for children; and exploring current motivations and barriers.

2 | METHODS

Participants (parents with a child with haemophilia aged eighteen or less) were recruited via an online survey managed by Haemnet, advertised using social media platforms accessed by the bleeding disorders community. The survey collected details on respondents' family history of haemophilia, views of gene therapy and their feelings about gene therapy for their children (Table 1). Respondents could also opt in to an online focus group. Of those who agreed to this, participants were purposely selected (haemophilia type, family history, current inhibitors, mother/father, age of children and geographical spread across the UK).

Two 90-min online video-based focus groups took place in May 2020. The discussion was led using an interview guide (Table 2) and the word cloud, with word size based on number of comments, formulated from the free text in the survey (Figure 1). To stimulate discussion, participants were shown visual prompts depicting gene therapy with a short explanation of the procedure (Figure 2) on which they were invited to reflect. The focus groups were recorded (following verbal consent), transcribed verbatim and thematically analysed. Ethical approval was deemed unnecessary according to the UK Heath Research Authority decision-making tool.[12] Direct quotes are anonymised to ExiP (Exigency parent) followed by participant number.

The focus group participants each received a gift voucher; three online survey participants who were drawn at random also received a gift voucher.

3 | RESULTS

In all, 158 participants initiated the online survey; 63 were fully completed (39%) taking an average of 5.13 minutes. Analysis of the apparently high drop-out rate reflects successful filtering of non-UK residents, non-parents and those who had no interest in or knowledge of gene therapy. Responses were received from all regions of the UK. Sixty respondents were mothers; 31 reported a previous family history of haemophilia (six haemophilia B, eight non-severe haemophilia; Table 2).

Nearly all respondents (60/63) had heard of gene therapy for haemophilia, with most (46/60 [76.6%]) receiving their information via haemophilia-specific social media. While few (17/60 [28.3%])

TABLE 2 Interview discussion guide

Gene therapy for children	
Primary question/point	Probes
When did you first hear about gene therapy?	
How did you first hear about gene therapy?	
Understanding around gene therapy not being available for children	Do you know why this is?
How do you feel about this?	
Is this something you would consider for your child/children if it were available?	Motivations and barriers to considering gene therapy
What are your hopes for gene therapy?	
Under what circumstances would you consider it?	Severity, number of bleeds, inhibitors, difficult treatment regime, impact on life, age of child, other
Do you think this will be a treatment that your child/children will want to have?	Why/why not? What do you think is good/bad about it?
What do you think HCPs should do to ensure your child/children is/are fit for gene therapy when they are older?	
What do you know about how (or if) gene therapy would cure your child?	What questions do you have about it?
What levels would you expect?	
How do you feel about the known and unknown risks?	
Do you have any worries about long-term safety?	
Share information about gene therapy to educate	Now what are your views?
Would your partner feel the same? How might views differ in the family?	
What is new to you?	
Any areas of concern?	
Any areas of interest?	
Anything else you would still want to know before deciding about gene therapy for their child/children?	
The genetic defect would still be there and would still be passed on to future generations	How do you feel about that?
Would it affect your decision on whether to undergo gene therapy?	
What would your children say about opting for gene therapy based on this information?	
Is there anything else you think your child/children would say about gene therapy?	
Communication from healthcare practitioners	
How do paediatric treaters need to inform parents/adolescents about gene therapy as potential therapy option?	Who should have this conversation with you?
Role of pharmaceutical companies	
Literature	
What key information would be needed?	
What questions would you be asking?	
What reassurances would you need?	
How much would you want to know/need to know?	
At what stage of life or the haemophilia 'journey' should these conversations happen to instil the correct knowledge at age-appropriate stages?	

felt they had a good understanding of the topic, most were positive about it; 53/60 (88.3%) said they would consider it for their child; 38/60 (63.3%) respondents did not know that gene therapy will not be available for children. Figure 1 represents words/phrases that expressed respondents' thoughts about gene therapy based on frequency of mentions. Discussions regarding gene therapy had principally taken place within the family (38/60; 63.3%) rather than with clinical teams (25/60; 41.6%); 13/60 (26.6%) participants reported that their child had asked for gene therapy.

Of 42/63 survey respondents who expressed a wish to join an online focus group, 19 were invited to participate and 10, all mothers, agreed. Each focus group discussion comprised five mothers from across England and Wales with a total of 12 affected children (aged 1–19 years, median age 9 years), all with severe haemophilia

FIGURE 1 Word cloud generated from responses to the online survey (size of word represents number of times word used)

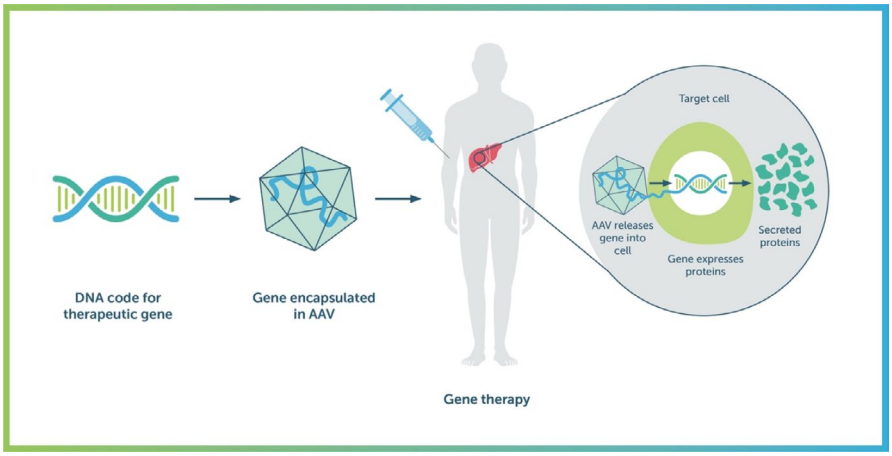


FIGURE 2 Illustration of the process of gene therapy (based on Pierce GF. The Science of Gene Therapy for Hemophilia; Medline; https://www.medscape.org/viewarticle/899793)

(one haemophilia B); half had no previous family history of haemophilia. Two families had multiple children with haemophilia including affected carrier daughters; thus, they discussed their views of gene therapy for their adult sons (both aged 19 years). All children received prophylaxis, mostly with recombinant factor VIII/IX, although three were treated with emicizumab (Hemlibra; Roche), one for a current inhibitor.

3.1 | Awareness about gene therapy

The focus groups revealed a lack of consistency in how families heard and learned about gene therapy (Table 3). Awareness was high but tended to be vague and fragmented.

Mothers of older children (aged nine years and above) felt they had been aware of gene therapy for "quite a long time" but could not be specific about when they first became aware. The majority, especially those with younger children (aged less than nine years), had typically heard about gene therapy within the last 1–2 years.

Most participants felt they were not well informed and had gathered knowledge randomly or from their own research (some immediately prior to the focus group), rather than through formal explanation. Most had only been told that gene therapy was something that may become available for their children as adults in the future.

3.2 | Understanding of gene therapy

The participants had a general understanding of gene therapy. Some were well informed but lacked confidence about the accuracy of the information they had acquired. Others reported consciously choosing not to engage with gene therapy: they felt it was not worth considering because it was too far in the future or not relevant for their child yet.

TABLE 3 Participant demographics.

Survey respondents					
Mother	**Father**	**total**	**Child/children diagnosis**	**Total affected children**	**Age of affected children**
			Haemophilia A		
4	0	4	Mild	7	1-12 years
3	0	3	Moderate	4	1-9 years
44	2	46	Severe	56	1-19 years
			Haemophilia B		
0	0	0	Mild	0	-
1	0	1	Moderate	1	7 years
8	1	9	Severe	10	0-24 years
60	3	63		78	
Focus group participants					
9	0	9	Haemophilia A (severe)	11	1-19 years
1	0	1	Haemophilia B (severe)	1	19 years
	10		12		

TABLE 4 Comments offered by participants about gene therapy.

Sources of awareness about gene therapy, in order of frequency of mentions	1. The haemophilia treatment centre (HTC) and medical team
	2. General media
	3. Facebook, usually haemophilia-related groups
	4. Personal blogs
	5. Friends and family
Participants' descriptions of gene therapy	Something to do with changing proteins to get the body to start producing clotting factor [ExiP7]
	An infusion into the liver cells that replaces the missing factor [ExiP10]
	A gene with 'normal' factor wrapped in a non-active virus that then reproduces the factor [ExiP8]
	Something injected into the vein through a drip, almost like an antibody, that goes to the liver and produces clotting factor [ExiP2]
	Piggybacking a bacterium to trigger factor production [ExiP6]
	Something that supresses the immune system' [ExiP2]
	Involves an intensive course of treatment to change the body. Involves a period of time in hospital to change the cells [ExiP5]
	Is administered more than once as it is not lifelong [ExiP5]
	Involves the need to come off treatment to get the body back to natural levels of factor [ExiP4]
	Completely cures haemophilia [ExiP3]
	Is far in the future and not anywhere near reality [ExiP4]
Participants' questions about gene therapy	How invasive would the treatment be? [ExiP5]
	What side-effects might there be, now and in the future? [ExiP5]
	How long does successful gene therapy last? Would more be needed after a certain amount of time, and would that even possible? [Exi10]
	How much of a commitment to the treatment would be needed? [ExiP3]
	Is any other treatment needed alongside gene therapy? [ExiP6]
	What clotting factor levels does gene therapy take those who have it up to, and do factor levels fluctuate after treatment? Would gene therapy only produce moderate factor levels, so although prophylaxis would not be needed, you might still need treatment on demand? [ExiP8]
	Do factor levels go up immediately or take time to rise? [ExiP9]
	Could you return to prophylaxis if the gene therapy was not successful, or are there any other options? [ExiP10]
	What would the advice be for surgery or trauma after gene therapy? [ExiP8]
	Can you still pass on the defective gene to children? [ExiP7]
	Could you be introducing a change to routine that might not be as effective? [ExiP10]

> I like the idea that it's going to exist, but also it feels quite abstract. I'm interested in it, but it just feels quite far away – possibly further than it actually is.
>
> [ExiP9]

Others wanted to feel informed and know the fundamentals of what gene therapy is and how it works. Those who had researched gene therapy online described the information as scientific and difficult to understand.

Individual comments suggested that participants understood the principles of gene therapy though the details were often incomplete or incorrect (Table 4). After viewing the visual depiction of gene therapy (Figure 1), participants noted that their awareness had lacked clarity and understanding:

> It looks a lot more simple. I know it's meant to in the picture. But it's definitely not what I thought it was.
>
> [ExiP4]

Not all participants were aware that gene therapy did not eradicate the hereditary genetic nature of haemophilia, believing it would end haemophilia within their family. However, this did not affect their interest in gene therapy as an option at the right time.

> It doesn't make me think, "Oh, it's completely worthless because the next generation are still going to have it".
>
> *[ExiP4]*

3.3 | Attitudes towards gene therapy

All participants felt their attitude towards gene therapy was conflicted. Individual participants felt full of hope and excitement but also worried about loss of control: gene therapy was life-changing but also scary. The main driver for this conflict was lack of long-term knowledge, with many of their fears and concerns based on unknowns rather than existing accounts of gene therapy not working or being dangerous (Table 5).

Some participants recounted lessons learned from contaminated blood products; patients and families had thought treatment was safe when it was not, and there was concern this could be repeated with gene therapy. Those who had participated in clinical drug trials were experienced in weighing risks and benefits to inform decision-making; however, this did not allay their concerns about gene therapy.

The word cloud generated from the responses to the online survey was discussed during the focus groups. All participants said the words represented their views.

3.4 | Parents' opinions about gene therapy for their children

The focus group participants knew that gene therapy was not available for CwH. Most had developed their own ideas about why this was, but none were certain or confident about them. They were reluctant to consider gene therapy while it was still new, associated with uncertainty, and while current treatments were working well.

> I think it would have to be a pretty bad situation to want to try it now. It would be a situation where it was probably one of our only options.
>
> [ExiP8]

Gene therapy raises ethical issues, worries and feelings of uncertainty:

TABLE 5 Drivers and barriers when considering gene therapy for a child.

Drivers	Barriers
Administration of prophylaxis is problematic	The responsibility of making a decision for a child because gene therapy fundamentally changes that person
Gene therapy offers the potential for fewer bleeds	The potential for future rebellion from the child due to the parent making the decision for them
Target factor levels cannot be achieved	Taking haemophilia away from a child when it could be a large defining part of them
An older child wanted to travel to a country or region where treatment was not available	Needing the child to decide for themselves
	Safety concerns
	There are too many unknowns
	Possible side effects
	Suppressing the immune system
	Disrupting a stable treatment routine that is associated with few or no bleeds
	Having an inhibitor

> We're almost being the guinea pigs, our generation. Do we want to look back in 40 years' time… to look back and go, 'Why did we even think that was an okay thing to do?'
>
> [ExiP5]

At the current stage of development, the number of medical and ethical barriers to gene therapy outweighed the number of drivers (Table 5). The responsibility for decision-making about gene therapy for CwH should not be underestimated and participants were concerned they might make the wrong choice – either because they consented and the outcome was poor, or they declined and denied their child life-changing treatment.

> We would absolutely not consider it until he was old enough to make that decision for himself. At the moment, we give him medication that makes it manageable, and he could stop that and that could be changed. I think because it's permanent and it's almost like it's changing him, and I'd want him to be able to make that decision, I think.
>
> [ExiP6]

Mothers of older children reported not wanting to make the decision on behalf of their child but also being worried about their child's own decision-making as this meant relinquishing control. However, they were keen that their child should be involved in the decision:

> Because I wouldn't want it to have any comebacks when he's older, if he gets to a certain age where he decides that he wouldn't have wanted to go through it. I would want him to be 100% happy with it.
>
> [ExiP2]

All participants said they would be devastated if their child prepared for gene therapy and was subsequently informed they could not proceed. However, they felt they would be able to cope with this if the process was transparent and psychological support was in place for both the child and family, as "gene therapy would affect the whole family".

Participants were aware that the cost of gene therapy was high and acknowledged the need for payers to recoup spending on investment. However, compared with prophylaxis, they believed it would be cost-effective over a lifetime.

Many participants expressed interest in finding out more about gene therapy, even if they would not consider it at this stage. They understood that gene therapy was a reality rather than a futuristic dream, and learning that the treatment was less invasive than they initially thought (albeit still a big commitment) made it feel slightly more appealing.

> I was quite positive to begin with. I think knowing for definite now that it doesn't get passed on to the next generation, the cure, is a bit… it's a bit of a downer. I suppose it is still quite a positive one on the whole.
>
> *[ExiP2]*

3.5 | Communicating information about gene therapy

There is an unmet need for simple, reliable sources of trusted and impartial information about gene therapy, including trial updates. Most participants felt their treatment teams were the best sources of advice and information; however, some believed they might not yet know enough to talk to parents informatively, partly because gene therapy is still relatively new. One participant felt that teams were focused on other new treatments for children and therefore might not prioritise discussion of gene therapy in paediatric clinics.

Participants felt that being kept informed gave them hope and would ensure they were prepared for a future when gene therapy was available. This was seen as valuable and reassuring, particularly in the early days after diagnosis or when struggling with treatment or inhibitors.

> The more exposure they have and we have every time we go to the centre, and go over it and learn a bit more, it gets time for us to take in that information bit by bit over the years, rather than all in one go.
>
> [ExiP1]

Some felt it would be important to start conversations about gene therapy with children from around the age of ten years. The rationale for including children in conversations about gene therapy was to deliver age-appropriate information, gradually building their knowledge so they would be fully informed and make their own decisions about treatment as adults.

> It's like sex education, that you start off young and you give children the facts, and as they're getting older they learn a bit more, and hopefully they make the right choices as they grow up.
>
> [ExiP5]

Participants wanted to have impartial facts about gene therapy in plain, simple language, without scientific detail. Some reported liking personal stories and social media blogs because they added colour and texture to their understanding

> Whereas at least with following [named person] on Instagram, […] he's not being paid by anyone to do it or anything, I can see a personal approach and how it's changing his life. That's more important to me.
>
> [ExiP4]

Discussion with haemophilia nursing teams was by far the most preferred source of communication about gene therapy: nurses were seen as the most trusted and best placed people to provide tailored, age-appropriate advice and support. Fact sheets from hospitals and gene therapy companies were also mentioned as an appropriate form of communication, though there was some hesitancy around literature from pharmaceutical companies with potentially vested interests.

4 | DISCUSSION

This study found that most parents were aware of gene therapy but were sometimes unclear about the details and principles of treatment. The focus groups included only mothers; their views may differ from those of fathers, and further research is needed to explore this. Participants had reservations about the balance of risks and benefits and were reluctant to make decisions to have gene therapy on their child's behalf. It is interesting to note that when gene therapy was discussed in relation to children, ethical concerns about personal choice were raised. When current treatment was effective and imposed a low burden on the family, the appeal of gene therapy was low. Nevertheless, participants wanted to remain informed about this future treatment, rating haemophilia nurses and patient organisations as the best sources of information.

Parental views about gene therapy for life-threatening genetic disorders are influenced by the severity of the condition and available treatment. Parents of children with Angelman syndrome, a genetic disorder causing severe intellectual and physical disability, overwhelmingly identified cure as a research priority.[13] By contrast, a survey of parents of children with Down syndrome found that while 61% favoured treatment that would reduce symptoms, only 41% supported a curative approach.[14] Parents of children with Duchenne muscular dystrophy weighed the potential benefits of gene therapy against their child's functional capacity and possible limitations on future access to treatment.[15,16]

This study has revealed a complexity in decision-making for parents of CwH, perhaps due to a lack of knowledge and education about gene therapy at this early stage or because haemophilia is a treatable long-term condition rather than a life-limiting disorder. People with haemophilia consider their disorder part of their identity, a belief reinforced by the psychological adaptations required by them and their families for self-management.[17,18] If gene therapy were to become a treatment option for children, they and their families would require age and developmentally appropriate information to enable them to make joint, informed decisions about this therapeutic option. Gene therapy has the potential to 'normalise' lives, effectively converting severe haemophilia to a condition that does not require routine treatment.[19] This is an appealing future, but one requiring a different approach to a life with less support from healthcare professionals. It is presently unclear how families should be supported when considering gene therapy where the impact extends beyond the affected individual.

5 | CONCLUSION

A coherent, community-wide strategy for communicating information and news about gene therapy should be provided for children and families living with haemophilia. This should come primarily from trusted haemophilia nursing teams, who can give tailored, age-appropriate, factual advice. Using a combination of information from relevant, trusted sources may be the best way to ensure that people with haemophilia and their families are able to obtain the knowledge needed to support informed decision-making about gene therapy now and in the future.

ACKNOWLEDGEMENTS

We would like to thank the participants of this study for sharing their views and time.

DISCLOSURES

The Exigency study programme is funded by an unrestricted educational grant by uniQure.

AUTHOR CONTRIBUTIONS

KK, SF and MH designed the study and analysed the questionnaire data. KK, SF and LS facilitated the focus groups and analysed the transcripts. KJ transcribed the interview recordings. All authors wrote and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Kate Khair https://orcid.org/0000-0003-2001-5958
Steve Chaplin https://orcid.org/0000-0001-7508-5609
Michael Holland https://orcid.org/0000-0002-9173-4100
Kathryn Jenner https://orcid.org/0000-0002-2704-0606
Simon Fletcher https://orcid.org/0000-0001-9018-6176

REFERENCES

1. Peyvandi F, Garagiola I. Clinical advances in gene therapy updates on clinical trials of gene therapy in haemophilia. *Haemophilia*. 2019;25:738–746.
2. Buckland KF, Bobby GH. Gene and cell therapy for children–new medicines, new challenges? *Adv Drug Deliv Rev*. 2014;73:162–169.
3. Ricci F, Vacchetti M, Brusa C, et al. New pharmacotherapies for genetic neuromuscular disorders: opportunities and challenges. *Expert Rev Clin Pharmacol*. 2019;12:757–770.
4. Maule G, Arosio D, Cereseto A. Gene therapy for cystic fibrosis: progress and challenges of genome editing. *Int J Mol Sci*. 2020;21:3903.
5. Thrasher AJ, Williams DA. Evolving gene therapy in primary immunodeficiency. *Mol Ther*. 2017;25:1132–1141.
6. Hacein-Bey Abina S, Gaspar HB, Blondeau J, et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. *JAMA*. 2015;313(15):1550–1563.

7. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med*. 2017;377(17):1630–1638.
8. Inglis A, Lohn Z, Austin JC, Hippman C. A 'cure' for Down syndrome: what do parents want? *Clin Genet*. 2014;86:310–317.
9. Landrum Peay H, Fischer R, Tzeng JP, et al. Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: a qualitative preference study of patients and parents. *PLoS One*. 2019;14(5):e0213649.
10. Paquin RS, Fischer R, Mansfield C, et al. Priorities when deciding on participation in early-phase gene therapy trials for Duchenne muscular dystrophy: a best-worst scaling experiment in caregivers and adult patients. *Orphanet J Rare Dis*. 2019;14(1):102.
11. DiMichele D, Miller FG, Fins JJ. Gene therapy ethics and haemophilia: an inevitable therapeutic future? *Haemophilia*. 2003;9:145–152.
12. *Health Research Authority Decision Making Tool*. [www.hra-decisionmakingtools.org.uk/research/], Accessed April 28, 2020.
13. Adams D, Roche L, Heussler H. Parent perceptions, beliefs, and fears around genetic treatments and cures for children with Angelman syndrome. *Am J Med Genet A*. 2020;182:1716–1724.
14. Inglis A, Lohn Z, Austin JC, Hippman C. A 'cure' for Down syndrome: what do parents want? *Clin Genet*. 2014;86:310–317.
15. Paquin RS, Fischer R, Mansfield C, et al. Priorities when deciding on participation in early-phase gene therapy trials for Duchenne muscular dystrophy: a best-worst scaling experiment in caregivers and adult patients. *Orphanet J Rare Dis*. 2019;14:102.
16. Landrum Peay H, Fischer R, Tzeng JP, et al. Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: a qualitative preference study of patients and parents. *PLoS One*. 2019;14:e0213649.
17. Canclini M, Saviolo-Negrin N, Zanon E, Bertoletti R, Girolami A, Pagnan A. Psychological aspects and coping in haemophilic patients: a case-control study. *Haemophilia*. 2003;9:619–624.
18. Khair K, Gibson F, Meerabeau L. 'Just an unfortunate coincidence: children's understanding of haemophilia genetic and inheritance. *Haemophilia*. 2011;17(3):470–475.
19. Miesbach W, Klamroth R. The patient experience of gene therapy for hemophilia: qualitative interviews with trial patients. *Patient Prefer Adherence*. 2020;14:767–770.

How to cite this article: Khair K, Steadman L, Chaplin S, Holland M, Jenner K, Fletcher S. Parental perspectives on gene therapy for children with haemophilia: The Exigency study. *Haemophilia*. 2020;00:1–9. https://doi.org/10.1111/hae.14188

Received: 8 April 2021 | Revised: 15 June 2021 | Accepted: 5 July 2021

DOI: 10.1111/hae.14378

Haemophilia WILEY

ORIGINAL ARTICLE

An exploration of why men with severe haemophilia might not want gene therapy: The exigency study

Simon Fletcher[1] | Kathryn Jenner[2] | Michael Holland[2] | Steve Chaplin[2] | Kate Khair[2]

[1] Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[2] Haemnet, London, UK

Correspondence
Simon Fletcher, Lead Research Nurse, Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE UK.
Email: simon.fletcher@ouh.nhs.uk

Abstract

Introduction: For many people with haemophilia (PwH) gene therapy offers a potential functional cure. However, some have stated that they do not wish to have gene therapy either now or in the future.

Aim: This sub-study, part of the larger Exigency programme, assesses the attitudes, views and understanding of those who do not wish to undergo gene therapy.

Methods: Participants were approached via social media and word of mouth referral and invited to participate in a focus group or individual interview to discuss their views. Interviews were recorded, transcribed verbatim and analysed thematically.

Results: Ten adult men with severe haemophilia (eight haemophilia A and two haemophilia B), mean age 34.3 years, participated in a 1-h focus group (n = 9) or interview (n = 1). All were on prophylaxis. None reported significant treatment burden, and all had annual bleeding rates of less than five in the previous 12 months. Four major themes emerged: self-identity and its loss, lack of long-term safety and efficacy data, ongoing concerns about past viral infection, and lack of current treatment burden.

Conclusion: There are many concerns about gene therapy, including eligibility, effectiveness and safety, which may result in individuals declining it as a therapy. These concerns may recede as more data are published. This study reveals a psychological dynamic around self-identity and belonging for PwH. The nature of this dynamic is poorly understood and needs exploration to facilitate support for those making decisions about gene therapy.

KEYWORDS
decision making, gene therapy, haemophilia, informed consent, self-identity, treatment burden

1 | INTRODUCTION

Recent developments in haemophilia treatments include the introduction of novel non-replacement therapies (factor VIII [FVIII] mimetics and coagulation pathway rebalancing products) with the potential to further improve quality of life in people with haemophilia (PwH).[1] However, to date, these cannot offer a complete or even functional cure (one that enables a person with haemophilia to live a life free from the effects of their condition and the treatment normally associated with it).[1,2]

Trials of gene therapy for both haemophilia A and B show its potential to offer affected individuals a clinically significant and sustained increase in factor expression which would reduce bleeding risk.[3,4,5] Current technologies for gene therapy for haemophilia utilise viral vectors to insert a functioning FVIII or factor IX (FIX) gene into the liver cells of people with severe haemophilia. Once the new gene has been

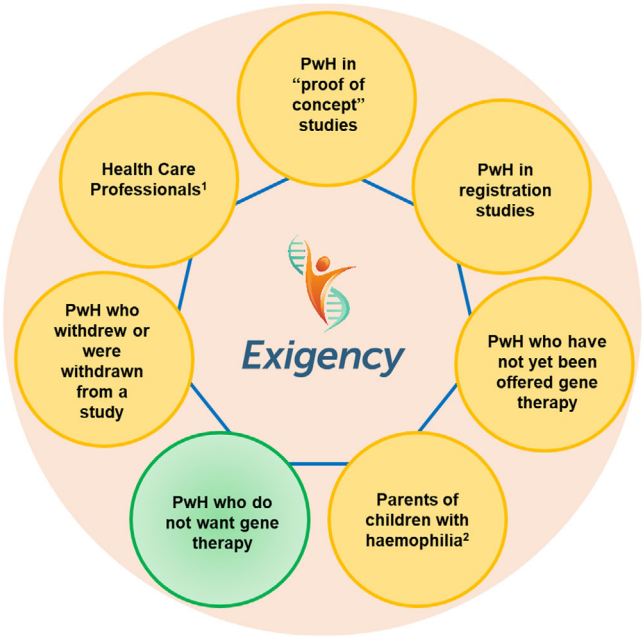


FIGURE 1 The exigency programme

delivered to the liver cells, they begin to express the missing clotting factor, normalising the individual's factor levels and preventing the bleeding associated with the underlying condition.[4] Gene therapy therefore holds out hope for lifelong freedom from prophylactic factor replacement therapy. It is not without a number of risks, including liver inflammation and the attendant need for immunosuppression in some individuals, as well as the as yet unquantifiable risk of hepatocellular carcinoma. It is also not suitable for all PwH as it is currently only in clinical trials for those adults with the severest forms, of whom one third may be ineligible as they have pre-existing antibodies to the viral vectors currently used to package and deliver the FVIII or FIX genes.[6,7]

Qualitative studies have begun to explore the reasons why PwH might consider gene therapy.[1,8,9,10,11] They show that while individuals are concerned about the reliability of gene expression, length of expression and safety, most remain willing to consider gene therapy a potential treatment option. To date, few studies have sought to investigate why some PwH decide that gene therapy is not an option for them and what influences their decisions. Understanding this will help ensure that clinicians are better placed to determine what educational or supportive strategies are required to enable PwH to make fully informed decisions either to undertake or decline gene therapy.

The Exigency programme has been designed to explore the knowledge, expectations for and experiences of gene therapy among a broad a range of people in the UK haemophilia community. Through canvassing the opinions of seven stakeholder groups, the programme aims to enhance our understanding of what motivates PwH to undertake gene therapy, the reality of what it is like to go through it, and the specific impacts of improvements on health-related quality of life (Figure 1). This sub-study assesses the attitudes and views of men with severe haemophilia who do not want to have gene therapy.

2 | MATERIALS AND METHODS

Two qualitative focus groups and a single qualitative interview were undertaken by SF and KK in October 2020 with 10 men (≥16 years of age) with severe haemophilia who self-identified as not wishing to have gene therapy. An interview guide (Table 1) was created based on a review of the current literature and the clinical experience of the two interviewers (SF is a Registered General Nurse with 10 years' experience in haemophilia care and clinical research and KK is a paediatric nurse with more than 20 years' experience in haemophilia care and clinical and academic research). This included questions on the individual's haemophilia history, including past and current treatment, their lifestyle and activities, and their views and understanding about gene therapy.

A sample size of 10 was set prior to commencement of the study. This decision was made pragmatically based on previous studies, including the PAVING study which showed that while there were PwH who were unwilling to have gene therapy the numbers were low (15%).[9] As this was the case, a sample size of ten was deemed large enough to achieve data saturation.

Participants were recruited through advertisements on social media accessed by the bleeding disorders community and word of mouth referral. Ten individuals responded and all agreed to take part in the study. Five were known prior to the study to one or other of the two interviewers and one was known to both. Fully informed written consent was received from each participant. Participants were assigned to focus groups as they were recruited; the first five were assigned to group one and the second five to group two. One participant was unable to attend the focus group to which he was assigned and was therefore offered an individual interview.

Due to the ongoing Covid-19 pandemic, all the focus groups and the individual interview were conducted using the Zoom online conferencing platform. In each case the two interviewers signed into Zoom from their own respective homes. No instructions were given to the either the focus group members or the individual interviewee as to the location they should join the call from. Each individual chose for themselves where this should be and in all cases it was their own home.

Both focus groups and the individual interview were recorded, transcribed verbatim and analysed thematically using an inductive coding methodology. Each focus group transcript was analysed by both interviewers separately, either manually (KK) or utilising NVivo 12 for Mac (SF). Once this had been done and prior to the next focus group or interview, the interviewers met to discuss, review and refine the emergent codes so that they could be explored in the following focus group and individual interview. Once the final individual interview had been completed and analysed the interviewers met to discuss all of the transcripts, further refine the codes and define the themes.

All participants received a gift voucher as a 'thank you' for the time they gave to attend interviews.

Ethical approval for all elements of the study was granted by the UK Healthcare Research Authority and Research Ethics Committee (SS/20/0061).

TABLE 1 Interview guide

Questions	Prompts
Can you tell me about your haemophilia–when were you diagnosed? What kind of treatment you are on now?	How many bleeds did you have in an average year?
	How are your joints? Did you have any joints that bleed more than others? How did you manage those?
	Have you ever had an operation in hospital? What was it for?
What impact has your haemophilia had on your life?	How do you feel about having haemophilia?
	How did it affect your schooling?
	How does it affect your work?
	Does your current treatment allow you to do what you want?
How active are you at the moment?	Do you play sports regularly?
	Are you able to tailor your current treatment to enable you to do this?
	Is that control of your treatment important to you?
What do you understand about gene therapy, and how do you see it as a treatment for haemophilia?	When and how did you first hear about gene therapy?
	What were your first thoughts about it?
	Were you/are you excited by the possibilities?
Have you discussed gene therapy with your family and what do they think about it?	Do they have any concerns about gene therapy and if so what are they?
	What do they think of your decision not to have it?
You've said that you don't think that gene therapy is something you want to take part in. Why is this?	What concerns do you have about it?
	Do you know of anyone who has taken part in any of the gene therapy studies?
	What have they said about it?
	Has this put you off?
	Has it changed your mind in any way?
Have you heard about any other treatments that might be available in the future?	What are your hopes for your future?
	How do you see haemophilia treatments going in the future?
What advice would you give to others considering having gene therapy?	
Is there anything else you would like to say or ask of me?	

3 | RESULTS

Ten male participants, mean age 34.3 years (range 19-62), were recruited to this sub-study. All had severe haemophilia (eight haemophilia A, two haemophilia B), were using prophylaxis (four standard and four extended half-life factor products, two FVIII mimetics), and reported fewer than five bleeds in the previous 12 months. Five had a history of blood-borne viral infections (hepatitis C and HIV) from contaminated factor treatment. Three participants were born to families with a known history of haemophilia. Nine participants took part in one of two focus groups. The mean age was 48.2 years (range 38-62) for Group A and 21.8 years (range 19-24) for Group B. One participant (42 years) took part in a one-to-one interview.

All participants were interested in the concept of gene therapy and believed it could offer a cure for haemophilia. Six had carried out their own research on gene therapy (including the processes involved, safety, efficacy, and durability) and understood the concept and practicalities of treatment, including the personal commitment required in terms of time and travel. Two participants had been formally invited by their treatment centre to take part in a gene therapy clinical trial; of these, one had declined to participate before receiving any further information and the other after discussing the study with the centre.

Four participants expressed concern that the cost of gene therapy might be prohibitive to payers, that its availability in the longer term would make it more rather than less limited, and that for some it was a 'now or never' opportunity. Despite this, all participants stated that

they did not want to have gene therapy. Different reasons for this were expressed, but four major themes arose, supported here with direct quotes anonymised to study number (ExiFG01-ExiFG10); further quotes are given in Table 2.

3.1 | Efficacy

Five participants felt too many unanswered questions remained about the efficacy of gene therapy to make it an attractive option for them. They were aware of the degree of variability in the levels of factor expressed following gene therapy, and that there was no guarantee they would achieve a normal factor level or even a level that would allow them to lead the lifestyle their current treatment regimen allowed.

> *'From what I've been told, my levels would go to about 15% on gene therapy, and currently with the sport I play – baseball and cricket, to quite a high level – that doesn't give me the flexibility that I want from it.' [ExiFG09]*

Four participants were particularly concerned about the duration of factor expression.

> *'What will my factor levels be at the end and then what will my expression levels be long- term? If it's only going to last five years, actually, I've given up six months of my life for what? And of course, we all know at the moment that, in theory at least, you can't have it again.'* [ExiFG02]

3.2 | Safety

Five older participants voiced concerns about gene therapy that are a legacy of the contaminated blood era:

> *'Safety, that's a big issue, of course, for all of us […] we've been through the very dark past of the haemophilia community, so that undoubtedly scars us to a large extent.' [ExiFG02]*

> '*It would be the most hideous irony if, in ten years' time, there was a problem with genetic cure […] I'd hate to be an agent in history repeating itself.'* [ExiFG04]

For the younger participants, who had not lived through the contaminated blood era, this appeared to be less of a concern:

> *'I don't think there'd be anything as bad as the contaminated blood scandal go on again. I'd like to hope that the government had kind of learned from their lesson. So, I would feel pretty safe trying any sort of new commissioned drug, so to say.' [ExiFG07]*

Two participants were concerned there might be a negative impact on their health, either as a result of the treatment itself or immunosuppression, that would affect their ability to look after their family. One explained:

> *'I'm healthy, I'm treated well, my haemophilia doesn't damage me day-to-day in terms of looking after my family – so did I need to risk anything to change that?'* [ExiFG10]

3.3 | Treatment burden

Six participants felt their current treatment regimens did not pose such a burden that it would make them want to consider gene therapy:

> *'For me it doesn't faze me if I've got to treat, inject intravenously for the rest of my life and live with haemophilia.'* [ExiFG06]

> *'I don't find needles a burden at all.'* [ExiFG08]

There was also a concern about the time commitment associated with the current gene therapy programmes and the likely burden this would impose, even if only in the short term:

> *'I think there's a lot of time that you need to invest in doing it, so to an extent it's not practical for me.'* [ExiFG02]

Three participants felt too many unanswered questions and too much uncertainty remained in the gene therapy trial protocols for them to consider it an option. One noted a concern that when told a particular therapy would '*involve X*', he was being sold '*a best-case scenario*' and that the researchers were *'not being open and honest with me about it*'' [ExiFG02].

Four respondents cited time lost from work as a barrier to them undertaking gene therapy:

> *'I don't really want to be seen as … my peers, like, "Oh, he's the one who's always slacking off work," even though that wouldn't be a case of slacking, as such. But I think it comes down to the perception as well. At the moment, I don't feel like I would be ready to commit all that time.' [ExiFG07]*

3.4 | Self-identity

Six participants said their haemophilia was an integral part of their identity and that their experiences of living with it defined who they were as individuals. Three felt that undergoing gene therapy would in some way remove that identity. One stated explicitly feeling that if he underwent gene therapy '*a little bit of* [his] *identity is going to be lost in a funny sort of way*' [ExiFG01]; one said he did not really want '*not to*

TABLE 2 Further quotes to support thematic analysis

Theme 1. Efficacy	
ExiFG01	'At the moment, whilst Emi is working and I'm not getting any side-effects or anything like that, then I'm really, really happy. So, I wouldn't really now want to consider gene therapy.'
ExiFG02	'Again, it comes down to similar to what I said about Emicizumab in relation to the lack of long-term data.'
ExiFG03	'Just that it has the potential to eventually wear off again, so it might be successful for the first number of years.'
ExiFG05	'I would have to see what the long-term effects, see other people, long-term effects, to see if it's worth me doing it or not. But it's a hard one. It really is a hard one. But I wouldn't at the minute.'
ExiFG06	'The other thing from what I've also done a bit of research into it is it's not guaranteed 100% it's going to work. '
	'I'd also probably add it got explained to me as like a one-hit wonder. So, you have literally got one shot, and if it doesn't work then it might not… you might not be able to ever have another go at it again. And that's probably another reason why I think, "Ooh… I'm a bit hesitant to start," because if it doesn't work now, and for whatever reason, ten years' time, I still don't have a family and my lifestyle is a lot less active, and then that's the right time to do it, have I blown my chance at potentially a life-changing medication? '
ExiFG07	'It's not guaranteed 100% it's going to work. So, I think if you're putting all this time and effort into it and you get to the line and then it's like, "Oh…" and you've gone through all of that for kind of nothing.'
Theme 2. Safety	
ExiFG02	'Obviously, it doesn't always go smoothly as you're promised.'
ExiFG03	'I think it's the liver, isn't it, that the virus has to attach to, the virus to get to your liver. I think, historically, that's bound to send shivers up the back of most haemophiliacs.'
	'I think there are too many questions around how it's delivered.'
ExiFG07	'But the main reason why I'm not interested at the moment is where we are with it. So, ten years, five/ten years down the line, maybe, where there is harder and more long-term evidence, I'd probably re-look at it. But as it stands right now, that's why I'm not really interested in it.'
	'To start with, I don't think there'd be anything as bad as the contaminated blood scandal go on again. I'd like to hope that the government had kind of learned from their lesson. So, I would feel pretty safe trying any sort of new commissioned drug, so to say.'
ExiFG10	'And then other little things like my daughter was just doing her GCSEs at the time and I thought, "Do you know what? If I'm exhausted, if there are any side-effects, I've got my own family to look after."'
Theme 3. Treatment burden	
ExiFG02	'And like so many others on the call now, I've got to a stage in… I have been for a long time, where I'm actually settled and content with my treatment regime. Yes, actually, going down to two times a week instead of three times a week has undoubtedly helped my venous access – that's been a benefit of sorts.'
	'But I daresay there are a fair few people who almost… I say almost, but have probably been duped into having it, to an extent, in the sense that they've been promised the earth and, actually, I think it's probably been a bit of a rollercoaster for some people.'
ExiFG03	'But weighing up the options of gene therapy and all of the bits and pieces that go with it – the six months out of your life, the hassle, the potential reversal to injecting yourself in the stomach – it wouldn't make much difference.'
ExiFG04	'Is it worth betting the farm again and doing something to every liver cell in my body just to achieve what? Nothing much different than at the moment. I take a tiny little bottle, whack it in my stomach, and the whole thing is done in five minutes, no side-effects, forget about it. I can't see it getting any better incrementally from here.'
ExiFG06	'So, I think if you're putting all this time and effort into it and you get to the line and then it's like, "Oh…" and you've gone through all of that for kind of nothing…'
	'At the moment, now, it's only twice a week, doesn't really faze me. Before I went onto Elocta I was having ReFacto, I was treating every other day, and going from ReFacto to Elocta, it didn't really faze me that I was having seven injections in two weeks compared to four injections in two weeks.'
ExiFG09	'I don't think it would be any more attractive than just going into my veins. Like everyone else has said, it doesn't bother me.'
ExiFG10	'Because it's the practicality that is the far overriding thing. If there was ever a point in the near future where I could sort that with work, then I would do it. But at the moment, I don't know how that is possible.'

(Continues)

TABLE 2 (Continued)

Theme 3. Treatment burden	
	'At the time, I lived an hour and a half away from work and an hour away from hospital, and actually, that would mean a really significant amount of my time and travel and an impact on my job, which is quite high-pressured and quite important to the business that I'm in.'
Theme 4. Identity	
ExiFG01	'I would feel as though a little bit of my identity is going to be lost in a funny sort of way.'
ExiFG03	'I think there's potential that you could feel you've lost part of your identity if you were no longer a proper haemophiliac, as such.'
	'I think it took me quite a long time to identify myself as a haemophiliac without having to sort of try and hide it away or rebuke it. So, I think I've only kind of come to terms with that in the last probably eight to ten years, and it's not really something I want to give up, as such, at the moment.'
	'If you'd told me about gene therapy when I was 18, I would have bit your arm off for it – but not so much now.'
ExiFG04	'I'm not bothered about if I'm a haemophiliac or not. I've spent most of my life swearing blind I wasn't anyway.'
ExiFG06	'Haemophilia defines me but it doesn't limit me, and it's just… I kind of compare having haemophilia with someone who's got dyslexia.'
ExiFG08	'We still belong to the community.'
ExiFG10	'It would be pretty remiss to say that haemophilia hasn't impacted my life – it kind of is my life.'
	'It probably sounds daft, but I actually feel that my 41 years of living with haemophilia has turned me into who I am.'

be a haemophiliac anymore' [ExiFG10], while another stated that even though he might technically still be a haemophiliac he would not think of himself as a '*proper haemophiliac*' [ExiFG03].

However, three participants felt that even if they did decide to have gene therapy and they would in some way no longer have haemophilia, their experiences as a person with haemophilia would remain part of them and they would still think of themselves as haemophiliacs:

> *'I strongly disagree when people say that if I was to have gene therapy I'd lose my sense of having haemophilia. That's my personal opinion on it. Genes are things we can't see, so I don't know how having gene therapy would completely remove you from the community of bleeding disorders, as such.'* [ExiFG07]

> *'It's part of who we are.'* [ExiFG08]

Of the six participants who said their haemophilia was an integral part of their life, none believed they had been limited by it. If anything, they felt that their current treatment enabled them to live their lives free from the constraints of their condition. One felt that his haemophilia gave him an advantage in terms of resilience:

> *'I think we had a soft skill that its only made me realise was an advantage a few years ago, in our ability to change at short notice, our flexibility and adapting is quite good.'* [ExiFG01]

Some participants' relationship with their haemophilia had not always been so comfortable. Three spoke of having tried to deny its existence and had rebelled against it in the past.

> *'As a teenager you go against that* [haemophilia]. *You deliberately – or I did, anyway – I rebelled, so when I should have done a jab I didn't do a jab and everything else. It's not going to control me; I'm going to control it. So you go into the old classic denial phase.' [ExiFG01]*

Most were now more reconciled to their condition, though one participant maintains a more ambivalent relationship with his haemophilia to this day, stating that he is '*not bothered about if I'm a haemophiliac or not*' [ExiFG02].

4 | DISCUSSION

A growing number of qualitative studies have shown that PwH express a spectrum of concerns when they are considering gene therapy, including its safety and efficacy.[1,8,9] However, these studies have also found that the majority of those interviewed remain willing to have, or indeed have actually undergone, gene therapy. At this time, only the PAVING Study[9] has shown that some PwH might not consider undertaking gene therapy in any circumstance. No studies prior to the Exigency programme have sought to explore this unwillingness and more fully understand the reasons why PwH may choose not to have gene therapy.

Participants in our study shared many concerns with those who have decided that gene therapy is a treatment they would consider, including cost of treatment,[11,12] the 'unknowns' of the process, the safety of the technology, potential side-effects and long-term durability[1,8,9]. However, the way in which they understood, weighed and processed these concerns appears to be different from those in previous studies.

One of the main themes discussed by participants was that of identity, and the role that haemophilia has in their life and the decisions they make. For many, their diagnosis was an important part of their understanding of who they are as individuals and as a member of a distinct community. It is known that haemophilia can impact negatively on health-related quality of life (anxiety, depression and low self-esteem have all been described[13,14,15,16,17]), but the concept of identity and the implications this might have for treatment decisions about future 'curative' therapies is not well understood.

Previous studies have explored the nature of chronic disease and identity formation in diseases such as diabetes, Crohn's disease, and juvenile idiopathic arthritis.[18,19,20] These show that long-term conditions can have a significant negative impact on identity development and the concept of self and can be associated with an increased risk of disease-related symptoms including increased pain and risk of co-morbidities. Several studies have shown that these issues can also be seen in individuals whose conditions (including cystic fibrosis, thalassaemia and haemophilia) have been lifelong rather than having developed during childhood and adolescence.[21,22,23] Despite these possible difficulties, the implication for individuals who stand to potentially 'lose' their diagnosis of haemophilia is not yet fully understood. Studies have shown that the loss of an underlying diagnosis can have a significant negative impact on the wellbeing of both the individual with the condition and on members of the immediate family.[24,25,26] However, it should be noted that the majority of these studies involved individuals who had undergone deep brain stimulation or psychosurgery for epilepsy, Parkinson's disease or OCD, and peculiarities of the surgery and the nature of the underlying conditions may be as important a feature as the loss of the condition itself.

Nevertheless, a similar negative impact might still be expected to be seen in some PwH post-gene therapy. Indeed, a number of the older participants had a strong attachment to their haemophilia and expressed concern that they would, in some ways, lose their identity if they had gene therapy. By contrast, while their identity as haemophiliacs was important to them, the younger participants were less concerned about its possible loss. Unlike many of the older participants, they have had access to prophylaxis since diagnosis which has reduced many of the long-term co-morbidities of haemophilia, such as arthropathy, immobility and chronic pain. Haemophilia has therefore had and continues to have less impact on their daily lives, and its loss may have a similar lack of impact. What the notion of identity might mean for any individual PwH who chooses to have gene therapy is not clear, but health care professionals involved in gene therapy should be aware of the possibility of psychological distress and have mechanisms in place to help deal with it.

A number of the participants were concerned about the amount of time they would need to invest in the process of gene therapy; that the commitment required was too great for them to consider it as a potential viable treatment. It should be noted that a large part of this personal input is the result of gene therapy currently being an investigational medicinal product. As such, participants are subject to increased scrutiny because of safety concerns. This burden may decrease when the therapy is finally licenced, and certain elements of the trial protocols may be eased. At this time, it is not known which requirements are likely to be eased, though it is likely there will still be a need to closely monitor liver enzymes and the effects of any immunosuppression required. Until such time as licensed treatment regimens are announced it is not possible to truly know how high the treatment burden is likely to be.

Half of the participants in our study, and in particular those older participants who had lived through the contaminated blood scandal, had concerns about long-term safety and variability in the expression of factor following gene therapy. These concerns, including the potential risk of hepatocellular carcinoma, have been raised in other studies[9,11,16] and show that there is a need for an ongoing, coherent, structured and multi-agency educational approach, which should seek to address the science, expectations and safety concerns of gene therapy.[27] Khair et al. have suggested that this should start in childhood.[10]

Although the intention of this study had been that all participants would take part in one of the two focus groups, one person was unable to take part in either of the groups. Because of the size of this participant group, the study team decided to offer this one individual the chance to take part in a single in-depth interview. The mixing of qualitative methods, in this manner, is an accepted practice within social science.[28,29] There are, however, inherent differences between the two methodologies, including the interaction between individual members of a focus group enhancing the discussion of sensitive subjects and facilitating greater engagement of the vulnerable. This should not make the interpretation of the data from the two methodologies significantly problematical, however.[30] The authors also sought to mitigate any methodological differences by performing the in-depth interview after both of the focus groups. In this way, both SF and KK were able to code the focus groups prior to the interview and use both the codes and themes identified as well as quotes from the focus groups as prompts in the in-depth interview.

This study has shown that the way individuals process and internalise their haemophilia plays an important part in how they understand and accept new treatment options, including gene therapy. While the psychological attachment of an individual to a diagnosis of haemophilia has been reported elsewhere,[31] our study suggests this may also play a significant factor in how individual PwH make treatment decisions now and in the future. Due to the small sample size of this UK-based study, with participants who are well-treated on prophylactic treatment regimens and report satisfaction with current treatment,[32,33] the implications and applications beyond this milieu may be limited. However, the PAVING Study[9] in the Netherlands, which has a similar socioeconomic and healthcare system to the UK, has shown that these results may not be isolated or specific to this cohort. Further studies are therefore needed to understand what a diagnosis of haemophilia means to individuals across different age groups, geographies, socioeconomic situations and treatment paradigms, how haemophilia is internalised and manifested, and what impact this may have on future treatment decisions.

5 | CONCLUSIONS

There is growing excitement in the haemophilia community that gene therapy may provide a functional cure. Concerns around effectiveness and safety, and the burden of treatment that exists in ongoing clinical trials, appear to be a barrier to some PwH at this time and may result in them declining gene therapy as a treatment option. Such concerns may recede as more safety and efficacy data are published along with personal testimony from those who have undergone gene therapy. PwH need access to these data, supported by education and counselling, to enable them to participate in shared decision-making around gene therapy as a treatment option.

This study has shown that diagnosis, identity and the concept of self are important considerations for PwH contemplating gene therapy. Some of these elements have been identified in other disease areas but have not previously been well described in PwH and are currently not addressed in clinical practice. Psychological support must therefore be an essential part of ongoing and future gene therapy trials as well as routine clinical care and follow-up, to support the significant decisions that PwH will need to make if they decide to undergo gene therapy.

ACKNOWLEDGEMENTS

We would like to thank the participants of this study for sharing their views and time. The Exigency study programme is funded by an unrestricted educational grant by uniQure Biopharma B.V.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AUTHOR CONTRIBUTIONS

Study design: Simon Fletcher, Kate Khair and Mike Holland. Interview guide design: Simon Fletcher and Kate Khair. Focus groups and interview facilitation: Simon Fletcher and Kate Khair. Analysis of transcripts and definition of themes: Simon Fletcher and Kate Khair. Transcription of interview recordings: Kathryn Jenner. Initial draft of manuscript: Simon Fletche. Review, amendment and approval of final manuscript: Simon Fletcher, Kathryn Jenner, Mike Holland, Steve Chaplin and Kate Khair. Simon Fletcher: https://orcid.org/0000-0001-9018-6176. Kathryn Jenner: https://orcid.org/0000-0002-2704-0606. Mike Holland: https://orcid.org/0000-0002-9173-4100. Steve Chaplin: https://orcid.org/0000-0001-7508-5609. Kate Khair: https://orcid.org/0000-0003-2001-5958

ORCID

Simon Fletcher https://orcid.org/0000-0001-9018-6176
Kate Khair https://orcid.org/0000-0003-2001-5958

REFERENCES

1. van Balen EC, Wesselo ML, Baker BL, et al. Patient perspectives on novel treatments in haemophilia: a qualitative study. *Patient*. 2020;13(2):201-210.
2. Peyvandi F, Garagiola I. Clinical advances in gene therapy updates on clinical trials of gene therapy in haemophilia. *Haemophilia*. 2019;25(5):738-746.
3. Machin N, Ragni MV. Measuring success in hemophilia gene therapy using a factor level & outcomes yardstick. *Expert Rev Hematol*. 2018;11(2):83-86.
4. High KA, Roncarolo MG. Gene therapy. *N Engl J Med*. 2019;381(5):455-464.
5. Pierce GF, Pasi KJ, Coffin D, et al, Members of the WFH Gene Therapy Round Table Program Organizing Committee. Towards a global multidisciplinary consensus framework on haemophilia gene therapy: report of the 2nd world federation of haemophilia gene therapy round table. *Haemophilia*. 2020;26(3):443-449.
6. 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(2):261-267.
7. Batty P, Lillicrap D. Advances and challenges for hemophilia gene therapy. *Hum Mol Genet*. 2019;28(R1):R95-R101.
8. Miesbach W, Klamroth R. The patient experience of gene therapy for hemophilia: qualitative interviews with trial patients. *Patient Prefer Adherence*. 2020;14:767-770.
9. van Overbeeke E, Michelsen S, Hauber B, et al. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. *Haemophilia*. 2020;27(1):129-136.
10. Khair K, Steadman L, Chaplin S, Holland M, Jenner K, Fletcher S. Parental perspectives on gene therapy for children with haemophilia: the Exigency study. *Haemophilia*. 2020.
11. Vasquez-Loarte TC, Lucas TL, Harris-Wai J, Bowen DJ. Beliefs and values about gene therapy and in-utero gene editing in patients with hemophilia and their relatives. *Patient*. 2020;13(5):633-642.
12. Noone D, Coffin D, Pierce GF. Reimbursing the value of gene therapy care in an era of uncertainty. *Haemophilia*. 2021;27(1):12-18.
13. Reinicke K, Søgaard IS, Mentzler S. Masculinity challenges for men with severe hemophilia. *Am J Mens Health*. 2019;13(4):1557988319872626.
14. Kalmar L, Oliffe JL, Currie LM, Jackson S, Gue D. Men, masculinities, and hemophilia. *Am J Mens Health*. 2016;10(6):NP22-NP32.
15. Canclini M, Zanon E, Girolami A. Factors which may influence coping with disease in haemophilia patients. *Haemophilia*. 2004;10(5):675.
16. Kodra Y, Cavazza M, Schieppati A, et al. The social burden and quality of life of patients with haemophilia in Italy. *Blood Transfus*. 2014;12(3):s567-s575.
17. Barr RD, Saleh M, Furlong W, et al. Health status and health-related quality of life associated with hemophilia. *Am J Hematol*. 2002;71(3):152-160.
18. Wicks S, Berger Z, Camic PM. It's how I am … it's what I am … it's a part of who I am: a narrative exploration of the impact of adolescent-onset chronic illness on identity formation in young people. *Clin Child Psychol Psychiatry*. 2019;24(1):40-52.
19. Turner J, Kelly B. Emotional dimensions of chronic disease. *West J Med*. 2000;172(2):124-128.
20. Charmaz C. Loss of self: a fundamental form of suffering in the chronically ill. *Sociol Health Illn*. 1983;5(2):168-195.
21. Williams B, Corlett J, Dowell JS, Coyle J, Mukhopadhyay S. I've never not had it so I don't really know what it's like not to: nondifference and biographical disruption among children and young people with cystic fibrosis. *Qual Health Res*. 2009;19(10):1443-1455.
22. Horky S, Sherman L, Polvinen JK, Saxena M, Rich M. I'm going to tell you a little about myself: illness centrality, self-image and identity in cystic fibrosis. *Patient Exp J*. 2017;4:3. 95–103.
23. García-Dasí M, Torres-Ortuño A, Cid-Sabatel R, Barbero J. Practical aspects of psychological support to the patient with haemophilia from

diagnosis in infancy through childhood and adolescence. *Haemophilia*. 2016;22(5):e349-e358.
24. Wilson S, Bladin P, Saling M. The "burden of normality": concepts of adjustment after surgery for seizures. *J Neurol Neurosurg Psychiatry*. 2001;70:649-656.
25. 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:e408-e412.
26. Bosanac P, Hamilton BE, Lucak J, Castle D. Identity challenges and 'burden of normality' after DBS for severe OCD: a narrative case study. *BMC Psychiatry*. 2018;18:186.
27. Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. 2019;25(4):545-557.
28. Alexander VD, Thomas H, Cronin A, Fielding J, Moran-Ellis J. Mixed methods. In: Gilbert N, ed. *Researching Social Life*. London: Sage; 2008:125-144.
29. Khair K, Collier C, Meerabeau L, Gibson I. Multimethodology research with boys with severe haemophilia. *Nurse Researcher*. 2013;20(6):40–44.
30. Barbour R. *Doing Focus Groups*. London: Sage; 2018.
31. Zhang S. The patients who don't want to be cured: a hemophiliac says his genetic disorder is part of his identity, and therapies like CRISPR threaten to erase it. *Atlantic*. 2018.
32. Khair K, Pollard D, Harrison C, Hook S, O'Driscoll M, Holland M. How patients view extended half-life products: impressions from real-world experience (The HOPE study). *Haemophilia*. 2019;25(5):814-820.
33. Kempton C, Trask P, Parnes A, et al. Development and testing of the satisfaction questionnaire with intravenous or subcutaneous hemophilia injection and results from the phase 3 HAVEN 3 study of emicizumab prophylaxis in persons with haemophilia A without FVIII inhibitors. *Haemophilia*. 2021;27(2):221-228.

How to cite this article: Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. *Haemophilia*. 2021;1-9. https://doi.org/10.1111/hae.14378

sciendo

COMMENTARY

Seeing the bigger picture: Qualitative research in the Zoom® age

Simon Fletcher

Participants in clinical trials for new haemophilia treatments are routinely asked to complete quality of life (QoL) questionnaires using validated and disease-specific instruments. Yet too often in clinical research we know very little about the life stories of individuals, making it difficult to know how they have been affected by a new therapy and what exactly has changed for the better – or for the worse. In my own research, I wanted to understand the differences that new treatments are really making to people's everyday lives. While traditional QoL instruments can be helpful, using a qualitative approach that involves speaking directly with people with haemophilia (PwH) and their family members has enabled me find out what has really been going on their lives, including impacts on the wider family. The Covid pandemic and the need to maintain social distancing changed the way in which my research has been carried out, but in fact provided an opportunity to see an even bigger picture. I believe that using videoconferencing platforms to conduct interviews and focus groups has both allowed me to see more of the world in which the participants live and has enabled participants to be more relaxed and open in their conversations, resulting in a potentially richer dataset. While this approach to qualitative QoL research should not replace interviews and focus groups, the use of videoconferencing should be considered as another methodology researchers can and should use to enable them to glean the richest data possible. Qualitative interviews offer an important complementary addition to the validated QoL measures used in clinical trials, enabling us to hear more about where improvements have occurred, where further improvements can be made, and the real-life impact of a new treatment for PwH and their families.

© Shutterstock

Qualitative research provides an opportunity to understand more about the real-life impact of new treatments for people with haemophilia – and using videoconferencing may enable the gathering of even richer data

Keywords: *haemophilia, gene therapy, qualitative research*

SIMON FLETCHER
Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Email: simon.fletcher@ouh.nhs.uk

As a research nurse based at a comprehensive care centre in the United Kingdom, I've been involved in clinical research in haemophilia for about nine years. Much of this has involved people with haemophilia (PwH) who are taking part in trials of novel therapies. Participants in such trials are routinely asked to complete quality of

life (QoL) questionnaires for regulatory purposes using instruments such as the EQ-5D, Haemo-QoL and, more recently, PROBE. Results using these instruments are often positive but can be poorly or inadequately reported. Consequently, we rarely know what effect any stated improvement means to individual people.

The World Health Organization defines quality of life as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [1]. As such, quality of life refers to subjective evaluations that are embedded in cultural, social and environmental contexts and norms.

Yet too often in clinical research we know very little about the life stories of individuals, making it difficult to know how they have been affected by a new therapy and what exactly has changed for the better – or, indeed, for the worse. This prompted me to consider a qualitative research approach when I decided to pursue a PhD by published works. I wanted to understand the differences that new treatments were really making to people's everyday lives.

Traditional QoL instruments can be helpful and sufficiently sensitive to describe changes in an individual's experiences of a disease or condition, especially if administered when they attend their care centre for clinical visits. There are, however, some inherent flaws in their design and application which can mean they can be inaccurate or misleading [2,3]. There is also a tendency to lose the individual in the aggregated scores. Many tools also focus on the presence or severity of the functional aspects of a condition but fail to take account societal attitudes, or issues of healthcare access, which may have a deeper impact on the lives of PwH [4]. It has been suggested that respondent-generated tools could help overcome this and also enable the capture of data on what really matters to individuals in terms of their QoL [5].

Rather than relying on these traditional QoL assessment tools, the research projects on which my PhD is based have involved speaking with PwH and their family members directly [6,7,8,9]. The aim has been to find out what has really been going on in their lives – what their thought processes were when they decided to go into a clinical trial, why they remained in that trial, what they gained from it, what improvements did it make to their lives, whether it had it made life worse in any way, and whether or not their expectations had been met. I'm interested to know both what has gone well and what hasn't gone as well as it might have done. The very act of listening to an individual narrative of lived experience has multiple benefits including increasing our understanding of a given patient group [10]. In the context of haemophilia care, it acknowledges the voices and experiences of PwH as they navigate a changing treatment landscape and enables them to be heard. And it allows us, as caregivers, to empathise – a process associated with improved patient outcomes [8,11,12].

My research has used a mixed methods approach that includes both focus groups and individual interviews. These different approaches to collecting qualitative data offer different benefits, but ultimately work together to build a rich picture [13,14]. An individual interview offers the opportunity to really focus, explore and probe each element of that person's story, while in a focus group participants will bounce off one another, the tale of one person's experience bringing up an idea with someone else. Within a focus group there is always a risk that one individual will be more vocal than the others. The focus groups in my studies have been small (five participants at most), making it easier to ensure that quieter participants join the conversation. It is also easier to avoid 'groupthink', and to employ strategies such as playing devil's advocate [15].

Those in clinical practice know that haemophilia and its management impacts both the affected individual as well as their wider family, and any change in QoL, whether for better or worse, will also affect others within the family. So in my research I always knew that it would be important to interview family members alongside those who have participated in clinical trials. While the ultimate decisions around joining a gene therapy trial may rest with the individual, I wanted to understand their decision-making process and what part their family played in it. I have heard, for instance, from some wives and partners of PwH who have had gene therapy that while they would never have disagreed with their partner's decision they had concerns about the process which they felt unable to discuss with them. It is important for us to hear and understand what impact any decision has on a family because as health care professionals we may not ordinarily see the wives, children and/or parents of the individuals we treat. But my research gives the opportunity to see and understand more about their lives and experiences – what is going on within the family, whether there are concerns among their children about their condition, what the family as a whole understands about it. There is a whole family behind each individual who walks through the door of the haemophilia centre and being able to hear from them enables us to see more of the bigger picture.

The Covid pandemic and the need to maintain social distancing practices has changed the way everyone in healthcare has had to work. It has also changed the way in which research has been carried out – the traditional methods of face-to-face interviews and large focus groups have had to be curtailed. Despite this, in some ways, these enforced changes have allowed me to see a bigger picture than I might have expected. My original plan had been to visit people's homes to interview them, or to find a venue where we could hold a conversation or conduct a focus group. When the pandemic struck, I had to radically rethink what was possible – and like so many others began using videoconferencing platforms. What could have been seen as a second-best option has in fact, I believe, given a richer data set as I've been able to see more of the world in which the participants live. Because I used a videoconferencing platform to carry out the interviews and focus groups, I have interviewed people in their kitchens while they were cooking or eating their tea; I have interviewed people cosied up for the evening in their loungewear; I have seen how they interact with other members of their family as they've momentarily stepped into the interview. Most importantly, though, I think they have been more relaxed in their conversations. The fact that there has been a computer screen between them and me seems to have somehow enabled them to be more open – perhaps because although I was there, I was not completely in their space.

Discussions about remote interviewing and the use of videoconferencing platforms for qualitative interview studies are increasing [16,17,18], and as we come out of the pandemic I think this is a trend that is only likely to increase. Videoconferencing is not an infallible technique – technical issues can occur, sound can drop out as interviewees move away from the microphone, or there can be issues with internet connections. Awareness of these issues, though, mean they can be mitigated if they occur.

My approach to analysing the study data has remained the same as it would have been if I had interviewed research participants in person. After each interview or focus group, I wrote up my field notes, identifying elements of the interview that struck me as immediately important, interesting or relevant, as well as personal comments about how I felt at the time or how some of the comments made me feel. While the notes were never formally analysed, they have provided a useful tool and guide when analysing the interviews, providing important contextual reminders. All of the interviews and focus group recordings have been transcribed, and I have gone through the transcripts line by line to identify common themes. I have often gone back to the recordings too, to listen to what an individual has said and the way in which it has been said. I want to know if a particular issue is raised by just one person, or whether it is something that is more commonly experienced. And if it is more commonly experienced, I want to know how people are describing it, whether they are describing it in the same way or differently. It is an ongoing and iterative process: having heard something in an earlier interview or focus group I have been able to introduce it into later groups so that it can be further explored. Again, this analysis helps to build a bigger picture.

Although familiarising myself with the technology and gaining proficiency in its use was initially a challenge, I personally feel there are few, if any, downsides to using videoconferencing platforms to conduct qualitative research: indeed, from what I have seen to date their use has been a positive experience. Face-to-face interviews and focus groups will always remain the dominant methodologies, but if we are to glean the richest data possible then researchers should use all available methodologies.

With respect to new treatments for haemophilia, I now believe that qualitative interviews offer an important complementary addition to the validated QoL measures used in clinical trials and that, as such, both regulatory authorities and the pharmaceutical companies should seek to incorporate them into future clinical studies. Without them, we may simply miss hearing about the improvements that have occurred and, more importantly, where further improvements can be made.

Undertaking this research has certainly given me a new view of my own role. Clinical research is very process-driven and too often researchers remain unaware of the real-life impact of a new treatment for PwH and their families. Qualitative interview-based research enables us to see and understand this – and it can be a joyous and rewarding experience.

ACKNOWLEDGEMENTS

The authors have advised no interests that might be perceived as posing a conflict or bias.

Informed consent was obtained from the participants in the study on which this article comments.

ORCID

Simon Fletcher https://orcid.org/0000-0001-9018-6176

REFERENCES

1. World Health Organization. WHOQOL: Measuring Quality of Life. Available at *https://www.who.int/toolkits/whoqol* (accessed December 2021).
2. Osborne TR, Ramsenthaler C, Siegert RJ, et al. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur J Haematol* 2012; 89: 437-457 doi:10.1111/ejh.12012.
3. Koot HM. The study of quality of life: concepts and methods. In: Koot HM., Wallender JL eds. *Quality of Life in Child and Adolescent Illness*. New York, Taylor and Francois Inc; 2001:3-21.
4. Parens E, Asch A. Disability rights critique of prenatal genetic testing: Reflections and recommendations. *Mental Retardation and Developmental Disabilities Research Reviews*. 2003;9(1):40-47 doi.org/10.1002/mrdd.10056.
5. Macduff C. Respondent-generated quality of life measures: useful tools for nursing or more fool's gold? *J Adv Nurs* 2000; 32(2): 375-382 doi:10.1046/j.1365-2648.2000.01486.x.
6. Fletcher S, Jenner K, Holland M, Khair K. The lived experience of a novel disruptive therapy in a group of men and boys with haemophilia A with inhibitors: Emi & Me. *Health Expect.* 2021;1-12. doi:10.1111/hex.13404.
7. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. *Haemophilia* 2021;27:760-768. doi: 10.1111/hae.14378.
8. Khair K, Steadman L, Chaplin S, Holland M, Jenner K, Fletcher S. Parental perspectives on gene therapy for children with haemophilia: the Exigency study. *Haemophilia* 2020; 27(1): 120-128. doi: 10.1111/hae.14188.
9. Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experience of people with haemophilia undergoing gene therapy in a clinical trial setting: Regaining Control, an Exigency Study (manuscript submitted for publication, 2021).
10. Charon R. Narrative medicine: a model for empathy, reflection, profession, and trust. *JAMA* 2001; 286(15): 1897-902. doi:10.1001/jama.286.15.1897.
11. Hojat M, Louis DZ, Markham FW, Wender R, Rabinowitz C, Gonnella JS. Physicians' empathy and clinical outcomes for diabetic patients. *Acad Med* 2011; 86(3): 359-64. doi:10.1097/ACM.0b013e3182086fe1.
12. Attar HS, Chandramani S. Impact of physician empathy on migraine disability and migraineur compliance. *Ann Indian Acad Neurol* 2012; 15(Suppl 1): S89-94. doi:10.4103/0972-2327.100025
13. Carey MA, Smith MW. Capturing the group effect in focus groups: a special concern in analysis. *Qualitative Health Research* 1994; 4(1): 123-127. doi.10.1177/104973239400400108
14. Kaplowitz MD, Hoehn JP. Do focus groups and individual interviews reveal the same information for natural resource valuation? *Ecological Economics* 2001; 36(2): 237-247 doi:10.1016/S0921-8009(00)00226-3.
15. MacDougall C, Baum F. The devil's advocate: a strategy to avoid groupthink and stimulate discussion in focus groups. *Qualitative Health Research* 1997; 7 (4): 532-541. doi10.1177/104973239700700407.
16. Khair K, Phillott A, Loran C, Pollard D, Forrester C, Alavian S, Hook S. HaemophiliaLIVE: an ethnographic study on the impact of haemophilia on daily life. *J Haem Pract* 2014;1(3): 14-20. doi: 10.17225/jhp.00030.
17. Archibald MM, Ambagtsheer RC, Casey MG, Lawless M. Using Zoom videoconferencing for qualitative data collection: perceptions and experiences of researchers and participants. *International Journal of Qualitative Methods 2019*; 18: 1-8. doi:10.1177/1609406919874596.
18. Gray LM, Wong-Wylie G, Rempel GR, Cook K. Expanding qualitative research interviewing strategies: Zoom video communications. *The Qualitative Report* 2020; 25(5): 1292-1301. doi: 10.46743/2160-3715/2020.4212.

HOW TO CITE THIS ARTICLE:
S Fletcher. Seeing the bigger picture: Qualitative research in the Zoom® age. *J Haem Pract 2021*; 8(1): 141-144. *https://doi.org/10.2478/jhp-2021-0019.*

Fletcher *et al.*
Orphanet Journal of Rare Diseases (2022) 17:155
https://doi.org/10.1186/s13023-022-02256-2

Orphanet Journal of Rare Diseases

RESEARCH

Open Access

The experiences of people with haemophilia and their families of gene therapy in a clinical trial setting: regaining control, the Exigency study

Simon Fletcher[1*], Kathryn Jenner[2], Luke Pembroke[2], Michael Holland[2] and Kate Khair[2]

Abstract

Background: Gene therapy has the potential to change the life experience of people with haemophilia and family members. Few studies have sought to explore the impact of gene therapy on both individuals and families. The aim of this study was to capture real-life experiences of gene therapy in People with haemophilia and their families.

Results: Sixteen participants with severe haemophilia (11 haemophilia A, five haemophilia B), mean age 41.4 years (range 23–75 years), took part in a single qualitative interview; ten were accompanied by a family member. Mean time since transfection was 3.56 years (range 1–10 years). Participants saw their involvement in gene therapy as a positive experience, freeing them from the personal burden of haemophilia and furthering treatment options for the wider haemophilia community. However, participants reported being unprepared for the side effects of immunosuppression. Some also reported feeling unsupported and having little control over what was happening as their factor levels became the focus of the process.

Conclusion: The results suggest that strategies need to be put into place to enable PwH fully to understand the process of gene therapy, and thereby make an informed choice as to whether it is a treatment they might wish for themselves. These include early and ongoing education, increased provision of psychosocial support and ongoing qualitative research.

Keywords: Haemophilia A, Haemophilia B, Genetic therapy, Decision making, Informed consent, Clinical trial

Background

Haemophilia affects 1:3333 men worldwide [1], resulting in recurrent joint and muscle bleeding leading to joint arthropathy, muscle contracture and significant disability [2, 3]. The treatment of affected individuals involves the prophylactic replacement of the missing factor, which reduces the incidence of spontaneous bleeding events and resultant joint damage [4, 5]. Replacement therapy has improved life expectancy and quality of life of people with haemophilia (PwH), though limitations such as high costs and the treatment burden of frequent intravenous infusions remain [6, 7]. The latter has decreased with the development of extended half-life factor replacement products and factor VIII (FVIII) mimetics [8–10]. With the development of a number of gene therapy platforms for both haemophilia A and B, a potential cure also appears to be ever closer.

Gene therapies for haemophilia currently use an adeno-associated virus to insert the gene of interest (B domain deleted FVIII or factor IX [FIX] Padua) into hepatocytes, which then begin to produce the relevant

*Correspondence: sfletcher26@aol.com
[1] Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE, UK
Full list of author information is available at the end of the article

clotting factor [11–14]. In the UK, 31 individuals (22 haemophilia A, nine haemophilia B) have so far undergone gene therapy in clinical trials examining the safety and efficacy of the technology [15]. Once biotechnology companies receive authorisation for their gene therapies [16] gene therapy may become a standard of care [17].

Qualitative studies have begun to explore the reasons why PwH might wish to consider gene therapy [18–20]. Some have sought to examine the impact gene therapy has had for those in clinical trials [21, 22], but none has considered the nature and impact of gene therapy itself and the immediate follow-up care it requires. While follow-up processes and requirements may change as gene therapy moves from clinical trials to a standard of care for haemophilia, many are likely to remain similar, including the need to monitor liver enzymes and factor levels and the need for immunosuppression. Without a clear understanding of the experiences of PwH who have had gene therapy, those who opt to have it in future and the haemophilia treatment centres that provide it will not truly understand the potential implications and may be ill prepared to deal with them.

The Exigency programme was designed to explore the knowledge, expectations and experiences of gene therapy among a range of stakeholders in the UK haemophilia community (Fig. 1). This sub-study assesses the experiences of men with severe haemophilia who have undergone gene therapy in clinical trials. It is the first investigation by a team not involved with or affiliated to a gene therapy dosing centre.

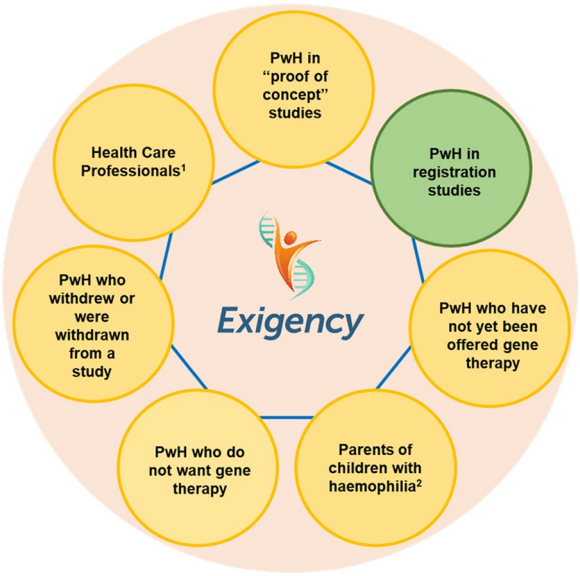


Fig. 1 Exigency diagram

Results

Sample characteristics

We invited 27 PwH (87.1% of those known to the UKHDCO) who had undergone gene therapy in the UK to participate. Sixteen PwH (51.6%) were interviewed along with 10 family members. Eleven participants had haemophilia A and five haemophilia B. The mean age of participants was 44.1 years (range 23–75 years). The mean time since gene therapy transfection was 3.56 years (range 1–10 years) and the mean self-reported factor level at the time of the interview was 0.33iu/ml (range < 0.01–1.37iu/ml). Three participants had been in phase 1 safety studies; the others had participated in subsequent phase 3 safety and efficacy studies. Recruitment was discontinued after 16 interviews as data saturation had been achieved. Three participants were known to SF and Six to KK prior to taking part in the study. None were known to both. For participant data see Table 1.

Overview of findings

Four major themes emerged from the interviews: altruism, side effects of immunosuppression, control, and liberation.

Altruism

All participants spoke of their reasons for wanting to take part in gene therapy. Nine spoke of their desire to help future generations of PwH.

> *"I've done it for the next generation. I don't want anyone to have to go through what I went through." [Exi06]*
> *"One of the big factors of moving it forward was, of course, our daughter being a carrier, because clearly, from our point of view, it was all about if by the time she gets to the point of having a family and fate rolls the dice and she has a haemophiliac then wouldn't it be amazing if someone went, 'That's not a problem." [Exi11]*

This was especially true for those who had participated in the phase 1 studies, who knew they would only see minimal increases in their factor levels.

> *"I don't want to sound like I'm a saint because I'm not a saint – but I felt I ought to give something back." [Exi09]*

For others the primary reason for trial participation was more personal; they were seeking a cure for themselves.

> *"I think to be a cure for me, to be honest." [Exi12]*

> *"I did [it] for my own little kind of mental state and my ability to be able to do things." [Exi06]*

Table 1 Participant demographics

Trial number	Age range	Factor prior to gene therapy	Current factor level*•	Haemophilia type	Years since gene therapy treatment†	Immunosuppression required
Exi01	45–54	EHL	1.37	Haem A	1	Yes
Exi02	18–24	EHL	0.21	Haem A	1	Yes
Exi03	25–34	SHL	0.50	Haem A	1	Yes
Exi04	45–54	EHL	0.90	Haem B	1	Yes
Exi05	25–34	SHL	0.11	Haem A	5	Yes
Exi06	25–34	SHL	0.05	Haem A	3	Yes
Exi07	35–44	SHL	0.06	Haem A	1	Yes
Exi08	35–44	SHL	0.02	Haem B	9	No
Exi09	75–84	SHL	0	Haem B	10	No
Exi10	65–74	SHL	0.25	Haem A	2	Yes
Exi11	35–44	SHL	0	Haem B	10	No
Exi12	25–34	SHL	0.07	Haem A	3	Yes
Exi13	55–64	SHL	0.13	Haem A	2	Yes
Exi14	25–34	SHL	0.40	Haem B	4	Yes
Exi15	35–44	SHL	1.20	Haem A	1	Yes
Exi16	25–34	EHL	0.06	Haem A	3	Yes

*iu/ml

• Self-reported figures

† Whole years at time of interview

Side effects of immunosuppression

Thirteen participants required immunosuppression (eleven haemophilia A and two haemophilia B) either prophylactically, to prevent transaminitis, or to treat a transaminitis that occurred. The mean length of time on immunosuppressive therapy was 16 weeks (17.9 weeks haemophilia A (range 6–36 weeks) and 21 weeks haemophilia B (range 6–36 weeks)), with some requiring multiple courses of therapy. Ten participants and six family members stated immunosuppression and its side effects were the worst part of the gene therapy experience. One participant described the experience as "*absolutely horrendous*" [Exi06]. Another said he would only think about having gene therapy again (if the technology reaches a point where redosing is possible) if he was certain he would not have to have immunosuppressive therapy:

> *"[If they said], 'You could have this gene therapy again, you don't need to go on steroids, we've found another drug you can do that, will do the same, there's no real side-effects,' I would probably take it again." [Exi03]*

Both participants and family members described insomnia (n = 7), anger (n = 5) and feelings of depression (n = 2).

> *"I did not sleep. I didn't need to." [Exi06]*

> *"I felt like it wouldn't take much for me to flip out at someone, so I'd think, 'If I just keep myself to myself, then I can't upset anybody.'" [Exi02]*

> *"That was a real dark, depressed... after a couple of weeks on them. I was angry, I was just... I broke down." [Exi03]*

Six participants said they had received immunosuppression for longer than they had expected and four had needed multiple courses.

> *"It was longer than I thought it was going to be for. I thought... I remember being told it would be six to eight weeks." [Exi02]*

> *"So, yes, in this next course of immune suppression – this is like chapter three of the immune suppression, the immune suppression diaries – that was the most intense time, for sure." [Exi07]*

While the overwhelming response to immunosuppression was negative, four participants reported some positive effects.

> *"Once I started taking the steroids and the*

Table 2 Side effects of immunosuppression

Side effects of immunosuppression*	Number of participants experiencing symptoms
Weight gain	7
Insomnia	7
Anger	5
Mood swings	3
Shaking hands	3
Hypersensitivity	2
Raised blood sugars	2
Depression	2
Pressure of speech	1
Constipation	1
Mania	1

*Self-reported symptoms

tacro[limus] I felt quite good [...] I had the sort of... the rush of blood to the head sort of energy of steroids." [Exi07]

Others reported relief from their usual hay fever (n = 1) and relief from pain caused by arthropathy (n = 4):

"My inflammation that I keep getting in my joints or my muscles just did not happen at all for one month. So, I felt extremely healthy." [Exi16]

For a full list of side effects experienced see Table 2.When asked to reflect on participation in gene therapy, all participants said it had been worthwhile, including those who now had no appreciable factor expression and were back on factor prophylaxis.

"I'd say yes, but just be prepared, really. Because it sounds really, really good – and it is good when it works – but you've got that period where – well, not for everyone – where it could be not very nice. Just be prepared for that, really." [Exi02]

Control

Half of the participants (n = 8), reported a need to control their haemophilia and its effect as important.

"It's a bit difficult for somebody who's not affected by the haemophilia to understand that you have to be able to control your life, and the home treatment was something that changed my life beyond all recognition. It allowed me to hold down a full-time job, which otherwise I would not have been able to do. It allowed me to go out of the house. It allowed me, or facilitated me rather, gradually overcoming my psychological fear of the world." [Exi09]

For some, this search for control involved pushing boundaries of what was 'allowable' or 'advisable' to see what they were capable of. Four participants said this was important to their own sense of identity and wellbeing, although they admitted it had also led them to ignore their haemophilia and caused more harm than good.

"I think I've probably only just recently calmed down a little bit more. I was definitely the one that... I would... I put my body through probably more than I should have." [Exi07]

"I'd had a really difficult probably three years of my life, with probably my physical and mental health, I suppose. And the haemophilia, I got really, really neglectful and I ended up... I ended up in hospital, very unwell." [Exi05]

Half of the participants (n = 8) reported that rather than gaining control they had lost both control and individuality as they became subject to study-specific requirements.

"It was just everything for the results, and the blood tests and everything were more important than anything." [Exi03]

"I suppose I'm saying that it's the protocols that treat you as a number rather than the people." [Exi04]

Some participants (n = 4) and family members (n = 2) felt this meant many of their concerns and issues were neither recognised nor adequately responded to.

"There was naturally stuff happening throughout the trial that I was noticing, and I was recognising and trying to have a conversation with them about – and it was like just falling on deaf ears." [Exi05]

"Looking back, I'm starting to question a bit more why was I not just taken off that treatment the minute I expressed the level of discomfort that I was feeling." [Exi07]

Two participants and their family members felt that mental health concerns were particularly poorly dealt with.

"Like, anything around mental health or psychological wellbeing was just like, nah... they did not want to know about that." [ExiF03]

"I felt like at the time the trial was more important, the results of the trial were more important than [husband's] mental health. I don't think we really had the support for his mental health at the time." [ExiF05]

Three participants thought some short-term loss of control was inevitable due to the constraining nature of study protocols. Four felt they had to wrest back some level of control, which took the form of refusing to attend appointments, weaning immunosuppression more quickly than advised, or refusing to have further courses of immunosuppression.

> *"They told me to prepare for it, because basically my liver enzymes kept rising and my factor's been on a consistent downward slope. So, there was that time where… I think they said to me if I didn't go on… Because they wanted me to go on immune suppression a fourth time and I said no. I said, 'I can't… for my own physical and mental health, and for my partner's mental health, I don't think we can go through that, so I'll take my chances.'" [Exi07]*

Liberation

Despite the issues discussed above, the majority of those interviewed (participants, n = 12; family members, n = 3) described gene therapy as life changing.

> *"I can do most of the physical actions that I couldn't do before. I can work in the garden, I can easily carry heavy bags from the grocery shop… And I don't have to worry that my elbows or my shoulder joint or anything like that will just give me a bleed. So, it's a peace of mind." [Exi15]*

> *"It's unbelievably life-changing. Life-changing." [ExiF08]*

For others (n = 3) their improvement was down to ease of travel (not have to take large volumes of factor with them and navigate customs with needles and syringes) or the ability to participate in sports in ways not previously open to them.

> *"I play golf twice a weekend, I carried a bag five and a half miles, swung a golf club, and I never had a single problem. I'd get back and be completely fine. I wouldn't even dream of doing that when I had haemophilia." [Exi06]*

Fourteen participants, including those in the early safety studies, had experienced a rise and then a decline in their factor levels. Four were on a prophylactic factor therapy regimen at the time of their interviews: two had returned to baseline levels of < 0.01iu/ml and two were experiencing bleeds despite having a factor level > 0.01iu/ml. The remaining 12 were not receiving factor replacement and 11 had not had any factor replacement therapy since transfection.

Of the 12 participants not currently on prophylaxis, all were aware there was a possibility of their levels dropping and that, at some point in the future, they may need to restart factor treatment, though there was hope this would not happen.

> *"I'm hoping that it comes down to such a level that I actually don't need factor anymore at any time in the future." [Exi01]*

One participant thought gene therapy had "*not really made much difference*" [Exi03], as it was not able to fix the problems he had with his joints. He felt that if he had had it at age 18 "*it would have been probably a different story*".

Further supporting quotes can be found in Additional file 1.

Discussion

A growing number of studies have sought to examine the impact of gene therapy on the lives of individuals who have undergone the procedure [21, 22]. Most have focused on the positive results, many of which were also seen in this study, including 'liberation' from their condition and the worry of bleeds, the ability to participate in sports in ways previously not open to them, and to holiday without worrying about taking factor with them. The nature of the questions asked in a number of these studies have, however, been leading, guiding participants to talk about certain predefined negative aspects rather than those that were important to them.

Previous studies have also been undertaken by research teams involved in the dosing of the participants, which is a concern. There are well documented ethical concerns about unequal power relationships in clinician-led research, including coercion and bias, as participants can feel indebted to the interviewers and therefore inhibited talking about concerns they have [23–26]. A strength of our study is that neither of the interviewers worked at any of the dosing sites, and although several participants were known to one or other of the interviewers, none were known to both.

There are clearly many positives to gene therapy, but this study has highlighted a number of concerns that have not been described elsewhere, with the side effects of immunosuppressive therapy being the most difficult and troubling element. Although not seen in all cases, post vector infusion transaminitis is a recognised side effect of gene therapy [27, 28]. The underlying pathophysiology of this inflammation, and why some individuals are affected and others not, has not yet been fully described [29, 30]. However, even moderate rises in transaminase levels are associated with dramatic falls in factor expression [13,

31]. Many gene therapy studies have therefore included the use of immunosuppression, either prophylactically or reactively, in an attempt to prevent this [29]. The duration of immunosuppression required is not fully understood and, as has been shown in this study, can vary between individuals.

Immunosuppression is associated with significant safety concerns due to the side effects profile of the medications, including weight gain, hypertension, hyperglycaemia, altered mood, muscle spasm, neuropathy and psychiatric reactions [32]. Many of these were reported by participants in this study. The use of immunosuppression and perceived pressure from research staff to continue immunosuppressive treatment, despite side effects, meant some participants felt they were losing control rather than gaining it. There was recognition and understanding that this pressure existed due to concerns that factor levels could drop, but a feeling that maintenance of expression became the primary focus for research staff and that other questions and concerns were ignored or downplayed. Four participants felt self-advocacy was the only way to regain control and took themselves off immunosuppression sooner and more quickly than study teams advised. The need for control (over individuals' lives, conditions and the research process) has been described in other studies [33].

Lack of psychosocial support, including lack of recognition of the need for it, was perceived by a number of participants as a concern. Provision of psychosocial support has been an ongoing concern within the UK haemophilia treatment community, with two thirds of comprehensive care centres and most haemophilia treatment centres having little or no access to services [34]. While access to support services is a wider issue, the concerns raised by the interviewees suggests that there should be greater emphasis on psychosocial needs, and that this should be integral to the package of care if gene therapy is to become a standard therapy. Psychosocial needs should also be acknowledged by the biotechnology companies running gene therapy studies and supportive measures incorporated into trials.

Future recipients of gene therapy, either in clinical trials or through licensed treatment must fully understand the therapeutic goals, the processes involved, and potential side effects. Known and unknown complications should be discussed alongside mitigation strategies that might be necessary. Consent to treatment should therefore be a process rather than an event, particularly as it is not possible to discontinue treatment once the vector has been given. This information process should begin in childhood and continue throughout life [35, 36]. In this way, when PwH decide that gene therapy is something they wish to receive, they will have a greater understanding and expectation of the process and potential outcomes.

Limitations

This study involved a self-selecting, UK-based sample of participants with ready access to prophylactic haemophilia treatment prior to their gene therapy. There could therefore be an inherent, unintended selection bias in this group. This bias has however been mitigated to a degree by the size of the sample (> 50% of the UK gene therapy cohort).

Data saturation usually requires 20–25 individual interviews [37, 38] but there is a degree of consistency in this study due to the homogeneity inherent in the gene therapy participant group. As no new codes or themes emerged in interviews 15 and 16, the research team felt that data saturation had been achieved. There may be a greater diversity of opinion and experience as gene therapy becomes more widely available, and it will be necessary to continue to interview future recipients and family members to continue to understand what affect it has.

The Exigency programme [19, 35] has been carried out in a high-income country where PwH have good access to intensive treatment. The concerns and issues raised may differ from those of low- and middle-income countries, or the emphasis placed on them may be different. Further research needs to be undertaken to delineate a greater understanding of these concerns. We believe it is important that such studies are undertaken by groups not linked to any single dosing centre to avoid researcher bias, thereby enabling participants to voice their concerns without fear that their comments could upset the teams looking after them.

Conclusion

When it becomes more widely available, gene therapy for haemophilia may become a standard of care, potentially changing the face of future haemophilia care. If this is to happen and is to be seen as a safe and attractive treatment, PwH need a greater understanding of the processes and implications of the therapy, some of which have been highlighted in this study. Strategies including early and ongoing education, and the adequate provision of psychosocial support throughout the process should be established. Ongoing longitudinal qualitative research will be needed to understand what impact gene therapy for haemophilia has throughout all life stages.

Methods

Study design

A qualitative interview study was conducted with men with severe haemophilia who had undergone gene therapy in the UK. Interviews were undertaken between 1 August 2020 and 31 August 2021.

The interviews followed an interview guide based on a review of the literature and the experience of the study team (see Additional file 2). Questions addressed the individual's haemophilia and treatment history, the decision-making process of opting for gene therapy, and their experience of gene therapy.

Recruitment and data collection

Participants were recruited through haemophilia centre referral, social media, and word of mouth referral. All participants took part in a single 1 h interview conducted by two researchers (SF and KK) via the video conferencing platform, Zoom®. Participants were given the option to be interviewed with a family member. The initial recruitment target was 25 individual interviews though recruitment could be discontinued at the discretion of the researchers if data saturation was achieved, or further recruitment was unlikely. The latter condition was added as UK data show that just 31 PwH have received gene therapy [16].

Analysis

Each interviewee was randomly assigned a study number (PwH, Exi01-Exi16; family members, ExiF01-ExiF10). All interviews, which were recorded and transcribed verbatim, were facilitated by SF and KK who each have more than 30 years' experience in nursing. Transcripts were thematically analysed by both researchers after each interview using inductive coding (SF: NVivo® for Mac; KK: manual coding). Prior to each scheduled interview the researchers met to discuss, review and refine emergent codes, enabling their exploration in subsequent interviews. On completion and analysis of the final interview, the researchers met to discuss all transcripts, further refine codes and identify final themes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-022-02256-2.

Additional file 1. Supporting Quotes.

Additional file 2. Interview Guide.

Acknowledgements

We would like to thank the centres who identified potential participants as well as the participants of this study for sharing their views and time.

Authors information

S Fletcher. This paper and others from the Exigency study programme will be offered in evidence for a phD by published works.

Authors' contributions

SF Study and interview guide design, interview facilitation, analysis of interviews primary authorship of manuscript. KJ Transcription of interviews. LP Study and interview guide design. MH, Study design. KK. Study and interview guide design, interview facilitation, and analysis of interviews. All authors read and approved the final manuscript.

Funding

The Exigency study programme is funded by an unrestricted education grant from uniQure Biopharma.

Data availability

The datasets generated and/or analysed during the current study are not publicly available as it contains un-anonymised participant information. Data sets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participants were sent detailed information sheets informing them of the nature and purposes of the research. Written informed consent was obtained. All participants received a gift voucher as a 'thank you' for the time they gave attending interviews. Ethical approval for all elements of the study was granted by the UK Healthcare Research Authority and the South East Scotland Research Ethics Committee (20/SS/0061).

Consent for publication

No applicable.

Competing interests

S Fletcher. Unrestricted educational grant from Roche Products Limited and Chugai Pharma UK Ltd, speaker honoraria from Roche Products Limited, Bayer and Novo Nordisk, meeting support from Novo Nordisk and Bayer. K Jenner. Unrestricted educational grant from Roche Products Limited and Chugai Pharma UK Ltd. L. Pembroke. Unrestricted educational grant from Roche Products Limited and Chugai Pharma UK Ltd, Consultancy fees from Roche Products Limited, Bayer, Biomarin and Sobi, Speaker Honoraria from Biomarin, Sobi, Novo Nordisk and Chugai. M Holland. Unrestricted educational grant from Roche Products Limited and Chugai Pharma UK Ltd. K Khair. Unrestricted educational grant from Roche Products Limited and Chugai Pharma UK Ltd, Consultancy fees from Bayer, Novo Nordisk, Sobi and Takeda, Speaker honoraria from Bayer, Biomarin, Novo Nordisk, Sobi, Pfizer and Takeda.

Author details

[1]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE, UK. [2]Haemnet, London N15 3JR, UK.

Received: 12 November 2021 Accepted: 13 February 2022
Published online: 04 April 2022

References

1. Stonebraker JS, Bolton-Maggs PHB, Brooker M, Evatt B, Iorio A, Makris M, O'Mahony B, Skinner MW, Coffin D, Pierce GF, Tootoonchian E. The world federation of Hemophilia Annual Global Survey 1999–2018. Haemophilia. 2020;27:591–600. https://doi.org/10.1111/hae.14012.
2. Curtis R, Baker J, Riske B, et al. Young adults with hemophilia in the U.S.: demographics, comorbidities, and health status. Am J Hematol. 2015;90:S11–6. https://doi.org/10.1002/ajh.24218.
3. Manco-Johnson M, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Cindy L, Bleak S, Cohen A, Mathew P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe Hemophilia. N Engl J Med. 2007;357(6):535–44. https://doi.org/10.1056/nejme078098.
4. Richards M, Williams M, Chalmers E, Liesner R, Collins P, Vidler V, Hanley J, on behalf of the Paediatric Working Party of the United Kingdom Haemophilia Doctors' Organisation. 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. https://doi.org/10.1111/j.1365-2141.2010.08139.x.
5. Srivastava A, Santagostino E, Dougall A, Kitchen SS, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Linás A, Goddard NJ, Mohan R, Poonose PM, Feldman BM, Lewis SZ, van den Berg H, Pierce GF, on behalf of the WFH Guidelines for the Management of Hemophilia panellists and co-authors. WFH guidelines for the management of Hemophilia, 3rd edition. Haemophilia. 2020;26:S1-158. https://doi.org/10.1111/hae.14046.
6. Farrugia A, Cassar J, Kimber MC, Bansal M, Fischer K, Auserswald G, O'Mahony B, Tolley K, Noone D, Balboniet S. Treatment for life for severe hemophilia A-A cost-utility model for prophylaxis vs. on-demand treatment. Haemophilia. 2013;19:e228–38. https://doi.org/10.1111/hae.12121.
7. Li N, Sawyer EK, Maruszczyk K, Guzauskas G, Slomka MT, Burke T, Martin AP, O'Hara J, Stevenson M, Recht M. Adult lifetime cost of hemophilia B management in the US: Payer and societal perspectives from a decision analytic model. J Med Econ. 2021;24:363–72. https://doi.org/10.1080/13696998.2021.1891088.
8. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Emicizumab prophylaxis in Hemophilia A with inhibitors. NEJM. 2017;377:809–18. https://doi.org/10.1056/NEJMoa1703068.
9. Young G, Liesner R, Chang T, Sidonio R Jr, Oldenburg J, Jiménez-Yuste V, Mahlangu J, Kruse-Jarres R, Wang M, Uguen M, Doral MY, Wright LY, Schmitt C, Levy GG, Shima M, Mancuso ME. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134:2127–38. https://doi.org/10.1182/blood.2019001869.
10. Pipe S, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K, Key N, Portron A, Schmitt C, Podolak-Dawidziak M, Bienz N, Hermans C, Campinha-Bacote A, Kiialainen A, Peerlinck K, Levy G, Jimenez-Yuste V. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019;6(6):e295–305. https://doi.org/10.1016/S2352-3026(19)30054-7.
11. Nathwani AC, Tuddenham EGD, Rangarajan S, Rosales C, McIntosh J, Linch DC. Adenovirus-associated virus vector-mediated gene transfer in haemophilia B. N Engl J Med. 2011;365:2357–65. https://doi.org/10.1056/NEJMoa1108046.
12. Nathwani AC, Reiss UM, Tuddenham EGD, Rosales C, Chowdary P, McIntosh J, Peruta MD, Lheriteau E, Patel N, Raj D, Riddell A, Pie J, Rangarajan S, Bevan D, Recht M, Shen YM, Halka KG, Basner-Tschakarjan E, Mingozzi F, High KA, Allay J, Kay MA, Ng CYC, Zhou J, Cancio M, Morton CL, Gray JT, Srivastava D, Nienhuis AW, Davidoff AM. Long-term safety and efficacy of factor IX gene therapy in haemophilia B. N Engl J Med. 2014;371:1994–2004. https://doi.org/10.1056/NEJMoa1407309.
13. Perin GQ, Herzog RW, Markusic DM. Update of clinical gene therapy for haemophilia. Blood. 2018;33:407–14. https://doi.org/10.1182/blood-2018-07-820720.
14. Rangarajan S, Walsh L, Lester W, Perry D, Madan B, Laffan M, Yu H, Vettermann C, Pierce GF, Wong WY, Pasi KJ. AAV5–factor VIII gene transfer in severe haemophilia A. N Engl J Med. 2017;377:2519–30. https://doi.org/10.1056/NEJMoa1708483.
15. United Kingdom Haemophilia Doctors' Organisation. The UKHCDO annual report and bleeding disorder statistics for the financial year 2019–2020. Manchester: United Kingdom Haemophilia Doctors' Organisation; 2021. http://www.ukhcdo.org/wp-content/uploads/2021/03/UKHCDO-Annual-Report-2020-2019-20-Data_FINAL.pdf. Accessed 12 Mar 2021.
16. Brown K, Green G. The haemophilia drug market. Nat Rev Drug Discov. 2018;17:541–2. https://doi.org/10.1182/blood-2018-07-820720.
17. Pierce G, Coffin D, Members of the WFH Gene Therapy Round Table Program Committee and Organizing Committee. The 1st WFH Gene Therapy Round Table: understanding the landscape and challenges of gene therapy for haemophilia around the world. Haemophilia. 2019;25:189–94. https://doi.org/10.1111/hae.13673.
18. van Overbeeke E, Michelsen S, Hauber B, et al. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. Haemophilia. 2020;27:129–36. https://doi.org/10.1111/hae.14190.
19. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: the exigency study. Haemophilia. 2021;27:760–8. https://doi.org/10.1111/hae.14378.
20. van Balen EC, Wesselo ML, Baker BL, Westerman MJ, Coppens M, Smit C, Driessens MHE, Leebeek FWG, van der Bom JG, Gouw SC. Patient perspectives on novel treatments in haemophilia: a qualitative study. Patient. 2020;13:201–10. https://doi.org/10.1007/s40271-019-00395-6.
21. Meisbach W, Klamroth R. The patient experience of gene therapy for haemophilia: qualitative interviews with trial patients. Patient Preference Adherence. 2020;14:767–70. https://doi.org/10.2147/PPA.S239810.
22. Aradom E, Gomez K. The patient gene therapy journey: findings from qualitative interviews with trial participants at one UK Haemophilia centre. J Haemophilia Pract. 2021. https://doi.org/10.17225/jhp00174.
23. Miller FG. Recruiting research participants. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wender D, editors. The Oxford textbook of clinical research ethics. Oxford: Oxford University Press; 2008. p. 397–403.
24. Whitmore E. To tell the truth: Working with oppressed groups in participatory approaches to inquiry. In: Reason P, editor. Participation in human inquiry. London: Sage; 1994. p. 82–98.
25. Berg DN, Smith KK. The clinical demands of research methods. In: Berg DN, Smith KK, editors. Exploring clinical methods for social research. Beverly Hills: Sage; 1985. p. 21–34.
26. Simmons M. Insider ethnography: tinker, tailor, researcher or spy? Nurse Res. 2007;14(4):7–17. https://doi.org/10.7748/nr2007.07.14.4.7.c6039.
27. Rangarajan S, Kim B, Lester W, Symington E, Madan B, Laffan M, Tavakkoli F, Pierce G, Wong WY, Pasi J. Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvovec (BMN 270): long-term efficacy and safety results in patients with severe hemophilia A. Haemophilia. 2018;24:S65.
28. High KA, George LA, Eyster E, Sullivan SK, Ragni MV, Croteau SE, Samelson-Jones BJ, Evans M, Joseney-Antoine M, Macdougall A, et al. A phase 1/2 trial of investigational Spk-8011 in hemophilia a demonstrates durable expression and prevention of bleeds. Blood. 2018;132:92–5856. https://doi.org/10.1182/BLOOD-2018-99-115495.
29. Batty P, Lillicrap D. Advances and challenges for hemophilia gene therapy. Hum Mol Genet. 2019;28:R95–101. https://doi.org/10.1093/hmg/ddz157.
30. Nathwani AC, Rosales C, McIntosh J, Rastegarlari G, Nathwani D, Raj D, Nawathe S, Waddington SN, Bronson R, Jackson S, Donahue RE, High KA, Mingozzi F, Ng CYC, Zhou J, Spence Y, McCarville MB, Valentine M, Allay J, Coleman J, Sleep S, Gray JT, Nienhuis AW, Davidoff AM. Long-term safety and efficacy following systemic administration of a self-complementary AAV vector encoding human FIX pseudotypedwith serotype 5 and 8 capsid proteins. Mol Ther. 2011;19:876–85.
31. Pipe S, Stine K, Rajasekhar A, Everington T, Poma A, Crombez E, Hay CRM. 101HEMB01 is a phase 1/2 open-label, single ascending dose-finding trial of DTX101 AAVrh10FIX in patients with moderate/severe hemophilia B that demonstrated meaningful but transient expression of human factor IX hFIX. Blood. 2017;130:S3331. https://doi.org/10.1182/blood.V130.Suppl_1.3331.3331.
32. National Institute of Health and Care Excellence. British National Formulary. 2021. https://bnf.nice.org.uk/treatment-summary/corticosteroids-general-use.html. Accessed 12 Sept 2021.
33. Dresser R. Silent partners: human subjects and research ethics. Oxford: Oxford University Press; 2016.
34. Quality Review Services. Inherited and acquired haemophilia and other bleeding disorders peer review programme: overview report. 2020. https://images.qualityreviewservicewm.nhs.uk/wp-content/uploads/2020/05/28154818/IABD-Overview-Report-2020-V1-20200527-1.pdf. Accessed 14 Sept 2021.
35. Khair K, Steadman L, Chaplin S, Holland M, Jenner K, Fletcher S. Parental perspectives on gene therapy for children with haemophilia: the Exigency study. Haemophilia. 2021;27:120–8. https://doi.org/10.1111/hae.14188.
36. Woollard L, Gorman R, Rosenfelt DJ. Improving patient informed consent for haemophilia gene therapy: the case for change. Ther Adv Rare Dis. 2021;2:1–16. https://doi.org/10.1177/26330040211047244.
37. Fusch PI, Ness LR. Are we there yet? Data saturation in qualitative research. Qual Rep. 2015;20:1408–16. https://doi.org/10.46743/2160-3715/2015.2281.

38. Bernard RH. Social research methods: qualitative and quantitative approaches. 2nd ed. Thousand Oaks: Sage; 2012.

Publisher's Note

sciendo

CASE STUDY

"I didn't know women could have haemophilia": A qualitative case study

Simon Fletcher

Introduction: There is a historic but persistent belief in haemophilia care that women do not suffer with the condition, they merely carry and transmit it. However, around 250 women worldwide are known to have factor levels within the severe to moderate haemophilia range (<1 IU/dL to 5 IU/dL), and the true figure may be greater than this. The experience of these women may be the same as or similar to those of men with similar factor levels, but there may be significant differences. What these differences are and what they mean to the women affected are not well understood as their voices are not heard. This case study highlights the issues and experiences of one woman living severe haemophilia. **Methods:** A single semi-structured qualitative interview was undertaken to explore the experiences of a young woman who has factor VIII levels of <1 IU/dL. The interview was recorded, transcribed and thematically analysed. **Results:** Four interlinked themes were identified: recognition, self-advocacy, identity and access to treatment. **Conclusion:** This case study indicates that, despite recent attempts to improve the diagnostic nomenclature, women and girls with haemophilia continue to find it difficult to access similar levels of care to men and boys. As such, they may fail to achieve parity in terms of safety, integrity and wellbeing, and have a reduced quality of life. If women and girls affected by haemophilia are to receive levels of treatment comparable to men, diagnostic criteria need to change further. Focusing on genotype, levels of factor expressed and phenotypical presentation rather than biological sex will acknowledge and validate their experiences, and improve treatment for all people with haemophilia in the future.

Keywords: *Haemophilia, Identity, Clinical trials, Women, Case study*

© Shutterstock

Based on the lived experience of a woman with severe haemophilia, this case study contends that diagnostic criteria and opportunities to participate in clinical research need to be improved if women and girls affected by haemophilia are to achieve equitable access to treatment.

SIMON FLETCHER
Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Email: simon.flether@ouh.nhs.uk

Haemophilia is an X-linked condition characterised by a reduction or absence of clotting factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B [1,2]. Resulting in an impaired or incomplete clotting pathway and attendant bleeding risk in affected persons, it is categorised according to the amount of factor

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0011

expressed (mild >5–45 IU/dL; moderate 1–5 IU/dL; severe <1 IU/dL) [3]. Bleeding tendency correlates with the severity of the condition, those with severe haemophilia bleeding more frequently than those with milder forms.

Affecting approximately 1:3,500 births worldwide [4], there are approximately 1.25 million men in the world with haemophilia, 420,000 of whom have severe haemophilia [5]. Current treatments consist of factor replacement, coagulation pathway rebalancing or, in the near future, gene therapy [6-8]. Haemophilia and its treatment come with significant individual, family and organisational burdens [9,10].

As haemophilia is an X-linked recessive condition, it has been accepted historically that women are largely unaffected and merely carry and transmit the condition [11]. However, this is far from the truth. Some women who carry the genetic mutation may, because of compound heterozygosity, incomplete X chromosomal inactivation or skewed lyonization, have factor levels commensurate with men with a diagnosis of haemophilia [12]. Miller and Bean [10] report that there are thought to be 250 women worldwide with factor levels in the severe to moderate range, though the true figure may be even higher, with many cases going unreported. The number of women who carry the haemophilia gene and are symptomatic to any degree is not known, but Kasper and Lin [13] suggest there may be nearly 2 million women worldwide who carry a mutation of haemophilia.

Similar to men with haemophilia, treatment for women with low factor levels depends on the severity of the presentation but can include factor replacement. Unlike men with haemophilia, however, the care of women with low factor levels can be complicated by the presence of additional haemostatic challenges throughout their lives [14], as well as a perceived inherent sexism in bleeding disorders care [15]. Treatment for women, therefore, depends upon adequate testing, accurate diagnosis and comprehensive follow-up.

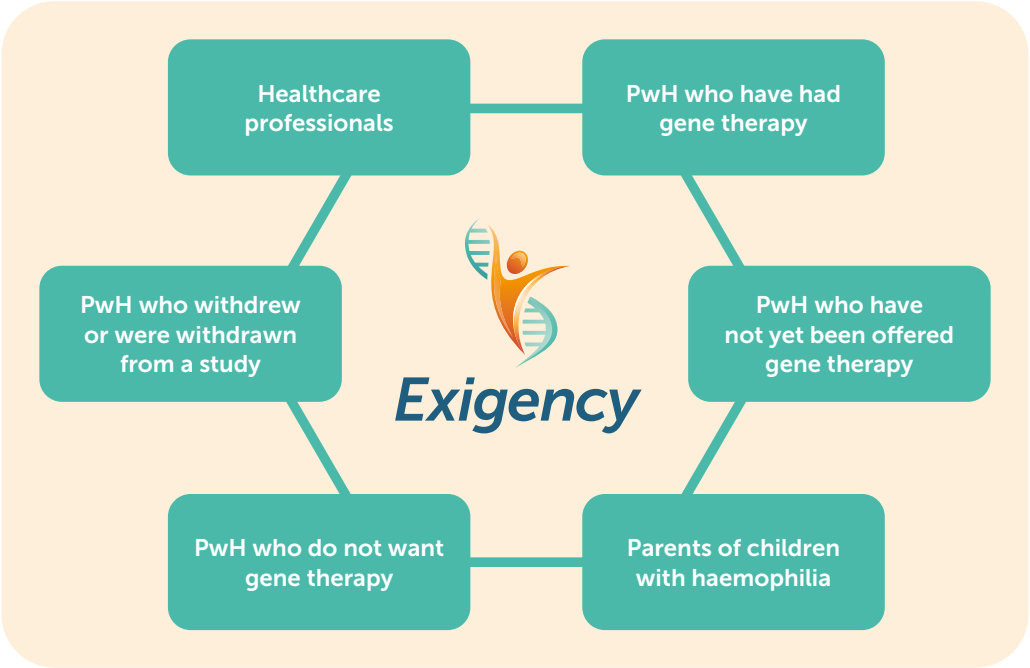
This case study presents the experience of a woman with severe haemophilia A and explores what implications these experiences might have for all healthcare professionals involved in the care of people with haemophilia (PwH) now and in the future.

METHODOLOGY

Case selection

This case study emerged from the ongoing Exigency programme [16-18], a nested group of studies looking into the views and experiences of gene therapy among six stakeholder groups: parents of children with haemophilia, PwH who have undergone gene therapy, PwH who have either withdrawn or were withdrawn from a gene therapy study, PwH who do not want

Figure 1. Diagrammatic representation of the Exigency study



gene therapy, PwH who have not yet been offered gene therapy, and healthcare professionals (Figure 1).

Other than parents of children with haemophilia and partners of men with haemophilia, women were excluded from the Exigency programme. This was a pragmatic decision based on the exclusion of women from haemophilia gene therapy studies. Despite this, Jayne (a pseudonym), a woman with haemophilia, contacted the study team asking to participate. Her approach prompted the study team to acknowledge that, rather than canvassing the views of PwH about gene therapy, they were only canvassing those of men with haemophilia, potentially giving an unintended skewed view. Jayne was therefore invited to participate in a separate intrinsic descriptive case study [19], in which her experiences – those of an individual from an excluded and potentially disadvantaged group [20] – could be heard.

Data collection and analysis

A single semi-structured qualitative interview was carried out by the author using the video-conferencing platform Zoom® in January 2022. The interview guide was adapted from that used in the Exigency study and addressed issues including Jayne's personal haemophilia story, her treatment history and ongoing care, and her thoughts on the future of haemophilia care (see Table 1 of the Appendix for the interview guide). Zoom® was used because of ongoing social distancing guidelines in the UK and because the travel requirements involved in meeting face to face would have been prohibitive. Zoom® has been found to be a useful and positive tool in qualitative research. [21,22].

The interview lasted 60 minutes, and was recorded, transcribed verbatim, and thematically coded using an inductive coding methodology [23].

Ethics

The Health Research Authority (HRA) decision-making tool was used to decide whether a formal application to the HRA and NHS Research Ethics Committee (REC) would be required for the interview [24]. As the interview would not generate any transferable or generalisable data and would not necessitate any change to Jayne's normal treatment regimen, it was deemed by the tool that no requirement for REC review and approval would be needed. The participant was asked to sign a consent form to confirm that she was happy to be interviewed and for pseudonymised quotes from the interview be used in any publications generated. It was stressed, however, that complete anonymisation may not be possible because, as a member of a rare subgroup of a rare condition, she may still be recognisable. A copy of this publication was sent to her prior to its submission to further confirm consent and correct any factual errors.

RESULTS

Biographical information

Jayne (pseudonym) is in her 20s and was born into a family with a known history of haemophilia A. Her maternal grandfather had severe haemophilia and her mother is therefore an obligate carrier. Her mother has a history of easy bruising and heavy menstrual bleeding; her factor levels were never formally tested, and although she was informed that she was a symptomatic carrier of haemophilia, no specific management options were made available to her.

When her mother became pregnant with Jayne, she informed her care team that she was a carrier of haemophilia. She was told by them that she had nothing to worry about as her child was a girl; it would not be a problem as *"only boys can get haemophilia"*. Jayne's birth was uneventful but it was soon noticed that, like her mother, she was prone to easy unexplained bruising. This was not picked up on by her health visitor, but at the age of six months Jayne developed a significant bleed at which point her GP suggested she should have her factor levels checked. When the results revealed a factor level of <1 IU/dL, further blood was taken and tested as it was thought there had been a mix-up and an incorrect result had been reported. The second sample confirmed a level of <1 IU/dL, her diagnosis was established and she was started on factor replacement therapy.

Jayne describes her childhood as one with few constraints: *"I can't say that I ever felt I was restricted in any way."* Her mother would ensure that she always sought advice if there was anything Jayne wished to do, but *"she found a way to do it"*. Despite ongoing factor replacement therapy, Jayne had regular breakthrough bleeds, most noticeably in her ankles, and felt like she was taking factor so frequently that she might as well have been taking it daily. At this time, she went through a period of rebellion and admits to having taken her factor less frequently than advised. She felt that she needed to have some control over her life and to be allowed *"to make the decisions for myself"*.

Jayne now uses an extended half-life factor prophylactically but states that she continues to have *"frequent bleeds"*, particularly into her ankles. She is hoping to be able to start emicuzumab in the near future, though has had difficulty convincing

her treatment centre to consider it as an option. The paucity of data on the use of emicizumab in women of childbearing age has meant that Jayne's treatment team were reticent to prescribe it until she decided to have no further children.

Jayne is married and has two children, neither of whom are affected by haemophilia.

Thematic analysis

Four major themes emerged during the interview: recognition, self-advocacy, identity, and access to treatment.

Recognition

Jayne spoke throughout her interview of the difficulty she has had in her condition and its severity being recognised. As described in the biographical sketch, this began at the point of diagnosis when her results came back: *"Their first thought was 'no, that can't be right'."*

This attitude of disbelief has continued to be a common occurrence. Jayne reports still being told by non-specialist healthcare staff when she informs them of her condition, *"Oh right, ok, yes [...] that's fine,"* and yet appropriate advice or the assistance of her haemophilia care team is rarely sought by them. She feels that, because of the relative rarity of haemophilia and it typically being understood as a condition that women *"can't actually have"*, there appears to be a disconnect between her reality and the understanding of haemophilia, even within a healthcare setting. This disconnect means that, at times, she has been left feeling unsafe in the care she has received.

> *"That's really upsetting, to think I don't feel safe [...] I don't feel like they're taking me seriously, I don't feel like they're getting the right advice. That's scary."*

Self-advocacy

Because of lack of recognition of the importance of her condition, Jayne feels she must constantly advocate for herself to ensure she receives appropriate care. This often means having to contact her treatment centre to inform them that she is about to have a procedure when the relevant care team have not done so. She feels that this is not something she should always have to think about and do.

> *"I shouldn't be having to think, 'Right, what do I need to tell them to do? Who do I need to tell them to contact?'"*

She accepts that, as a woman with severe haemophilia, her condition is rare within an already rare condition and that it's *"just one of those thing[s] where they just don't see it enough"*, but that equally it does not *"really excuse the fact that it's happening"*.

Jayne wonders whether an increase in training, not just in the bleeding disorders community but *"in women's services and things that are only really affecting women"*, is what is needed to improve both her own experience and that of all women with bleeding disorders.

Identity

Jayne spoke about the differences that exist for her as a result of her haemophilia. This manifested most clearly in adolescence, around the time of her menarche.

> *"I found that quite embarrassing, because it's something that every woman has to go through but you don't usually have to talk with doctors and nurses about it at such a young age in detail [...] Other girls didn't have to speak to a doctor about it unless... unless they had to go to the doctors about it for some reason. Even before I'd started they [the doctors and nurses] were talking about it."*

She also spoke about being seen as different from men with severe haemophilia:

> *"If it's a man and he says, 'I've got a bleeding disorder,' it is like, 'Oh right, ok, 100% we understand that,' but if it's a woman it will be like, 'Oh, right, ok... So, are you a carrier?'"*

Jayne sees herself as more a member of a community of women with bleeding disorders than a member of the haemophilia community.

> *"I understand that in my situation, yes, it is quite rare [...] but are they not taught about bleeding disorders and women with bleeding disorders and how to deal with it?"*

It is not that she feels deliberately excluded from the haemophilia community, but that being seen as 'only' a carrier lessens and demeans her experiences.

Access to treatment

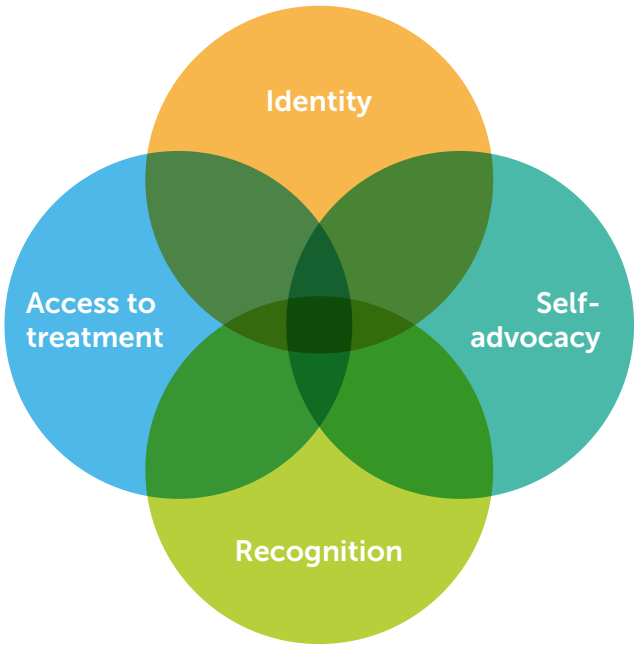
A major issue for Jayne is access to new treatments and the disparity that exists because she is a woman rather than a man.

Discussing new treatments and those currently in development, including gene therapy, Jayne is concerned that few, if any, women affected by haemophliia will be able to access them. Citing her own experience, she reports that it has taken a lot of negotiation with her care team for them to consider emicizumab as a treatment option: *"They're too scared [...] because what if it affects fertility or what if it affects periods, things like that."*

Much of the problem, she believes, stems from the fact that women are not included in many, if any, clinical trials of new therapies for haemophilia. She wonders whether this is due to a combination of women with haemophilia being rarer or not recognised, or that pharmaceutical companies are too cautious. Jayne says she has applied to take part in studies and believes there are other women who might be similarly willing but have been told that, as women, they are not able to participate. She says the exclusion of women in this way has to change because it feels like they are being *"punished for having children or wanting to have children or having periods"*. The right to choose to have a treatment or not, as some men with haemophilia are choosing not to with gene therapy [17], should be fundamental. To have those decisions enforced because of a lack of available safety data resulting from exclusion from clinical trials would appear to be unjust.

Further quotes supporting the themes arising from Jayne's interview can be found in Table 2 of the Appendix.

Figure 2. Thematic interactions observed in the case study



DISCUSSION

Though four major themes emerged in the interview – identity, recognition, self-advocacy and access to treatment – it became apparent that they were not completely distinct and that there was a great deal of interaction between them. It was impossible, for example, to think about identity without recognising how that impacted upon and in turn was impacted by recognition, access to treatment and self-advocacy (Figure 2). The themes' overlapping nature means that it is difficult to discuss one single element of Jayne's condition without reference to another.

One of the major issues Jayne discussed is difficulty accessing treatment because of the reluctance of her medical team to prescribe treatments that have not been tested on women. The problem, as she noted, is that women have generally been underrepresented in clinical trials and almost entirely excluded from haemophilia clinical trials.

Seen as vulnerable group, women have traditionally been excluded from clinical research [14,25,26]. This led to the rise of the male norm bias [27], where women's participation in clinical research was seen as unimportant due to the belief that data from studies which included only men could also be applied to women. More recently, sex-related differences, including differences between the progression and physiological characteristics of diseases, have been noted [28-30]. As such, the importance of including women in clinical research has again come to the fore.

The underrepresentation of women in haemophilia care is, in some senses, understandable for two reasons. The first, as highlighted above, is that historically only men have been thought to be affected, and as such the inclusion of women in clinical trials for haemophilia treatments was not seen to be necessary. The second is that, even though some women may benefit from a particular treatment, there are too few to make their inclusion in a trial practical or even possible. While both of these issues perhaps make the recruitment of women into haemophilia clinical trials complex, neither should necessarily have excluded them. Ineligibility purely on the basis of sex when other inclusion criteria are met – including the presence of the genetic mutation, a severe bleeding phenotype, factor usage, bleed data and willingness to participate – would seem to be wrong. A second X chromosome should not preclude women from taking part in clinical studies [15]. The advent of improved testing and new treatments, some of which may have applications in other (non-haemophilia) bleeding disorders, also

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0011

highlights a growing need to redress this balance and ensure that women are recruited to any future studies so that there is an adequate body of evidence to allow parity of treatment with men.

More recently, sex-related diagnostic criteria have been called into question with the recognition of gender dysphoria and transgenderism [31,32]. Valk's 2018 case study [33], in particular, of a person with mild haemophilia (10 IU/dL) transitioning from female to male, and therefore from a carrier with low factor levels to person with haemophilia, shows that any diagnosis for haemophilia based purely on sex may no longer be valid or morally and legally defensible.

Identity as a woman with haemophilia has always been difficult for Jayne but it has also been an issue for many other women with haemophilia and other bleeding disorders. Sanigorska et al. [34] have shown that for many women the term 'carrier' has negative connotations, dismissing and devaluing their experiences, and resulting in feelings of insecurity and the avoidance of healthcare settings.

In an attempt to mitigate some of these concerns, the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) has proposed a number of changes to the nomenclature for affected women and girls [35]. However, these changes, while seeking to improve both diagnosis and clinical care for women and girls with haemophilia, may achieve less than hoped as they continue to perpetuate the sex-based discrimination that exists. Rather than streamlining and simplifying the definition of haemophilia for women, the guideline has created five new definitions, maintaining the distinction that while women may be symptomatic they fundamentally remain carriers rather than people with haemophilia.

Limitations

As with all case studies, the focus on a single individual whose concerns and issues may not be the same as other women with haemophilia means this case study has limited generalisability [36]. However, while Jayne's case may be the voice of an individual, it is the voice of an individual from an excluded and disadvantaged group [14]. There are obviously fewer women with severe haemophilia than there are women affected by haemophilia – but if a woman with a diagnosis of severe haemophilia is not recognised and cannot access care and treatments at parity with men, what hope do women less severely affected have?

The rarity of this case and other women with severe haemophilia makes the generation of any data important. This can add greatly to our knowledge of the aetiology, natural history and treatment [37,38], as well as our understanding of women with bleeding disorders' experience through narrative analysis [39].

CONCLUSION

Women with severe haemophilia form a rare group within an already rare disease. As such, their condition and/or specific needs are poorly understood. This case study shows how one woman with a phenotypically severe form of haemophilia feels about her condition and treatment. She feels that she and other women in the bleeding disorders community, including those with milder forms of haemophilia, are being disadvantaged in the treatment options available to them both now and in the future.

If there is to be equitable availability of treatment for women and girls affected by haemophilia, then two issues need to be addressed. The first is that the diagnostic criteria, based predominantly on an individual's sex, need to be reviewed and formally amended. Women should not be penalised for having a second X chromosome but should be treated according to their level of expressed factor and the severity of their symptoms. Secondly, women with haemophilia should have equal opportunity to be involved in clinical research and contribute to the safety and efficacy data of any new treatment in the same way as men with similar factor levels can.

ACKNOWLEDGEMENTS

Informed consent has been obtained from the individual reported in this case study.

The author has advised no interests that might be perceived as posing a conflict or bias.

ORCID

Simon Fletcher https://orcid.org/0000-0001-9018-6176

REFERENCES

1. Callaghan MU, Kaufman RJ. Cellular processing of factor VIII and factor IX. In: Lee C, Berntorp E, Hoots K, eds. *Textbook of Haemophilia*, 2nd edn. 2010. Oxford, UK: Wiley-Blackwell.
2. Kitchen S, de Paula Cereta F, de Lima Montalvão SA, et al. Laboratory diagnosis and monitoring. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26(S6): 35-48. doi: 10.1111/hae.14046.
3. Hatton C, Hay D, Keeling DM. Haemostasis, abnormal bleeding and anticoagulant therapy. In: Hatton C, Hay D, Keeling DM, eds. *Haematology: Lecture Notes*, 10th edn. 2018. Chichester, UK: Wiley-Blackwell.
4. Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The World Federation of Hemophilia Annual Global Survey 1999–2018. *Haemophilia* 2020; 27: 591-600. doi: 10.1111/hae.14012.

5. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C. Establishing the male prevalence and prevalence at birth of hemophilia: A meta-analytic approach using national registries. *Ann Intern Med* 2019; 171(8): 540-546]. doi: 10.7326/M19-1208.
6. Pipe SW, Carcao M, Chew K, et al. Hemostatic agents. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26(S6): 59-71. doi: 10.1111/hae.14046.
7. Francini M, Mannucci M. Non-factor replacement therapy for haemophilia: a current update. *Blood Transfus* 2018; 16: 457-61. doi: 10.2450/2018.0272-17.
8. Garrison LP, Kleinermans D. Is the world ready for gene therapy? *Haemophilia* 2022; 28(Supp 2): 5-8. doi: 10.1111/hae.14439.
9. DeKoven M, Karkare S, Lee WC, et al. Impact of haemophilia with inhibitors on caregiver burden in the United States. *Haemophilia* 2014; 20: 822-830. doi: 10.1111/hae.12501.
10. Khair K, Kulkowska A, Myrin Westersson L, et al. The burden of bleeds and other clinical determinants on caregivers of children with haemophilia (the BBC Study). *Haemophilia* 2019; 25: 416-423. doi: 10.1111/hae.13736.
11. Miller CH, Bean CJ. Genetic causes of haemophilia in women and girls. *Haemophilia* 2021; 27: e164-e179. doi: 10.1111/hae.14186.
12. Shoukat HMH , Ghulam Ghous G, Tarar ZI, Shoukat MM, Ajma N. Skewed inactivation of X chromosome: a cause of hemophilia manifestation in carrier females. *Cureus* 2020; 12(10):e11216. doi: 10.7759/cureus.11216.
13. Kasper CK, Lin JC. How many carriers are there? *Haemophilia* 2010; 16(5): 842. doi: 10.1111/j.1365-2516.2010.02210.x
14. van Galen K, Lavin M, Skouw-Rasmussen N, et al.; European Haemophilia Consortium (EHC), European Association for Haemophilia and Allied Disorders (EAHAD). European principles of care for women and girls with inherited bleeding disorders. *Haemophilia* 2021; 27(5): 837-847. doi: 10.1111/hae.14379.
15. Weyand AC, James PD. Sexism in the management of bleeding disorders. *Res Pract Thromb Haemost* 2021; 5: 51-54. doi: 10.1002/rth2.12468.
16. Khair K, Steadman L, Chaplin S, et al. Parental perspectives on gene therapy for children with haemophilia: the Exigency study. *Haemophilia* 2021; 27(1): 120-128. doi: 10.1111/hae.14188.
17. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: the Exigency study. *Haemophilia* 2021; 27(5): 760-768. doi: 10.1111/hae.14378.
18. Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experiences of people with haemophilia, and their families, of gene therapy in a clinical trial setting: regaining control, the Exigency study. *Orphanet J Rare Dis* 2022; 17: 155. doi: 10.1186/s13023-022-02256-2.
19. Stake RE. *The Art of Case Study Research*. 1995. London: Sage Publications.
20. Schwandt TA, Gates EF. Case study methodology. In Denzin NK, Lincoln YS, eds. *The SAGE Handbook of Qualitative Research*, 5th edn. 2017. London: Sage Publications.
21. Archibald MM, Ambagtsheer RC, Casey MG, Lawless M. Using Zoom videoconferencing for qualitative data collection: perceptions and experiences of researchers and participants. *International Journal of Qualitative Methods* 2019; 18: 1-8. doi: 10.1177/1609406919874596.
22. S Fletcher. Seeing the bigger picture: Qualitative research in the Zoom® age. *J Haem Pract* 2021; 8(1): 141-144. doi: 10.2478/jhp-2021-0019.
23. Alhojailan MI. Thematic analysis: A critical review of its process and evaluation. *West East Journal of Social Sciences* 2012; 1(1): 39-47.
24. NHS Health Research Authority. Is My Study Research? October 2017. Available from *http://www.hra-decisiontools.org.uk/research/* (accessed 3 January 2022).
25. Denny C, Grady C. Research involving women. In: Emanuel EJ, Grady C, Crouch RA, et al., eds. *The Oxford Textbook of Clinical Research Ethics*. 2008. Oxford, UK: Oxford University Press.
26. Steinberg JR, Turner BE, Weeks BT, et al. Analysis of female enrollment and participant sex by burden of disease in US clinical trials between 2000 and 2020. *JAMA Netw Open 2021*; 4(6): e2113749. doi: 10.1001/jamanetworkopen.2021.13749.
27. Mastroianni AC, Faden R, Federman D. Executive summary. In Mastroianni AC, Faden R, Federman, D. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, vol. 1. 1994. Washington (DC): National Academies Press.
28. Sterling TR, Vlahov AJ, Astemborski J, et al. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med* 2001; 344: 720-725. doi: 10.1056nejm2000103083441003.
29. Campaigne BMN, Wishner KL. Gender-specific health care in diabetes melitus. *J Gend Specif Med* 2000; 3(1): 51-58. PMID: 11253237.
30. Walsh SJ, Rau LM. Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States. *Am J Public Health* 2000; 90: 1463-1466. doi: 10.2105/ajph90.9.1463.
31. Thomas R, Page F, Khosia R, Vester A, Hana T, Say L. Ensuring an inclusive global health agenda for transgender people. *Bull World Health Organ* 2017; 95: 154-156. doi: 10.2471/blt.16.183913.
32. Joseph A, Cliffe C, Hillyard M, Majeed A. Gender identity and the management of the transgender patient: a guide for non-specialists. *J R Soc Med* 2017; 110: 144-52. doi: 10.1177/0141076817696054.
33. Valk C. A transgender person with haemophiia. *J Haem Pract* 2018; 5(1): 147-151. doi: 10.17225/jhp00128.
34. Sanigorska A, Chaplin S, Holland M, Khair K, Pollard D. The lived experience of women with a bleeding disorder: A systematic review. *Res Pract Thromb Haemost* 2022; 6: e12652. doi: 10.1002/rth2.12652.
35. van Galen KPM, d'Oiron R, James P, et al. A new hemophilia carrier nomenclature to define hemophilia in women and girls: Communication from the SSC of the ISTH. *J Thromb Haemost* 2021; 19: 1883-1887. doi: 10.1111/jth.15397.
36. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. *BMC Res Notes* 2014, 7: 264. doi: 10.1186/1756-0500-7-264.
37. Carey JC. The importance of case reports in advancing scientific knowledge of rare diseases. *Adv Exp Med Biol* 2010; 686: 77-86. doi: 10.1007/978-90-481-9485-8_5.

38. Nakamura T, Igarashi H, Ito T, Jensen RT. Important of case-reports/series, in rare diseases: Using neuroendocrine tumors as an example. *World J Clin Cases* 2014; 2(11): 608–613. doi: 10.12998/wjcc.v2.i11.608.
39. Khair K, Pollard D, Steadman L, Jenner K, Chaplin S. The views of women with bleeding disorders: Results from the Cinderella study. *Haemophilia* 2022;28(2): 316-325. doi: 10.1111/hae.14514.

HOW TO CITE THIS ARTICLE:
Fletcher S. "I didn't know women could have haemophlia": A qualitative case study. *J Haem Pract* 2022; 9(1): 85-95. *https://doi.org/10.2478/jhp-2022-0011.*

Table 1. Interview guide

Thank you for agreeing to take part in this interview. Everything you tell us in this interview will be treated with complete confidence but some comments may be used in a publication, subject to your prior review – your identity will never be revealed.

In this interview we want to know, as a woman, what your experience of haemophilia is, what it has been like growing up with it, and how it impacts on your day-to-day life.

Are you OK to proceed and are you happy that we record the interview?

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? • Do you have a history of haemophilia in your family? • How did your parents cope with the diagnosis?
Can you tell me about what it was like growing up with haemophilia?	• What was school like? • Did you feel excluded because of your haemophilia? • When did your periods start and how was that for you?
Can you recall how many bleeds you have on average?	
How are your joints?	• Do you have any joints that bleed more than others? • How do/did you manage those bleeds?

What about pain? Do you have any pain now?
 	
Imagine a scale of 1 to 6, where 1 is very little pain and 6 is the worst pain. How bad is that pain?
	• How has it been over the past month?
	  • Do you get pain every day?
	  • Is it joint-related/arthritic, or is it haemophilia-related?
	• How does arthritic pain differ from the pain of a bleed (if applicable)?

What impact has having haemophiila had on you and your family?	• Have there been any negative impacts? • Do you think there are any positive impacts? • How worried are you about an injury? • Was it difficult talking about your haemophilia to boyfriends/your spouse?
Do you feel that because you are a woman your care is different from that of men with haemophilia.	• In what ways?
	• How long have you been on it? • Have you been on any other treatments?
What treatment are you on?	
Have you ever had an operation in hospital? What was it for?	
Do you have any children of your own?	
Have you heard about any other treatments that might be available in the future?	• What do you know about them? • Do you think any of them are an option for you? • If not, why not?
Is there anything else you would like to say or ask of me?	

Thank you for taking part in this interview.

It is my intention to publish the interview as a case study in a haemophilia journal. As mentioned at the start of the interview, I will endeavour to keep protect your identity by removing any identifying data and using a pseudonym for you. Once it is written I will send you copy for you to comment on.

If you have any questions between then and now, please don't hesitate to contact me.

Table 2. Supporting quotes

Recognition	She [mother] took me to the GP, and it was the GP that said, "I think we should test her for haemophilia."
	I don't know how the GP... I don't know if it happened that my mum said, "Oh, I do have haemophilia in my family but they said it couldn't be that," and whether they just thought we've got to rule it out. I don't know how it happened, really. But I just know that the GP was the one who sent my mum and me to the hospital to get the blood tests done.
	I don't know what the things were like [all those years ago], but perhaps they could have thought at the very least that maybe I was a carrier and would still have... just maybe have low levels but not enough to make me a haemophiliac.
	I've found they've been like, "Oh – really?" and "I've never had a woman with haemophilia." The attitude has been not necessarily that they don't believe me, but the attitude has been, "Well, I don't know anything about haemophilia, never had a woman with haemophilia, so I don't know."
	Well, I mean, haemophilia isn't the only bleeding disorder, so you can't say that the next day they wouldn't see someone, see a woman, with a different bleeding disorder. I understand that in my situation, yes, it is quite rare. But why aren't they... I don't know, obviously, what goes on in their medical training and how much time they spend on different areas, but are they not taught about bleeding disorders and women with bleeding disorders and how to deal with it?
Self-advocacy	It was like, ok, so they diagnosed me with that, they said what they wanted to do – they wanted to do surgery. And it was like, "Ok, but I have haemophilia A."
	And he said, "Probably going to be surgery." I said, "Right, ok. I have haemophilia A, severe," and they were like, "Oh, right, ok." I said, "You need to contact my centre. Or you need to speak to an on-call haematologist here. But you need to speak to someone. I'm not happy to have surgery without you having spoken to someone and have a plan in place."
	When they took us aside to speak to the midwife about what to expect and everything, I said, "What about my haemophilia? Is that going to have an effect? Should I do anything different?" And she went, "Oh. I don't know because I've never had a woman with haemophilia," and it was just left at that. And it was kind of like... well, ok, it's good that you're admitting that you don't know, but could you find out, could you speak to someone? And instead I went home and I actually contacted my haemophilia centre myself, and obviously had to explain to them what had happened and ask them for advice or what I should do. And I just feel like I probably shouldn't have had to do that. Something that was so upsetting at the time, why did I need to go and seek out my own medical care, my own advice and things like that?
	I'd say all my life me or my mum have had to advocate for me.
Identity	I mean, I think one of the big things is that so many people still think that women don't get these certain bleeding disorders, and that's probably the biggest thing.
	I've spoken to people when I've been doing interviews or surveys and things like that, and they've sort of been like, "We're really excited to speak to you because we didn't know that women... we didn't know there'd be a woman with haemophilia." So, they don't even sort of wonder if it's out there. They don't wonder if there's women out there with haemophilia or certain bleeding disorders. They've been told that there's not, so they don't include them, I'm guessing.
	I've spoken to a lot of mums whose daughters might have haemophilia mildly or they've been told that they're a carrier and they're experiencing some symptoms, and I talk to them and they seem to have a lot of the experiences that I have in terms of heavy periods, bleeding in joints and things like that, which I can say, "Oh, well, yes. Because it's actually documented that I have haemophilia, this is what I... this is the medication that I can use, or this is what the doctor prescribed me, or this is what I do." And they still find that helpful.

Identity	**Interviewer:** Do you think there should be a move now... You talked earlier about women who are symptomatic carriers, they have low levels of factor VIII, whatever it may be, whether it corresponds with a mild or a moderate or a severe. Do you think we should stop calling symptomatic carriers symptomatic carriers, we should call them women with haemophilia? **Jayne:** Yes. **Interviewer:** Because it's the same thing? **Jayne:** Because, yes, because I think if we started calling them or diagnosing them with haemophilia, all of a sudden there would be all these women with haemophilia who people could talk to and could be included in clinical studies
	And on the Friday when I'd been up to have blood tests I'd said to them I've got haemophilia A, severe. They were like, "Oh right, ok, yes." And I was like, "Yes. Ok?" and they were like, "Yes, yes, that's fine. Never met a woman with haemophilia A."
Access to treatment	I do want to go to Hemlibra, but [...] it's been delayed and delayed. And that's what's prompted me to be like, "Why is there never any data on women?" I know that it's probably a lot harder to find women with haemophilia, but I don't know... I kind of feel like is there not another way to find some data around women and these different drugs?
	I don't have a lot of understanding on it [gene therapy] because it's not something that I've ever been approached about. I didn't really even know anything about Hemlibra until I read that it was... it had been approved on the NHS for severe and people with inhibitors. I sort of... I think I'd sort of seen that maybe something like that was in the works, but I didn't know that it was here, that it was an option, until it sort of was.
	Interviewer: So the information you're getting you're having to get yourself. **Jayne:** Yes. **Interviewer:** It sounds like it's not being offered because nobody's really sure whether it's appropriate or not at the moment. **Jayne:** Yes.
	Why are they never... When they put the feelers out for, you know, "We want to speak to men of this age, this background," or whatever they're looking for to include in their study, why isn't it... why are there never feelers out for women? I know that it might be harder to find them, but can they not reach out to centres and say, "Do you have any patients with any of these conditions – or anything like that – and would they be interested in taking part?" I mean, some people wouldn't be and that's just personal preference. They might not be suitable, whatever they've got as the criteria. But there must be ways to find women. But when I see studies it is like... it's asking for men. And most of the time, if I apply – when it starts involving medical treatments and things like that, it's like they're too scared to ask.

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0011

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

Simon Fletcher ,[1] Luke Pembroke,[2] Mike Holland,[2] Kate Khair[2]

To cite: Fletcher S, Pembroke L, Holland M, *et al*. 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. *BMJ Open* 2022;**12**:e060351. doi:10.1136/bmjopen-2021-060351

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-060351).

Received 03 January 2022
Accepted 14 July 2022

[1]Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Haemnet Ltd, London, UK

Correspondence to
Simon Fletcher;
simon.fletcher@ouh.nhs.uk

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.

Funding This study was funded through an unrestricted educational grant from uniQure Biopharma BV.

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.

ORCID iD

Simon Fletcher http://orcid.org/0000-0001-9018-6176

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.

Received: 30 August 2022 | Revised: 21 February 2023 | Accepted: 21 February 2023

DOI: 10.1111/hae.14774

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Expectation and loss when gene therapy for haemophilia is not an option: An exigency sub-study

Simon Fletcher[1] | Kathryn Jenner[2] | Michael Holland[2] | Kate Khair[2]

[1]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[2]Haemnet, London, UK

Correspondence
Simon Fletcher (MA, BA (Hons), Dip N, RGN), Lead Research Nurse (Immunohaematology), Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford OX3 7LE, UK.
Email: simon.fletcher@ouh.nhs.uk

Funding information
The Exigency study programme is funded by an unrestricted educational grant by uniQure Biopharma B.V. to Haemnet

Abstract

Background: Qualitative studies have explored why people with haemophilia (PwH) might consider or forgo gene therapy, the impact it has had on those who have received it, and what support might be needed throughout the process. No studies have yet examined what withdrawal prior to transfection might mean for PwH and their families.

Aims: To understand the experiences of PwH and their families of withdrawal from gene therapy and to understand what support mechanisms might be required.

Methods: Qualitative interviews were conducted with people with severe haemophilia who consented to take part in a gene therapy study in the UK but either withdrew or were withdrawn before transfection.

Results: Nine PwH and a family member were invited to this sub-study. Eight participants were recruited: six PwH (five haemophilia A and one haemophilia B) and two family members. Four participants were excluded from a study after consenting but before transfection, having failed to meet all the inclusion criteria; two withdrew after consenting but before transfection due to concerns including duration of factor expression and the time commitment involved in follow-up. The mean age of participants was 40.5 years (range 25–63 years). Two major themes emerged during the interviews: Expectation and loss.

Conclusions: PwH have many expectations about the difference gene therapy can make to their lives. Studies show that these expectations may not be fully realised. For those who have either withdrawn or been withdrawn from gene therapy, any expectations they had may now be unachievable. The nature of these expectations and the loss expressed by the participants indicate that support needs to be provided to help them and their families manage it.

KEYWORDS
clinical trials, decision making, gene therapy, grief and loss, haemophilia

1 | INTRODUCTION

Haemophilia is an X-linked recessive clotting disorder affecting 1:3333 men worldwide,[1] which results in a reduction or absence of factor VIII (FVIII) or factor IX (FIX). Untreated, it can cause spontaneous joint and muscle bleeds, progressive joint arthropathy, muscle contractures and disability.[2,3] Treatment involves replacement of the missing factor to reduce the incidence and severity of bleeding events.[4,5] Life expectancy and quality of life have improved for people with haemophilia (PwH) with the availability of replacement therapy, but limitations remain, including high treatment cost, risk of inhibitors and high treatment burden.[6,7] The recent introduction of extended

half-life factor products and FVIII mimetics has helped reduce treatment burden.[8,9] However, until the development of gene therapy platforms for haemophilia, the possibility of a cure, functional or complete, has been beyond reach for PwH.[10,11]

In current gene therapies for haemophilia, the gene of interest (a truncated FVIII gene or a full-length FIX (Padua) gene) is transferred into the nuclei of hepatocytes via an adeno-associated virus (AAV), instigating production of the relevant clotting factor.[12,13] The number of people worldwide who have received gene therapy is not readily available; UK records indicate that 31 PwH (22 haemophilia A, nine haemophilia B) have had gene therapy in ongoing clinical trials.[14] Access to gene therapy remains limited, restricted to a clinical trial setting. However, with the European Medicines Agency's provisional approval of valoctocogene roxaparvovec (Roctavian; BioMarin) for haemophilia A[15] and the US Food and Drug Administration's accelerated approval of etranacogene dezaparvovec (Hemgenix; CSL Behring) for haemophilia B,[16] the number of PwH wanting and having access to gene therapy is expected to increase dramatically. Van Overbeek et al.[17] indicate that over 80% of people with severe haemophilia would consider gene therapy if it were available. Some PwH will be unable to have gene therapy due to pre-existing or historic factor inhibitors or significant concomitant liver damage.[18] Others may be precluded because they have pre-existing neutralising antibodies to the AAVs used,[19,20] but they will not know this until they put themselves forward for gene therapy.

Qualitative studies are now exploring PwH's views and experiences of gene therapy, why they might choose or decline it,[21,22] and the impact it has had on those who have received it.[23–25] These show that the side-effects of adjunct supportive treatments, increased treatment burden during and immediately post-therapy period, and perceived changes to individual identity are among the most important considerations. To date, no studies have examined what withdrawal from a gene therapy study might mean for individual PwH and their families.

As part of the Exigency programme, exploring the knowledge, expectations and experiences of gene therapy among a range of stakeholders in the UK haemophilia community,[26] this sub-study seeks to explore the experiences of men with severe haemophilia who either withdrew from a gene therapy clinical trial or who were excluded during the screening process. Against the background of gene therapy being approved as a treatment option, it is important to understand what the impact of withdrawal or exclusion from gene therapy might mean for these individuals and their families, and what support mechanisms may be needed.

2 | METHODS

2.1 | Study design

Qualitative interviews were conducted with people with severe haemophilia who had consented to participate in a gene therapy study in the UK and who either withdrew or were excluded from a clinical trial before transfection. Each participant was given the option to be interviewed with a member of their family.

The interviews followed an interview guide[26] designed by the study team and a patient representative (a person with haemophilia who has had gene therapy). Questions addressed the individual's condition and treatment history, their decision to undergo gene therapy, the screening process, the reasons for withdrawing or being excluded, and how they felt following the experience.

2.2 | Recruitment and data collection

Participants were recruited through haemophilia centre referral, social media advertising, and word-of-mouth referral. All participants took part in a single interview with the principal investigator (SF) using the Zoom video meeting platform.

2.3 | Analysis

A study number was sequentially assigned to participants at consent (Exi101–Exi106 for those with haemophilia; ExiF101–ExiF102 for family members). All interviews were recorded, transcribed verbatim and inductively analysed to identify emergent codes and themes. After each interview, all codes and themes generated were reviewed before the subsequent interview. This iterative process enabled the exploration of themes as they emerged. Once all interviews were completed, all emergent codes were re-reviewed, further refined, and the final themes identified. No pre-defined code trees were created to ensure that all codes and themes defined emerged from the interviews rather than pre-existing researcher experience or the literature.[27,28]

3 | RESULTS

Nine PwH were invited to take part in this sub-study. Seven PwH and two family members were recruited. Six PwH and two family members were interviewed between January 2021 and January 2022. One participant withdrew before interview. At this point, based on available data for the number of PwH who had been excluded or withdrew from gene therapy clinical studies, a pragmatic decision was made to discontinue recruitment.

Five participants had haemophilia A and one haemophilia B. Four were on prophylaxis with a standard half-life product and two with an extended half-life product. The mean age of participants was 40.5 years (range 25–63 years). Demographic data are provided in Table 1; no demographic data for family members have been reported though relevant comments have been included. Four participants were excluded from a gene therapy study after consenting but before transfection: one failed screening due to a transient FVIII inhibitor history in childhood (unknown to the team prior to his consenting visit), one due to liver enzyme abnormalities, and two because they had AAV inhibitory antibodies. Two withdrew after consenting but before transfection: one was concerned about the durability of the treatment and follow-up sampling requirements; one withdrew over concerns about the

TABLE 1 Biographical information.

Participants with haemophilia					
Subject number	**Age range**	**Ethnicity**	**Haemophilia type**	**Treatment**	**Reason for withdrawal**
Exi101	20-29	White British	Haemophilia A	EHL	Liver enzymes out of range
Exi102	30-39	White British	Haemophilia A	SHL	Previous transient FVIII inhibitor
Exi103	20-29	White British	Haemophilia A	EHL	Personal choice
Exi104	40-49	White British	Haemophilia A	SHL	Personal choice
Exi105	40-49	White British	Haemophilia B	SHL	AAV antibody positive
Exi106	60-69	White African	Haemophilia A	SHL	AAV antibody positive
Family members					
Subject Number		**Age Range**		**Ethncity**	**Sex**
ExiF101		20-29		White British	Female
ExiF102		60-69		White African	Female

variability of factor expression and the unquantifiable risk of cancer. Both were also concerned about the time commitment requirements of the follow-up processes.

Two major themes emerged during the interviews: Expectation and Loss.

3.1 | Expectation

Each of the participants had clear reasons for wanting to participate in a gene therapy clinical trial and clear expectations about what they wanted from it. Two participants wanted to be able to do things that others take for granted.

> *'Part of the reason that gene therapy sounded so appealing is that it would mean I would be able to maybe go abroad without having to take loads of stuff with me'*
>
> [Exi103]

> *'Not be reliant on having to treat myself with prophylaxis, not being reliant on the treatment in order to govern my life, and to be able to be normal, and to be able to do things that other people do.'*
>
> [Exi106]

For two participants, the notion of gene therapy as a cure for their haemophilia was a strong motivating factor.

> Investigator: 'You mentioned earlier the "C" word, the "cure" word. Did you think of gene therapy as a cure?'
>
> PwH: *'Yes.'* Investigator: *'So, you'd thought of it as this was going to give you normal levels for the rest of your life.'*
>
> PwH: *'That's right, yes.'*
>
> [Exi101]

Two participants reported altruistic reasons for wanting to take part in a gene therapy study, thinking of future generations and family members rather than themselves.

> 'I wanted to go for that trial for all the reasons I said before and to be able to look my daughter in the eye, and to be able to look my grandkids in the eye, and to say, "So that you could have a better treatment I've trialled it. I'm one of these pioneers…"'
>
> [Exi105]

None of the family members interviewed spoke of specific expectations for gene therapy; they spoke more of affirming their partners' decision and supporting them through the process. One spoke of putting her desire to have children on hold to enable her partner to have gene therapy. Although disappointed for him, not having gene therapy meant that they could now focus on this:

> *'I sort of thought to myself, maybe selfishly, I thought, "Well, actually, maybe this clears the way for us to now start our family," and I thought, "Well, one door closes, another door opens," sort of thing, and that's what was meant to be, really.'*
>
> [ExiF101]

3.2 | Loss

Participants expressed various *feelings* associated with grief and loss, including denial, anger, bargaining, depression and acceptance.[29]

- *Denial*

One participant and his *partner* described a feeling of having had '*the rug pulled out from underneath*' and feeling like their hopes had been taken away [Exi106; ExiF102]. One participant described how,

following his exclusion, he began to stop '*expecting the new good thing, better treatment or whatever*' [Exi102]. Another spoke of going through a period of denial of his condition, to the point of not adhering to his treatment:

> *'I had a few weeks of me absolutely loathing the whole idea of haemophilia and anything to do with it.'*
>
> [Exi101]

The wider family were reported as having experienced similar emotions. One participant's wife described her parents' upset, saying her mother was '*heartbroken*' [ExiF101]. Another participant said that while it was '*a downer*' [Exi05] he feels it was worse for his parents than for him.

- *Anger*

All four participants who had been excluded from studies talked of being angry after being informed. One described it as *'a kick in the teeth'* [Exi101].

This anger was not always directed at the haemophilia care teams or research teams:

> *'I was a bit angry at myself for allowing myself to think that that would be it [a cure]. Having that hope and having it taken away is horrible.'*
>
> [Exi102]

Family members also experienced anger, one spouse describing her husband's exclusion as '*galling*' [ExiF101].

- *Depression*

One participant described how, despite being pragmatic at first, he went through a period of depression following his exclusion from a study.

> *'I remember being OK about it. For some reason, in the room I was just like, "Oh that's rubbish" and just sort of…But as soon as I left the centre, I honestly had a bit of an emotional breakdown, basically. I was devastated.'*
>
> [Exi102]

One described a period in which he stopped taking his prophylaxis.

> *'There were a few weeks where I just didn't even take an injection afterwards, until the point where my ankle pain started and I kind of had to go back to it.'*
>
> [Exi101]

His spouse spoke of being uncertain of how to help him and her concern that he was doing himself significant harm.

> *'I know that if I had medication that I'm supposed to be taking every day, if I stop taking it that would be it. So, I was a bit panicked. I remember feeling quite panicked. And it was just… it was quite sort of dark times.'*
>
> [ExiF101]

- *Bargaining*

Two participants rationalised their decision not to have gene therapy in light of questions about the technology, its safety and their current situations.

> *'The main thing that kind of stuck with me was the cancer risk. And that's…that's probably one of the main reasons I decided against it because I feel I can go on injecting myself twice a week. It takes 10, 15 minutes out of my week for both injections and I continue to lead a normal life.'*
>
> [Exi104]

Having initially been excluded from a trial due to having antibodies to the viral vector, Exi105 turned down an opportunity to take part in a subsequent phase of the same trial that allowed PwH with antibodies below a certain level to participate.

> *'If it wasn't for Covid, I would have done it this time around, hands down, without hesitation. But because of Covid, I can't reconcile it.'*
>
> [Exi105]

- *Acceptance*

All participants spoke of having to accept the inevitability and reality of exclusion or withdrawal from gene therapy.

> *'Everything happens for a reason, and I just had to say, "Okay, that hasn't happened, but life does go on. You've lived with this for years of your life anyway, so what's changed?"'*
>
> [Exi101]

This included acceptance of the 'experimental' nature of the studies they had hoped to participate in.

> *'For me, it was always, "Well, there's no guarantees." There's no guarantees with science.'*
>
> [Exi105]

> *'In hindsight I'm glad I sort of… I stepped in when I did. Because it's a trial and they're trying to gauge what works and what doesn't work, and that's why you're part of a trial.'*
>
> [Exi106]

However, for five participants, the process of moving on – and therefore dealing with their sense of loss – involved re-evaluating their lives

and resetting personal goals. Acceptance for two participants (Exi102, Exi105), involved the belief that, if the technology changes, it may be possible for them to have a different form of gene therapy in the future. Consideration of other novel treatments or the possibility of accessing a new replacement factor was key for two participants.

> *'There's an 'Elocta-Plus' coming out and potentially I'll go down to doing my treatment once a week.'*
>
> [Exi104]

Further supporting comments for all themes, with associated codes, can be found in Table 2.

4 | DISCUSSION

Discussions about the effect of participant withdrawal and exclusion in clinical trials have tended to focus primarily on the loss of reliable data, under-representation of minority groups and poor generalisability.[30,31] These are known and well-understood problems. What is less well understood is the effect that withdrawal and/or exclusion has had on trial participants. This issue has been studied in palliative care and malignant haematology, highlighting concerns about goals of care, emotional coping, and professional trust and support.[32,33] It has not been studied to any degree in haemophilia care, possibly because a 'curative' treatment for haemophilia has not previously been available. In treatment areas where it has been discussed, the family voice has rarely, if ever, been heard. Consequently, the potential impact of withdrawal and exclusion on PwH and what support they and their families might require is not understood.

Studies show that important considerations for PwH when thinking about whether they wish to have gene therapy include the possibility that it may change the way they understand their haemophilia and how they see themselves as individuals with haemophilia.[21,22] Four participants in this sub-study mentioned a desire to be 'normal', to be able to do the things everyone else can, among the reasons they wanted to have gene therapy. This raises the issue of PwH entering gene therapy with high and possibly unrealistic expectations around the difference it will bring to their lives, including normalisation, reduction in disease burden, and even a cure.[22,25] The presence of associated comorbidities and variances in treatment effect are among the reasons why these expectations may not be fully realised.[25,34]

The discussion as to whether gene therapy in its current form is truly curative is disputable. Studies have demonstrated both variability in overall levels of expression and a gradual decline in expression over time.[35,35] While FIX expression following haemophilia B gene therapy seems to be more stable and durable than FVIII with haemophilia A,[13,36,37] it remains too early to tell whether these results will be maintained over a longer timeframe. Despite this, gene therapy is being seen as a curative treatment among the patient community and general public,[38,39] and two participants in this sub-study spoke of gene therapy being a cure. As such, the implications and expectations for PwH considering gene therapy may be higher than for other currently available treatment modalities. Managing expectations is therefore key and should form part of a broader education around known and unknown possibilities.

There is increasing recognition of the potential need for psychological support for people who have undergone gene therapy as more becomes known about its impact.[40,41] However, little, if any, thought has been given to the support that individuals who are unable to have gene therapy may need. In this sub-study, all participants experienced feelings of expectation, loss and grief to varying degrees. Although more pronounced in participants who had been excluded from studies, these feelings were also demonstrated by those who withdrew from a study before transfection. In many ways, this should come as little surprise. The potential need for some level of psychological support should have been foreseen and offered as part of the clinical trials.

One of the factors associated with the loss caused by withdrawal or exclusion from a gene therapy trial is the suddenness of the event. Many PwH only find out they are ineligible after they have decided that it is something they wish to undertake and have had their expectations raised. The provision of regular AAV antibody testing, in advance of when the individual wants to have gene therapy, can help mitigate this and facilitate ongoing discussion and education around gene therapy as a potential treatment option.[42]

The need for ongoing AAV testing, psychosocial support and education will have significant implications for the provision of care when gene therapy becomes a standard of treatment. All proposed modalities, including the hub-and-spoke model favoured by the European Haemophilia Consortium and European Association of Haemophilia and Allied Disorders,[40,41] refer to the provision of support for PwH who have received gene therapy. They do not discuss the implications for PwH who may be unable to have gene therapy, and the impact of withdrawal or exclusion from gene therapy on partners, spouses and the wider family. These impacts need to be acknowledged and considered in any proposed model of care moving forward.

4.1 | Strengths and limitations

Although our study includes only a small number of participants, it is likely to represent a significant proportion of the PwH who were either excluded or withdrew from gene therapy clinical studies in the UK. Figures on those excluded or withdrawn have not been routinely published, despite being a standard reporting requirement.[45] One of the few groups to publish data report a 28% withdrawal/exclusion rate.[46] If this is consistent across all gene therapy studies and territories, the withdrawal/exclusion rate in the UK would be nine (28% of 32 known to have received gene therapy), though the true figure may be higher.

Despite this, the small sample size makes it difficult to infer that the results seen here are applicable beyond the UK. Further qualitative studies should be undertaken to ascertain whether similar concerns are evident in other territories, including lower and middle-income countries. Through understanding these issues more fully,

TABLE 2 Supporting quotes.

Theme	Participant number	Quote	Code
Expectations	Exi101	But I'm more than happy to be a guineapig to find out if it will work for my little brother	Altruism
		And I thought if we can make sure it works, we can get him on it and make his life way better, if you know what I mean	
	Exi106	To be able to be normal, and to be able to do things that other people do	Normality
	Exi102	I would just be normal, if you like. And that was great. That was sort of the goal of it all, to my mind anyway, in terms of haemophilia, was to get to a point where it's not even a thing anymore	
	Exi103	In my case, it's just much less stressful not having to worry about whether I can find a vein or not, and also because I'm now doing 26 injections a year rather than about 180	Reduction in burden
		I was just like, "Please say it's gene therapy, because if it is then I'm in." She was explaining it and I just thought, "Yes. Why not?" Because these injections are a bit of a pain. It was, "Yes, I want to do this." At that point, factor VIII injections had been such a toll and super-stressful and not good mentally either. It was just like if there was anything I could do to stop taking injections, I'll take it. I was in pretty much straight away	
Loss	Exi101	But like I said, there was that kind of… you know, "I've done all this, I've done all these different checkpoints."	Denial
	ExiF101	It was, it was gutting, wasn't it. It was, really.	
		It was quite sort of dark times. I just remember that sort of hue of depression over [him] and [he] just couldn't shake it. Yes, it was quite… it was quite sad to see him go through it	
		Your dad was really gutted for you when it didn't happen, and he was really supportive	
		Well, I just found it a bit… to me, him not even taking his medication was a bit scary	
	Exi102	I think it was just like there never was that possibility there because I had the inhibitor. It wasn't like that just then I was being told no; I actually didn't have a chance to have it at that point. So, to be upset, if you like, was understandable	Anger
		I think it was just that I'd allowed myself to think that that was it in terms of the haemophilia. And then, to have that gone was…	
	Exi106	It disappointed me. It disappointed my parents more. It disappointed my wife	
	Exi101	Yes, it was just the pain, the swelling, you know. I knew I was doing myself more harm. You know, self-harm isn't good, and not taking the injection is self-harm, in a sense. And I had a lot of support from my wife and I think that helped as well, so…	Depression
	Exi102	It was just an unfortunate misunderstanding rather than anything else, I guess. But no, I was proper devastated after that.	
	Exi101	And also my wife is about to go for IVF in the next few weeks at Oxford	Acceptance
		But it's great that, you know, she starts her treatment in a few weeks' time, and it's finally, hopefully happening, in a sense	
	Exi102	Yes, that's exactly it. It comes at you in waves, doesn't it, where you're just sort of… you come to terms with it and you think you are, and then no, you're not. I don't know. A good while	
		Only a few months after that I remember starting reading stuff about Hemlibra, and then obviously they've got the extended half-life products now	
		Yes, I think that's… yes, you're right. It was more upset at me being upset, if that makes sense. She knew how much it meant to me, but also that… She's very much the voice of reason, in that, like I say, it wasn't that I could have had it and then I didn't; it was that I never actually could have done at the point, how it was, so to sort of come to terms with that	
		Well, it's more like I would be just sort of a bit more wary about allowing myself that sort of… you know, to not be… not congratulating myself before I've crossed the finish line. Do you know what I mean? Just like it's done when it's done, but not to have too much hope riding on it until it is actually done and it is actually a thing	
	Exi105	My world wasn't rocked. I was like, "[sighs frustratedly] At least I've tried. At least I went for it. And there may be something else coming through the pipeline."	
	Exi106	I'm a little past it now and it would have been really nice to have it earlier, but I've still got… you know, I'm still relatively unscathed compared to some other people. And I want it to keep that way	

pharmaceutical and biotechnology companies will be able to better identify the support required in gene therapy trials going forward, especially as those for other haematological conditions such as von Willebrand's disease become available.[47]

5 | CONCLUSION

Despite its small sample size, this is the first study of its kind to explore the experience of PwH who have either withdrawn or been excluded from a gene therapy clinical trial. It shows that PwH entering into gene therapy have many expectations about the difference it will make to their lives, some of which may never be fully realised even if they are able to have it. For those who have either withdrawn or been excluded from trials, these expectations become unobtainable in many ways and are associated with a degree of loss. The sense of loss expressed by participants in this sub-study indicates that supportive measures need to be put in place and available before, during and after trial involvement, and similarly in models of care once gene therapy is more widely available, for both the individual and their family.

AUTHOR CONTRIBUTIONS

Study design, Simon Fletcher, Kate Khair and Mike Holland; Interview guide design;Simon Fletcher, Kate Khair; Interview facilitation; Simon Fletcher; Analysis of transcripts and definition of themes.;Simon Fletcher;Transcription of interview recordings; Kathryn Jenner; Initial draft of manuscript; Simon Fletcher; Review, amendment and approval of final manuscript; Simon Fletcher, Kathryn Jenner, Mike Holland and Kate Khair.

ACKNOWLEDGEMENTS

The authors would like to thank the participants of this study for sharing their views and time. Kate Khair, Kathryn Jenner and Michael Holland, are employees of Haemnet Ltd.;Simon Fletcher is undertaking a PhD funded by Haemnet Ltd.; The Exigency study programme is funded by an unrestricted educational grant by uniQure Biopharma B.V. to Haemnet; All relevant conflicts of interest have been acknowledged in the individual author declaration statements.; Trial registered on ClincalTrials.gov Jan 2021 - https://clinicaltrials.gov/ct2/show/NCT04723680

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All participants received information sheets detailing the purpose of the research. Written informed consent was obtained before each interview and confirmed verbally at each interview. All participants received a gift voucher for taking part. Ethical approval for the study was granted by the UK Healthcare Research Authority and the Southeast Scotland Research Ethics Committee (20/SS/0061).

ORCID

Simon Fletcher https://orcid.org/0000-0001-9018-6176

Kate Khair https://orcid.org/0000-0003-2001-5958

REFERENCES

1. Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The world federation of hemophilia annual global survey 1999–2018 *Haemophilia*. 2020;27:591-600. doi:10.1111/hae.14012
2. Curtis R, Baker J, Riske B, et al. Young adults with hemophilia in the U.S.: demographics, comorbidities, and health status. *Am J Hematol*. 2015;90:S11–6. doi:10.1002/ajh.24218
3. Manco-Johnson M, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357:535-544. doi:10.1056/nejme078098
4. 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. doi:10.1111/j.1365-2141.2010.08139.x
5. Srivastava A, Santagostino E, Dougall A, et al, Pierce GF on behalf of the WFH Guidelines for the Management of Hemophilia panellists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26:S1-S158. doi:10.1111/hae.14046
6. Farrugia A, Cassar J, Kimber MC, et al. Treatment for life for severe hemophilia A-A cost-utility model for prophylaxis vs. on-demand treatment. *Haemophilia*. 2013;19:e228–38. doi:10.1111/hae.12121
7. Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013;368:231-9. doi:10.1056/NEJMoa1208024
8. Maris M, Hermans C. A golden age for Haemophilia treatment? *Haemophilia*. 2018;24:175-176. doi:10.1111/hae.13411
9. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017:377:809-818 doi:10.1056/NEJMoa1703068
10. Nathwani AC, Tuddenham EGD, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in haemophilia B. *N Engl J Med*. 2011;365: 2357–2365. doi:10.1056/NEJMoa1108046
11. George LA, Sullivan SK, Giermasz A, et al. Haemophilia gene therapy with a high specific-activity factor XI variant. *N Engl J Med*. 2017;377:2215-2227. doi:10.1056/NEJMoa1708538
12. Chowdary P, Shapiro S, Makris M, et al. Phase 1–2 trial of AAVS3 gene therapy in patients with hemophilia B. *N Engl J Med*. 2022;387:237-2347. doi:10.1056/NEJMoa2119913
13. Rangarajan S, Walsh L, Lester W, et al. AAV5–factor VIII gene transfer in severe haemophilia A. *N Engl J Med*. 2017;377:2519-2530. doi:10.1056/NEJMoa1708483
14. United Kingdom Haemophilia Doctors' Organisation. *The UKHCDO Annual Report and Bleeding Disorder Statistics for the Financial Year 2019–2020*. Manchester: United Kingdom Haemophilia Doctors' Organisation; 2021 Available from: Accessed 12/03/2021. http://www.ukhcdo.org/wp-content/uploads/2021/03/UKHCDO-Annual-Report-2020-2019-20-Data_FINAL.pdf
15. European Medicines Agency. *First gene therapy to treat severe haemophilia A*. 24 June 2022. Accessed 9th Dec 2022. https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia#:~:text=Roctavian%20is%20the%20first%20gene,not%20cause%20disease%20in%20humans
16. Naddaf M. *Researchers welcome $3.5-million haemophilia gene therapy — but questions remain. Nature* 6 December 2022. Accessed 9th Dec 2022. https://www.doi.org/10.1038/d41586-022-04327-7
17. van Overbeeke E, Hauber B, Michelsen S, et al. Patient Preferences for gene therapy in haemophilia: Results from the PAVING

threshold technique survey. *Haemophilia*. 2021;27:957-966. doi:10.1111/hae.14401
18. Meisbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia: a patient and physician perspective. *Haemophilia*. 2019;25(4):545-557. doi:10.1111/hae.13769
19. Pipe SW. Delivering on the promise of gene therapy for haemophilia. *Haemophilia*. 2021;27(Suppl. 3):114–121. doi:10.1111/hae.14027
20. Standford 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;3:161-167. https://doi.ogr/10.1002/rth2.12177
21. van Overbeeke E, Hauber B, Michelsen S, et al. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. *Haemophilia*. 2020;27:129-136. doi:10.1111/hae.14190
22. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. *Haemophilia*. 2021;27:760-768. doi:10.1111/hae.14378
23. Meisbach W, Klamroth R. The patient experience of gene therapy for haemophilia: qualitative interviews with trial patients. *Patient Pref Adher*. 2020;14:767-770. doi:10.2147/PPA.S239810
24. Aradom E, Gomez K. The patient gene therapy journey: Findings from qualitative interviews with trial participants at one UK Haemophilia centre. *J Haem Pract*. 2021:32-44. https://doi.org10.17225/jhp00174
25. Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experiences of people with haemophilia and their families of gene therapy in a clinical trial setting: regaining control, the Exigency study. *Orphanet J Rare Dis*. 2022;17:155 doi:10.1186/s13023-022-02256-2
26. Fletcher S, Pembroke L, Holland M, Khair K. An 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. *BMJ Open*. 2022;12:e060351. doi:10.1136/bmjopen-2021-060351
27. Glaser BG, Strauss AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. Aldine Publishing Company; 1967.
28. Charmaz K. *Constructing Grounded Theory. Introducing Qualitative Methods Series*. 2nd ed. SAGE Publications; 2014.
29. Kübler-Ross E. *On Death and Dying*. Macmillan; 1969.
30. Hadidi N, Lindquist R, Treat-Jacobson D, Swanson P. Participant withdrawal: challenges and practical solutions for recruitment and retention in clinical trials. *Creat Nurs*. 2013;19:37-41. doi:10.1891/1078-4535.19.1.37
31. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. *J Clin Nurs*. 2010;19:227-233. doi:10.1111/j.1365-2702.2009.03041.x
32. Dresser R. *Silent Partners: Human Subjects and Research Ethics*. Oxford University Press; 2017.
33. Ulrich CM, Knafl K, Foxwell AM, et al. Experiences of patients after withdrawal from cancer clinical trials. *JAMA Netw Open*. 2021;4:1-12. doi:10.1001/2Fjamanetworkopen.2021.20052
34. Fletcher S, Jenner K, Holland M, Khair K. The lived experience of a novel disruptive therapy in a group of men and boys with haemophilia A with inhibitors: Emi & Me. *Health Expect*. 2021;1-12. doi:10.1111/hex.13404
35. Makris M. Gene therapy 1•0 in haemophilia: effective and safe, but with many uncertainties. *Lancet Haematol*. 2020;7(3): e186-e188. doi:10.1016/S2352-3026(20)30035-1
36. Pierce GF. Gene therapy for hemophilia: are expectations matching reality? *Mol Ther*. 2020;28(10):2097-2098. doi:10.1016/j.ymthe.2020.09.019
37. Pasi KJ, Rangarajan S, Mitchell N, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382(1):29–40. doi:10.1056/NEJMoa1908490
38. Ozelo MC, Mahlangu J, Pasi KJ, et al. For the GENEr8-1 trial group. Valoctocogene Roxaparvovec gene therapy for hemophilia A. *N Engl J Med*. 2022;386:1013–1025. http://doi.org/10.1056/NEJMoa2113708
39. Vasques-Loarte TC, Lucas TL, Harris-Wai J, Bowen DJ. Beliefs and values about gene therapy and in-utero gene editing in patients with hemophilia and their relatives. *The Patient – Patient-Centered Outcomes Research*. 202113:633–642. doi:10.1007/s40271-020-00442-7
40. Gallagher J. Transformational therapy cures haemophilia B. BBC. 2022. Accessed 25th June 2022. https://www.bbc.co.uk/news/health-62240061
41. Krumb E, Hermans C. Living with a "hemophilia-free mind" – the new ambition of hemophilia care? *Res Pract Thromb Haemost*. 2021;5:e12567. doi:10.1002/rth2.12567
42. Hermans C. Haemophilia gene therapy: experiences and lessons from treated patients. *Orphanet J Rare Dis*. 2022;17:154. doi:10.1186/s13023-022-02313.w
43. Khair K, Steadman L, Chaplin S, Holland M, Jenner K, Fletcher S. Parental perspectives on gene therapy for children with haemophilia: the exigency study. *Haemophilia*. 2020;27:120–128. doi:10.1111/hae.14188
44. Bok A, Noone D, Skouw-Rasmussen N, on behalf of the EHC Think Tank. Key challenges for hub and spoke models of care – a report from the 1st workshop of the EHC Think Tank on Hub and Spoke Treatment Models. *J Haem Pract*. 2022;9:20-26. doi:10.2478/jhp-2022-0003
45. Meisbach W, Chowdary P Coppens M, et al. Delivery of AAV-based gene therapy through haemophilia centres – a need for re-evaluation of infrastructure and comprehensive care: a joint publication of EAHAD and EHC. *Haemophilia*. 2021:27;967-973. doi:10.1111/hae.14420
46. International Committee of Medical Journal Editors (ICMJE). *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals*. 2022 Accessed 31st May 2022. https://www.icmje.org/recommendations/
47. George LA, Sullivan SK, Giermasz A, et al. Hemophilia B gene therapy with a high-specific-activity factor IX variant. *N Engl J Med*. 2017;377:2215-2227. doi:10.1056/NEJMoa1708538
48. Barbon E. *Engineering of Adeno-associated Viruses to Enhance Cell-specific Transduction*. ISTH 2022 12 July, London.

How to cite this article: Fletcher S, Jenner K, Holland M, Khair K. Expectation and loss when gene therapy for haemophilia is not an option: An exigency sub-study. *Haemophilia*. 2023;1-8. https://doi.org/10.1111/hae.14774

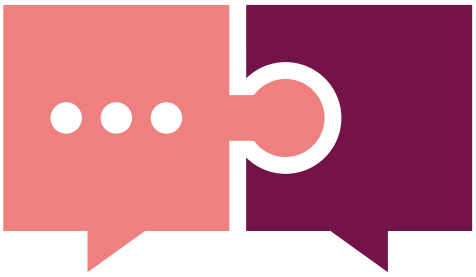
sciendo

CLINICAL PRACTICE

Shared decision-making for gene therapy in haemophilia care

Simon Fletcher, Kathryn Jenner, Kate Khair

Shared decision-making (SDM) is an important part of patient-centred care in which healthcare professionals (HCPs) and patients/caregivers jointly reach care decisions through a two-way exchange and synthesis of information based on clinical evidence and patient preference. SDM was described in haemophilia care in 2014 as two-sided intervention to aid patient decision-making. However, as the range of haemophilia treatments has expanded, identifying the optimal haemophilia treatment for an individual has become more complex. This is particularly so in the case of gene therapy, a one-time-only, irreversible treatment. In this context, it is vital that people with haemophilia (PwH) and their families continue to be involved in care decisions in an informed and interactive way. For gene therapy, this must include being well informed about the gene therapy process, enabling the patient to engage in fully informed SDM and consent, and ensuring that issues around long-term durability, potential side effects, the need for long-term follow-up are understood with a recognition that the 'unknown unknowns' are also unknown to HCPs. Both HCPs and patient organisations have a key role to play in providing PwH with access to relevant information and education, tailored to individual needs and free of jargon. Considerable education and support are required before PwH can make a truly informed decision about having gene therapy. Use of structured SDM tools such as the SHARE approach can help to support this. There is a need for SDM educational tools that include written/visual information and the use of standardised checklists may be helpful for both PwH and HCPs. The most important part of this process is that PwH want to undergo gene therapy – and this is only an option if they are fully educated and informed by fully educated and informed healthcare teams.



SHARED DECISION-MAKING

©Shutterstock/AlexKaplun

Education and support during the shared decision-making process is key to ensuring that people with haemophilia are able to make informed therapeutic choices as gene therapy becomes more widely available as a treatment option

SIMON FLETCHER
Haemnet Ltd, London, UK. Email: simon@haemnet.com

KATHRYN JENNER
Haemnet Ltd, London, UK

KATE KHAIR
Haemnet Ltd, London, UK

Keywords: *Shared decision-making, Haemophilia, Gene therapy, Patient education, Informed consent*

Shared decision-making (SDM) is a process by which healthcare professionals (HCPs) and patients or their caregivers jointly reach a decision about care, described in haemophilia care by Athale et al. in 2014 as a two-sided intervention including tools to aid patient decision-making [1]. As such, it forms a core part of patient-centred care [2].

Approaches to SDM vary according to its context, including both generic models and models developed for specific healthcare settings [3,4]. However, in all contexts, it is based on a two-way exchange and synthesis of information between HCP and patient, recognising the combined value of the medical knowledge of the HCP and the experiential knowledge of the patient [3,5]. The exchange should encompass clinical evidence and individual patient/caregiver preferences, beliefs and values, and must include consideration of the risks, benefits and possible consequences of different treatment options [2]. The patient/caregiver must understand these and the range of therapeutic options available to them; the HCP must be equipped to provide information to the patient/caregiver to support their understanding. While SDM is widely recommended in healthcare policy, the extent to which it is truly practised is unclear [6,7].

WHY IS SHARED DECISION-MAKING IMPORTANT IN HAEMOPHILIA CARE?

For many years, the choices for healthcare providers around haemophilia treatment options have been relatively simple: treatment on-demand to replace the missing coagulation factor when bleeds occur or, for people with severe haemophilia who bleed more frequently, initiating prophylaxis where sufficient factor concentrates are available [8]. The choice of treatment product, until recently, was limited to plasma-derived or recombinant products. Reducing the number of bleeds experienced was the greatest priority for people with haemophilia (PwH) [9], although the frequency of infusions under a prophylactic regimen led to greater treatment burden. Over time, the introduction of personalised prophylaxis, the modification of coagulation factor molecules to facilitate longer-acting treatments, and the development of non-factor replacement therapies have contributed to reducing this burden [10,11].

As contemporary haemophilia care has moved from factor replacement to novel therapies [12] and gene therapy [13], identifying the optimal haemophilia treatment for an individual is now a 'difficult and multifaceted process' [14]. It is therefore important that PwH and their families are involved in decisions around their care in an 'informed and interactive way'. Ensuring that bleed protection continues is essential but must be considered alongside the hopes and expectations of PwH with regard to new treatments. Healthcare providers must also recognise that, as patients with a long-term condition, PwH have acquired expertise through their own lived experiences and may have differing opinions about treatment from those of their healthcare providers [15].

SHARED DECISION-MAKING AND GENE THERAPY FOR HAEMOPHILIA

Gene therapy is a new therapeutic option that may become part of routine clinical care for haemophilia. The nature of haemophilia gene therapy necessitates a commitment to a long-term treatment journey on the part of the patient, as once the vector is infused, it cannot be removed. It is a one-time only, irreversible treatment. In this context, SDM becomes both more complex and more necessary.

PwH need to be well informed about the process of gene therapy and must be enabled to engage in fully informed decision-making and consent [16]. Issues around long-term durability of factor expression and potential side effects (which are not fully known) must be understood by PwH. It is not possible to predict outcomes for haemophilia gene therapy, and a good initial response does not preclude loss of expression leading to reduced factor expression or failure of gene therapy [17]. Data on longer-term outcomes remain unknown at present due to the limited long term follow up of PwH in gene therapy trials. The known side effects of gene therapy currently include infusion related reactions, liver function abnormality or toxicity, and side effects of corticosteroids or other immunosuppression [17]. There is a theoretical risk of integration of the vector into the host genome which may predispose to malignancy [18]. Currently immune response to the vector, inducing vector antibody formation, means that re-dosing with the same vector is not possible [17]. Potential recipients of gene therapy must understand the risks and the need for long-term (potentially life-long) follow-up within their decision-making process. It is, therefore, imperative that the understanding and expectations of PwH are central to all discussions about gene therapy as a treatment option, including 'unknown unknowns' about long-term impact [19].

HCPs and patient organisations both have a role in guiding and supporting PwH through their decisions around gene therapy as a treatment option [20], enabling them to be a full partner in the decision-making

process [14,21]. This should include ensuring that they are empowered to choose not to have gene therapy at any time in their gene therapy journey prior to infusion [22]. There is an assumption that HCPs will be able to support non-biased shared decision making. Valentino et al. [23] recommend the provision of education and training around SDM for all those who 'evaluate, administer and follow' candidates who may receive haemophilia gene therapy. This is important in minimising potential therapeutic biases that could result in HCPs who do not perceive benefits of gene therapy swaying SDM and vice versa, and unconscious bias linked with the ethnicity, culture or educational level of individual PwH [2].

Patient preferences must be understood in order to ensure decision-making that supports the individual situations of PwH. Within this, it is important to understand the cognitive biases that the patient may also bring to the SDM process [24]. Attentional bias, for example, may lead to a selective focus on the benefits of gene therapy versus the risks or vice versa [22]. Social biases may include the influence of family members who have different treatment preferences; and as gene therapy is a new mode of treatment, familial and community links with the contaminated blood scandal may raise concerns [22,25]. Information or misinformation about gene therapy in the public domain is another potential social bias. Self-perception bias linked with an individual's view of themselves as a person with haemophilia may also be a factor [22]. SDM provides a framework for discussing patient preferences and values in the context of available evidence [26].

HOW DO WE ENSURE SHARED DECISION-MAKING IS A REALITY?

For PwH to be fully involved in SDM in relation to gene therapy, they must have access to clear, relevant information and education. This should be based on tailored communication to ensure that those with 'low levels of health literacy or socioeconomic disadvantage' are not excluded [16,20].

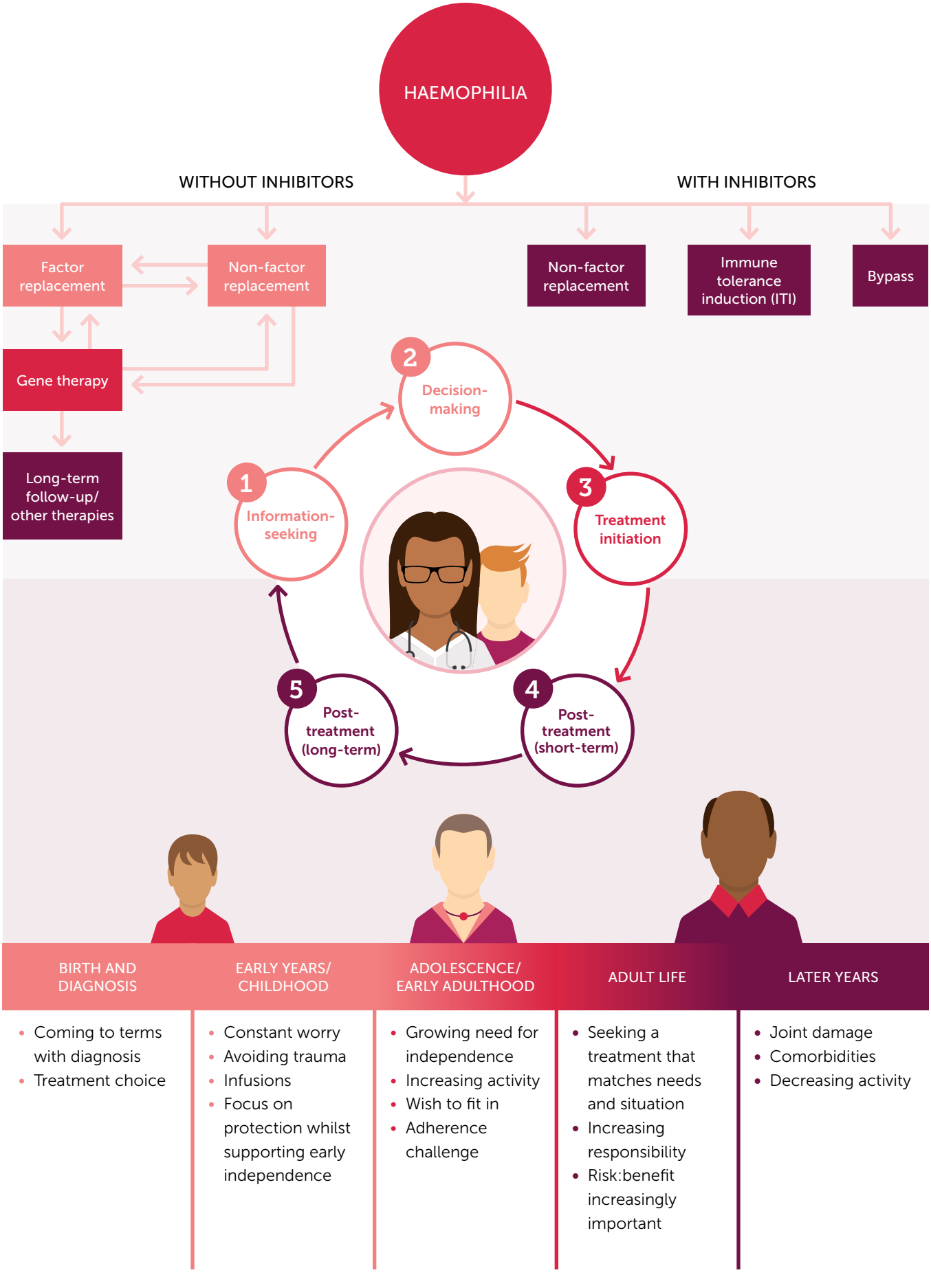
Hermans et al. [14] describe patient involvement and education as two key principles in SDM. This includes a focus on 'what really matters to patients and families in terms of treatment priorities, expectations and ambitions', and the use of 'jargon-free terminology'. All members of the healthcare team should be educated about new treatment options in order to be able to support PwH through the SDM process.

Supporting PwH in decision-making around gene therapy as a treatment option is a process (or journey) that may take a considerable amount of time from first discussion to dosing [21]. Wang et al. describe five pillars of the decision-making journey: 'pre-gene therapy information seeking', 'pre-gene therapy decision-making', 'treatment initiation', short-term post-gene therapy follow-up (≤ 1 year)', long-term post-gene therapy follow-up (> 1 year)' [19]. All of these elements must be considered when embarking on SDM discussions around haemophilia gene therapy and the process must not be rushed. Gene therapy is a complex treatment that, due to its nature, involves a complex and multifaceted decision-making journey that will be different for each individual (Figure 1). PwH will therefore require considerable education and support before they are able to make a truly informed decision.

The use of SDM structured tools to support patient decision-making is recommended as good practice [6]. The SHARE approach, designed by the US Agency for Healthcare Research and Quality, is commonly cited as an appropriate model in the context of haemophilia gene therapy [2,20,21]. This five-stage process is based on 'Seeking patients' participation, Helping patients explore and compare management options, Assessing patients' values and preferences, Reaching a decision with patients, and Evaluating the patient's decision' [27]. While this model provides an important point of reference for the role and responsibilities of HCPs in SDM, it assumes that interaction is led by the HCP rather than the patient. However, the discussions that occur as part of the SDM process do not necessarily have to begin with HCPs. PwH may seek to initiate conversations around gene therapy, including SDM, and it is important that HCPs foster an environment in which this can happen. In either case, PwH must also be aware of their role in the SDM process, including education (supported by the HCP), careful consideration of benefits and risks, and open communication with the HCP around treatment goals and preferences [28].

There is a need for SDM educational tools that include written/visual information about the benefits and risks of gene therapy treatment, expectations and realities, and the need for long-term monitoring and follow-up [14,16,21]. Standardised checklists may be helpful for both PwH and HCPs, within and outside of the clinical setting. Having a point of reference of this kind can help to ensure that all elements that need to be discussed in clinic are discussed [18]. In the US, Limjoco and Thornburg have consulted people with haemophilia A and HCPs on the development of an SDM tool or tools for gene therapy, incorporating a checklist and taking both perspectives into account [29,30]. PwH felt that having access to an SDM

Figure 1. The patient decision-making journey in the current treatment landscape (cf. Wang et al., 2022) [19]



tool laying out the pros and cons of gene therapy would support their decision-making outside of clinic through enabling further review and discussion with their families. The proposed checklist included education about gene therapy, risks, comparison with other treatments, follow up, impact on mental health and quality of life [29]. A tool aimed at facilitating HCP discussion has been developed, which can be used during patient discussions on gene therapy in combination with the SDM tool developed by the World Federation of Hemophilia (WFH) [27,30,31]. The WFH SDM tool is designed to assist with treatment selection and includes a significant number of downloadable patient education materials comparing currently available treatments alongside gene therapy [31]. It describes the SDM journey of reflecting on current personal goals and available treatments, considering future options and confirming a decision about treatment. As this tool will be widely accessible, it has the potential to support both HCP and PwH through the decision-making process. Going forward, the role and value of tools such as these should continue to be assessed from the perspectives of both PwH and healthcare providers [16,20].

For some PwH, SDM may be a new concept. They may have had little engagement in decision-making about their treatment previously and may perceive SDM as an intimidating prospect [2]. Patient organisations can play a valuable role in respect of both explaining new treatment paradigms such as gene therapy and supporting PwH in SDM [20]. This may include, for example, providing educational materials that support health literacy [16] and peer support groups to facilitate discussion about the process of gene therapy [21]. Support should be available for PwH for whom gene therapy proves not to be an accessible treatment option [32], and for PwH who would like to have gene therapy but whose choice is not supported by their healthcare provider or organisational policies.

CONCLUSION

SDM is an important aspect of haemophilia care and is a necessity as gene therapy becomes a more widely available treatment option. With haemophilia gene therapy, healthcare professionals are asking PwH to make decisions about a treatment that may not work as well as they had hoped, that can currently only be undertaken once, and for which we cannot offer long-term safety guarantees. It is therefore essential that they are equipped with the knowledge, skills and confidence to support SDM. Recent recommendations from the UK National Institute for Health and Care Excellence (NICE) for research around measuring the effectiveness and sustained implementation of SDM in the clinical setting [6] should be considered in the context of haemophilia treatment choices and SDM for haemophilia gene therapy.

Education and support of PwH during the SDM process using currently available and developing SDM tools [27,30,31] are paramount to ensure fully informed individual decision-making and consent. The development of tools to ensure equitable access to education and information about haemophilia gene therapy and the patient journey are now starting to be developed. Patient organisations are key in supporting their members to make appropriate decisions about gene therapy, as well as campaigning for access and funding as these treatments become clinically available. The most important part of this process is that PwH want to undergo gene therapy – and this is only an option if they are fully educated and informed by fully educated and informed healthcare teams.

ACKNOWLEDGEMENTS

Simon Fletcher, Kathryn Jenner and Khair Khair are employees of Haemnet Ltd. Kate Khair is a shareholder of Haemnet Ltd and Editor-in-Chief of *The Journal of Haemophilia Practice*. Kathryn Jenner is Technical Editor of *The Journal of Haemophilia Practice*.

This paper does not contain any studies involving human participants or animals performed by any of the authors.

ORCID

Simon Fletcher https://orcid.org/0000-0001-9018-6176
Kathryn Jenner https://orcid.org/0000-0002-2704-0606
Kate Khair https://orcid.org/0000-0003-2001-5958

REFERENCES

1. Athale A, Giguere A, Barbara A, Krassova S, Iorio A. Developing a two-sided intervention to facilitate shared decision-making in haemophilia: decision boxes for clinicians and patient decision aids for patients. *Haemophilia*. 2014 Nov;20(6):800-6.
2. Valentino LA, Blanchette V, Negrier C, O'Mahoney B, Vias V, Sannie T, Skinner M. Personalising haemophilia management with shared decision making. *J Haem Pract* 2021; 8(1) 69-79. doi:10.17225/jhp/00178
3. Bomhof-Roordink H, Gärtner FR, Stiggelbout AM, Pieterse AR. Key components of shared decision making models: a systematic review. *BMJ Open* 2019; 9: e031763. doi: 10.1136/bmj.open-2019-031763.
4. Légaré F, Härter M, Stiggelbout AM, Thomson R, Stacey D. Choosing treatments and the role of shared decision-making. In: North J, Nolte E, Merkur S, Anell a (eds.), *Achieving Person-*

Centred Health Systems: Evidence, Strategies and Challenges. 2020. Cambridge: Cambridge University Press. 283-316. doi: 10.1017/9781108855464.014.
5. Charles C, Gafni A, Whelan A. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. *Soc Sci Med* 1999; 49(5): 651-61. doi: 10.1016/s0277-9536(99)00145-8.
6. National Institute for Health and Care Excellence. Shared decision making. NICE guideline [NG197]. Published 17 June 2021. Available from *https://www.nice.org.uk/guidance/ng197* (accessed July 2023).
7. Elwyn G, Durand MA, Song J, et al. A three-talk model for shared decision making: multistage consultation process. *BMJ* 2017; 359: j4891. doi: 10.1136/bmj.j4891.
8. Srivastava A, Santagostino E, Dougall A, et al.; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26 Suppl 6:1-158. doi: 10.1111/hae.14046.
9. Mühlbacher AC, Sadler A, Lamprecht B, Juhnke C. Patient preferences in the treatment of hemophilia A: A Best-Worst Scaling Case 3 analysis. *Value Health* 2020 Jul;23(7):862-869. doi: 10.1016/j.jval.2020.02.013.
10. Coppola A, Franchini M, Pappagallo G, et al. Current choices and management of treatment in persons with severe hemophilia A without inhibitors: a mini-Delphi consensus. *J Clin Med* 2022; 11(3): 801. doi: 10.3390/jcm11030801.
11. Fletcher S, Jenner K, Holland M, Khair K. The lived experience of a novel disruptive therapy in a group of men and boys with haemophilia A with inhibitors: Emi & Me. *Health Expect* 2022; 25(1): 443-454. doi: 10.1111/hex.13404.
12. Gualtierotti R, Pasca S, Ciavarella A, et al. Updates on novel non-replacement drugs for hemophilia. *Pharmaceuticals (Basel)* 2022; 15(10): 1183. doi: 10.3390/ph15101183..
13. Gogia P, Tarantino M, Schramm W, Aledort L. New directions to develop therapies for people with hemophilia. *Expert Rev Hematol* 2023 Mar 8:1-17. doi: 10.1080/17474086.2023.2184341. Epub ahead of print.
14. Hermans C, Noone D, Benson G, et al. Hemophilia treatment in 2021: Choosing the "optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians. *Blood Rev* 2022; 52: 100890. doi: 10.1016/j.blre.2021.100890.
15. 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. doi: 10.1111/j.1365-2516.2008.01926.x.
16. Woollard L, Gorman R, Rosenfelt DJ. Addressing patient education priorities in the era of gene therapy for haemophilia: Towards evidence-informed shared decision-making. *Haemophilia* 2021; 27(2): e302-e304. doi: 10.1111/hae.14214.
17. Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. *Blood*. 2021 Sep 16;138(11):923-931
18. Miesbach W, Foster GR, Peyvandi F. Liver-related aspects of gene therapy for haemophilia: Call to action for collaboration between haematologists and hepatologists. *J Hepatol* 2023; 78(3): 467-470. doi: 10.1016/jhep.2022.11.014.
19. Wang M, Negrier C, Driessler F, Goodman C, Skinner MW. The hemophilia gene therapy patient journey: questions and answers for shared decision-making. *Patient Prefer Adherence* 2022; 16: 1439-1447. doi: 10.2147/PPA.S355627.
20. Limjoco J, Calatroni A, Aristizabal P, Thornburg CD. Gene therapy preferences and informed decision-making: Results from a National Hemophilia Foundation Community Voices in Research survey. *Haemophilia* 2023; 29 (1): 51-60. doi: 10.1111/hae.14706.
21. Noone D, Astermark J, O'Mahoney B, et al. The journey of gene therapy in haemophilia – putting the patient at the centre of the hub and spoke model. *J Haem Pract* 2022; 9(1): 156-166. doi10.2478/jhp-2002-0021.
22. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The Exigency study. *Haemophilia* 2021; 27(5): 760-768. doi: 10.1111/hae.14378.
23. Valentino LA, Kaczmarek R, Pierce GF, Noone D, O'Mahoney B, Page D, Rotellini D, Skinner MW. Hemophilia gene therapy: First do no harm. *J Thromb Haemost* 2023 June 21. doi: 10.1016/j.tha.2023.06.016. [Epub ahead of print].
24. Savioni L, Triberti S. Cognitive biases in chronic illness and their impact on patients' commitment. *Front Psychol* 2020; 11: 579455. doi: 10.3389/fpsyg.2020.579455.
25. Khair K, Steadman L, Chaplin S, et al. Parental perspectives on gene therapy for children with haemophilia: The Exigency study. *Haemophilia* 2020; 27(1): 120-128. doi: 10.1111.
26. Politi MC, Dizon DS, Frosch DL, Kuzemchak MD, Stiggelbout AM. Importance of clarifying patients' desired role in shared decision making to match their level of engagement with their preferences. *BMJ* 2013; 347: f7066. doi: 10.1136/bmj.f7066.
27. The SHARE Approach. Agency for Healthcare Research and Quality, Rockville, MD. *https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html* (last accessed March 2023).
28. Nossair F, Thornburg CD. The role of patient and healthcare professionals in the era of new haemophilia treatments in developed and developing countries. *Ther Adv Hematol* 2018; 9(8): 239-249. doi: 10.1177/2040620718784830.
29. Limjoco J, Thornburg CD. Gene therapy for hemophilia A: A mixed methods study of patient preferences and shared decision-making. *Patient Prefer Adherence* 2023 Apr 19;17:1093-1105. doi: 10.2147/PPA.S406894.
30. Limjoco J, Thornburg CD. Development of a haemophilia A gene therapy shared decision-making tool for clinicians. *Haemophilia* 2023 July 4. doi: 10.1111/hae.14822. Epub ahead of print.
31. Noone D, Chadwick J, Coffin D, Hayes B, Kaeser G, Naccache M, Skinner M, Sannie T, Thornburg C, Pierce G. A new tool to assist in treatment selection – the World Federation of Hemophilia (WFH) shared decision making (SDM) tool. Presented at ISTH 2023 (in press).
32. Fletcher S, Jenner K, Holland M, Khair K. Expectation and loss when gene therapy for haemophilia is not an option: An Exigency sub-study. *Haemophilia* 2023; 29(3): 776-783. doi: 10.1111/hae.14774.

HOW TO CITE THIS ARTICLE:
Fletcher S, Jenner K, Khair K. Shared decision-making for gene therapy in haemophilia care. *J Haem Pract* 2023; 10(1): 62-67. *https://doi.org/10.2478/jhp-2023-0009*.

Fletcher *et al.*
Orphanet Journal of Rare Diseases (2024) 19:59
https://doi.org/10.1186/s13023-024-03068-2

Orphanet Journal of Rare Diseases

RESEARCH

Open Access

Barriers to gene therapy, understanding the concerns people with haemophilia have: an exigency sub-study

Simon Fletcher[1,2*], Kathryn Jenner[1], Michael Holland[1] and Kate Khair[1]

Abstract

Background Gene therapy has the potential to offer people with haemophilia (PwH) a life free from bleeding and the burden posed by current treatment regimens. To date, gene therapy has only been available in clinical trial settings, to PwH without pre-existing or historical factor inhibitors, significant concomitant liver damage or pre-existing neutralising antibodies to the adeno-associated viruses used to deliver the therapy. Thus, most PwH treated at centres not currently involved in gene therapy trials, either as a referral/follow-up centre or as a dosing centre, have been unable to access the therapy. This Exigency sub-study aims to gain a greater understanding of the opinions of PwH in the United Kingdom who have not had access to gene therapy: asking what they understand, what concerns they have, and whether they perceive any barriers preventing their access to gene therapy.

Results Twenty-three PwH were approached; 14 consented, and one withdrew prior to interview. The mean age of the participants was 35.7 years (range 25–74 years). Eleven had haemophilia A and two haemophilia B. Two were treated with standard half-life factor products, five with extended half-life products, five with a FVIII mimetic and one with a clinical trial product. One family member (a participant's partner) was also interviewed. The participants identified four barriers to gene therapy: concerns about the process of gene therapy (Expectations), uncertainty about the results (outcomes), (Access) to treatment, and a lack of understanding about gene therapy (education).

Conclusions This Exigency study subgroup sees gene therapy as a positive treatment development that promises an improved quality of life. For this participant group, four issues impact their decision to undergo gene therapy. If the promise of gene therapy is to be realised, these barriers need to be acknowledged and addressed by healthcare professionals, patient organisations, and gene therapy providers.

Keywords Haemophilia, Gene therapy, Shared decision-making, Outcomes, Quality of life

Background

Gene therapy offers people with haemophilia (PwH) the potential of a life free from prophylactic factor replacement therapy and spontaneous joint bleeding [1, 2]. The availability of gene therapy for haemophilia has, however, been constrained as it has only been available as part of a clinical trials programme. Restrictive inclusion and exclusion criteria including age (≥18 years), pre-existing or historical inhibitors, significant concomitant liver damage and pre-existing neutralising antibodies to the adeno-associated vector (AAV) used have also limited its availability [1, 3–5].

Two gene therapy products have now been granted marketing approval in Europe and the United States [6, 7] with more expected in the next 12 months [8]. While it

*Correspondence:
Simon Fletcher
sfletcher26@aol.com
[1] Haemnet, London N15 3JR, UK
[2] Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE, UK

is likely that many of the restrictive inclusion and exclusion criteria seen in the clinical trials will be maintained in the marketed product, a growing number of PwH will soon be able to access gene therapy. The hub and spoke model of care proposed by the European Haemophilia Consortium and the European Association of Haemophilia and Allied Disorders [9, 10], will mean that those centres not previously part of a trials programme will be able to access the specialist expertise necessary to facilitate access to gene therapy for the PwH in their care.

Qualitative studies have explored the impact of gene therapy on those who have had it [11–13] and those who were excluded from having it [14]. A number of studies have also examined what the wider haemophilia community thinks of gene therapy and whether it is a treatment they would consider [15, 16]. This sub-study, part of the larger Exigency study [17], seeks to build on this body of knowledge by investigating perceptions of and concerns about gene therapy among PwH in the United Kingdom (UK) who have not yet been able to access it, and to identify the barriers to access they perceive if and when it becomes a standard of care (SoC) treatment option.

Results

We approached 23 PwH and consented 14. One withdrew before interview. Recruitment was discontinued after 13 interviews (participant codes Exi201–Exi213) as we deemed data saturation had been achieved. The method described by Guest, Namey and Chen, was used to assess saturation [18]. Five data collection events were used to calculate the base size (105), with three data collection events per run length of two interviews. A < 5% new information threshold was used for the level of saturation confidence (see Table 1).

The mean age of participants was 35.7 years (range 25–74 years). Eleven had haemophilia A; two had haemophilia B. All participants were on prophylaxis, two on standard half-life (SHL) factor products, five on extended half-life (EHL) products, four on a FVIII mimetic and one on a clinical trial product. Demographic and treatment details for the participants are given in Table 2**.**

All participants saw gene therapy as a positive development and one that had the potential to improve the quality of life (QoL) of PwH,

> *'I think its advancement in treatment. It's the next stage in treatment.'*
> *[Exi204]*
> *There's people who'd benefit from that [gene therapy] to give them a better quality of life.*
> *[Exi207]*

There were, however, four key barriers which they suggested might prevent them and others from having gene therapy:

- *Expectations*: concerns about the process of gene therapy
- *Outcomes*: uncertainty about the results
- *Access* to treatment
- *Information*: a lack of information about gene therapy.

Expectations

Despite having a limited understanding of all the processes involved in gene therapy, many participants were aware of some and had concerns about them. Ten were worried about possible side effects and associated consequences of having gene therapy. Three participants knew of people who had had gene therapy and required steroids to maintain factor expression. Their concerns centred on the side effects they had seen, including weight gain, insomnia and immunosuppression, a particular concern during the Covid-19 pandemic.

> *'I did some reading and then I also know just from social media what it was like to go through the process, and I just thought the process looked awful, really, to be honest.'*
> *[Exi205]*
> *'And granted, the circumstances of [the individual] but also when he went on it he had to go on immu-*

Table 1 Data saturation calculation

Interview Number	1	2	3	4	5	6	7	8	9	10	11	12	13
New themes per interview	22	19	23	18	23	14	12	9	8	5	2	3	1
# Base themes					105								
New themes per run						26		17		7		4	
% New terms						24.8%		16.2%		6.7%		3.8%	

Table 2 Biographical and treatment data

	Exi201	Exi202	Exi203	Exi204	Exi205	Exi206	Exi207	Exi208	Exi209	Exi210	Exi211	Exi212	Exi213
Age	74	32	57	42	23	29	26	25	25	53	24	24	30
Haemophilia Type	A	A	A	A	B	A	A	A	A	A	A	A	B
Ethnicity	White	White	White	Asian	White	White	White	White	White	White	White	White	White
Treatment Centre	HTC	CCC	CCC	CCC	CCC	CCC	HTC	HTC	HTC	CCC	HTC	CCC	CCC
Current treatment	Extended Half-Life Product	FVIII Mimetic	FVIII Mimetic	FVIII Mimetic	Extended Half-Life Product	FVIII Mimetic	Extended Half-Life Product	Standard Half-life Product	Extended Half-Life Product	Standard Half-life Product	Extended Half-Life Product	FVIII Mimetic	Clinical Trial Product

HTC haemophilia treatment centre, *CCC* comprehensive care centre

nosuppressants, which at the time of Covid and all that stuff it… Covid in itself was just another big issue.'
[Exi212]

Three participants were concerned about the level of commitment and engagement that gene therapy would involve. Two acknowledged that it had the potential to improve their overall QoL but believed it would also increase their treatment burden, particularly in the short term.

'The fact is I really enjoy the treatment I'm on. I chose this treatment because I can't be bothered dealing with haemophilia – I want to just treat and forget. And obviously, that's maybe one of the selling points of gene therapy, but not in its current formation when there's so much baggage attached to it.'
[Exi202]
'I just can't be bothered with the faff [inconvenience], to be honest.'
[Exi211]

Three participants thought that the commitment required for follow-up was manageable on a personal level, but two did not think their employers would be as accommodating, potentially impacting their ability to have gene therapy.

'For me, it would be fine. Whether my employer had the same sort of mindset.'
[Exi208]

Outcomes

Five participants expressed concerns about the outcomes of gene therapy, with two citing rumours that the factor levels achieved were not as good as they would wish:

'To be fair, if someone said to me, "Ok, we'll go for gene therapy, your levels are going to be 60," I'd jump at it now. But the fact of, "Ok, we don't know what's going to happen and how you're going to react to it," it's too much of a risk for me at this moment in time.'
[Exi206]

Others had heard that the treatment was not as durable as they would hope. One reported he would sooner *'wait until there was more longevity data available'* [Exi208] before being ready to decide to have gene therapy.

Four participants stated that gene therapy would impact their independence and lead to an increased reliance on their treatment centre:

'I knew exactly how to look after myself, for lack of a better term. It wasn't the best treatment for me because I was treating daily. However, I knew exactly how to play it, and I knew if I did my injection in the morning I was covered. When I moved to [FVIII mimetic], I went from treating every day to once a week and then to fortnightly, and I'll go away for a weekend or I'll go and do something and I get paranoid that I'm not covered because I'm so used to having that injection and knowing that I've topped my levels up and I can go and do this thing. So, I think taking gene therapy and taking the injections entirely out of the equation might be a little bit too much.'
[Exi206]
'Right now, I think, my life is quite settled in the sense of I'm treating every fortnight, I'm doing it on my own, I don't need to go to my treatment centre other than for my six-month check-up.'
[Exi212]

Three participants were concerned that rather than reduce their treatment burden, gene therapy would add an administrative burden to their lives they were unwilling to accept:

'The biggest impact haemophilia has on me isn't the bleeding, it's not even the joint damage, it's all the paperwork, it's all the bureaucracy, the admin, managing hospital appointments, managing home deliveries that never quite go right. So, any more paperwork, like haemophilia admin […] I don't see the need to take on any more bureaucracy. I don't see what gene therapy is going to add to pay that value, pay that extra cost.'
[Exi202]
'[There would be] a lack of independence because I'd have to ring my centre – "I've got a bleed. What do I do?" where I've spent so long being like, "I'll do what I want. I'm going to do something stupid, so I'll take an extra dose."'
[Exi206]
'I think there's going to be so much health surveillance attached to it right now, compared to I do a subcut injection twice a month and have a five-minute clinic conversation once every six months. Why would I trade that in?'
[Exi207]

One participant even stated the treatment he received, as someone with severe haemophilia, was better than he would have after gene therapy as a person with mild haemophilia.

'I'm very much of the belief that because treatment's available to severe haemophiliacs I sometimes have a better quality of life than some

with mild and moderate [Haemophilia]. So, I wouldn't want to go through all that to then become essentially a mild haemophiliac, if you will, when mine is much more manageable because the treatment is there.'
[Exi206]

Access

Eleven participants had concerns about who would decide which PwH would be offered gene therapy and on what grounds any decision would be made.

None of the participants in this sub-study were treated at centres involved in gene therapy clinical trials and they had, therefore, been unable to access gene therapy. Two acknowledged that their centre was not large enough to have been involved in gene therapy studies; however, three believed their centre was large enough to have been involved but had actively decided not to participate in the gene therapy clinical trials. They also thought their centre would be unlikely to offer gene therapy if and when it becomes available as a SoC treatment option.

'I think [my centre] has made a decision that "We're going to get all our patients we can onto [names product]".
[Exi204]
'It's almost like you are steered towards a particular treatment or a particular brand of treatment.'
[Exi203]

Three participants stated that their care team made treatment decisions in good faith, based on benefit to the individual; for example, because they *'last longer in your system, you're getting fewer bleeds now'* [Exi203]. Three, however, said this was not always the case, and two said that despite having compelling reasons to switch treatment, their care teams were not always willing or able to consider it.

'The treatment that I am on, I had to argue heavily to get onto it. I'd spent a few years asking for an extended half-life, was getting told, "No, your current treatment's working for you." And it was working for me because I was fiddling the doses I was taking, and I told them that.'
[Exi206]

One described having never been aware that a choice was available, saying it had always been a case of,

'"this [treatment] is coming, we're about to sign a contract, this is the plan." So, it's more about, "This is the plan, this is what we're going to do, and at some point you'll move across to this."'
[Exi204]

Five were aware that, ultimately, cost drives treatment choice and availability of treatment.

'I know the NHS is always focused on this cost-price analysis about…you know, the utilitarian argument about how do we get the best gain with the smallest amount of money.'
[Exi205]

As a result, they felt that, in reality, they had little say over what treatments they could access. Most did not think the advent of gene therapy would change this due to its cost.

'Unfortunately, I personally believe it's always going to come down to cost as number one. And I know that might make me come across a bit bitter, but I think it will always be cost one, patient two.'
[Exi208]
'From everything I've heard about gene therapy, it costs a lot of money.
[Exi205]

Two participants thought the cost of gene therapy would be so prohibitive that it would be better to direct research into treatments that have the greatest impact on the greatest number of people with haemophilia.

Information

Though all the participants had been aware of gene therapy for more than a decade, seven said they were concerned about the lack of easily accessible and understandable information. Although four had searched for information about gene therapy online, one said the propensity for *'misinformation on the internet*' [Emi210] made him reluctant to use it as a resource. Four participants stated that even when information was available, much of it was too complicated.

'I think if there'd have been more communication, different communication, more layman's term communication, that would have enabled haemophiliacs to make a more informed choice on their treatment, that would have been great.'
[Exi203]
'The language [is] still very medically orientated and not for the layman.'
[Exi207]

One participant said that some healthcare professionals (HCPs) were bad at explaining the therapy's complexities in an easily digestible form.

'I ask a question…a 30-second question and get a 25-minute answer. [my consultant] can be half an

hour, 40 minutes, 50 minutes, and by that time… What I would love is simple stuff. Simple, just easy for me to break down, easy for me to understand, easy for me to make a decision on.'
[Exi203]

Two participants thought there was a lack of information simply because it was not known.

'I think they should be putting more information out, but I'd like to know if they actually have the information themselves. That's the thing I'm really curious about because I'm not so sure they do. I'm not sure they've potentially got this actual data to show us all yet.'
[Exi205]

Three participants said that clinicians at their centres did not have the time to provide information about gene therapy, meaning they lacked the knowledge needed to make any decision about gene therapy as a treatment option.

'I only have a five-minute conversation with my consultant anyway, about every six months. He phones me up and says, "Are you doing all right?" and I say yes. He says, "Have you had any bleeds?" and I say no. And that's it.'
[Exi201]
'I have briefly mentioned it over the phone and I don't think it sits right with my consultant at that moment in time – but since then there's been no discussions around it.'
[Exi208]

Further supporting quotes can be found in Table 3.

Discussion

All participants in this study saw gene therapy as a positive development in the treatment of haemophilia. However, they also expressed concerns that present barriers to gene therapy.

The most significant concern, related to the need for steroids following gene therapy and their potential side effects. Even though not all clinical trials necessitated the use of steroids [19, 20], there was a widespread perception that, following gene therapy, there would be a need to take of steroids for prolonged periods. The level of concern expressed about the side effects, particularly immunosuppression, may always be a general concern but may also have been heightened during the Covid-19 pandemic when the interviews were taking place. The concern may, therefore, decrease as the pandemic continues to wane. The prospect of further pandemics [21, 22] may, however, mean there will always be concern about immunosuppressive medication following gene therapy. Further research is needed to ascertain whether immunosuppression will remain a necessary feature of gene therapy or whether alternative strategies can be used.

In common with other studies [3, 23, 24], many participants had concerns about the outcomes of gene therapy. However, rather than focusing on factor expression and durability, these related more to the need for an increased level of engagement with clinical services in the first 6–12 months, and a perceived additional burden related to the treatment of bleeds.

The ability to treat bleeds quickly and effectively has been a key advantage of home treatment [25]. Participants appeared to be concerned that treating bleeds after receiving gene therapy would involve contact with or a need to attend their haemophilia centre, which represented a 'backwards step', even if bleed frequency was reduced.

Many participants also felt their current treatments did not significantly impact their lives and were, therefore, reluctant to consider a change that might increase the frequency of interaction with their treatment centre, even if it was only in the short term. Consequently, some said they would be hesitant to pursue gene therapy as a treatment option. Similar concerns were expressed in other Exigency sub-studies [13, 16]. This may highlight a genuine concern among PwH, but may also reflect another perceived barrier the participants discussed: a lack of accessible, patient-focused information.

A number of participants stated that the language used to discuss gene therapy was too complicated and not pitched at a level they could easily understand. As a result, some said they were unable to decide whether gene therapy would or would not be an appropriate treatment for them. There is, therefore, a need for gene therapy providers, haemophilia care teams and patient organisations to do more to enable all PwH to fully understand its nature and implications. This should include plain language summaries, patient education leaflets, visual materials and engagement events, with consideration given to individual communication needs [26].

Recent discussion about gene therapy, education and decision-making has focused on shared decision-making (SDM). The concept of SDM was first described in the late 1980s as a reaction against the paternalistic nature of decision-making [27, 28], but it was first used in the context of haemophilia care in 2014 [29]. SDM is based on a two-way exchange of information between patients and HCPs [30–32], and seeks mutual understanding and agreement between the medical knowledge of HCPs and the beliefs, preferences, and experiences of patients/caregivers [33–35]. There is a concern, however, that SDM may retain features of the paternalistic decision-making

Table 3 Supporting quotes

Expectations	
Exi202	Why would I trade [what I have] for having to hike up to London every week or something for bloods for six months?
Exi203	I think if it's a cure… It doesn't cure all the joint replacements, it doesn't cure the arthritis, it doesn't cure the hepatitis, it doesn't cure the cirrhosis—it just solves a problem, which is bleeding. That's what it does, it solves a problem. It means that you don't bleed anymore. Does that mean that haemophilia is cured? It may do. I just don't… The word doesn't sit right with me for some reason
Exi205	And then also, just the process itself. I thought at the time… I mean, when I was doing some reading, I was still at Uni and I thought no way I'm doing anything like this at Uni, going in and out of that process
	But just the process of going in and out of hospital multiple times… And then even when I went to [names hospital] last year and did some more reading about it at that stage, I thought it was going to get mentioned in some form of a conversation about what it is and the future, as it always does now. But I just thought I'm not so sure I want to make my immune system go to tatters when we're part of a worldwide pandemic, and also, I'm not so sure this is the most responsible thing to be doing in an NHS Covid crisis, really
	There's not enough evidence, not enough data behind that, and not enough people really going through the process of it yet
Exi208	At the moment, it's a little bit, I feel, like… not a waste of time, but I just feel like if you're going through it you'll put a lot of strain probably on your family as well as your work. I just feel that's probably quite a massive reason why I wouldn't feel comfortable going along with it
	My lifestyle at the moment, it fits around my treatment process. So, I just kind of want to keep it as much as normal as I can
Exi211	They might be quite open to it, but I've only just started this job so… I'd have to… probably give it a while before I…
Exi212	Yes… I mean, thinking of where personally I am now with college and where I'll be next year, if—if—I were to be, say, going on it next year, next year is one of the most important years for not only graduating college but then also setting up my professional life. So, that's not something I'd really want to sabotage by going onto this, and then having the next X, Y, Z. The pay-off just wouldn't be worth it when the medication that I'm on is allowing me to live the lifestyle that I currently am
Exi213	If we're speaking exclusively on haemophilia, then I think it's quite a gold mine because there's just so many options out there. It's better now to be growing up with haemophilia than it was ten years ago, and obviously ten years before that and so forth. Hopefully, children that are born with haemophilia A now, for example, they're not going to have as much joint damage as I do
Outcomes	
Exi201	It's an interesting question, because certainly when they talked about [grandson] having gene therapy, his mother had said a flat no until another few years until they see if there are any side-effects that come out
	Her reason is give it 20 years and see what happens. Because the last time we discussed it was in the very early days and she was saying we don't know what the side-effects are, we don't know what the long-term effects are, we don't know how long the effects will last, we don't know whether it will be worse after if they do come back
Exi202	Maybe in ten years when it is one and done, maybe that will be different
	If my treatment wasn't performing as well, maybe that would be a different question, a different equation almost
Exi203	If they turned around and said, 'Right, gene therapy is for you for all these reasons,' and I ask, 'Well, what are the chances of it working? What are the chances of it failing? What's the chance of me never needing to inject again?' You know, the fact that I'm 57… 'What's the risk of bleeds?' To me, all the answers there are all unknowns because it's gene therapy, it's new
	I don't think. I think, for me, it's the way… I guess the way the language is all about curing haemophilia, and I find that a little bit uncomfortable in that haemophilia is therefore defined as this problem to be fixed, and therefore I am… there's something wrong with me that needs to be corrected, rather than 'Here's some drugs that can allow you to live a flourishing life'
Exi205	For starters, everyone's saying it could work, it might not work, so ok we're in a 50/50 situation, flip of the coin anyway. And then it might work but you might only get to 12 percent. You might only get to 12% potentially, or you might be 95%. I mean, it really is a flip of the coin, and we don't really know… And there's no logical reason… there doesn't seem to be a logical reason right now about where you sit
	I think there are so many other things that could come first to make haemophilia better at a far more reasonable cost and would have a far more direct impact on 99 percent of people if we started doing it tomorrow morning
Exi206	The same with gene therapy. There's a lot of talk of roughly eight years because that's as much data as we have, and maybe levels dwindle. So, especially getting older, would I take that one jab for eight decent years and then go back to being a normal haemophiliac? Maybe. It's difficult to quantify it and to make the decision based on that because… it does work for a lot of people… it's just you don't know… It's like a lottery, though—you go into it and you don't know what level you're going to get
	I think it's the finality of gene therapy. Moving onto [Names FVIII Mimetic Product], if it doesn't quite work for me—I know, and I've discussed it with my centre about switching to an extended half-life because that's still an option. But if you go onto gene therapy and it doesn't quite work, what situation are you left in?
Exi212	But then I also think… well, I also kind of like the security that I have with my medication, knowing that if I take my medication like I'm supposed to then nothing's going to happen. Whereas with gene therapy I feel like there's still a lot that's kind of unknown
Access	
Exi202	It's not been mentioned to me. Again, I have struggles trying to get them to elaborate on basic things like what's happened to those scans you did, no I don't want to be changed from the current treatment I'm on. So, no—no discussions about gene therapy
	I changed centre during Covid, so that's been a huge barrier to just accessing a lot of things in general
Exi203	And I don't know the politics behind the decision-making that different treatment centres have got. I don't want to get involved in that, but I assume and I'm guessing that different treatment centres have got different views because of different levels of funding or whatever it might be

Table 3 (continued)

	But it is kind of 'We think this is going to be good for you for these reasons,' and I go, 'Yes, if it stops me from bleeding then great, fantastic.' I did push the [names treatment] one though. I did say, 'I want to do this as soon as possible.' So, that's the only one time that I've gone in and said, 'Can we stop faffing around with this once-every-two-days stuff? I want to change because I'm hearing great things.' And they just said, 'Yes, we'll do it as soon you're fit and ready.' And we did and it's been great
Exi204	So there is a financial part of it, but [my centre] is a big centre, similar to other areas, so I presume they have leverage in terms of how it would work… So, it's just understanding how the decisions are made. But we're not given a choice
	I think the NHS has to ultimately derive the greatest value from the smallest amount of money
Exi206	There are still some times where we butt heads, which… rightly so, because they'll say one thing and I will try and argue my point against it. But it's a much more open conversation. I'm not being dictated to as to what I need to do. They will listen to me and offer their advice, so it's much better
	From everything I've heard about gene therapy, it costs a lot of money and it's a bit of a 50/50 thing
Exi207	The centre I was at was not very helpful, would not refer me to the centre to get onto the trial—which at the time I was very annoyed about
Exi208	I don't think I'd be one of the main patients to benefit from it in their eyes. So, when you look at the list of priorities—because it's not going to go to everyone on that patient list—I wouldn't be top of that list
Exi211	So, I didn't even know it was a thing until I went on Facebook, to be honest. And then I spoke to a few more people around my age and they said they're all on it, so I just wondered why I've not been offered it
Exi212	It was that they got a cheaper deal buying a bigger bunch of, say… I can't remember what any of them are called, but they get a bigger deal for buying more of the same product, so they'll buy that, put more patients out on it, because obviously it saves them more money at the end of the day. So, I understand that it's not really a possibility to have "Oh, here's all these different products for all these different patients who need what they need." I understand the constraints on that
Exi213	At all the centres that I've been to it's just not something that's been brought up with me at all
Information	
Exi201	I learnt about it when my daughter told me about it. I've always ignored my haemophilia, I'm not part of any real haemophilia group or…I'm not a member of the Haemophilia Society and I don't read things about it. And I don't have any things that come into my inbox about it. It's just one of those things I've tried to… well, I just have ignored. So, I heard about it when [she] told me about it
	Not that I'm aware of it. Mind you, I only have a five-minute conversation with my guy anyway, about every six months. He phones me up and says, "Are you doing all right?" and I say yes. He says, "Have you had any bleeds?" and I say no. And that's it
Exi203	I think what has always frustrated me a little bit is there's no sort of education about the different treatments in layman's terms. I'm headlines and not detail, just like a lot of other people—I do the headline and the detail I expect layman's terms information
Exi205	I think they should be putting more information out, but I'd like to know if they actually have the information themselves. That's the thing I'm really curious about because I'm not so sure they do. I think that's why they might all be… none of them are putting information out because I'm not sure they've potentially got this actual data to show us all yet
	And doing some reading about it… The thing I've found with reading about it is… like I said, being a person who's focused by data, there just never was anywhere that told me the exact… not an exact number, but ranges were very coy and ranges were too big that I don't want to get involved in that
Exi207	I don't think so. I'd have to go search it and do a bit of a… like, you'd have to do a dive in the studies because it's still in trial period, so the information's not that easy to ask, like at the snap of your fingers
	So, my first consultation there took about three and a half hours because we literally sat there and went through everything. There are still some times where we butt heads, which… rightly so, because they'll say one thing and I will try and argue my point against it. But it's a much more open conversation
Exi208	But I think the thing for me is… I think I'd want to just see a bit more of the longevity results. And I think if I was to ever make the move… I think this time last year I was a definite no, but I think the idea around it is actually… I think it is going to probably be the future. So, for me, I'd probably actually want to speak to someone –when I say 'someone' I mean not my direct team but maybe someone who's gone through the process, as such—first. But short term, the next 12 to 24 months, I probably would still be a no if it was offered
	Yes. I mean, I'm sure there is a vast amount of evidence and results out there. But the next step is probably accessing it and how easy it is to access it. I'd like to think I'm at a reasonable level, where I can go out and find that sort of stuff. But other than the AGM for The Haemophilia Society, I have found it quite hard to kind of find information, or up-to-date information anyway
Exi209	So, I think it's a mixture of there is the info out there, but you've got to look for it, it's not fed to you on a plate, and also hearing experiences from people who have actually been through it. I think if you're not proactive to find someone like that then there's not enough information
Exi211	I feel like there's still not enough to go on here—which is fine, because it's still new, they still don't have as big a pool of people that are on it to say, "Here's what our research shows"
	Getting the consultants to speak about it a bit more, really. [My consultant] doesn't actually really tell me about anything that's new. The nurse tries to but the consultant obviously leads the consultation, so…

process it initially sought to resolve, including limiting the number of available options, framing and nudging [36–38], many of which seem to have been experienced by many participants in the study. Despite these concerns, the core concepts of SDM—active dialogue, mutual understanding and agreement—must remain central to the educational process to enable PwH to choose the most appropriate treatment option for them at any given time, whether gene therapy or another of the available therapies [39].

SDM to support access to haemophilia gene therapy, however, may be impacted by another concern raised by the participants: cost. Aware that treatment for haemophilia is expensive, and that their access to treatment has always been limited by its cost, many participants were anxious that haemophilia gene therapy may be yet more expensive. They were concerned that gene therapy might not be considered cost-effective and that, as a result, its availability would be limited or even prohibited, as has been seen in other conditions [40]. Indeed, at the time of writing, draft guidance from the National Institute for Health and Care Excellence (NICE) has not recommended the first gene therapy product as a treatment option in the UK [41]. It may be that until more long-term data regarding expression, durability, and efficacy is available, many PwH will remain unable to access gene therapy. Until such time that access is available to all, some commentators have suggested that stakeholders—patients, patient advocacy groups and clinicians—should seek to evidence the everyday realities and difficulties of living with haemophilia, including treatment burden and anxiety induced by the ongoing fear of potential bleeds [42].

Strengths and limitations

Some aspects of this study may affect the generalisability of its findings. These relate to the size and structure of the study sample, the study setting, and the qualitative aspect of its methodology.

Participants in the study were under the care of centres not involved in gene therapy clinical trials. However, as this means they would have had less access to the information about gene therapy, the authors believe this makes them more representative of the majority of PwH in the UK. The sample included fewer people with haemophilia B than people with haemophilia A. This was not seen as a concern as the majority of the issues raised related to gene therapy processes, outcomes, education and access, and were not therefore, therapy or condition specific.

That the study was conducted in a high-income country where access to factor prophylaxis is readily available. Findings therefore may not be representative of the views of PwH in lower and middle-income countries. Further research should be undertaken in other economic territories to address this.

The nature of qualitative research makes it difficult to generalise any data collected. Its strength lies in the ability of qualitative inquiry to provide meaning and deeper understanding in specific situations [43, 44]. Through both meta-analyses and syntheses, qualitative sources can have application beyond their immediate context [45, 46]. This paper, therefore, should not be seen in isolation but within the growing body of qualitative haemophilia gene therapy studies [11, 13, 15, 47].

Conclusion

This Exigency study subgroup sees gene therapy as a positive treatment development that promises a greatly improved QoL. However, four significant issues were identified that could present barriers to participants considering gene therapy as a treatment option: the processes involved, the outcomes of gene therapy, access to gene therapy, and the availability of information. If the promise of haemophilia gene therapy is to be realised, these barriers need to be acknowledged and addressed by HCPs, patient organisations, and gene therapy providers. If, however, it is not possible to resolve these barriers fully, it is essential that PwH are enabled, through a SDM process, to access an available treatment option that offers the QoL they seek.

Material and methods

Design

Exigency is a mixed methods study designed to explore the opinions of PwH and their families in the UK about gene therapy [17]. This sub-study focuses on PwH who have not yet had the opportunity to participate in a gene therapy programme because they are under the care of a centre not currently involved in ongoing clinical trials.

Following a brief indicative literature review, the study team and a patient representative designed a semi-structured interview schedule (See Additional file 1: Appendix 1). The guide addressed issues including the participant's condition, their treatment history, their understanding of gene therapy for haemophilia, why they think they have not yet been offered the possibility of taking part in a gene therapy study, and how gene therapy might be accessible in the future as a treatment option (18). The guide was used as a template for the interviews, but the interviewer (Principal Investigator) was free to explore any of the issues raised in more depth. He we also encouraged to explore any issue discussed in a previous interview if it had been discussed (unprompted) on at least two previous occasions.

Recruitment

Participants were recruited through participant identification centre referral, social media advertising and word-of-mouth referral. The eligibility criteria allowed for the recruitment of all people with either haemophilia A or B who could give written informed consent and had a good command of English. All participants and a family member, if available, took part in a single one-hour semi-structured interview using a video conferencing platform. All interviews were carried out by the principal researcher (SF). Three of the 13 participants were known to the principal researcher prior to their participation in the study. Video conferencing was used during the Covid-19 pandemic as a social distancing strategy. It was continued post-pandemic as it was convenient and popular and has been shown to provide rich qualitative data [48–50].

Data collection

Analysis

At consent, each participant was assigned an individual study number. All interviews were recorded (audio and video), transcribed, and thematically analysed inductively. NVivo for Mac (version 12) was used to facilitate the coding process. Field notes were made following each interview. All interviews were coded within five working days by the principal investigator. Seven of the interviews were randomly re-coded by a second investigator (KK) and both investigators met once a month

Table 4 Coding diagram

Primary codes	Secondary codes	Themes
Changing goalposts	Concerns about the processes of gene therapy	Expectations
Immunosuppression		
COVID-19		
Increased burden		
Employment concerns		
Identity		
Increased medicalisation		
Reduced choices		
	Uncertainty about the results of gene therapy	Outcomes
Increased bureaucracy		
Cure		
Durability		
Benefits of		
Factor levels		
Not just gene therapy		
Anxiety		
	Access to treatment	Access
Infected blood		
Inhibitor		
Cost		
Gatekeeping		
Clinical trials		
Treatment centre		
	A lack of understanding of gene therapy	Information
Discussions about GT		
First Introduction to GT		
Understanding of GT		
Not enough information		
HCP don't understand it		
Unwillingness/Inability to discuss		
"I don't understand it"		
Not enough information		
Too complicated		

to discuss all completed interviews to ensure the reliability of the interview process and code generation. Previously created field notes were also be reviewed to provide added context to the discussion. This process was continued until saturation was achieved and the interviews discontinued. Upon completion of the interviews, the study team reviewed all the emergent codes, refined them further, and identified the final themes (see Table 4).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-024-03068-2.

Additional file 1. Exigency Interview guide.

Acknowledgements
The authors would like to thank the participants of this study for sharing their views and time.

Author contributions
Study design—SF, KK, and MH; Interview guide design—SF and KK; Interview facilitation—SF; Analysis of transcripts and definition of themes—SF; Transcription of interview recordings—KJ; Production of manuscript—SF; Review, amendment and approval of final manuscript—SF, KJ, MH and KK.

Funding
An unrestricted educational grant by uniQure Biopharma BV to Haemnet funds the Exigency study programme.

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available, as none of the participants consented to this. The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Each participant was sent a copy of the study PIS detailing the rationale and goals of the study. Written informed consent was then obtained prior to interview and confirmed verbally at the interview. The study was reviewed by the UK Healthcare Research Authority and the Southeast Scotland Research Ethics Committee (20/SS/0061), and approval was granted for all study elements.

Consent for publication
All participants have consented to their anonymised data being used in any presentation or publication.

Competing interests
Simon Fletcher, Kate Khair, Kathryn Jenner and Michael Holland are employees of Haemnet Ltd. Simon Fletcher is undertaking a Ph.D. funded by Haemnet Ltd.

PPI Statement
The Exigency Protocol was written with the assistance of a patient representative (a person with haemophilia who has subsequently gone on to have gene therapy). This representative was also involved in the design of the interview schedule. The protocol was also reviewed before REC submission by two patient representatives: a woman with Haemophilia with an affected son, and a partner of a person with haemophilia.

Received: 3 October 2023 Accepted: 3 February 2024
Published online: 10 February 2024

References

1. Nathwani AC, Tuddenham EGD, Rangarajan S, Rosales C, McIntosh J, Linch DC, Chowdary P, Riddell A, Pie AJ, Harrington C, O'Beirne J, Smith K, Pasi J, Glader B, Rustagi P, Ng CYC, Kay MA, Zhou J, Spence Y, Morton CL, Allay J, Coleman J, Sleep S, Cunningham JM, Srivastava D, Basner-Tschakarjan E, Mingozzi F, High KA, Gray JT, Reiss UM, Nienhuis AW, Davidoff AM. Adenovirus-associated virus vector-mediated gene transfer in haemophilia B. N Engl J Med. 2011;365:2357–65. https://doi.org/10.1056/NEJMoa1108046.
2. George LA, Sullivan SK, Giermasz A, Rasko JEJ, Samelson-Jones BJ, Ducore J, Cuker A, Sullivan LM, Majumdar S, Teitel J, McGuinn CEM, Ragni V, Luk AY, Hui D, Wright JF, Chen Y, Liu Y, Wachtel K, Winters A, Tiefenbacher S, Arruda VR, van der Loo JCM, Zelenaia O, Takefman D, Carr ME, Couto LB, Anguela XM, High KA. Haemophilia gene therapy with a high specific-activity factor XI variant. N Engl J Med. 2017;377(23):2215–27. https://doi.org/10.1056/NEJMoa1708538.
3. George LA, Monahan PE, Eyster ME, Sullivan SK, Ragni MV, Croteau SE, Rasko JEJ, Recht M, Samelson-Jones BJ, MacDougall A, Jaworski K, Noble R, Curran M, Kuranda K, Mingozzi F, Chang T, Reape KZ, Anguela XM, High KA. Multiyear factor VIII expression after AAV gene transfer for hemophilia A. N Engl J Med. 2021;385:1961–73. https://doi.org/10.1056/NEJMoa2104205.
4. Rangarajan S, Walsh L, Lester W, Perry D, Madan B, Laffan M, Yu H, Vettermann C, Pierce GF, Wong WY, Pasi KJ. AAV5–factor VIII gene transfer in severe haemophilia A. N Engl J Med. 2017;377:2519–30. https://doi.org/10.1056/NEJMoa1708483.
5. Perin GQ, Herzog RW, Markusic DM. Update of clinical gene therapy for haemophilia. Blood. 2018;33:407–14. https://doi.org/10.1182/blood-2018-07-820720.
6. European Medicines Agency. First gene therapy to treat severe haemophilia A. 24 June 2022. Accessed 9th Mar 2023. Available from: https://www.ema.europa.eu/en/news/first-gene-therapy-treat-severe-haemophilia#:~:text=Roctavian%20is%20the%20first%20gene,not%20cause%20disease%20in%20humans.
7. Naddaf M. Researchers welcome $3.5-million haemophilia gene therapy—but questions remain. Nature. 2022;612:388–9. https://doi.org/10.1038/d41586-022-04327-7.
8. McName A. Pfizer takes on haemophilia B gene therapy market with new FDA application Fidanacogene elaparvovec could be a strong contender against CSL's Hemgenix gene therapy. Pharmaceutical Technology [internet] June 27, 2023Accessed 4th September 2023. Available from www.Pharmaceutical-technology.com/news/pfizer-haemophilia-b-gene-therapy-fda-application/#:~:text=Pfizer%20has%20announced%20that%20the,(MAA)%20currently%20under%20review
9. Miesbach W, Chowdary P, Coppens M, Hart DP, Jimenez-Yuste V, Klamroth R, Makris M, Noone D, Peyvandi F. Delivery of AAV-based gene therapy through haemophilia centres—a need for re-evaluation of infrastructure and comprehensive care: a Joint publication of EAHAD and EHC. Haemophilia. 2021;27:967–73. https://doi.org/10.1111/hae.14420.
10. Srivastava S. Cell and gene therapy is transforming healthcare. Part 2. Cell & Gene; 2020. Accessed 15th April 2023. Available from: https://www.cellandgene.com/doc/part-cell-and-gene-therapy-istransforming-healthcare-0001.
11. Meisbach W, Klamroth R. The patient experience of gene therapy for haemophilia: qualitative interviews with trial patients. Patient Prefer Adherence. 2020;14:767–70. https://doi.org/10.2147/PPA.S239810.
12. Aradom E, Gomez K. The patient gene therapy journey: Findings from qualitative interviews with trial participants at one UK Haemophilia centre. Journal of Haemophilia Practice. 2021;8:32–44. https://doi.org/10.17225/jhp00174.
13. Fletcher S, Jenner K, Pembroke L, Holland M, Khair K. The experiences of people with haemophilia, and their families, of gene therapy in a clinical trial setting: regaining control, the Exigency study. Orphanet J Rare Dis. 2022;17:155. https://doi.org/10.1186/s13023-022-02256-2.
14. Fletcher S, Jenner K, Holland M, Khair K. Expectation and loss when gene therapy for haemophilia is not an option: an exigency sub-study. Haemophilia. 2023. https://doi.org/10.1111/hae.14774.
15. van Overbeeke E, Hauber B, Michelsen S, Peerlinck K, Lambert C, Hermans C, Le PQ, Goldman M, Simoens S, Huys I. Patient perspectives regarding gene therapy in haemophilia: interviews from the PAVING study. Haemophilia. 2020;27:129–36. https://doi.org/10.1111/hae.14190.

16. Fletcher S, Jenner K, Holland M, Chaplin S, Khair K. An exploration of why men with severe haemophilia might not want gene therapy: The exigency study. Haemophilia. 2021;1:9. https://doi.org/10.1111/hae.14378.
17. Fletcher S, Pembroke L, Holland M, Khair K. 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. BMJ Open. 2022;12:e060351. https://doi.org/10.1136/bmjopen-2021-060351.
18. Guest G, Namey E, Chen M. A simple method to assess and report thematic saturation in qualitative research. PLoS ONE. 2020;15(5):e0232076. https://doi.org/10.1371/journal.pone.0232076.
19. George LA, Sullivan SK, Giermasz A, Rasko JEJ, Samelson-Jones BJ, Ducore J, Cuker A, Sullivan LM, Majumdar S, Teitel J, McGuinn CE, Ragni MV, Luk AY, Hui D, Wright JF, Chen Y, Liu Y, Wachtel K, Winters A, Tiefenbacher S, Arruda VR, van der Loo JCM, Zelenaia O, Takefman D, Carr ME, Couto LB, Anguela XM, High KA. Hemophilia B gene therapy with a high-specific-activity factor IX variant. N Engl J Med. 2017;377(23):2215–27. https://doi.org/10.1056/NEJMoa1708538.
20. Pipe SW, Leebeek FWG, Recht M, Key NS, Castaman G, Miesbach W, Lattimore S, Peerlinck K, Van der Valk P, Coppens M, Kampmann P, Meijer K, O'Connell N, Pasi KJ, Hart DP, Kazmi R, Astermark J, Hermans CRJC, Klamroth R, Lemons R, Visweshwar N, von Drygalski A, Young G, Crary SE, Escobar M, Gomez E, Kruse-Jarres R, Quon DV, Symington E, Wang M, Wheeler AP, Gut R, Liu YP, Dolmetsch RE, Cooper DL, Li Y, Goldstein B, Monahan PE. Gene therapy with etranacogene dezaparvovec for hemophilia B. N Engl J Med. 2023;388:706–18. https://doi.org/10.1056/NEJMoa2211644.
21. Akhter S, Akhtar S. Emerging corona virus diseases and future perspectives. VirusDis. 2020;31:113–20. https://doi.org/10.1007/s13337-020-00590-2.
22. Basnet BB, Basnet R, Panday R. Prospects for controlling future pandemics of SARS in highlights of SARS-CoV2. VirusDis. 2021;32:770–3. https://doi.org/10.1007/s13337-021-00715-1.
23. Nathwani AC, Tuddenham E, Chowdary P, McIntosh J, Lee D, Rosales C, Phillips M, Pie J, Junfang Z, Meagher MM, Reiss U, Davidoff AM, Morton CL, Riddell A. 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. Blood. 2018;132:489. https://doi.org/10.1182/blood-2018-99-118256.
24. Chowdary P, Shapiro S, Davidoff AM, Reiss U, Alade R, Brooks G, Dane A, McIntosh J, Short G, Tuddenham E. 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. Blood. 2018;132:631. https://doi.org/10.1182/blood-2018-99-118050.
25. Mahlangu J, Dolan G, Dougall A, Goddard NJ, Hernandez EDP, Ragni MV, Rayner B, Windyga J, Pierce GF, Srivastava A. Chapter 7: Treatment of specific hemorrhages. In: A Srivastava, E Santagostino, A Dougall, S Kitchen, M Sutherland, SW Pipe, M Carcao, et al on behalf of the WFH Guidelines for the Management of Hemophilia panellists and co-authors. WFH Guidelines for the Management of Hemophilia. Haemophilia. 2020:26(Suppl 6): 85–94. https://doi.org/10.1111/hae.14046
26. Noone D, Astermark J, O'Mahony B, Peyvandi F, Khair K, Pembroke L, Jenner K. The journey of gene therapy in haemophlia. Putting the patient at the centre of the hub and spoke model. J Haem Pract. 2022;9(1):156–66. https://doi.org/10.2478/jhp-2022-0021.
27. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: What does it mean? (Or it takes at least two to Tango). Soc Sci Med. 1997;44(5):681–92. https://doi.org/10.1016/S0277-9536(96)00221-3.
28. Waldron T, Carr T, McMullen L, et al. Development of a program theory for shared decision-making: a realist synthesis. BMC Health Serv Res. 2020;20:59. https://doi.org/10.1186/s12913-019-4649-1.
29. Athale A, Giguere A, Barbara A, Krassova S, Iorio A. Developing a two-sided intervention to facilitate shared decision-making in haemophilia: decision boxes for clinicians and patient decision aids for patients. Haemophilia. 2014;20(6):800–6. https://doi.org/10.1111/hae.12495.
30. Sandman L, Munthe C. Shared decision making, paternalism and patient choice. Health Care Anal. 2010;18(1):60–84. https://doi.org/10.1007/s10728-008-0108-6.
31. Bomhof-Roordink H, Gärtner FR, Stiggelbout AM, Pieterse AR. Key components of shared decision making models: a systematic review. BMJ Open. 2019;9:e031763. https://doi.org/10.1136/bmj.open-2019-031763.
32. Valentino LA, Blanchette V, Negrier C, O'Mahoney B, Vias V, Sannie T, Skinner M. Personalising haemophilia management with shared decision making. J Haem Pract. 2021;8(1):69–79. https://doi.org/10.17225/jhp/00178.
33. Woollard L, Gorman R, Rosenfelt DJ. Addressing patient education priorities in the era of gene therapy for haemophilia: towards evidence-informed shared decision-making. Haemophilia. 2021;27(2):e302–4. https://doi.org/10.1111/hae.14214.
34. Wang M, Negrier C, Driessler F, Goodman C, Skinner MW. The hemophilia gene therapy patient journey: questions and answers for shared decision-making. Patient Prefer Adherence. 2022;16:1439–47. https://doi.org/10.2147/PPA.S355627.
35. Hermans C, Noone D, Benson G, et al. Hemophilia treatment in 2021: Choosing the "optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians. Blood Rev. 2022;52:100890. https://doi.org/10.1016/j.blre.2021.100890.
36. Hamann J, Heres S. Adapting shared decision making for individuals with severe mental illness. Psychiatr Serv. 2014;65:1483–6. https://doi.org/10.1176/appi.ps.201400307.
37. Drolet BC, White CL. Selective paternalism. AMA J Ethics. 2012;4:582–8. https://doi.org/10.1001/virtualmentor.2012.14.7.oped2-1207.
38. Bailo L, Vergani L, Pravettoni G. Patient preferences as guidance for information framing in a medical shared decision-making approach: the bridge between nudging and patient preferences. Patient Prefer Adherence. 2019;13:2225–31. https://doi.org/10.2147/PPA.S205819.
39. Fletcher S, Jenner K, Khair K. Shared decision-making forgene therapy in haemophilia care. J Haem Pract. 2023;10(1):62–7. https://doi.org/10.2478/jhp-2023-0009.
40. Pagliarulo N. Bluebird, winding down in Europe, withdraws another rare disease gene therapy. BioPharm Dive. 21 Oct 2021. Accessed 26 Aug 2022. https://www.biopharmadive.com/news/bluebird-withdraw-gene-therapy-europe-skysona/608666/.
41. National Institute for Health and Care Excellence Draft guidance consultation: Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B. National Institute for Health and Care Excellence. 02 Aug 2023. Accessed 06 Aug 2023. https://www.nice.org.uk/guidance/gid-ta10699/documents/draft-guidance.
42. Khair K, Redfren N. Beyond approval: considerations and challenges in access to gene therapy. London: Haemnet; 28 Nov 2022. Accessed 19 Jan 2023. https://anchor.fm/haemnet.
43. Leung L. Validity, reliability, and generalizability in qualitative research. J Family Med Prim Care. 2015;4(3):324–7. https://doi.org/10.4103/2249-4863.161306.
44. Carminati L. Generalizability in qualitative research: a tale of two traditions. Qual Health Res. 2018;28(13):2094–101. https://doi.org/10.1177/1049732318788379.
45. Zimmer L. Qualitative meta-synthesis: a question of dialoguing with texts. J Adv Nurs. 2006;53:311–8. https://doi.org/10.1111/j.1365-2648.2006.03721.x.
46. Finfgeld-Connett D. Generalizability and transferability of meta-synthesis research findings. J Adv Nurs. 2010;66:246–54. https://doi.org/10.1111/j.1365-2648.2009.05250.x.
47. Baas L, van der Graaf R, van Hoorn ES, Bredenoord AL, Meijer K. for the SYMPHONY consortium. The ethics of gene therapy for hemophilia: a narrative review. J Thromb Haemost. 2023. https://doi.org/10.1016/j.jtha.2022.12.027.
48. Archibald MM, Ambagtsheer RC, Casey MG, Lawless M. Using Zoom videoconferencing for qualitative data collection: perceptions and experiences of researchers and participants. Int J Qual Methods. 2019;18:1–8. https://doi.org/10.1177/1609406919874596.
49. Lobe B, Morgan D, Hoffman KA. Qualitative data collection in an era of social distancing. Int J Qual Methods. 2020. https://doi.org/10.1177/1609406920937875.
50. Fletcher S. Seeing the bigger picture: qualitative research in the Zoom® age. J Haem Pract. 2021;8(1):141–4. https://doi.org/10.2478/jhp-2021-0019.

Publisher's Note


haemnet


OXFORD
BROOKES
UNIVERSITY


NHS
Oxford University Hospitals
NHS Foundation Trust


UNIVERSITY OF OXFORD
DOMI NUS ILLV
MINA TIO MEA