Exigency

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

Principal investigators:	Simon Fletcher
Co-Investigators:	Dr Kate Khair, Luke Pembroke
Study Sponsor:	Haemnet (Registered Charity No 1152241)
Study Coordinator:	Mike Holland, Haemnet
Version date:	13th November 2020
Version number:	Version 3

CONFIDENTIAL

haemnet

List of Abbreviations

Abbreviation	Definition
AAV	Adeno-associated viruses
PIC	Participant identification centres
PWH	People with haemophilia
QoL	Quality of life

Study Synopsis

Title	Exigency: an exploration of the impact of gene therapy on the lives of people with haemophilia and their families
Short Title	Exigency
Study Aim	This study programme aims to examine the real-world experience and impact of gene therapy in a diverse community of people and families affected by haemophilia who have been or will be exposed to gene therapy.
Primary Objective	To explore the expectations that patients, and families in the UK have of gene therapy and its position in contemporary and future haemophilia management
Secondary Objectives	To understand the lived experience of people who have undergone gene therapy To understand the as yet "unseen" impact of gene therapy on the extended family To understand the impact of ineligibility for gene therapy trials To understand the impact of withdrawal from gene therapy on individuals and their ongoing attitude to their haemophilia care To understand why some patients and families opt not to participate in gene therapy trials as a treatment option
Design	Non-interventional qualitative study
Number of Centres	Seven PIC sites for Phases 1 and 2: • Oxford University Hospitals NHS Foundation Trust • Royal Free London 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 Further recruitment will be undertaken via social media.
Duration	24 months total; data collection over 14-18 months
Number of Subjects	105, to include 65 people with haemophilia, and 40 family members
Inclusion Criteria	People with haemophilia A or B who consented to and have undergone gene therapy in the early dose-finding studies and a member of their family People with haemophilia A or B who consented to a gene therapy trial following the results of the early studies and a member of their family People with haemophilia A or B who consented to a gene therapy trial but who withdrew, were withdrawn from, or were ineligible for the

	study, and a member of their family People with haemophilia A or B who are definitely not interested in or unaware of gene therapy and a member of their family People with haemophilia A or B who are interested in but have not been offered gene therapy Those who have given written consent to be in the study All participants will be ≥16 years.
Exclusion Criteria	Participants will be excluded if they do not speak English (for the interviews) or do not consent to be in the study.
Statistical Analysis	This is a qualitative study using established qualitative research methodologies (grounded theory). Statistical evaluation is not appropriate.
Operational Procedures	
Ethical Approval	NHS ethical approval will be sought from the HRA
Data Analysis	To be conducted by Haemnet
Write-up and Publication	Lead researcher and research team

Exigency

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

Index

1 Background

1.1 Disease introduction

Haemophilia A and B are rare congenital disorders caused by an inherited genetic defect of the X chromosome that results 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 5,000 males [Srivastava et al, 2013]. Different types of severity are recognised:

- “severe” (factor activity is less than 1%)
- “moderate” (factor activity is 1-5%)
- “mild” (factor activity is 6-25%).

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 [Richards et al, 2010]. 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 and introduction 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 seven years in 10 men with severe haemophilia B [Nathwani et al, 2011; Nathwani et al, 2014]. However, following the introduction of gene for the Padua variant of the factor IX gene, near normal levels of factor expression have been seen in more recent cohorts [Perin et al, 2018]. Infusion of an AAV5 vector encoding a B-domain-deleted human factor VIII gene was associated with the sustained normalisation of factor VIII activity level over a period of one 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 [Rangarajan et al, 2017].

With many more gene therapy trials in development, and with the possibility of licensure in the near future [Brown and Green, 2018], gene therapy may soon be introduced as a standard of care treatment [Pierce et al, 2019].

However, challenges remain. AAVs naturally cause infection in humans, provoking an immune response that generates antibodies; individuals with AAV antibodies are ineligible for some gene therapies. UK haemophilia centres have estimated the prevalence of antibodies to two AAV subtypes (5 and 8) among 100 adults with haemophilia [Standford et al, 2019]. The overall prevalence of antibodies or inhibitors was 30% for AAV5 and 40% for AAV8, suggesting a substantial proportion of people may be screened out of first-line gene therapy but may be eligible for newer gene therapy studies where AAV5 positivity is not an exclusion criterion.

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

1.2 Rationale for the study

In potentially offering a “cure” for haemophilia, it is of little surprise that optimistic views have been expressed about gene therapy on haemophilia-specific social media websites and forums. Expectations within the community are high, with many patients voicing optimism 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 (although patients will inevitably be required to comply with regular safety monitoring).

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 [Iorio et al, 2018]. 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 but has not yet been described in haemophilia care, as no group involved in gene therapy studies has sought to undertake any in-depth qualitative research into the impact of this treatment in this group.

Gene therapy represents a substantial shift in the entire life experience of living with haemophilia for the patient and his family. As such, there is a need to look beyond the quantitative data collected in clinical trials and to assess the real impact of gene therapy on the everyday lives of patients and their families. This data is best captured using qualitative research techniques.

Patients are rarely homogeneous in how they react. For some patients and families, gene therapy is likely to hold little interest, while 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 to be that around one third of the population with haemophilia will not be eligible for gene therapy. Being screened for a potentially life-changing therapy only to find it is not available is likely to result in significant disappointment, for which health care professionals will need to offer support. It may affect current treatment-taking behaviours and is also likely to have an impact on the lives of close family members (carers/adult children/adult siblings).

2 Aim and Objectives

2.1 Aim

The Exigency study programme aims to examine the real-world experience and impact of gene therapy in a diverse community of people, and families affected by haemophilia who have been or will be exposed to gene therapy.

2.2 Primary objective

- To explore the expectations that patients, and families in the UK have of gene therapy and its position in contemporary and future haemophilia management.

2.3 Secondary objectives

- To understand the lived experience of people who have undergone gene therapy
- To understand the as yet "unseen" impact of gene therapy on the extended family
- To understand the impact of not being able to participate in gene therapy trials
- To understand the impact of withdrawal from gene therapy on individuals and their ongoing attitude to their haemophilia care
- To understand why some patients and families decide not to choose gene therapy as a treatment option

3 Study Design

3.1 General design

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

The study is designed to allow English-speaking patients and their families to tell their own life stories through narrative accounts. The narratives represent a true sharing of experiences valued by the tellers, listeners and gatherers [Hardy et al, 2009], and therefore offer insight into how these patients and families cope with haemophilia.

Most experienced practitioners familiar with haemophilia have preconceived ideas and theories that may potentially bias data capture. Grounded theory is a research methodology that allows identification and description of the broad spectrum of life with haemophilia from the perspectives of the patient and their families. This methodology enables rich data capture across a large age range and allows for deep consideration of data, allowing research questions to be re-shaped as evolving themes and new concepts emerge.

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

3.2 Primary endpoints

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

3.3 Secondary endpoints

- To understand the motivation of people with haemophilia 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 people with haemophilia, and whether these have been met.
- To understand how gene therapy impacts the lives of people with haemophilia and their families with regard to levels of factor expression and the post-gene therapy monitoring regimen.
- To understand the impact on people with haemophilia of being told they are ineligible for gene therapy, and how this affects their subsequent approaches to treatment.
- To understand why some people with haemophilia 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 people with haemophilia who are interested in gene therapy but have not been offered a trial.
- To understand the concerns of people with haemophilia 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.

3.4 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 of 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, with the patient co-researcher in attendance to help facilitate and take process field notes. The focus groups will take a grounded theory approach to explore a variety of issues relating to gene therapy and its impact upon 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. This is a standard qualitative research methodology that allows for open discussion. Initial subject interviews will follow a guide developed by the research team (see Appendix 1). Each interview will be conducted by the lead researcher.

3.5 Statistical analysis and sample size calculation

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

All focus groups and individual interviews will be recorded digitally so that the researcher can pay full attention to the subject, without the need to write down verbatim comments [Balen et al, 2000].

Immediately following each interview, the researcher and patient co-researcher will record any thoughts, reflections or observations that arose during the interview. These will be analysed as part of the framework analysis described below [Ritchie et al, 2003].

After each of the focus groups and interviews, the sound files will be transcribed verbatim. The lead investigators will then analyse the transcripts using a grounded theory approach. The texts will be read and re-read, 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 [Spencer et al, 2003]. 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 (e.g. patients vs.). Correlation between groups may be achievable with explanatory factors (e.g. age, treatment regimen, bleeds, joint health, etc.).

4 Study Group

The study population will comprise people over the age of 16, who fall into the categories outlined under Section 4.1 below. We hope to recruit up to 140 participants to the study in total, to include:

- Approximately 65 men with haemophilia
- Approximately 40 family members (spouse/partner/parent/carer or sibling of the person with haemophilia) to form patient/family member dyads

4.1 Inclusion criteria

- People with haemophilia A or B who consented to and have undergone gene therapy in the early dose-finding studies
- People with haemophilia A or B who consented to a gene therapy trial following the results of the early studies
- People with haemophilia A or B consented to a gene therapy trial but who withdrew, were withdrawn from, or were ineligible for the study
- People with haemophilia A or B who are definitely not interested in gene therapy
- People with haemophilia A or B who are interested in but have not been offered gene therapy
- Those who have given written consent to be in the study.

4.2 Exclusion criteria

- Non-English speakers
- Those who do not consent to be in the study.

5 Recruitment, Screening and Study Procedures

Once ethical approval has been received, people with haemophilia A or B who have undergone gene therapy and people with haemophilia A or B who withdrew from, were withdrawn from or who were ineligible for gene therapy will be recruited through Six PIC sites (i.e. 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 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.

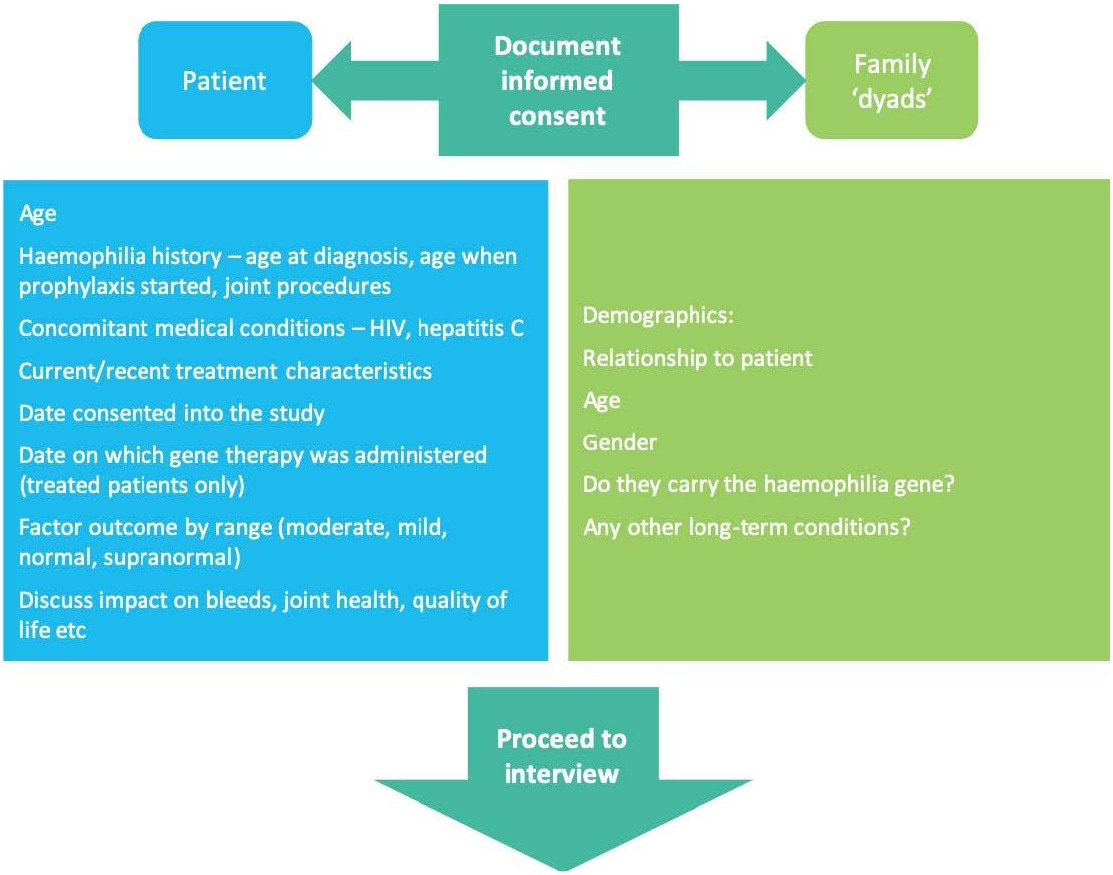
Once identified, potential participants will be given information about the study by their clinical team and will be invited to participate. If they agree to participate, they will be contacted by the research team from the Oxford Haemophilia and Thrombosis Centre at the Oxford University Hospitals NHS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

The study will also be advertised on social media platforms to recruit those people with haemophilia 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 social media advertisement in Appendix 2).

5.1 Study visits (inclusion)

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 video conference. The Haemnet lone worker policy (Appendix 3) will be followed to ensure interviewer safety.

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

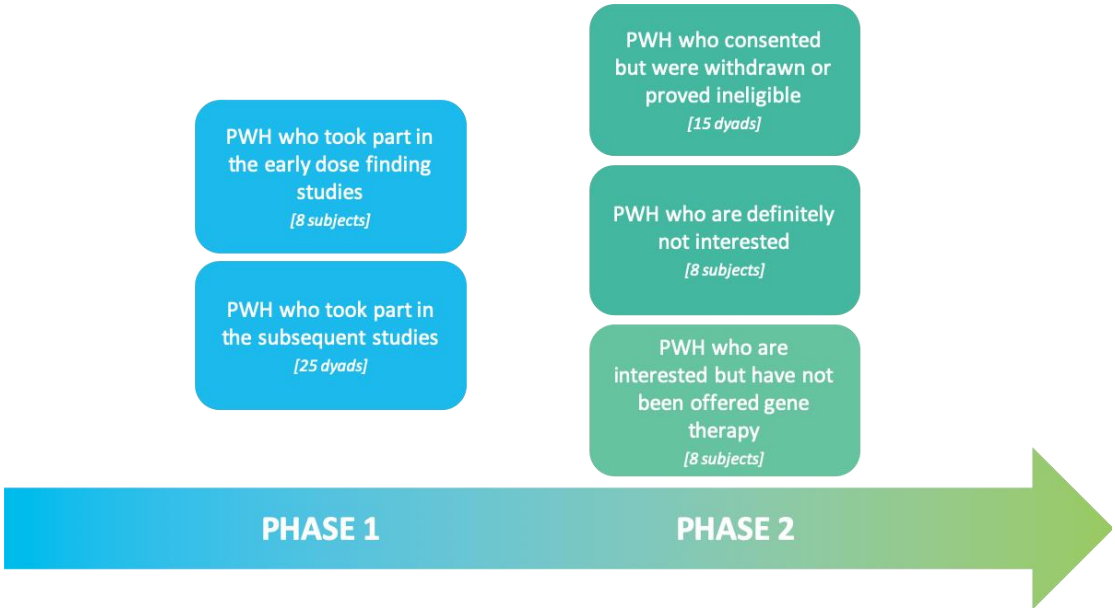


5.2 Study sequence

Subject to patient availability, data-gathering activities will be conducted in two phases, as shown in the panel below.

Two focus groups lasting one to two hours will each comprise eight to ten individuals from two subgroups: those who did not want to be part of gene therapy trials, and those not yet offered a gene therapy trial. Focus groups may be conducted either face-to-face or via video conference.

Approximately 40 in-depth qualitative individual interviews, each lasting around two hours, will be conducted with patient/family member dyads from two subgroups: those who have undergone gene therapy, or those who were withdrawn or withdrew themselves after initial consent. In all cases, each participant/dyad will be interviewed once only, either face-to-face or via video conference.



5.3 Study duration

The study will last for 24 months. It is estimated that data collection will take around 14–18 months.

6 Data Analysis

The data generated in this study will be analysed using grounded theory. 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, and finally theories are developed about the data that has emerged [Charmaz, 2014]. Grounded theory has been used extensively in research with children and families [Neill, 2007] and within haemophilia [Khair et al, 2019].

Audio-recorded interviews:

- Focus groups and interviews will be transcribed, verbatim, by a professional transcriptionist unknown to study participants. All data will be anonymised during the transcription process.
- The transcripts will be read and re-read by the research team. The transcribed data will be coded into themes for further analysis using a transformational framework, identifying themes or concepts, summarising and synthesising the data, and using descriptive framework analysis to represent the view expressed [Spencer et al, 2003].
- A table of themes will be produced, characterising recurring ideas and thoughts captured during the focus groups and interviews. These will form the basis for further analysis.
- Individual quotes may be used – these will be anonymised. Participants will be informed of this in the information sheet(s) and consent.

Field notes:

- Immediately after the interviews and focus groups, the researcher and patient co-researcher will record any thoughts, reflections or observations made during the interview or focus group. In particular, any thoughts or ideas about emerging themes will be recorded.

- These notes will be analysed as part of the framework analysis [Ritchie et al, 2003].

7 Ethics

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.

7.1 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 upon their haemophilia care. Consent will be reaffirmed before the interviews take place.

7.2 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.

7.3 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 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.

Ethical approval is not necessary for the health care professional focus groups; however, an information sheet has been developed for their knowledge about the study and participation.

7.4 Reward for participants

Participants who agree to attend focus groups will receive a £100 gift voucher for their participation, along with reimbursement of travel costs.

Participants who agree to be interviewed for the study will be given a £50 gift voucher for their participation, up to a maximum of £100 per household, along with reimbursement of any travel costs.

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

8 Data Protection

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

- All audio recordings 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 audio recordings) will be kept in locked cupboards by Haemnet for the duration of the study.
- Recordings will be deleted by Haemnet 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.

Haemnet will act as sponsor to the study and will monitor data quality and undertake site audits as necessary.

9 Finance and Funding

Funding for the study has been provided by uniQure

All study funds will be managed by Haemnet.

9.1 Study sponsor

The study is sponsored by and indemnified by Haemnet.

10 Dissemination

Abstracts will be submitted to the 2021/2022 national and international haemophilia conferences, including the European Association for Haemophilia and Allied Disorders (EAHAD) Congress 2021, the Haemophilia Nurses Association (HNA) Conference 2021, and the Word Federation of Hemophilia Congress 2022.

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

The study results will be disseminated directly to study participants through a final summary report. Results will also be shared on social media and through the UK Haemophilia Society and European Haemophilia Consortium (EHC) websites, and through member newsletters.

All investigators will contribute to study publications and will be named as co-authors. Authorship will be confirmed in line with journal publication guidance, such as International Committee of Medical Journal Editors (ICMJE) recommendations.

11 Study Personnel

11.1 Study Lead Investigators

Simon Fletcher
Lead Research Nurse at the Haemophilia and Thrombosis Centre at the Churchill Hospital, Oxford. Simon has been in post for six years and has extensive knowledge of clinical research and the care of people with haemophilia. He will oversee the study including ethical approval, study staff training, participant enrolment, study completion including evaluation of all outcome measures used, and ensure timely results presentation and publication. This work would contribute to his "PhD by publication" programme. simon.fletcher@ouh.nhs.uk

Dr Kate Khair
Director of Research at Haemnet; Visiting Professor of Health and Social Care, London South Bank University; Clinical Academic Careers Fellow, The Centre for Outcomes and Experience Research in Childhood Health, Illness and Disability, Great Ormond Street Hospital (GOSH) for Children, London. Formerly Nurse Consultant in Haemophilia at GOSH, Kate has extensive knowledge in qualitative research with children and young people with haemophilia. kate@haemnet.com

11.2 Study Co-Investigator

Luke Pembroke
Project Manager and "Patient Researcher" at Haemnet. Luke has experience working within the medical education sector of the healthcare communications industry. Living with haemophilia himself, Luke is an active patient advocate, and has worked extensively with a network of patient groups within the UK, Europe and globally. luke@haement.com

11.3 About Haemnet

Haemnet is a registered charity (No 1152241) that supports health and social care professionals to ensure that excellent care becomes an everyday experience for people with bleeding disorders. The charity provides education, undertakes research and drives service innovation. Haemnet Ltd (Company No 12211003) is the trading arm of the charity.

Haemnet will act as the study sponsor. **Mike Holland** is CEO of Haemnet and will oversee and manage all logistical aspects of the study. mike@haemnet.com

Haemnet is currently engaged in a multi-methods study assessing the prevalence and impact of chronic pain in PWH, and a study looking at educating personal trainers to work with PWH. Previous research studies and publications have also included:

- 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(5): 814-820. doi: 10.1111/hae.13803.
- Khair K, Holland M. The Kids' immune thrombocytopenia Tool is not suitable for assessing quality of life in children with platelet function disorders. Haemophilia 2018; 24(4): e259-e261. doi: 10.1111/hae.13528.
- Khair K, Klukowska A, Myrin Westesson L, et al. The burden of bleeds and other clinical determinants on caregivers of children with haemophilia (the BBC Study). Haemophilia 2019; 25(3): 416-423. doi: 10.1111/hae.13736.

- von Mackensen S, Myrin Westesson L, Kavakli K, et al. The impact of psychosocial determinants on caregivers' burden of children with haemophilia (results of the BBC study). Haemophilia 2019; 25(3): 424-432. doi: 10.1111/hae.13684.
- Khair K, Holland M, Bladen M, et al; SO-FIT Study Group. Study of physical function in adolescents with haemophilia: The SO-FIT study. Haemophilia 2017; 23(6): 918-925. doi: 10.1111/hae.13323.
- Khair K, Holland M, Pollard D. The experience of girls and young women with inherited bleeding disorders. Haemophilia 2013; 19(5): e276-81. doi: 10.1111/hae.12155.
- Forrester C, Bielby H, Johns S, Efford J, Holland M, Khair K; United Kingdom Haemophilia Nurse's Association. Potential for development of haemophilia link nurse role within UK hospitals. Haemophilia 2013; 19(4): 578-82. doi: 10.1111/hae.12144.
- Khair K, Holland M, Vidler V, Loran C, Harrington C. Why don't haemophilia nurses do research? Haemophilia 2012; 18(4): 540-3. doi: 10.1111/j.1365-2516.2012.02749.x.
- Khair K, Holland M, Carrington S. Social networking for adolescents with severe haemophilia. Haemophilia 2012; 18(3): e290-6. doi: 10.1111/j.1365-2516.2011.02689.x.

Haemnet also runs an annual conference for haemophilia nurses, and two training courses aimed at members of the haemophilia multidisciplinary care team: “Contemporary Care of People with Bleeding Disorders” (a four-day residential training course) and the ASPIRE leadership development programme.

12 References

Balen R, Holdroyd C, Mountain G, et al. Giving children a voice: methodological and practical implications of research involving children. Paediatric Nursing 2000; 12(10): 24-8.

Brown K, Green G. The haemophilia drug market. Nat Rev Drug Discov 2018; 17(8): 541-42.

Charmaz K. *Constructing Grounded Theory*. 2nd edition. Introducing Qualitative Methods series. 2014. London: SAGE Publications.

Hardy S, Gregory S, Ramjeet J. An exploration of intent for narrative methods of inquiry. Nurse Researcher 2009; 16 (4) 7-19.

Iorio A, Skinner MW, Clearfield E, et al; coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia 2018; 24(4): e167-e172. doi: 10.1111/hae.13504.

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): 814-20. doi: 10.1111/hae.13803.

Nathwani AC, Tuddenham EGD, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in haemophilia B. N Engl J Med 2011; 365: 2357-65.

Nathwani AC, Reiss UM, Tuddenham EGD, et al. Long-term safety and efficacy of factor IX gene therapy in haemophilia B. N Engl J Med 2014; 371: 1994-2004.

Neill S. Grounded theory sampling: 'whole' family research. Journal of Research in Nursing 2007; 12; 435-443.

Perin GQ, Herzog RW, Markusic DM. Update of clinical gene therapy for haemophilia. Blood. 2018; 33(7): 407-14.

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): 60-67. doi: 10.1111/hae.13489.

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(2): 189-94. doi: 10.1111/hae.13673.

Rangarajan S, Walsh L, Lester W, et al. AAV5–factor VIII gene transfer in severe haemophilia A. N Engl J Med 2017; 377: 2519-30.

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(4): 498-507.

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. 2003. London: SAGE Publications.

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. 2003. London: SAGE Publications.

Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of the World Federation of Haemophilia. Guidelines for the management of haemophilia. Haemophilia 2013; 19(1): e1-47.

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: 161-67. doi: 10.1002/rth2.12177.

Appendix 1: Social Media Advertisements

Appendix 2: Haemnet Lone Worker Policy

Haemnet staff will frequently work by themselves without close or direct supervision. Such work is usually home-office based. However, there may be occasions when Haemnet staff will need to work alone, visiting and interviewing service users, or running meetings with previously unknown colleagues, whether in or out of usual office hours.

The Haemnet Lone Worker policy aims to ensure the health, safety and welfare of all staff who are required to work in such circumstances. The health and safety of lone workers depends on good risk assessment practices, effective communication, and shared responsibility.

When working as a lone worker on Haemnet-related work, lone workers must:

- ensure that someone else knows the whereabouts of the lone workers and what they are doing;
- ensure they do not take unnecessary risks;
- care for their own health and safety and that of others who may be affected by their acts or omissions;
- seek and follow advice from their manager;
- follow all health and safety policies;
- comply with requests for information on whereabouts from managers;
- report any incidents including threats and potentially dangerous situations;
- ensure that the Team Administrator is aware of any changes to their contact details.