An Exploration of the Impact of Emicizumab on the Lives of People with Haemophilia and Inhibitors 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
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List of Abbreviations

Abbreviation	Definition
CCC	Comprehensive Care Centre
EAMS	Early Access to Medicines Scheme
Emi	Emicizumab
Haemo-QOL	Haemophilia Quality of Life scale
Hep-Test-Q	Haemophilia and Exercise Project Test Questionnaire
HJHS	Haemophilia Joint Health Score
HRQoL	Health-Related Quality of Life
HTC	Haemophilia Treatment Centre
PWH	People with Haemophilia
QoL	Quality of Life
SO-FIT	Study Of physical Function In adolescenTs with haemophilia

Study Synopsis

Title	Emi and Me: an exploration of the impact of emicizumab on the lives of people with haemophilia and inhibitors and their families
Short Title	Emi and Me
Study aim	This study aims to examine the real-life experience and impact of using emicizumab in a cohort of patients with haemophilia and inhibitors, who are being prescribed emicizumab in routine clinical practice as well as those who have been in the clinical trials. We also intend to capture the impact of emicizumab use on the lives of close family members (parents/carers/children/siblings).
Primary Objective	To capture the real-life experience of using emicizumab for haemophilia inhibitor therapy for the patient with haemophilia and his close family members
Secondary Objectives	To describe difference patient satisfaction with injections (numbers of injections, how to remember treatment dates, and so on). To understand user's expectations of emicizumab and how they see future haemophilia care (less frequent injections, impact on home storage, number of bleeds, reduced hospitalisations and so on). To describe the as yet 'unseen' impact on the extended family – and to seek their views of innovative therapy for haemophilia.
Design	Non-interventional qualitative study
Number of Centres	N/A (recruitment via social media)
Duration	6 months data collection 12 months total study duration
Number of Subjects	25 'dyad' pairs
Inclusion Criteria	Study participants will be people with inhibitors using emicizumab (prescribed by treating clinicians) in usual clinical care. Family members of participants will also be included.
Exclusion Criteria	Participants will be excluded from the study if they do not have an inhibitor, are not being treated with emicizumab, do not speak English (for the interviews) or do not consent.
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 HRA
Data analysis	To be conducted by Haemnet
Write up and publication	Lead researcher and research team

Emi and Me

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1 Background

1.1 Disease Introduction

Haemophilia A is a rare congenital disorder caused by an inherited genetic defect of the X chromosome that results in a deficiency in factor VIII production. Factor VIII plays a pivotal role in the coagulation cascade, bringing together the clotting factors IXa and X, a critical step in the formation of a blood clot to help stop bleeding. Haemophilia A 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 is with FVIII prophylaxis, which decreases spontaneous bleeding events and resultant joint damage [Richards et al, 2010]. Prophylaxis requires frequent intravenous infusions, which can be as often as daily but are usually 2-3 times per week.

A serious complication of treatment is the development of inhibitors to infused factor VIII replacement therapies. Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII, making it difficult, if not impossible to obtain a level of factor VIII sufficient to control bleeding. Up to 40% of patients receiving replacement factor develop inhibitors [Iorio et al, 2017].

Of these patients, who are predominantly children, between 50 and 86% can be tolerised through extended periods of very high treatment [Holstein et al, 2016]. Unfortunately, for a small number of these children, this treatment fails leaving a cohort of young children/adolescents who join a group of adults who never had access to this treatment [Khair et al, 2018]. For this ever-growing cohort of individuals treatment is with bypassing agent therapy either when bleed occur (on-demand or episodic therapy) or as prophylaxis [Dekoven et al, 2013].

Treatment of inhibitors is burdensome for the patient and his family [Lindvall et al, 2014; DeKoven et al, 2014] as it requires repeated intravenous infusions. Furthermore, treatment does not always alleviate bleeding, which can result in haemophiliac arthropathy, reduced mobility and pain and frequent episodes of hospital delivered care [Berntorp et al, 2011].

Emicizumab is a bispecific factor IXa- and factor X-directed humanised monoclonal antibody that has been co-developed by Chugai, Roche and Genentech. It has been designed to mimic the activity of factor VIII bring together factor IXa and factor X, proteins that are required to activate the natural coagulation cascade and restore the blood clotting process for haemophilia A patients. Emicizumab is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly or potentially once monthly following initial weekly 'loading' doses [Shima et al, 2016]. In a pivotal phase III study, which compared emicizumab with on-demand (no prophylaxis) and prophylaxis use of bypassing agents (BPAs) in adults and adolescents with haemophilia A with inhibitors, the primary endpoint showed a clinically meaningful and statistically significant reduction in treated bleeds of 87% (risk rate [RR]=0.13, $p<0.0001$) with emicizumab prophylaxis [Oldenburg et al, 2017]. Furthermore, over a median observation time of 31 weeks, substantially more patients experienced zero bleeds with emicizumab prophylaxis.

Consequently, patient expectation of emicizumab is significant. On haemophilia-specific social media websites, many patients have expressed optimism for a treatment likely to result in reduced treatment burden and fewer bleeds, with a consequent impact on mobility and pain. Treatment burden also includes the time commitment required for treatment, which is reported to impact on treatment adherence [Thornburg, 2018]. The frequency of infusion of current therapy is often cited as influencing adherence to treatment; decreased frequency of infusions and sub-cutaneous administration may encourage adherence and better treatment outcomes [Hacker et al, 2001].

1.2 Rationale for the study

Emicizumab offers patients protection from bleeding with fewer injections, this should reduce treatment burden. While patient expectation is high (as evidenced by the conversations on UK haemophilia social media sites) there are risks that patients may forget to treat and thus experience bleeds. During clinical trials participants have been monitored closely and, through questionnaire completion, have described improvement in quality of life [Mancuso et al, 2018, Oldenburg et al 2019].

What is also apparent to clinical teams is the dramatic change to life experience of not just the patient but his family – the ability to travel, to plan attending events knowing that bleeds will not occur, even potentially to have another child because of the reduction in treatment burden, particularly the time needed for treatment and rehabilitation.

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

Emicizumab has been available in the UK in clinical trials and as part of an Early Access to Medicines Scheme (EAMS) for non-trial eligible patients since spring 2018. It was recently licensed in the UK and is now available for routine clinical care for any person with haemophilia A and an inhibitor.

We hypothesise that patients and their carers/families will be excited about this new treatment option and that for most, if not all, the promise of improved care and quality of life will be a reality.

2 Aim and Objectives

2.1 Aim

This study aims to examine the real-life experience and impact of using emicizumab in a cohort of patients with haemophilia and inhibitors, who are being prescribed emicizumab in routine clinical care or as part of the EAMS process as well as those who have been in the clinical trials. We also intend to capture the impact of emicizumab use on the lives of close family members (parents/carers/children/siblings). Each participant and his family members will be deemed a study ‘dyad’.

2.2 Primary Objective

To capture the real-life experience of using emicizumab for haemophilia inhibitor therapy for the patient with haemophilia and his close family members.

2.3 Secondary Objectives

- To describe difference patient satisfaction with injections (numbers of injections, how to remember treatment dates etc).
- To understand user's expectations of emicizumab and how they see future haemophilia care (less frequent injections, impact on home storage, number of bleeds, reduced hospitalisations etc).
- To describe the as yet 'unseen' impact on the extended family – and to seek their views of innovative therapy for haemophilia.

3 Study design

3.1 General Design

This is a prospective, observational cohort qualitative research study to be conducted among patients using emicizumab in routine clinical practice.

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 PI and supervised by Dr Kate Khair.

3.2 Primary Endpoints

To gather a deep and thorough understanding about how switching from factor based products to emicizumab for routine treatment in "real-world" settings meets the needs and changes the perspectives of the patient with haemophilia and his immediate family members.

3.3 Secondary endpoints

- To gather a deeper understanding about how emicizumab is used in real life, how patients remember to treat, and what impact this has had on their ability to engage fully in daily activities.
- To describe patients' views about treatment patterns; given days vs. tailored individualised treatment (once weekly to once monthly injections)
- To understand differences and experiences between participant sub-groups (children/siblings, carers, adult and child patients).
- To develop a greater understanding of where emicizumab fits in the future treatment landscape, which might include use in patients with haemophilia without inhibitors.

3.4 Statistical analysis and sample size calculation

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

We will start with an interview guide developed by the lead researcher and a patient co-researcher, and tested on three pilot participants (one child, one teenager, one adult).

All 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]. Following each interview, the researcher will also make notes of any thoughts, reflections or observations that arose during the interview.

After each of the interviews, the sound files will be transcribed verbatim; the lead investigators will then analyse the transcripts using a grounded theory approach. Direct quotes are analysed into topics, and topics are coded into themes to identify recurring themes seen as important aspects of life with haemophilia. Each interview is coded as it occurs, following analysis the interview guide is then amended so that emerging themes may be further investigated in later interviews [Charmaz 2006].

This continues until no new data are described (data saturation). This is recognised as being a very effective way to gain deep insightful and rich data from study participants [Bryant and Charmaz, 2010; Charmaz, 2013; Charmaz, 1990, Sim et al, 2018]. The study team have used this methodology in previous haemophilia research studies [Khair et al, 2013; Khair et al 2019 (HOPE study, in press)].

Inferential testing will be used to describe how outcomes differ between groups (e.g. patients vs. parents). 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 with haemophilia A, of any age or severity, in the UK who have an inhibitor, and their family members. According to the UKHCDO annual report for April 2016 to March 2017, there are 217 people with an inhibitor listed on the National Haemophilia Database (UKHCDO, 2017).

We estimate that in the UK, around 20 patients have been treated with emicizumab in clinical trials (principally in the major London centres). Around 40 people received therapy with emicizumab as part of the Early Access to Medicines Scheme (EAMS) for non-clinical trial eligible patients. Another small cohort of people have received emicizumab since it was licensed in the UK in May 2018.

From this sub-population of <100 people, we would hope to recruit around 25 to the study, together with at least one family member.

Prescribed doses and frequency of treatment will be decided and prescribed by the patient's clinical team. No patient will switch to emicizumab to gain entry to this study.

4.1 Inclusion Criteria

- People with haemophilia A and an inhibitor aged >8 yrs who are prescribed emicizumab therapy in routine clinical practice.
- Parents and siblings of children aged <16 years with haemophilia A who are prescribed emicizumab.

- Partners/carers/siblings/children of adults with haemophilia A who are prescribed emicizumab will become patient 'dyads'
- Those who have given written consent to be in the study.

4.2 Exclusion Criteria

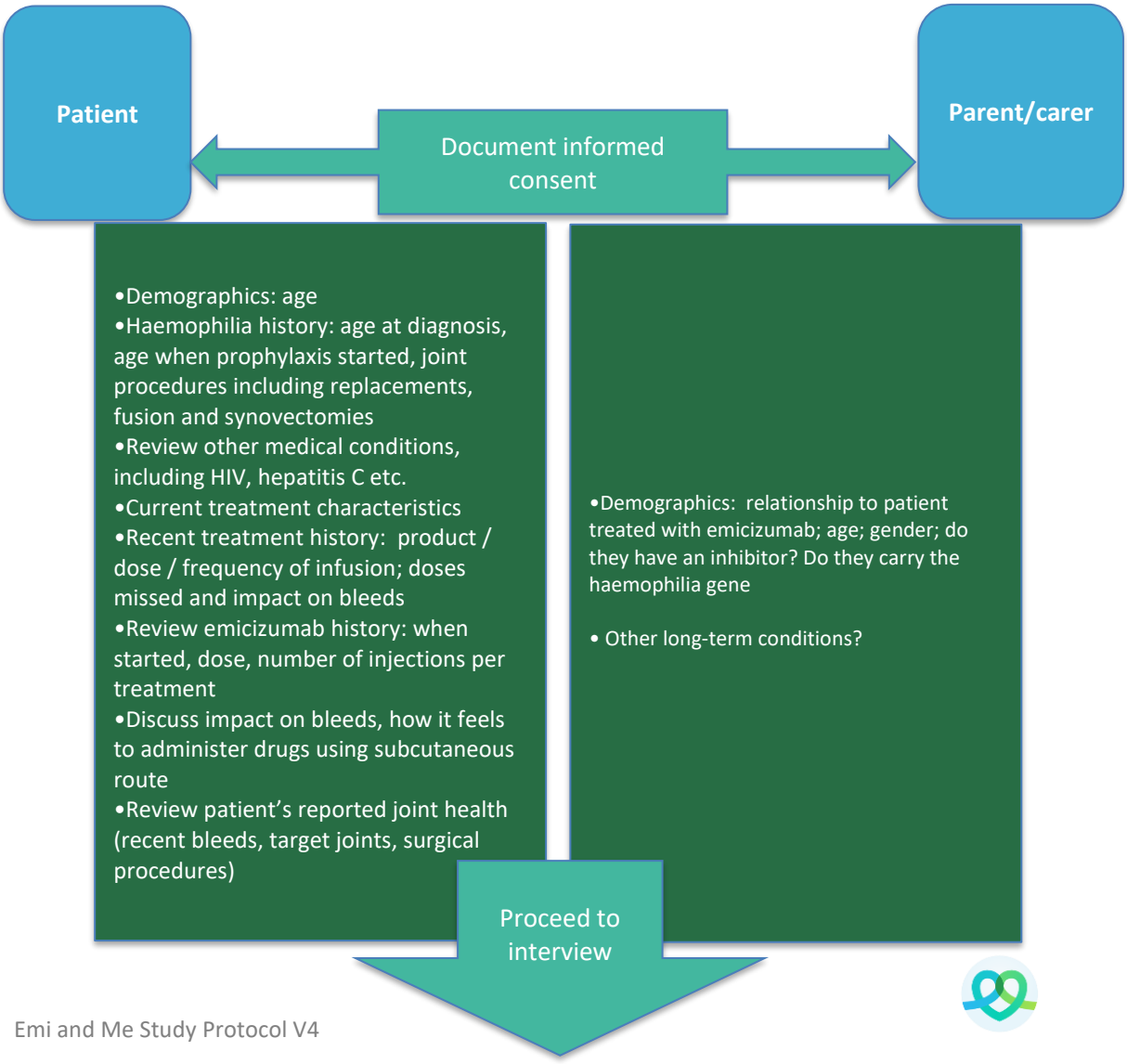
- Patients prescribed treatment other than emicizumab for their haemophilia
- Non-English speakers
- Those who do not consent to be in the study.

5 Recruitment, Screening and Study Procedures

The study will be advertised via Haemnet to nurses in haemophilia centres where patients who are being prescribed emicizumab will be seen for direct clinical care. 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 to organize a mutually convenient time for their interview which could be undertaken at hospital, home or other mutually convenient site. The Haemnet lone worker policy (appendix 2) will be followed to ensure interviewer safety.

5.1 Study visits 1 (inclusion)

There will be a single study visit, at which all study data will be collected. This is summarised in the panel.



5.2 Study duration

The study will last for 6 months, during which time each dyad will be interviewed once only.

5.3 Safety reporting

Emicizumab is a newly licensed therapeutic option for people with haemophilia as such safety data is still being collected.

Although adverse event information is not being actively solicited via this protocol, physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) (see Appendix 3) that come to their attention either to the marketing authorization holder of the suspected medicinal product, via the Roche Adverse Event and Special Situation Reporting Form to be supplied to the physician (for Roche medicinal products) (see Appendix 4), or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a subject is not exposed to a marketed medicinal product, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

If during one of the interviews a participant mentions an adverse event, or any of the special situations described above, the interview will continue without interruption. Once the interview is complete, an appropriate adverse event report will be prepared and submitted.

6 Data analysis plan

6.1 Data analysis

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 identifying themes, coding and analysing these finally developing theories about the data that has emerged [Charmaz, 2006]. Grounded theory has been used extensively in research with children and families [Neill, 2007].

Taped Interviews:

- The interviews will be transcribed and anonymised during the transcription process.
- Once the interviews are transcribed, the text will be read and re-read whilst listening to the recordings to ensure correct transcription. Following this review process and analysis the tapes will be destroyed and the transcripts will become the source data
- The interviews will be coded into themes by the whole research team, the themes will then be analysed further using a transformational framework, identifying over-arching themes or concepts, summarising and synthesising the data and using descriptive analysis to represent the findings/dyads views [Spencer et al, 2003].
- A table of the themes will be produced
- These themes will characterise recurring ideas and thoughts from the participants and will form the basis for further analysis and publications.
- Individual quotes may be used – these will be anonymised, this will be in the information sheet(s) and consent.

Field notes:

- Immediately after the interview, the researcher will record any thoughts, reflections or observations made during the interview. In particular any thoughts/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 one interview to discuss their hopes, fears, expectations and the realities of the new treatment.

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.

National guidance on interviewing children [MRC, 2004; RCPCH, 2000] will be followed.

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; as such consent will be reaffirmed before the interviews take place. Informed consent will be required from the adult participants and parents of all child participants.

Age appropriate information will be used to gain assent from child participants, this will either be in a written format, for those old enough to comprehend the written assent form, or verbal from those who are pre-literate. [Gibson and Twycross, 2007]. If a child says ‘no’ this will be taken as non-assent and they will not be requested to participate again.

7.2 Anonymity/confidentiality

The use of 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 researcher.

7.3 Ethical approval

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

Ethical approval will be sought from the Health Research Authority using the standard IRAS application forms.

This study will be registered with the research and development department at GOS.

7.4 Reward for participants

At the end of each interview, participants will be given a £50 voucher as a 'thank you' present for participation (maximum £100 per family). This will be included in the participant information sheets.

7.5 Stakeholder consultation

This Steering Committee developing this project will include patient representation: our patient representative will also assist in recruiting study participants and conducting the patient interviews. All appropriate Disclosure and Barring Service (DBS) checks will be undertaken. The primary patient interview schedule will be derived from three current users of emicizumab (one child, one teenager, one adult) and their family members

8 Data Protection

Participants in the Emi and Me 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.
- All personal identifiable data will be kept for 12 months after the study. After this period they will be shredded.
- All anonymised data, including transcripts of interviews will be kept for 15 years after the study. After this period 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 is being sought under the Roche/Chugai investigator initiated research programme. All study funds will be managed by Haemnet.

9.1 Study sponsor

The study will be sponsored by and indemnified by Haemnet.

10 Dissemination

We will submit abstracts to the 2020/2021 national and international haemophilia conferences, such as EAHAD, WFH, and ISTH.

In addition, we will submit the study results for publication in peer-reviewed journals serving medical/nursing/allied health professionals who work with people with haemophilia.

We will also disseminate our results directly to study participants through a final report. We will also publicise the results via the UK Haemophilia Society 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 ICMJE.

11 Study Personnel

11.1 Steering Committee Members

The following people have contributed to the preparation of the study design and protocol:

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

Simon Fletcher: is a clinical trials/research nurse in the haemophilia centre at The Churchill Hospital in Oxford. He is interested in the impact of new therapies on patients with bleeding disorders and is undertaking a PhD by published works; this study will form part of this body of work. He has research expertise including assent/consent, data analysis and presentation/publication skills. He also has clinical expertise in the care of adults with haemophilia and inhibitors.

Luke Pembroke is Communications Officer and "patient researcher" with 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 writes educational materials for HCPs and patients, as well as creative blogs, social media posts, and clinical papers.

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 has previously managed and successfully delivered the Pfizer EUROASPIRE-funded SO-FIT study, as well studies and projects funded by Novo Nordisk (the SO-HEROIC study), the Roald Dahl Marvellous Children's Charity (the SO-LIFE study), and the Burdett Trust for Nursing (the Transforming Transition programme).
Haemnet is currently engaged in a multi-methods study assessing the prevalence and impact of chronic pain in PWH. Previous research studies and publications have also included:

- 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). In press.
- 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.
- Khair K, Klukowska A, Myrin Westesson L, Kavakli K, Escuriola C, Uitslager N, Santoro C, Holland M, von Mackensen S. The burden of bleeds and other clinical determinants on caregivers of children with haemophilia (the BBC Study). Haemophilia 2019 March 29. doi: 10.1111/hae.13736.
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- 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 a core education course (Contemporary Care of People with Bleeding Disorders), a nurse leadership programme (ASPIRE), and hosts a European nurses network facilitating development of haemophilia practice across Europe.

11.2 Study Lead Investigators

Simon Fletcher

Research nurse in the haemophilia centre at The Churchill Hospital in Oxford.
Simon.fletcher@ouh.nhs.uk

Dr Kate Khair

Clinical Academic Careers Fellow, The Centre for Outcomes and Experience Research in Childhood Health, Illness and Disability, Great Ormond Street Hospital for Children, London
kate@haemnet.com

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Appendix 1: 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.

Appendix 2: Safety Reporting Definitions

Adverse Events (AE)

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any reports of new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).

  Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Assessment of Causality of Adverse Events

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal products.

The PI will use her knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to a medicinal product. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Appendix 3: Roche Adverse Event and Special Situation Reporting Form

Instructions:

This form is to be used for reporting Adverse Events (AEs) and Special Situations originating from a spontaneous source, a Non-Interventional Study (NIS), a Market Research and Patient Support Program (MAP), a Pre-Approval Access (PAA) / Compassionate Use (CU) Program and a Post-Trial Access Program (PTAP).

AEs and Special Situations will be collectively referred to as "adverse events" hereafter.
For AEs and Special Situations originating from:

- Spontaneous sources: Omit section A, B,C and D and start to complete the form with Section 1 – Reporter Details.
- NIS: Complete section A first in addition to the other sections.
- MAP: Complete section B first in addition to the other sections.
- PAA/CU Program: Complete section C first in addition to the other sections.
- PTAP: Complete section D first in addition to the other sections.

The four essential elements for AE/Special Situations reporting are marked with * .

Once completed, forward the form to your Roche Local Safety Unit (LSU) or to Roche Safety Operations as applicable.

For dates, spell out the first three letters of the month, DD/MMM/YYYY, e.g., 07/APR/2015.

Note: The format/wording of this form may be modified by the Roche LSU as needed as long as the requirements on essential data that needs to be collected is not omitted.

A. Non-Interventional Study (NIS) REPORTS ONLY

NIS Protocol Number:	
Site Number:	
Patient Number:	

Did the patient receive a studied medicinal product as per the NIS protocol? ☐ Yes ☐ No

Are any of the adverse events reported on this form exempted from collection as per the NIS protocol? ☐ Yes ☐ No

B. Market Research and Patient Support Program (MAP) REPORTS ONLY

Note: Even if there is no identifiable patient, complete as many details as possible.

MAP Identifier:		Project Title:	
MAP Service Provider:		Respondent ID:	
Address:		E-mail Address:	
		Telephone Number:	
Country:		Fax Number:	

C. Pre-Approval Access (PAA)/Compassionate Use (CU) Program REPORTS ONLY

Program Number:	
Patient Identifier:	

D. Post-Trial Access Program (PTAP) REPORTS ONLY

Program Number:	
Patient Identifier:	

1. REPORTER DETAILS * *Note: If available please provide reporter's occupation. If data privacy allows please provide name, address and/or phone number.*

Reporter First Name:		Occupation:
Reporter Surname:		☐ Physician (specify speciality):
Address:		☐ Pharmacist

Postal/Zip Code:		☐ Nurse
Country:		☐ Consumer/Patient
E-mail Address:		☐ Legal
Telephone Number:		☐ Company Representative
Fax Number:		☐ Other (specify):

Has the Regulatory Authority been notified of this report? ☐ Yes ☐ No ☐ Unknown

2. PERMISSION TO CONTACT HEALTHCARE PROFESSIONAL (HCP)

If the reporter is a consumer/patient, permission to contact HCP regarding adverse event(s)? ☐ Yes ☐ No	HCP Contact Details:

3. PATIENT DETAILS *

Note: If data privacy allows please provide at least one descriptor. Please ensure the patient's age or age group is captured wherever possible.

Name/Initials:		Weight:	☐kg ☐lb
Gender:	☐ Male ☐ Female ☐ Unknown	Height:	☐cm ☐inch
Date of Birth: or age at time of event:	☐ Year(s) ☐ Month(s) ☐ Day(s)	Ethnic Origin:	☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other (specify):

4. SUSPECT PRODUCT * *- If more than 4, continue in Additional Relevant Information, Section 8.*

Product Name (report brand name if available)	**Indication/ condition** for which the product has been prescribed	**Dose and Unit**	**Route**	**Frequency**	**Start Date**	**Stop Date** (or ongoing)	**Batch/ Lot Number**
A							
B							
C							
D							

A

Was the suspect product discontinued due to the adverse event? ☐ Yes ☐ No

If so, did the patient's condition resolve/improve? ☐ Yes ☐ No ☐ Unknown

Was the suspect product reintroduced? ☐ Yes ☐ No

If so, did the event recur? ☐ Yes ☐ No ☐ Unknown

B

Was the suspect product discontinued due to the adverse event? ☐ Yes ☐ No

If so, did the patient's condition resolve/improve? ☐ Yes ☐ No ☐ Unknown

Was the suspect product reintroduced? ☐ Yes ☐ No

If so, did the event recur? ☐ Yes ☐ No ☐ Unknown

C

Was the suspect product discontinued due to the adverse event? ☐ Yes ☐ No

If so, did the patient's condition resolve/improve? ☐ Yes ☐ No ☐ Unknown

Was the suspect product reintroduced? ☐ Yes ☐ No

If so, did the event recur? ☐ Yes ☐ No ☐ Unknown

D

Was the suspect product discontinued due to the adverse event? ☐ Yes ☐ No

If so, did the patient's condition resolve/improve? ☐ Yes ☐ No ☐ Unknown

Was the suspect product reintroduced? ☐ Yes ☐ No

If so, did the event recur? ☐ Yes ☐ No ☐ Unknown

5. ADVERSE EVENT(S)/SPECIAL SITUATION(S) * *- If required, continue in Additional Relevant Information, Section 8.*

Adverse Event (AE) (list primary first)	**Onset Date**	**Outcome** (enter number as per the key below)	**Resolved/ Improved Date**	**Seriousness**	**Causality** **Y=Yes, N=No, U=Unknown, NP=Not Provided** (specify all suspect products that may have caused the adverse event). If causality is

		If outcome is unknown, use key 6 and add further details in Section 8		(enter one or more numbers as per the key below)	unknown, specify "unknown" and add further details in Section 8			
					Suspect Product			
					A	**B**	**C**	**D**

Key for outcomes:

1. Fatal, 2. Not Recovered/Not Resolved, 3. Recovered/Resolved, 4. Recovered/Resolved with sequelae, 5. Recovering/Resolving, 6. Unknown

Key for seriousness:

1. Death (if yes, provide date): **2. Life-Threatening** (use only if patient was at immediate risk of death due to adverse event) **3. Initial/Prolonged Hospital Admission** **4.Congenital Anomaly/Birth Defect** **5. Persistent or Significant Disability** **6. Medically Significant** (important medical event that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes) **7. Non-serious Adverse Events of Special Interest (AESI**) as per NIS protocol **8. Non-serious**

6. CONCOMITANT MEDICATIONS

Also include herbal, homeopathic medications and supplements as well as OTC products. If more than 6, continue in Additional Relevant Information, Section 8.

Product Name (report brand name if available)	**Indication**	**Dose and Unit**	**Route**	**Frequency**	**Start Date**	**Stop Date** (or ongoing)

7. TEST(S) PERFORMED TO EVALUATE ADVERSE EVENT(S)

E.g., baseline results prior to product. If required, continue in Additional Relevant Information, Section 8.

Test	**Date of Test**	**Test Result** (include units if applicable)	**Reference Range**	**Result Pending?**
				☐
				☐
				☐
				☐
				☐
				☐

8. ADDITIONAL RELEVANT INFORMATION

Provide a description of the adverse event(s), severity, concurrent conditions and relevant medical history (including start and end date if applicable), clinical course, causality (if unknown), treatment for adverse event(s) and outcome.

9. MEDICATION ERROR INFORMATION

Please complete for all reports of intercepted or confirmed medication error. If any other information is considered of relevance, please provide it in section 8.

A. Brief description of the medication error:

B. Stage where the error first occurred:

☐ Storage
☐ Prescribing
☐ Dispensing
☐ Preparation for administration
☐ Administration
☐ Drug monitoring

C. Was the patient exposed to the error?
☐ Yes ☐ No
If the answer is Yes, continue to section C1. If the answer is No, continue to sections C2 and C3.
C1. Did the error have any clinical consequences?
☐ Yes ☐ No

If the answer is yes, please provide the numbers of the associated adverse events (as per section 5) below:

C2. Stage where the error was intercepted:

☐ Storage
☐ Prescribing
☐ Dispensing
☐ Preparation for administration
☐ Administration
☐ Drug monitoring

C3. Please describe the potential for harm that might have occurred if the error had reached the patient:

D. Setting(s) where the error occurred (list more than one if applicable, e.g. pharmacy, hospital, private home…):

E. Contributing factors and root causes:

F. Mitigating factors that prevented or moderated the progression of the error towards harming the patient:

G. Corrective and/or preventative actions taken in response to the error:

ROCHE USE ONLY OR VENDORS ACTING ON BEHALF OF ROCHE

LRN: AER: Local Received Date: Company Received Date:

Report Type ☐ Initial ☐ Follow-Up ☐ Spontaneous ☐ Literature ☐ Other (specify): NIS Protocol Number: MAP ID: PAA/CU Program Number: PTAP Program Number:	**Ancillary Documentation?** ☐ Yes ☐ No **Supplementary Form attached?** ☐ Yes ☐ No