HOw Patients view Extended half-life products: Impressions from real-world experience (The HOPE study)

Kate Khair 1
Debra Pollard 2
Catherine Harrison 3
Susan Hook 4
Mike O'Driscoll 5
Michael Holland 6

1The Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), Great Ormond Street Hospital for Children, London, UK

2The KD Haemophilia Centre & Thrombosis Unit, Royal Free Hampstead NHS Trust, London, UK

3Haemophilia & Thrombosis Centre/P100, Royal Hallamshire Hospital, Sheffield, UK

4Royal Edinburgh Infirmary, Edinburgh, UK

5School of Health and Education, Middlesex University, London, UK

6Haemnet, London, UK

Correspondence

Kate Khair, The Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), Great Ormond Street Hospital for Children, London WC1N 3JH, UK.

Email: Kate.khair@gosh.nhs.uk

Funding information

Sobi

Abstract

Introduction: Extended half-life (EHL) clotting factors have been shown to offer people with haemophilia (PwH) protection from bleeding with fewer infusions, which might reduce treatment burden.

Aim: The HOw Patients view Extended half-life products (HOPE) study aimed to explore, understand and describe patient expectations around the prophylactic use of EHL products and to establish whether these expectations were met through individual follow-up analysis.

Methods: The HOPE study was a prospective, qualitative cohort study conducted among PwH who had switched to Fc fusion protein EHL products in routine clinical care and who had not been recruited to clinical trials of these products. Semi-structured audio-recorded interviews were undertaken over two time points; transcripts were analysed to systematically generate theory from data that contains both inductive and deductive thinking.

Results: Forty-three interviews were conducted with 25 participants. Most participants were positive about EHL treatment and intended to continue using them. Reduced frequency of infusions meant lives were less disrupted or dominated by haemophilia, and there was less perceived stress on overused veins. For those PwH who did not reduce infusion frequency, there were other perceived benefits from EHLs with respect to greater protection with higher trough levels and fewer bleeds.

Conclusion: Patients switching to EHL treatments believe these products will result in fewer infusions and less disruption of everyday life, leaving them feeling more protected with fewer bleeds and increased activity levels, as well as enhanced well-being and mental health. Understanding patient expectation and experience around using products adds real-world data to clinical trial experience.

KEYWORDS

extended half-life factors, haemophilia, patient expectation, patient experience, qualitative

research

1 INTRODUCTION

Extended half-life (EHL) clotting factors may offer people with haemophilia (PwH) protection from bleeding with fewer infusions, which might reduce treatment burden.1,2 While patient expectation is high (as suggested by posts on social media), there are potential risks that PwH may forget to perform less regular infusions and thus experience more bleeds than

currently. The HOw Patients view Extended half- life products (HOPE) study aimed to provide in depth qualitative data on the expectations of PwH about EHL products, and whether those expectations were met. The study was timed to start as EHL factors became commercially available in the UK (summer/autumn 2016).

Clinical trials have demonstrated the efficacy of EHL products,3-6 but little is known about why PwH would choose to switch to a new therapy. Understanding the rationale for switching from standard to EHL factor is an important aspect of haemophilia care.

The HOPE study was designed to capture the expectations and the realities of PwH in the UK switching or recently switched to EHL factors, who had not been recruited to clinical trials of these products. The working hypothesis was that PwH would be keen to use these products and that for most, if not all, the promise of improved care would be met.

The primary objective was to explore, understand and describe patient expectations around the prophylactic use of EHL products and to establish whether these expectations were met through individual follow-up analysis. In addition, we sought to understand how patients used these products in everyday life.

2 MATERIALS AND METHODS

The HOPE study was a prospective, qualitative cohort study conducted among PwH who had switched to Fc fusion protein EHL products (subsequently EHL only) outside of clinical trials. The aim was to determine hopes and expectations of switching; and participants were recruited be- fore or as they switched products. Eligible participants were adults aged

>16 years or parents of children aged <16 years with moderate or severe haemophilia A or B currently on prophylaxis with standard half-life products who were likely candidates to be prescribed EHL coagulation factors as prophylaxis, and who were receiving treatment in a UK haemophilia centre. Sixteen is the legal age at which young people are deemed to have capacity and can consent to treatment by the National Health Service without parental consent. Patients prescribed EHL clotting factor products in a clinical trial setting and non-English speakers were excluded.

The study was registered (Registration Number 2049) as a Clinical Audit/Service Evaluation project with the Clinical Governance and Safety Team at the lead site, which advised that it did not require approval from a local research ethics committee. This advice was echoed by other centres. Furthermore, the Kings Fund Experience Based Co-Design Toolkit7 states that as this study will not change clinical practice, it is deemed not necessary to obtain research ethics approval. Nevertheless, study participants were required to verbally consent to be in the study. This consent could be withdrawn at any stage and would not impact upon their haemophilia care; as such, consent was reaffirmed before the second interview.

The HOPE study was advertised via waiting room flyers in the investigators' centres, additionally 'switching' patients were identified by clinical staff in centres as potential study participants and were given information about study participation. Participants contacted the research team by telephone or email to arrange an interview. Participants were also recruited via social media; the project was advertised via a flyer on UK haemophilia-specific sites on Facebook. The HOPE study used a qualitative research design of semi- structured interviews with a longitudinal element using thematic analysis to systematically generate theory from data that contains both inductive and deductive thinking to formulate hypotheses that aim to discover participants' views. The question the researcher repeatedly asks is 'What's going on?'.8 Usually this is done in face- to-face encounters; however, it has also been used with telephone interviews.9 We undertook a series of semi-structured interviews in phase one (P1). We then made a further approach to each participant for a phase 2 (P2) interview at least 6 months later, looking for consistency with and changes from their earlier comments.

The study coordinators and a patient co-researcher developed the P1 interview schedule. The P2 interview schedule was based on P1 and included issues that had emerged in P1. P2 attempted to capture change from the baseline of P1 in certain respects and to understand the experiences (or 'journey') from P1 to P2. This approach gives a very rich data set reflecting real-life experiences of participants. The same researcher undertook all interviews.

Interviews varied in duration from 15 to 30 minutes and were digitally recorded and transcribed verbatim by a professional transcriptionist unknown to the study participants to maintain anonymity. The transcripts were analysed using NVIVO qualitative data analysis software. Participants were anonymized and known by study number only.

2.1 Data analysis

Descriptive statistics were extracted from the qualitative data on name of treatment product used at P1 and P2, length of time on EHL, participant age, haemophilia type and severity and inhibitor status. These statistics were analysed using SPSS software (v.22).

Data were coded line by line in each interview using NVIVO soft- ware (v.11) and then analysed using inductive thematic analysis,10 which identifies recurring patterns in the data. Ideas, comments or statements that recurred were organized into a hierarchical pattern of themes. Codes and themes were reviewed and refined through- out the analysis process.

3 RESULTS

3.1 Patient characteristics

A total of 43 interviews were conducted with 25 people. Patient disposition is summarized in Figure 1. The first wave of interviews was conducted with PwH (or their parents) who were about to start, or had recently started, treatment with an EHL factor. In all, there were 22 phase 1 interviews. These participants (subject to their con- sent) were then followed up approximately 6 months later when a P2 interview was conducted. At P2, three participants declined to be interviewed and one was withdrawn from the study following recruitment into a clinical trial. There were therefore 18 pairs of P1/P2 interviews. Three new participants were interviewed for the first time at P2; therefore, seven people provided one interview (four P1 and three P2).

Table 1 summarizes the characteristics of each participant. Participants were either adults or parents of children with haemophilia (CwH). Two-thirds of the interviews (67%, n = 16) were by proxy – through the mothers (in all instances) of a CWH, and the remaining third (n = 8) were conducted directly with PWH. The mean age of CWH was 6.25 ± 4.31 years (range 1-14). The mean age of PWH was 36.8 ± 13.7 years (range 16-56).

More than half of participants (58.3%, n = 14) had haemophilia A (Table 1). Overall, 7 (29%) of participants were treated with an EHL product at P1 (5 with EHL-FVIII and 2 with EHL-FIX) and 17 (71%) were treated with an EHL product at P2 (15 with EHL-FII and 2 with EHL-FIX). The recruiting criteria for the study were participants who were about to switch to EHL therapy; seven individuals had already switched 1-10 weeks pre interview, five of these were parents of children with haemophilia who had switched 4-10 weeks prior to interview. It also became apparent that one participant was using a non-Fc fusion protein EHL, this was more than half-way through the P1 interview. The study team decided pragmatically that these interviews would be included as the parents would have good recall of their switching decisions and the patient interview had generated new data that was relevant to using EHL therapy per-se.

The themes that emerged from the interviews are discussed here:

3.1.1 Expectations

All patients being considered for EHL treatment in the UK were required to undergo pharmacokinetic (PK) assessment and dosing; this was done as part of routine clinical care and was not part of the HOPE study. Having undergone PK assessment participants expected that EHL products would require less frequent dosing, less disruption and less demand on veins or central venous access de- vices (CVADs). Some hoped they would offer better protection and therefore would experience fewer bleeds. There was initial

uncertainty about future benefits because dose frequency could not be predicted at the pre/switch time point of P1.

3.1.2 Experiences

In all, 17 participants were using EHLs at P2. The majority of sentiments expressed towards EHL were positive; however, a small number of participants also expressed mixed sentiments about aspects of their treatment.

Seventy-three per cent of participants were positive about EHL products stating less disruption, fewer treatment administrations, fewer bleeds, feeling more protected, improved mental health and improved sense of well-being. This meant reduced dosing; reduced burden of venous access; greater benefits in families with more than one child using an EHL; and greater flexibility about staying away from home. Participants felt that EHLs had lived up to their expectations and in one case had exceeded them. Several reserved judgement, saying it was too soon to comment or they were uncertain about the longer term suitability of their treatment.

Neutral experiences were reported by 20%: this included expectations not being met, with little change in protection against bleeds (based on trough levels), dose frequency or disruption. A small number of participants (7%) reported negative experiences including a lack of confidence in an unfamiliar medicine.

TABLE 1 Characteristics of participants, treatment and interviews completed

Participant[a] and number			Age[b] (y)	Haemophilia	Inhibitor history[c]	Treatment P1	Interview P2	Interview P1
H1	Carer	12	A	Previous	Elocta	Elocta	●	●
H2[d]	PWH	44	B		Idelvion	Idelvion	●	●
H3	PWH	44	A		Refacto	Elocta	●	●
H4	PWH	36	A		Advate	Elocta	●	●
H5	PWH	33	A		Refacto	Refacto	●	●
H6	Carer	2	A	Previous	Advate	Advate	●	●
H7	Carer	12	A		Refacto	Refacto	●	●
H8	Carer	2.5	A		Advate	Elocta	●	●
H9	Carer	1.5	A		Elocta	Elocta	●	●
H10	Carer	5	A		Advate	Elocta	●	●
H11	Carer	1	A		Elocta	Elocta	●	●

H12	Carer	8	A	Previous	Advate	Elocta	●	●
H13	Carer	14	A		Refacto	Elocta	●	●
H14	Carer	6	A		Refacto	Refacto	●	●
H15	PWH	46	A		Advate	No P2	●	-
H16[e]	Carer	3	A		Elocta	No P2	●	-
H17	PWH	16	B		Alprolix	Alprolix	●	●
H18[e]	Carer	3	A	Current	Advate	No P2	●	-
H19	Carer	10	A		Elocta	Elocta	●	●
H20	Carer	1	A	Previous	Advate	Elocta	●	●
H21	PWH	56	A		Refacto	Elocta	●	●
H22	PWH	19	A		No P1	Elocta	-	●
H23	Carer	5	A		Refacto	No P2	●	-
H24	Carer	9	A		No P1	Elocta	-	●
H25	Carer	5	A	Previous	No P1	Elocta	-	●

Abbreviation: PWH, person with haemophilia.

A Person who was interviewed.

B Age of PwH at time of interview.

C Inhibitor history at PI – no patients developed inhibitors during the study.

dPatient H2 confirmed his eligibility in screening but his treatment (Idelvion) emerged only in interviews; although not on a Sobi product he was not withdrawn as analysis revealed many interesting comments.

ePatient H18 was withdrawn as he switched to emicizumab.

Most participants did not fully understand the term ‘pharmacokinetics’ or their trough levels and thus the rationale for the new infusion frequency. Of those whose experiences were neutral or negative, two were unsure whether they wanted to continue to use EHL products.

3.1.3 Treatment frequency

Many who had switched to EHLs had experienced reductions in dose frequency. At P1, this was the source of some uncertainty as participants refined and adapted to a new treatment pattern. Others reported (at P1 or P2) no change in dose but felt they were better covered because factor levels were higher than with traditional factors. The reduction in number of treatments needed per week was seen as a positive outcome of using EHL therapy – even if this was ‘only’ one infusion less per week.

3.1.4 Adherence

Participants were aware that treatment adherence is a concern for clinicians and most reported adhering to their treatment plan and never or rarely missing doses. Most administered their EHL treatment in the morning, though there was greater flexibility at week- ends. The main reason cited for missing a dose was work, tiredness or being too busy with other tasks. This was most noticeable in parent/carers.

In children, age was an important factor in the decision to tailor treatment. Most parents of very young children saw no need to tailor dosage because they perceived a low risk of trauma. School- age children tended to be very active, and in some cases, additional treatments were given before an activity but many parents managed risk by tailoring both activities and factor administration. There was little evidence overall that PWH avoided activities though not all tailored their treatment to manage bleed risk.

When initiating EHL treatment, participants had to adjust treatment routines, which made adherence difficult for some. Some felt that haemophilia centres exerted pressure on them to adhere: they knew the products were expensive and that access was controlled and some stated that the EHL would be withdrawn if they did not follow the treatment plan stating that in the past it may have been possible to conceal a missed dose, but this was no longer an option because treatment was now more closely monitored.

Home treatment with EHLs is monitored with the Haemtrack app, which logs the date and time of dose administration. The re- cord is scrutinized by clinicians, who can identify missed doses. Some participants felt under pressure to use Haemtrack but most were positive: they considered it convenient and easy to use. A minority of users reported technical problems with updates and reliability and improvements were suggested. Participants reported being contacted by a clinician requesting an explanation when their Haemtrack data revealed missed doses; some reported being told that they would not have bleeds if they adhered to the treatment plan. One parent reported making a special effort with data recording adherence to secure treatment with an EHL; however, her child still did not receive EHL therapy.

3.1.5 Bleeds

This study was not designed to quantify the effect of EHLs on bleeding frequency. At P1, several participants reported 1-2 bleeds per month; some participants reported at P2 that their bleeding frequency had decreased after starting EHL treatment. Participants tended to manage a bleed with additional doses of factor even when this was not part of their treatment plan; clinical advice was sought when this and other measures had failed. Some participants felt that treatment with an EHL made their decisions about managing bleeds more complex, including comments about timing of repeat doses during the early stages of EHL use.

3.1.6 Switching decision

The discussion about switching to an EHL was most likely to be, but not exclusively, initiated by a clinician. The main barriers to switching from the participants' perspective were a lack of detailed information about EHL products and not wanting to change an established and effective treatment. One mother reported being at the point of switching for her 6-year-old son, but had concerns about potential side effects of a new molecule (inhibitor and cancer risks) and decided to wait until there was more data on use in children. Some participants suggested that EHLs were not available in some geo- graphical areas, one stated that their hospital had offered EHL but was 'still tied up in a contract for his "old" factor and he wouldn't be able to switch for a further 6 months' or that some people were not eligible for treatment switching. One parent had initially been reluctant to join a clinical trial and the haemophilia centre never broached the possibility again; so the child was unable to switch until the product was commercially available. A switch was delayed for one child in the hope that an inhibitor would be eradicated.

More concerns were expressed at P1, when some participants had just started using an EHL, than at P2. The reduced treatment frequency prompted concerns that 'cover' would be insufficient, with one participant describing previous daily dosing as a 'safety blanket'. Some were concerned about the possible unidentified risks of a new and unfamiliar treatment. The different pharmacokinetic properties of EHLs raised perceived concerns at P1, including shorter half-life than suggested by the product literature and misunderstanding about metabolism of EHLs.

Extended half-lifes are more expensive than SHL factors in the UK, and NHS providers have been selective who is eligible for treatment, effectively restricting access to some patients or delaying the local introduction of EHLs.2 Though there was understanding about the pressure on the NHS to manage resources, some participants and carers were sceptical that access to EHLs was determined on primarily clinical grounds, suspecting that limiting cost was the main determinant: the conditions imposed on EHL treatment were perceived to be designed to ensure 'cost neutrality' – that is to prevent costs increasing. Once prescribed, continued access to treatment with EHLs is generally conditional on adherence to an agreed treatment plan and monitoring with Haemtrack.

4 DISCUSSION

Our interview methodology involved reporting things to participants that others had said (eg 'we have heard XYZ – has that ever happened to you?') This is a recognized qualitative interviewing technique, but risks leading discussion. The interviewers were aware of this and were cautious with wording of questions and amended questions frequently throughout the interview phase of the study, which continued until we reached a point of

data saturation where no new discussions could be coded against a theme or topic. This enables us to report the experience of this study cohort.

Patient experience is an important aspect of measuring the effectiveness of NHS health care11 but the outcomes usually collected are quantitative in nature, through clinical trials or through quantitative measures more generally (number of joint bleeds, number of infusions, amount of treatment used) rather than based on qualitative assessment. We have used a qualitative research methodology involving semi-structured interviews with a longitudinal element to explore and describe patient expectation and experience around using EHL products in routine clinical care, adding real-world data to clinical trial experience of these products. These participants were 'early adopters' of EHL therapy in a non-trial situation; they may have hoped for greater benefit from switching early based on perceived benefit of their peers in clinical trials. Patients switching to EHL treatments believe these products will result in fewer infusions and less disruption of everyday life, leaving them feeling more protected with fewer bleeds and increased activity levels, as well as enhanced well-being and mental health. This was also described in a recent survey of over 1000 patients/parents.12

Patient satisfaction is recognized to be an important determinant of treatment adherence.13 Most participants who were receiving EHL treatments in our study were positive about it and intended to continue with it. The majority of participants experienced reduced frequency of treatment which meant that their lifestyles were less disrupted or less dominated by haemophilia, with less perceived stress on overused veins. Some were able to dispense with CVADs, something that has been demonstrated to reduce caregiver bur- den.14 Even in those cases where there was not reduced frequency of treatment after switching to EHL treatments, there were often other perceived benefits such as higher troughs with greater levels of protection and fewer bleeds.

A number of participants wanted more information about EHL treatments – in some cases about its availability in their area, or regarding research about outcomes over the longer term. There may be a case for hospitals and haemophilia centres, perhaps in conjunction with providers of EHL treatments, to evaluate their current pro- vision of information about EHL treatments and to consider whether any changes or improvements are appropriate. This was particularly apparent in discussing understanding of PK (which all participants had undergone as part of the clinical switching programme); there was a clear lack of knowledge about factor levels, timing of infusions and treatment for bleeding episodes. This is an area that requires additional patient/carer education.

Some participants were hoping to switch from standard half- life products at P1 but had still not done so at P2, because of cost or because they felt, haemophilia centres seemed reluctant to make the change. The decision to offer EHL treatment should not be on a simplistic basis of a cost comparison with non-EHL treatments. Our analysis suggests that there are distinct advantages to EHL treatment, such as feelings of better protection and some evidence of greater activity levels, reduced bleeds and pain. The HOPE study was a qualitative study, which explored and described experiences of PWH using EHL treatments – a causal relation- ship between EHL treatment and these outcomes is not claimed. Nevertheless, there is certainly a case for a more rigorous study designed to assess whether

there are such relationships, and if so, then clearly ‘value’ should be attributed to these benefits when making the decision to offer EHL treatment.

There seemed to be considerable barriers to PWH obtaining or staying on EHL treatment, which relate to perceived cost or ‘rationing’ of treatment by haemophilia centres. This study was con- ducted during a period of historically high levels of financial stress within NHS funding, particularly when compared to other western European countries. There has also been an apparent resurgence of the postcode lottery as commissioning has become increasingly local, discretionary and therefore variable following the Health and Social Care Act 2012.15 This was reported by two participants, from the same geographical region, who reported being unable to switch due to contracting/budgetary issues. Haemophilia care in the UK is commissioned through the specialized commissioning route, and the availability of factor products is subject to competitive tendering, which can place limits to the range of products clinicians are able to offer patients. Nevertheless, it is important for clinicians to remember that the value of a treatment is not represented by its cost alone.

Clinicians should be careful not to place undue pressure on PWH in terms of creating a perception that anything less than complete adherence may result in the withdrawal of a treatment. In some cases, the need of haemophilia centres to gather evidence about cost-effectiveness appeared to result in strong pressure on PWH to adhere very strictly to the agreed treatment plan (monitored remotely through Haemtrack), at the perceived risk of having the treatment withdrawn. This meant that the HOPE study participants felt unable to tailor their own treatment around ‘risky’ activities as they had done when using SHL factors; this led to anxiety about bleeding risk and limited some activities. There needs to be more and better information about EHL treatments, including pharmacokinetics and individual treatment plans. This study was undertaken as Fc fusion protein EHL factors be- came commercially available in the UK. Any patient who switched had undergone PK assessment as part of the switching programme and may have had different views about his new therapy based on this knowledge. The numbers are too small to compare between parent and patient experience or between haemophilia A and haemophilia B where the benefits of once weekly prophylaxis might have been expected to be greater. We believe there is a need for a comparative study designed to adequately capture real-world haemophilia treatment burden and to demonstrate the potential bene- fit that can be attributed to EHL products. Such a study would add further evidence from real-world data to support that obtained in quality of life outcomes in clinical trials.16,17 This would help to ensure that the patient voice is heard in shared decision-making about therapeutic options in keeping with the ‘no decision about me without me’ mantra in the NHS consultation.15

ACKNOWLEDGEMENT

We would like to thank all participants of the HOPE study for their time and opinions about using EHL products and providing this real-world data.

DISCLOSURES

The HOPE study was managed by the study sponsor, Haemnet (www. haemnet.com), a UK-registered charity (No 1152241) that supports and promotes haemophilia nurse education and research. Financial support was provided from Sobi (Swedish Orphan Biovitrum AB, Stockholm) by an Investigator Initiated Research (IIR) grant. KK, DP, CH and SH have all received speaker fees from Sobi. SH is now an employee of Novo Nordisk UK. Research at Great Ormond Street Hospital is supported by the NIHR/BRC.

AUTHOR CONTRIBUTIONS

The study was designed by KK and MH, and the design was approved by all authors. Data collection was performed by MO'D. Data analysis was performed by KK and MO'D. The first draft of the manuscript was written by Steve Chaplin, a medical writer. All authors recruited participants, contributed to and agreed the final version of the manuscript.

ORCID

Kate Khair https://orcid.org/0000-0003-2001-5958

Debra Pollard https://orcid.org/0000-0002-7797-3500

Catherine Harrison https://orcid.org/0000-0002-9336-5249

Mike O'Driscoll https://orcid.org/0000-0001-9221-6164

Michael Holland https://orcid.org/0000-0002-9173-4100

REFERENCES

1. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015;126:1078-1085.

2. Collins P, Chalmers E, Chowdary P, et al. The use of enhanced half- life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. Haemophilia. 2016;22:487-498.

3. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. Blood. 2012;119:3031-3037.

4. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317-325.

5. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369(24):2313-2323.

6. Santagostino E, Martinowitz U, Lissitchkov T, et al. Long acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. Blood. 2016;127(14):1761-1769.

7. Kings Fund. The Kings Fund Experience Based Co-Design Toolkit. https://www.kingsfund.org.uk/projects/ebcd. Accessed October 20, 2018.

8. Charmaz K. Constructing Grounded Theory, 2nd edn. Thousand Oaks, CA: Sage; 2014.

9. Ward K, Gott M, Hoare K. Participants views of telephone interviews within a grounded theory study. J Adv Nurs. 2015;71(12):2775-2785.

10. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101.

11. Jenkinson C, Coulter A, Bruster S. The Picker Patient Experience questionnaire: development and validation using data from in-patient surveys in five countries. Int J Qual Health Care. 2002;14(5):353-358.

12. von Mackensen S, Kalnins W, Krucker J, et al. Haemophilia patients' unmet needs and their expectations of the new extended half-life factor concentrates. Haemophilia. 2017;4:566-574.

13. Chaugule SS, Hay JW, Young G. Understanding patient prefer- ences and willingness to pay for hemophilia therapies. Patient Prefer Adherence. 2015;9:1623-1630.

14. Schwartz C, Powell VE, Su J, Zhang J, Eldar-Lissai A. The impact of extended half-life versus conventional factor product on haemophilia caregiver burden. Qual Life Res. 2018;27(5):1335-1345.

15. GOV.UK. Health and Social Care Act 2012: fact sheets - Publications

- GOV.UK. [online] 2012; https://www.gov.uk/government/publi cations/health-and-social-care-act-2012-fact-sheets. Accessed October 20, 2018.

16. Chowdary P, Kearney S, Regnault A, Hoxer CS, Yees DL. Improvement in health-related quality of life in patients treated with ninacog betal pegol, a new extended half-life recombinant FIX product. Haemophilia. 2016;4:e267-e274.

17. Mancuso ME, Santagostino E. Outcome of clinical trials with new extended half-life FVIII/IX concentrates. J Clin Med. 2017;6(4):39.