VWD360

The Lived Experience of People with von Willebrand Disease

Protocol Prepared by

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haemnet

Study Synopsis

Title	The Lived Experience of People with von Willebrand Disease
Short Title	vWD360
Study Aims	To identify the lived experience of people with von Willebrand Disease (vWD) and including: ▪ Experiences of bleeding ▪ Impact on quality of life ▪ Access to therapeutic options ▪ Satisfaction with current treatments and management ▪ Areas of unmet need.
Primary Objective	To understand the lived experience of people with vWD including the impact of bleeding on quality of life.
Secondary Objectives	To identify levels of satisfaction with current treatments and management approaches. To identify areas of unmet need among people with vWD.
Primary Endpoint	To identify differences in bleeding, daily activities, pain/discomfort and anxiety/depression between sub-types of vWD based on self-reported validated survey data collected both retrospectively and prospectively.
Secondary Endpoints	Descriptive narratives of the lives of people with vWD sought from interviews using thematic analysis of current treatments and unmet need.
Design	An observational multi-country, mixed methods natural history study combining both retrospective and prospective data collection with qualitative (interviews) data collection.
Duration (end of study)	12 months from study commencement or all recruitment targets (see below) have been achieved, whichever comes first.
Number of Subjects	We aim to secure cross-sectional survey responses from around 450 verified participants through clinical trial recruitment centre sites in ▪ United Kingdom (150 participants) ▪ Republic of Ireland (100 participants) ▪ United States (200 participants). Within this total, we expect to purposively recruit:

	▪ 30 participants to a qualitative interview-based substudy ▪ 50 participants to a 30-day bleed diary substudy.
Inclusion Criteria	Adults aged 16 and above (UK and Ireland) and adults aged over 18 (in USA) with a confirmed diagnosis of inherited vWD of known diagnostic subtype and vWF level. For the **qualitative interview-based substudy**, 30 adults who have completed the survey and who wish to be interviewed will be purposively selected for a broad range of ages and diagnostic subtype. For the **bleed diary substudy**, 50 adults who have completed the survey and who wish to take part will be purposively selected for a broad range of ages and diagnostic subtype.
Exclusion Criteria	Participants will be excluded from the study if they: ▪ Have acquired vWD ▪ Have other inherited bleeding disorders ▪ Do not wish to participate in or to consent to the study. ▪ Are under 16 (UK & Ireland) or 18 (US). Those for whom written/spoken English would prohibit participation will also be excluded.
Statistical Analysis	The sample size in this study is not based on formal statistical hypothesis testing. The planned number of subjects is considered adequate to meet the study objective of understanding the lived experience of people with vWD and the impact of bleeding on quality of life. All collected data will be reported using listings, summary tables and figures, as appropriate. For the **qualitative interview-based substudy** data will be analysed thematically, using NVivo. For the **bleed diary substudy** we will report descriptive statistical analyses including categorical classification and mean, median and ranges.
Operational procedures	
Data Analysis	To be conducted by the Haemnet research team
Dissemination	The Haemnet research team

Schedule of Study Assessments

Study Procedures	Enrollment	Baseline	Interview	30-day Bleed Diary
Days	D-1	D1	D1 to D42	D8 to D56
Informed consent [1]	X	X		
Cross-sectional survey questionnaire	X	X		
Further study options presented [2]		X		
Informed consent [3]			X	X
Interview			X	
Daily bleed record [4]				X

1 Informed consent will be sought signed prior to any study-specific procedures
2 Subjects will be presented with options to join the study interview programme or 30-day bleed diary
3 Further informed consent will be sought signed prior to commencement of study activities
4 Subjects to be provided with access to a 30-day daily bleed diary. Those who consent will each day receive a prompt asking: “Have you had a bruise or bleed you would like to report?”. If “yes”, additional data will be collected, to include anatomical site, symptoms, treatment received, location for treatment.

1 Background

von Willebrand disease (vWD) is reported to be the most common bleeding disorder, with prevalence estimated at 1% of the general population.[1] Despite this, little is known about its natural history, or of the impact it has on affected individuals and their families.

The Haemnet vWD360 programme is a mixed-methods, natural history study designed to gain a greater understanding of vWD and its impact on individuals and their families. It comprises both qualitative and quantitative approaches and is designed to include the perspectives of individuals with a diagnosis of any subtype of vWD.

The vWD360 study includes three components:

- Quantitative cross-sectional survey
- Qualitative one-to-one interviews with affected individuals
- 30-day bleed diary.

1.1 Context

von Willebrand Disease (vWD) is an inherited blood clotting (coagulation) disorder characterized by a reduction (quantitative) or poor function (qualitative) defect of factor VIII (FVIII) and/or von Willebrand factor (vWF). There are numerous subtypes categorised as:

- **Type 1**: a quantitative defect characterised by decreased levels of vWF in the circulation. Many affected individuals have a mild bleeding phenotype but may have heavy menstrual bleeding (HMB) and bleed following trauma/surgery.
- **Type 2**: a qualitative defect that is further divided into four subtypes
  - Type 2A – vWF is unable to bind to form the large vWF multimers required for coagulation
  - Type 2B – vWF has enhanced binding to platelet glycoprotein Ib (GPIb), causing rapid clearance of platelets and an associated thrombocytopenia
  - Type 2M – vWF has a decreased ability to bind to GPIb
  - Type 2N – there is a deficiency of vWF binding to FVIII
- **Type 3**: the most severe vWD subtype, characterised by complete absence of vWF production and an inability to bind with FVIII, resulting in a severely reduced FVIII level.[2]

Acquired vWD can develop as an autoimmune disorder, as a result of cancer, some cardiac conditions or following of certain drugs. It will not be considered as part of this study.

[1] https://www.cdc.gov/ncbddd/vwd/data.html#ref

[2] James PD, Connell NT, Ameer B, Di Paola J, Eikenboom J, Giraud N, Haberichter S, Jacobs-Pratt V, Konkle B, McLintock C, McRae S, R Montgomery R, O'Donnell JS, Scappe N, Sidonio R, Flood VH, Husainat N, Kalot MA, Mustafa RA. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv* 2021 Jan 12;5(1):280-300. doi: 10.1182/bloodadvances.2020003265.

vWD is characterized by prolonged or spontaneous bleeding from birth. Affected individuals tend to bruise easily, may have frequent nosebleeds (epistaxis), may bleed from the gums, bleeding within tissues (haematoma), in the gastrointestinal tract (more common later in life) and joint bleeds (in Type 3). vWD causes prolonged bleeding following injury, trauma, or surgery (including dental work). Women with vWD can have prolonged heavy menstrual bleeding, they may also have an increased risk of excessive blood loss during pregnancy and childbirth.

The severity and frequency of the bleeding episodes in vWD can vary greatly among affected individuals, even within the same family. The bleeding phenotype correlates to some degree with the subtype of VWD, with those with the severest form (Type 3) having the most bleeding.

Treatment varies based on the diagnosis. In Types 1 and 2 vWD treatment is usually 'on-demand' (after bleeding occurs) with some patients receiving prophylaxis if they have significant frequent bleeding. On demand treatment may be with oral, intra-nasal or subcutaneous treatments or with intravenous infusions of clotting factor concentrates containing FVIII/vWF. This is the method of treatment for all bleeding and prophylaxis in Type 3 vWD, where for some patients, treatment may be given at home.[3]

The lack of routine prophylaxis in Type 1 and 2 vWD means that most patients are reliant on hospital delivered care, which may involve frequent clinic appointments, causing prolonged bleeding due to a lack of timely administration of treatment. This can result in concurrent illnesses such as iron deficiency anaemia, which further impacts on the quality of life of affected individuals and their families.

There remains a need for a comprehensive understanding of the experience of people with vWD across the whole spectrum of subtypes in order to identify:

- The nature and range of symptoms that people experience and how these vary with the different disease subtypes
- The variability in pathways through which patients progress to access appropriate care
- The impact of living with vWD on the individual's quality of life.

Aims and Objectives

The vWD360 study is a mixed methods study which explores the lived experience of those affected by vWD.

The primary objective of this study is to understand the lived experience of people with vWD including the impact of bleeding on quality of life.

The secondary objectives of the study are to:

[3] Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, Grow JM, Kouides P, Laffan M, Lavin M, Leebeek FWG, O'Brien SH, Ozelo MC, Tosetto A, Weyand AC, James PD, Kalot MA, Husainat N, Mustafa RA. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv* 2021 Jan 12;5(1):301-325. doi: 10.1182/bloodadvances.2020003264.

- Identify levels of satisfaction with current treatments and management approaches
- Identify areas of unmet need among people with vWD.

2 Study Endpoints

2.1 Primary Endpoint

To identify differences in bleeding, daily activities, pain/discomfort and anxiety/depression between sub-types of vWD based on self-reported survey data collected both retrospectively and prospectively.

2.2 Secondary Endpoint

Descriptive narratives of the lives of people with vWD sought from interviews using thematic analysis of current treatments and unmet need.

3 Methodology

Haemnet's 360 methodology is a mixed methods approach designed to give an all-around perspective on the lived experience of rare bleeding disorders. It has previously been used in a study into Glanzmann's thrombasthenia (REC no 22-SC-0095).[4] It was found to be acceptable to participants and generated insightful data. This has been presented to the scientific community, and publications are currently underway.

3.1 Orientation

A project steering committee will manage the overall study approach and confirm the parameters to be analysed in the surveys. This group will be an independent panel composed of patient and physician stakeholders.

Members are:

- Dr Kate Khair – Director of Research, Haemnet
- Dr Robert Sidonio – Assistant Professor, Department of Pediatrics, Emory University School of Medicine
- Brian O'Mahony, Irish Haemophilia Society
- Dr Michelle Lavin – Consultant Haematologist, Ireland
- Manon Degenaar-Dujardin, Patient Advocate, The Netherlands
- Sunjeev Maini, Patient Advocate, UK
- Simon Fletcher, Principal Researcher, Haemnet.

Recruitment to the vWD360 study will principally be by patient identification recruitment centres in each country. Key eligibility criteria will include:

- Confirmed diagnosis of inherited vWD of known (to the recruiting centre) subtype
- Adults aged 16 years and older (18 years and older in US)

[4] Khair K, Glanzmann's 360 Study. Haemophilia 2023, 29: 5-13. https://doi.org/10.1111/hae.14713

- Ability to read/write/speak English/ for questionnaire and interview completion (English speaking only)
- Ability to provide informed consent.

Investigators at each participating recruitment centre will be supplied with a preset number of voucher codes, each reflecting a specific vWD subtype and vWF level. Sample codes are shown in the table.

	10 or less	**11-20**	**21-30**	**Over 30**
Type 1	HN3601a	HN3601b	HN3601c	HN3601d
Type 2A	HN3602Aa	HN3602Ab	HN3602Ac	HN3602Ad
Type 2B	HN3602Ba	HN3602Bb	HN3602Bc	HN3602Bd
Type 2M	HN3602Ma	HN3602Mb	HN3602Mc	HN3602Md
Type 2N	HN3602Na	HN3602Nb	HN3602Nc	HN3602Nd
Type 3	HN3603a	HN3603b	HN3603c	HN3603d

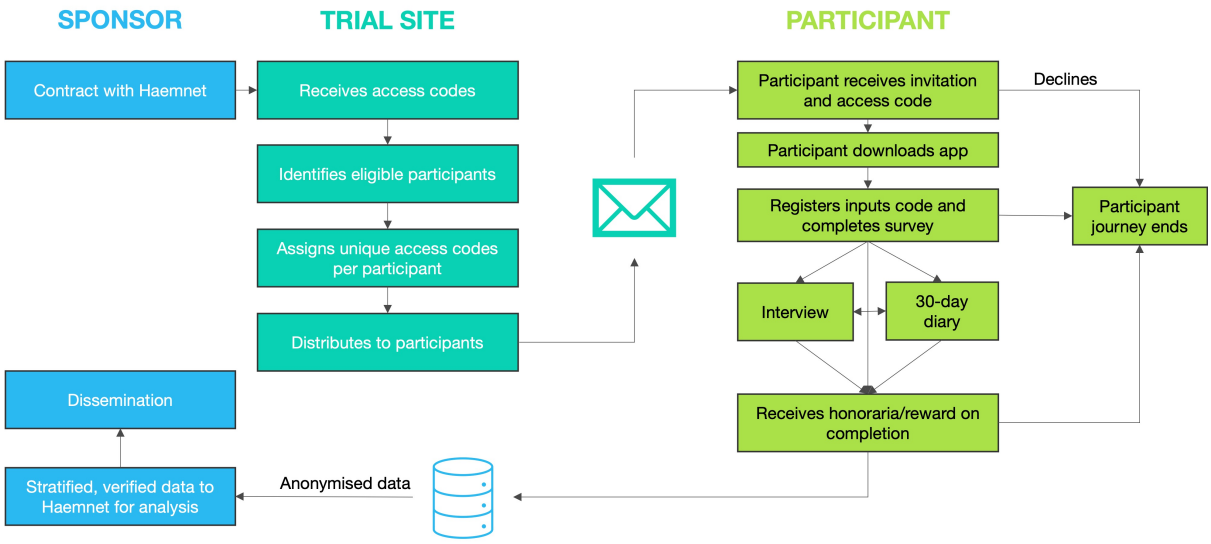
Investigators will assign the appropriate voucher codes to eligible participants, who will receive it as part of a study invitation pack. If the potential participant chooses to participate in the study, they will download the Haemnet application that houses the study data collection app (or access it online if a smartphone is not available). They will be asked to register with app and then enter the voucher code, along with an email address and first name. This will give them access to the study materials:

- Consent documents
- Access to the general (one-time) survey.

Following completion of the survey, participants will also be given the option to opt-in to:

- A one-to-one interview (for which there would be a separate reward)
- A 30-day bleed diary (for which there would be a separate reward).

This approach will minimise workload to the recruiting centre and should generate data on subjects with clinician-verified vWD subtype and vWF levels without the centre supplying any patient-identifiable data to the study sponsor. The anticipated flow is shown in the illustration.



3.2 Data Collection

A mobile smartphone and web-based digital app will be used to collect survey data from participants. It will offer a single access point to the elements of the study and will reduce the burden of participation on those who choose to take part.

The app has been designed to satisfy the General Data Protection Regulation (UK and EU versions), as well as data protection laws in USA.

Organisational and technical measures will ensure that the confidentiality, integrity and availability of the data derived from the app is upheld.

Access will be strictly controlled both from the front end and back end, further ensuring the privacy and security of the data collected.

Features include:

- eConsent
- Single dashboard providing pathways to various elements of the study
- Interactive and engaging user interfaces
- Patient self-reported data collection
- Diary data collection

Cross-sectional survey data

We will collect quantitative data on:

- Number, site of bleeds and other symptoms
- Treatments used and healthcare utilisation
- Impact on daily activities, quality of life, pain/discomfort and anxiety/depression, self-esteem and self-efficacy.

The survey includes six validated tools:

- Generic health related quality of life (EQ-5D)[5]
- Self-Efficacy to Manage Chronic Disease Scale (SEMCD)[6]
- Rosenberg's Self-Esteem Score[7]
- Psychological Health and Well-being (PH8)[8]
- Generalised Anxiety Disorder Assessment (GAD-7)[9]
- Menorrhagia Impact Questionnaire (MIQ).[10]

Qualitative interview-based substudy

Thirty individuals will be invited to share their experiences of living with vWD by participating in one-to-one in-depth qualitative interviews. They will be purposively selected to reflect age, gender and diagnostic sub-type.

Interviews give the opportunity to capture the intangible variables that enrich the data needed for a natural history study. We will conduct face-to-face or digital platform interviews, depending on each participant's choice.

Each interview will be undertaken by the Haemnet research team (Dr Kate Khair and/or Simon Fletcher). Each will be structured in order to better understand:

- Impact on quality of life (to identify the holistic impact factors)
- Knowledge within families
- Impact on education/career choices/working ability
- Societal and cultural issues.

Audio recordings of each interview will be captured and transcribed verbatim by a professional transcriptionist. Interview transcripts will be analysed using established thematic analysis. Consent to use anonymised quotes in publications will be obtained (see section 4.1).

Bleed diary substudy

Fifty individuals will be invited to enter daily bleeds into the phone-based app for 30 days. They will be purposively selected to reflect age, gender and diagnostic sub-type.

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[5] Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.

[6] Ritter PL, Lorig K. The English and Spanish Self-Efficacy to Manage Chronic Disease Scale measures were validated using multiple studies. J Clin Epidemiol. 2014; 67(11): 1265-1273.

[7] Rosenberg M. Conceiving the Self. New York: Basic Books, 1979.

[8] Kroenke, Kurt, et al. The Patient Health Questionnaire-2: Validity of a Two-Item Depression Screener. *Medical Care*, vol. 41, no. 11, Lippincott Williams & Wilkins, 2003, pp. 1284–92, http://www.jstor.org/stable/3768417.

[9] Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-1097.

[10] Bushnell DM, Martin ML, Moore KA, Richter HE, Rubin A, Patrick DL. Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin 2010; 12:2745-55. doi: 10.1185/03007995.2010.532200.

Individual participants who consent to take part will receive a daily prompt, enquiring whether or not they have had a new bruise or bleed, or wish to provide updated information on a previously reported bruise or bleed.

- If the participant has no new information to record, they will simply select “No” to the questions and will not be prompted until the following day.
- If the participant has new information to record, they will select “yes” and will be guided through a structured survey for the bleed site, bleeds, treatment/s and the where the treatment was given (home/hospital etc) and social outcomes (missed work, school and/or activities). They will also be given the opportunity to enter follow up data on treatment and activity relating to previous bleeds.

Data protection measures are set out in section 4.5.

3.3 Expected Participant Numbers

The sample size in this study is not based on formal statistical hypothesis testing. The planned number of subjects represents a pragmatic distribution across three countries that is considered adequate to meet the study objectives of capturing the lived experience of people with vWD.

Accordingly, we aim to secure cross-sectional survey responses from around 450 verified participants through patient identification recruitment centre sites in:

- The United Kingdom (150 participants)
- The Republic of Ireland (100 participants)
- The United States (200 participants).

We expect to recruit:

- 30 participants to the qualitative interview-based substudy
- 50 participants to the bleed diary substudy.

3.4 Data Analysis

Cross-sectional survey data

Descriptive data of socio-demographic characteristics and clinical data will be shown as frequency distribution in per cent or as mean ± standard division SD (range), median and interquartile ranges (IQR). Descriptive statistics of the sociodemographic and clinical data (age, severity, treatment regimen, number of bleeds per week, hospital contact and admission) will be presented to give an overview of the characteristics of the study population.

Data on participants’ quality of life, menorrhagia, mental health, self-efficacy and self-esteem will be analysed. The comparison of differences between groups will be examined by Student’s test, Mann-Whitney U-test or ANOVA according to distribution. Analyses will be exploratory in nature.

All data will be tested for normal distribution using the Shapiro Wilk test.

Qualitative interview-based substudy

Interview data will be analysed using established qualitative research methodologies. We will start with an interview guide developed by the lead researcher and a patient co-researcher. After each of the interviews, the sound files will be transcribed verbatim; the investigators will then analyse the transcripts using NVivo software. Direct quotes are analysed into topics, and topics are coded into themes to identify recurring themes seen as important aspects of life with vWD. This is recognised as being an effective way to gain insightful data from study participants.

Qualitative research 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.[11] Such approaches have been used extensively in research with children and families[12] and within haemophilia.[13]

Audio-recorded interviews:

- All 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. Interview transcripts will also be analysed using NVivo (a qualitative data analysis software package that enables qualitative researchers to organize, analyse and find insights in unstructured or qualitative data).[14]
- 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.[15]
- A table of themes will be produced, characterising recurring ideas and thoughts captured during the 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 consented accordingly.

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

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

[13] 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.

[14] Creswell JW. *Qualitative Inquiry and Research Design, Choosing among Five Approaches*. 2nd Edition, Sage Publications Inc., Thousand Oaks, 2007.

[15] 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.

- Field notes: Immediately after the interviews, the researchers will record any thoughts, reflections or observations made during the interview. In particular, any thoughts or ideas about emerging themes will be recorded. These notes will be analysed as part of the framework analysis.[16] [17]

Bleed diary substudy

Descriptive statistics of prospectively collected bleed diary data will be shown as mean ± standard division SD (range), median and interquartile ranges (IQR) for the different vWD subtypes. The comparison of differences between groups will be examined by Student's test, Mann-Whitney U-test or ANOVA according to distribution. Such analyses will be exploratory in nature.

All data will be tested for normal distribution using the Shapiro Wilk test.

4 Ethics and Data

4.1 Risk to Participants

There is minimal risk to participants or researchers from participating in this study. In the event that any patient becomes distressed by this, they will be referred (with consent) to the appropriate professionals at the haemophilia centres from which they have been recruited

4.2 Reward for Study Sites and Participants

Patient identification recruitment centres will be reimbursed at standard tariff rates for participants recruited to the study.

Individual study participants who complete the cross-sectional survey will be entered into a prize draw for one of 50 gift vouchers worth £100 (or equivalent (US dollars or Euro)).

- Those who take part in the qualitative interview-based substudy will each receive an additional gift voucher to the value of £100 (or equivalent).
- Those who take part in the bleed diary substudy will receive an additional gift voucher to the value of £100 (or equivalent).

4.3 Informed Consent

Potential study participants will receive an invitation pack from their patient identification recruitment centre. Those who wish to join the study, will do so either by scanning a QR

[16] 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.

[17] Bowling A. *Research Methods in Health: health: investigating health and health services*. McGraw Hill 2009; 3rd Edn. Chapter 16 Unstructured interviewing and focus groups.

code with their smartphone or enter a link into the browser on their laptop or desktop PC. Both approaches will lead the user to the study data collection app.

The participant will be required to register with the Haemnet app. Following app registration, the participant will be asked to enter the study code received from their recruiting centre. This will present them with the overall study information sheet (PIS). If they wish to proceed the cross-sectional survey will then be accessible via the app dashboard.

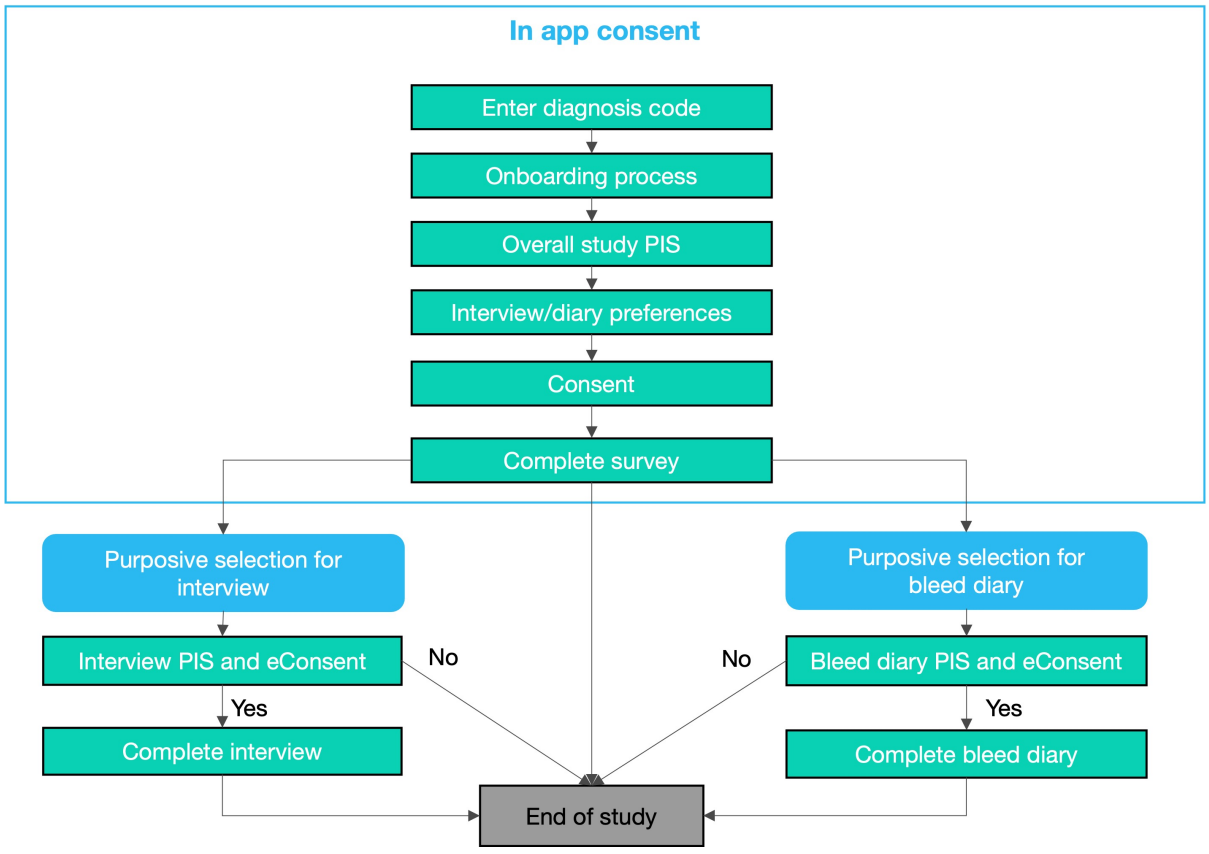
The survey will include a tick box inviting participants to register their interest in taking part in the qualitative interview-based substudy or the bleed diary substudy.

Consent to take part in the survey can be withdrawn at any stage via the "withdraw consent" option within the app (data already entered will be retained and used in analyses).

Following completion of the cross-sectional survey, survey information will be reviewed for purposive sampling by the Haemnet research team. Those selected for the qualitative interview-based substudy will then receive further information and consent documentation (by email) from the Haemnet research team. Electronic consent will be taken before the interview takes place. This will include consent to use anonymised direct quotes in publications. Verbal re-consent for recording will be taken before the interview begins.

Those selected for the bleed diary substudy will be contacted and sent an information sheet. Consent will be taken electronically, after which access to the 30-day bleed diary will be available via the app dashboard.

The consent process is summarised in the diagram.



4.4 Participant Confidentiality

App ID: Those who register with the app will be assigned a unique app pseudo ID number. This is used to keep the registration data e.g. name and email separate from the study data. This ID will only be known to the Haemnet research team.

Interview and/or bleed diary participants: Those who choose to …. will be assigned a further unique study number, that will be known only to the researchers and study participant. This study number will be on the informed consent forms for each substudy. All study data will be anonymised prior to analysis.

The use of interview-based data raises particular issues of confidentiality when direct quotes and/or the circumstances of quotes may be used in reports and publications. It is therefore imperative that individuals are anonymised to all those but the Haemnet research team. Any individual reports and publications that include direct quotes will refer to participants only by study number; these will be known only to the research team.

The anonymised (to participant number by the research team) audio recorded interviews will be sent to an external transcriptionist via a secure, password protected link. The transcripts will then be returned to the principal investigator who will upload them to a protected folder on the Haemnet server.

4.5 Data Protection

Participants' study data will anonymised prior to analysis and managed in line with the UK & EU General Data Protection Regulation (GDPR) (successor to the UK Data Protection Act 1998).

Participants privacy will be preserved throughout the study.

- All audio recordings will be transcribed verbatim by a professional transcriptionist unknown to the study participants. All transfers will be via a secure, password protected link. Transcripts will then be returned to the principal investigator who will store them on a protected folder on the Haemnet server.
- All data will be kept in access-controlled, password-protected electronic files by Haemnet for the duration of the study.
- Interview recordings will be deleted by Haemnet once the study has been analysed. Transcripts will be stored for 15 years and may be reanalysed during that period (an optional consent within the consent form).

4.6 Ethical Approval

United Kingdom: Ethical approval will be sought from the Health Research Authority in the UK using standard IRAS application forms. The study will be registered with the research and development office at Oxford University Hospitals NHS Foundation Trust.

Ethical approval for the Ireland and USA arms of the study will be sought via appropriate channels.

5 Timelines and Deliverables

5.1 Study Timeline

The planned first patient first 'visit' is 1 September 2023.

Participants who chose to complete only the cross-sectional survey may be in the study for as little as one day.

- Those who choose to join the qualitative interview-based substudy will remain in the study until interview completion (predicted to be a maximum of 6 weeks)
- Those who choose to join the bleed diary substudy will remain in the study for 30 days data collection, (predicted to be a maximum of 8 weeks).
- Those who choose to join both the qualitative interview-based substudy and the bleed diary substudy will remain in the study for a maximum of 10 weeks, although both sections may also run concurrently.

All data collection should be completed by 31 December 2024.

5.2 Study Dissemination

Outputs from the study that are suitable for wider dissemination in journals or at conferences will be developed for publication in clinical and health policy journals, along with abstracts and posters for use at conferences. Study publications will be shared electronically with those study participants who give permission for further contact.

5.3 Study Conduct

The study sponsor is Haemnet Ltd (company registration number 12211003).

Haemnet has full public liability insurance cover. All members of staff are fully checked annually through the UK's Disclosure and Barring Service (DBS).

Haemnet's study team will ensure the study adheres to the stated timelines. The study team will also monitor data quality and undertake site audits as necessary.

The study is funded by Hemab Therapeutics (www.hemab.com) a biotechnology company developing treatments for bleeding and thrombotic disorders.

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6 About Haemnet

6.1 Project Team

Dr Kate Khair

Director of Research. Formerly Nurse Consultant at Great Ormond Street Hospital for Children NHS Foundation Trust, London, Kate has extensive understanding of qualitative research and an unparalleled track record of study completion and publication.

Simon Fletcher

Principal Researcher. He was formerly the Lead Research Nurse at the Haemophilia and Thrombosis Centre at the Churchill Hospital, Oxford. Simon has extensive knowledge of clinical research and the care of people with bleeding disorders.

Samuel Bristow

Digital Strategy and Compliance Lead. Sam's expertise is in digital technologies and data collection capabilities. He will ensure the study remains on track with respect to research governance and regulatory compliance.

6.2 Haemnet

Haemnet works with healthcare professionals, patient communities, industry and other key stakeholders within the area of rare bleeding disorders and other chronic conditions. It is a specialist consultancy that conducts research, designs and delivers education, and produces creative content and media.

The Haemnet team has previously managed and successfully delivered a wide range of studies and projects, which have been published in peer-reviewed journals and have informed practice and provided the basis for educational resources used by clinical teams with patients. These include:

The Cinderella study

- Khair K, Pollard D, Steadman L, Jenner K, Chaplin S. The views of women with bleeding disorders: Results from the Cinderella study. *Haemophilia* 2022;1–10. https://doi.org/10.1111/hae.14514
- 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.

The Exigency study

- 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 *Orphanet J Rare Dis* 2022 Apr 4;17(1):155. doi: 10.1186/s13023-022-02256-2.

- 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;27:760–768. https://doi.org/10.1111/hae.14378
- 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.

Project GYM

- McLaughlin P, Holland M, Dodgson S, Khair K. Project GYM: A randomized feasibility study investigating effect on motivation of personal trainer-led exercise in young men with hemophilia. *Res Pract Thromb Haemost* 2021 Nov 26;5(8):e12613. doi: 10.1002/rth2.12613.
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