



ORIGINAL ARTICLE

Assessing patients' and caregivers' perspectives on stability of factor VIII products for haemophilia A: a web-based study in the United States and Canada

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Summary. Haemophilia A is a rare inherited bleeding disorder characterized by an inability of the blood to clot normally. Patients can experience spontaneous or trauma-induced joint and soft tissue bleeding and must keep coagulation factor VIII (FVIII) accessible at all times; thus, FVIII product storage and stability are critical. Our primary objective was to assess haemophilia A patients' and caregivers' experiences and preferences with FVIII product storage and stability. A secondary objective was to evaluate the use of the social media site Facebook in recruitment. In this cross-sectional study, 145 English-speaking adult patients and caregivers of children with haemophilia A were recruited through two state-based haemophilia organizations in the United States (US) and one national organization in Canada for a web-based survey assessing demographics and FVIII product ordering, usage, and storage practices. Of the 101 individuals who completed the survey, 60% resided

in Canada; 57% were recruited through Facebook. Caregivers and patients responded similarly to questions about ordering practices and product usage, with some distinction between groups in storage practices. Two-thirds of participants noted challenges with storing FVIII products, especially storage away from home. More than half preferred storing FVIII products at room temperature vs. in the refrigerator for long periods of time. FVIII product accessibility, usage and storage affect disease management. Results support the need for more convenient and accessible FVIII products for patients in daily life and while travelling. In addition, the use of social media has potential value in recruiting this population.

Keywords: factor ordering, factor stability, factor storage, factor VIII products, haemophilia, patient and caregiver survey

Introduction

Haemophilia A is a rare inherited bleeding disorder in which the affected individual lacks or has limited production of coagulation factor VIII (FVIII) products, resulting in the inability of the blood to clot normally. The disorder is recessive and sex-linked (X chromosome), occurring almost exclusively in males. The severity level and predicted bleeding frequency

associated with haemophilia depend on the amount of clotting factor that is missing from the individual's plasma. The normal range for factor activity in the blood is 50–150%; factor activity is 5–40% for mild haemophilia A, 1–5% for moderate haemophilia A and <1% for severe haemophilia A [1].

Patients with haemophilia, particularly with severe haemophilia, must keep FVIII products accessible at all times to prevent or treat bleeding episodes; thus, FVIII product storage and stability are of critical importance, especially given the range of manufacturer-recommended storage guidelines. Guidelines for some products indicate a maximum of 2 months of room temperature storage (e.g., Alphanate [Grifols Biologics, Inc, Los Angeles, CA, 90032, USA]) [2], whereas others indicate up to 12 months of room temperature storage (e.g., Kogenate FS [Bayer HealthCare LLC, Tarrytown, NY, USA]) [3]. The Appendix presents storage and shelf life information for selected FVIII products.

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There are limited published data on patient or caregiver perspectives on FVIII product storage. However, obtaining patients' and caregivers' perspectives is critical to understanding disease management, particularly with rare conditions such as haemophilia A.

Thus, the primary objective of this study was to assess haemophilia A patients' and caregivers' experiences and preferences associated with FVIII product storage and stability attributes in the United States (US) and Canada via a web-based survey. In addition, the rarity of diseases such as haemophilia A makes traditional methods of study recruitment difficult. As such, a secondary objective was to evaluate the use of the social media site Facebook in recruiting adult patients and caregivers of children with haemophilia A.

Materials and methods

Study Design and Participants

A cross-sectional study of English-speaking adult patients with haemophilia A and caregivers (parents) of children younger than 18 years with haemophilia A was undertaken. Members of two state-based haemophilia organizations in the US [Texas Central Hemophilia Association (Dallas, Texas) and Hemophilia Association of New York, Inc. (New York, New York)] and one national organization in Canada [Canadian Hemophilia Society National Office (Montreal, Quebec) and its local chapters] were invited to complete a survey assessing respondent demographics and selected FVIII product ordering, usage, and storage practices and preferences.

Recruitment advertisements were posted on the organizations' websites and/or sent via e-mail to their member lists. In addition, two organizations posted study advertisements on their respective Facebook pages. The organizations received a donation for their assistance in study recruitment.

Questionnaire administration and content

Survey administration. Participants completed several screening items to confirm their eligibility and their status as either a patient with haemophilia A or as a caregiver of a child younger than 18 years with haemophilia A. Eligible participants then provided informed consent and were invited to complete the self-administered, web-based survey questionnaire as a patient or caregiver/parent. The target sample size was 100 completed questionnaires, and the survey was closed after the 101st survey was completed.

All eligible participants received a \$50 American Express reward card for completing the survey. The study was fielded from October 2012 through November 2012 following RTI's institutional review board (IRB) committee (ethics committee) approval.

Survey content. In addition to selected demographics (e.g., year of birth, education), the 23 survey questionnaire items assessed the following FVIII product-related information:

1. Current product usage
2. Ordering practices
3. Storage routines and challenges
4. Storage preferences

Programming logic was included in the questionnaire to route participants to the appropriate questions for patients or for caregivers, and question stems were tailored to respondent type (i.e., patient or caregiver). Only caregivers were administered a question about their sex because all patient survey respondents were presumed to be male.

Data analysis

Data analysis was primarily descriptive in nature. Responses to each of the survey questions were summarized by respondent type (patient or caregiver) and for the overall sample. Two items included open-ended response choices, and responses were assessed as frequency counts. To test for differences between patients and caregivers, a *t* test was applied for continuous variables and a chi-square test was applied for comparison of binary outcomes. Of 33 possible chi-square tests, 15 had fewer than five observations in each cell of the cross tabulation and were not tested. In total, one *t* test and 18 chi-square tests were conducted. A type I error rate of 5% ($\alpha = 0.05$) was applied to each individual hypothesis test. Owing to the exploratory nature of the study, no correction for multiple tests was performed. All analyses were conducted using SAS software Version 9.3 for Windows [4].

Results

Unless otherwise specified, the statistical tests did not detect significant differences between groups or could not be performed because of sample size limitations.

Recruitment

Of the 145 individuals who responded to survey invitations, 101 (70%) individuals completed the survey questionnaire [68 caregivers (67%), 33 patients (33%)]. The majority of participants who completed the questionnaire were recruited from the Canadian Hemophilia Society and its local chapter affiliates (68%). More than half (57%) of the sample were recruited through Facebook (Table 1). Participant characteristics were generally similar between those recruited via Facebook and those recruited using other means (data not shown). The organization that did not post a study advertisement on Facebook recruited

Table 1. Respondent type by recruitment mode (N = 101).

Respondent type	Non-Facebook (n = 43), n (%)	Facebook (n = 58), n (%)
Caregivers	26 (60.5)	42 (72.4)
Patients	17 (39.5)	16 (27.6)

the fewest participants (only 13% of the total respondents).

Demographics

Of the 101 participants who completed the survey, approximately 60% resided in Canada. The mean age of adult patients (n = 33) was approximately 34 years, whereas the mean age of caregivers was about 38 years (Table 2). Among the caregiver respondents, 82% were female. Caregivers reported that the mean age of their sons with haemophilia A (n = 68) was 8.2 years [standard deviation (SD), 4.8 years], ranging from 1 to 18 years.¹ More than half of the participants were employed (52%) and reported a college or university education or higher (54%). Approximately 60% of the US sample was white, and 62% were married. (Marriage status and ethnicity/race data were not collected for Canadian participants).

Product usage

Overall, caregivers and patients responded similarly to questions about product usage, with the exception of the number of FVIII product vials typically infused at one time. Approximately 75% of all respondents reported typically infusing a single FVIII product vial at any one time; however, a chi-square test detected a statically significant difference between patients and caregivers, with more patients than caregivers infusing with multiple vials (42% vs. 16%, respectively; P = 0.004).

The majority (77.2%) of participants reported using one of two FVIII products: Advate (Baxter Healthcare Corporation, CA, 91362, USA) [5] or Kogenate FS [3]. Nearly 80% reported having used their current FVIII product for 2 or more years. More than two-thirds of the sample (69%) reported that they used their FVIII product primarily as prophylaxis, and nearly one-quarter (24%) used it primarily on demand. More than half of the overall sample (56%) reported infusing their FVIII product 3 days a week, followed by twice a week (21%), or 4 or more days a week (17%).

¹While the caregiver survey was intended for those caring for children with haemophilia A who were younger than 18 years, caregivers were asked about their child's year of birth only and not the actual birth date. Thus, the upper limit of the age range extended to 18 years.

Table 2. Participant characteristics.

Characteristic	Caregivers* (n = 68)	Patients (n = 33)	Total sample (N = 101)
Sex (derived), n (%) [†]			
Male	12 (17.6)	33 (100.0)	45 (44.6)
Female	56 (82.4)	0 (0)	56 (55.4)
Age in years (derived) [‡]			
Mean (SD)	38.2 (7.6)	33.9 (12.2)	
Range	19–57	18–58	
Ethnicity, n (%) [§]			
Asian	1 (3.8)	0 (0)	1 (2.7)
African American/black	2 (7.7)	0 (0)	2 (5.4)
Hispanic or latino	8 (30.8)	1 (9.1)	9 (24.3)
White	13 (50.0)	9 (81.8)	22 (59.5)
Other	2 (7.7)	1 (9.1)	3 (8.1)
Missing	0	1	1
Education, n (%)			
Less than high school degree or equivalent (e.g. GED)	1 (1.5)	1 (3.0)	2 (2.0)
High school or equivalent (e.g. GED)	16 (23.5)	12 (36.4)	28 (27.7)
Technical school or associate's degree (2-year college degree)	11 (16.2)	5 (15.2)	16 (15.8)
College or university	35 (51.5)	12 (36.4)	47 (46.5)
Graduate or professional	5 (7.4)	3 (9.1)	8 (7.9)

GED = general equivalency diploma; SD = standard deviation.

*The caregiver column displays demographic characteristics for the caregivers themselves, rather than the patients for whom they care.

[†]Administered to caregiver-only participants. Patients were presumed to be male.

[‡]Derived age based on year of birth.

[§]Administered to US participants only.

[¶]'Missing' numbers are not included in the denominator for percentage calculations.

FVIII product ordering practices

Overall, caregivers and patients generally responded similarly to questions regarding FVIII product ordering practices. Nearly half of the participants reported ordering FVIII products monthly, and nearly one-quarter ordered it less frequently (Fig. 1). Participants reported a mean of 22 (SD, 21) FVIII concentrate vials in each order. More than half of the overall sample noted that they ordered FVIII products directly from haemophilia treatment centres; the next most frequently reported ordering source was a home health-care provider. Only 15% of participants provided write-in responses indicating their ordering source for FVIII products. Of the write-in responses provided, blood banks and specialty pharmacies were the most frequently reported.

FVIII product storage practices and challenges

More than half of the overall sample reported storing FVIII products primarily in the refrigerator (55%), and 32% stored it at room temperature. However, some distinction was found between patient and caregiver storage practices: patients reported a higher frequency of refrigerator storage than caregivers (61% vs. 42%, respectively) and a higher frequency of mixed room

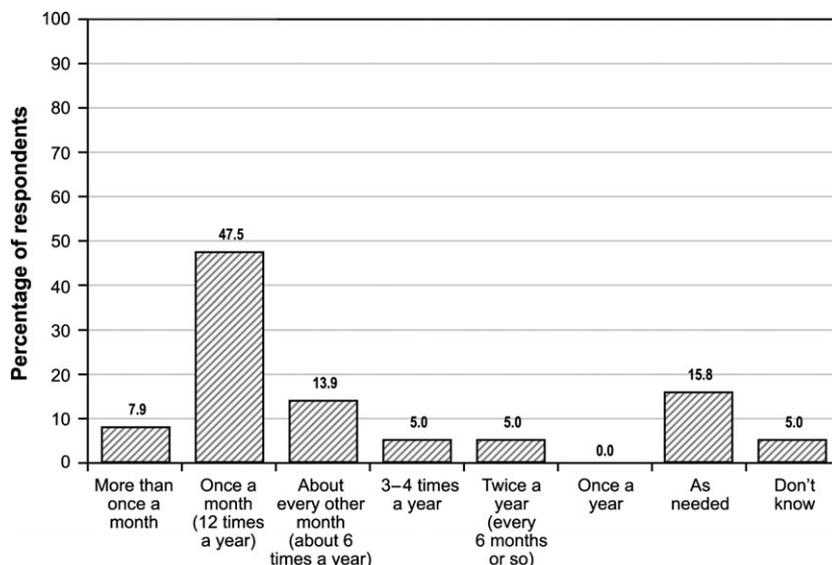


Fig. 1. Frequency of FVIII ordering.

Table 3. FVIII product storage routines and challenges.

Characteristic	Total sample (<i>n</i> = 101), <i>n</i> (%) [*]
What are the biggest storage challenges, if any, associated with [your/your child's] current Factor VIII product? Select all that apply.	
The need to keep the factor refrigerated	19 (18.8)
The need to plan for refrigerating the factor when I travel for work or vacation	28 (27.7)
The length of time the factor can stay at room temperature	16 (15.8)
The length of time the factor can be refrigerated	4 (4.0)
The inability to return room temperature factor to the refrigerator	15 (14.9)
The inability to order a lot of factor at one time	19 (18.8)
The inability to store a lot of factor at one time	16 (15.8)
The length of time between mixing and using the factor	6 (5.9)
The need to carry an insulated tote bag for factor storage when I leave the house	27 (26.7)
None of the above	32 (31.7)

^{*}Column percentages do not sum to 100 because participants were asked to select all options that apply.

temperature and refrigerator storage (24% vs. 7%, respectively; $P = 0.044$).

Nearly one-third of the sample reported no challenges with storing FVIII products. However, most participants reported storage challenges, and more than one-quarter reported the need to plan for refrigeration when travelling for work or vacation (28%) and the need to carry an insulated tote bag when leaving the house (27%) as the biggest challenges with FVIII product storage (Table 3).

Most participants reported using FVIII product vials before vial expiration; however, eight survey respondents (7.9% of overall sample) indicated that they had FVIII product vials that expired and could not be used. Of those who had vials that expired before they could be used, seven participants reported using FVIII products primarily on demand and one participant reported using FVIII products as prophylaxis.

FVIII product storage preferences

Participants were asked to indicate the most important aspect about FVIII product storage for a new FVIII product with improved storage ability. More than half (54%) of the sample noted that the ability to store a FVIII product at room temperature for a longer duration was the most important attribute compared with the ability to store the product longer in the refrigerator, indicated by only 5% of participants (Fig. 2).

When asked about interest in a new FVIII product that worked just as well as their current FVIII product but had different storage options, 80% of the overall sample indicated that they were very or somewhat interested in a FVIII product that could be stored at a higher temperature (room temperature) for up to 12 months, compared with a FVIII product that could be refrigerated for up to 2 or 3 years (56 and 54% respectively). Although there were no statistically significant differences between caregiver and patient responses for any of the three storage options, a greater percentage of both patients and caregivers indicated a strong preference for storage at room temperature compared with the refrigeration options (Fig. 3).

The primary reasons for interest in a new FVIII product that could be stored at a higher room temperature for up to 12 months included the ability to keep more factor at home (50.6%) and the ability to travel more easily (64%).

Discussion

The primary objective of this cross-sectional, web-based survey of haemophilia A patients and caregivers was to assess their experiences and preferences around FVIII product storage and stability attributes. A secondary objective of the study was to evaluate the use

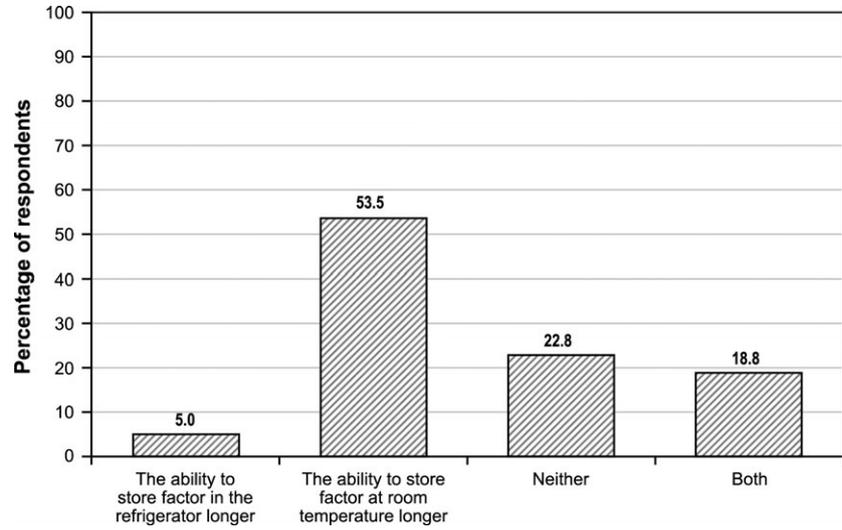


Fig. 2. If a new factor VIII product were available, which one of the following statements about factor storage would be most important to you?

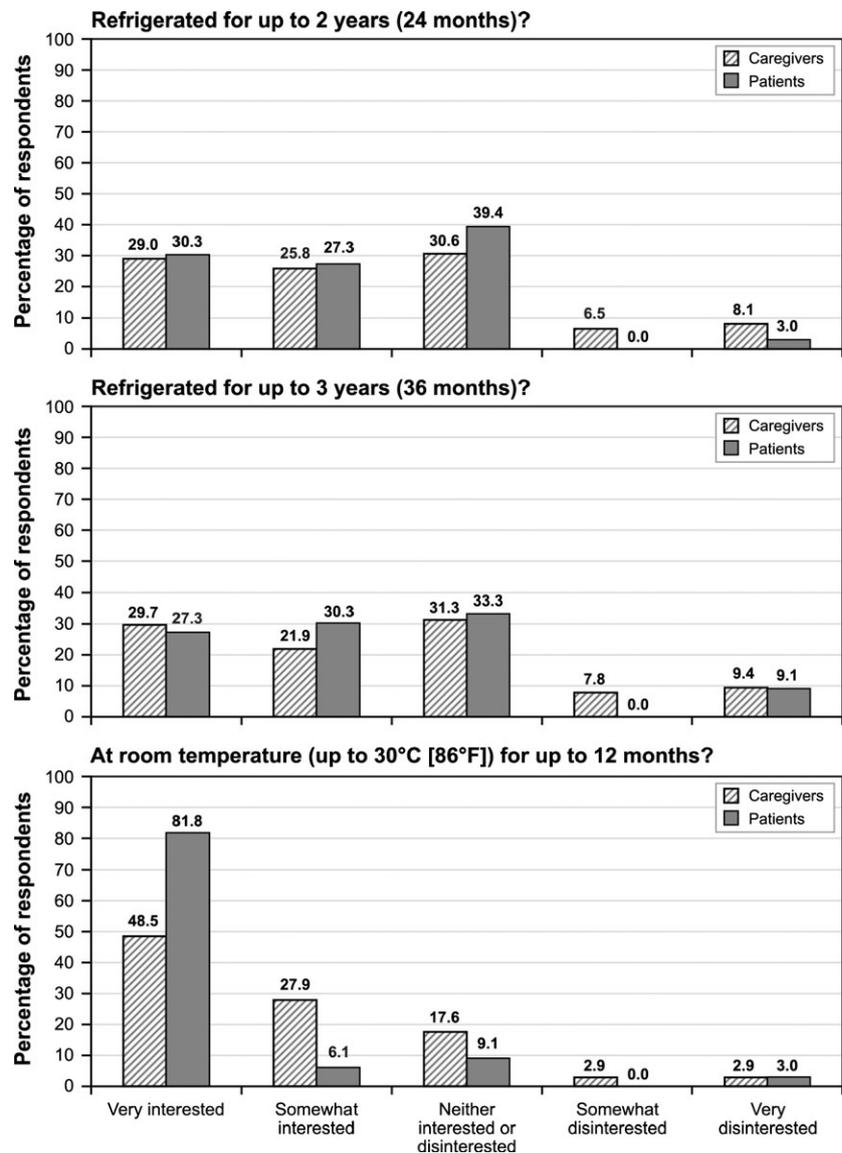


Fig. 3. Interest in a new factor VIII product that could be stored...

of the social media site Facebook in recruiting this population.

Participants generally reported ordering FVIII products regularly (approximately once a month), storing it in the refrigerator, and using it prophylactically. Although the majority of the overall sample reported infusing a single vial at a time, more patients than caregivers infused multiple vials at a time (42% of patients vs. 16% of caregivers). This finding may suggest that patients are infusing more FVIII products than caregivers (e.g., in response to breakthrough bleeds, to achieve the correct dose based on weight of adult patients or before at-risk activities such as sports); thus, patients, in particular, may require fast access to FVIII products.

The greatest storage challenges noted by both patients and caregivers included the need to plan for refrigerating FVIII products when travelling and carrying an insulated tote bag when leaving the house. Furthermore, a small percentage of participants (particularly those reporting FVIII product use primarily on demand vs. as prophylaxis) reported having FVIII product vials that expired before they could be used. Regardless of how FVIII product is used primarily (on demand vs. prophylaxis), manufacturer guidelines note that expired FVIII products should not be used. Improperly stored or expired factor may be ineffective in treating bleeding episodes. This study did not explore the reasons for product wastage (e.g., ordering more FVIII products than needed, not infusing as often as anticipated), although flexibility in FVIII product storage options could potentially reduce the frequency of FVIII product wastage. Caution should be used in generalizing these findings because the sample sizes for those with expired FVIII product vials was very small in this study; nevertheless, this finding is interesting and potentially worth further investigation.

Patients and caregivers did not differ significantly in preferences for extended storage options (a FVIII product that could be either stored at the higher range of room temperature for up to 12 months or refrigerated for up to 2 or 3 years). However, a vast majority of both patients and caregivers expressed interest in a product that can be stored at room temperature for longer durations [up to 30°C (86°F) for up to 12 months], primarily for travelling with greater ease, keeping more factor at home, and having better access when needed. The introduction of new and effective FVIII products increases treatment options and may provide the flexibility desired by FVIII product consumers (e.g., prolonged ability to store the product at room temperature) [6–8].

These results should be considered in the context of a number of potential weaknesses or limitations of the study design, including the lack of data collected on severity of haemophilia, use of FVIII products prior to

planned activities such as sports, and vial size. In addition, the small size and makeup of the sample (e.g., participants were primarily caregivers from Canada) could limit generalizability to the population of haemophilia A patients and caregivers. Finally, there is the potential for concern regarding the authentication of respondents recruited via Facebook. Whenever feasible, steps were taken to mitigate some of these potential limitations, and suggestions for further areas of study are provided.

We did assess participants' primary use of FVIII products (on demand vs. prophylaxis) and, where sample sizes permitted, compared the two groups; however, the study objectives did not include more detailed assessment of other uses, such as prophylactic use prior to certain activities such as sports. It remains unclear how results from on-demand patients, who also may periodically use FVIII products prophylactically, might differ from our findings. Future studies may wish to examine these differences, should sample sizes permit.

The survey did not assess FVIII product vial sizes, which could affect storage practices and preferences. For instance, some FVIII product distributors may not have a patient's exact vial size in stock at the time of the order and might dispense more than one vial for the dose required, thus necessitating more storage space. It remains unknown how vial size might influence results of this study, but this impact is potentially worth exploring.

Although the overall sample size of this study ($N = 101$) may be considered small compared with many web-based surveys assessing patterns of product ordering and use, the sample size in this study is considered adequate given the exploratory nature of the study, the rarity of haemophilia A, and the known challenges in recruiting participants with rare diseases. In light of these challenges, several methods were used to recruit potential participants, including use of advertisements e-mailed to haemophilia organization mailing lists or posted on their websites, and advertisements posted directly on the Facebook pages of haemophilia organizations.

The use of social media is a potentially useful tool in recruiting haemophilia patients (especially those who do not belong to haemophilia organizations). However, the use of Facebook, e.g., does have its limitations, such as difficulty in authenticating participants' eligibility or ensuring that participants do not complete the survey questionnaire more than once (i.e., in response to the advertisement from both the haemophilia organization's e-mail or webpage posting and the Facebook page). In this study, participants were asked a series of screening questions to ensure that they themselves had haemophilia A or cared for a child with haemophilia A. In addition, cookies were pushed onto respondents' computers to alert

researchers if the survey was accessed more than once from the same computer. Finally, as an additional check, an external party verified that each gift card went to a unique mailing address. Although these procedures do not guarantee fully validated respondents, they are indeed reasonable steps in mitigating the potential concerns of recruiting through social media. Furthermore, in our previous experience, very few individuals have tried to 'fake' their way into a haemophilia study.

Although this study was not designed to assess multiple and varied relationships, further areas for investigation could focus on the relationship of haemophilia A severity to FVIII product use and storage, the relationship of FVIII product storage (at room temperature or refrigerated) to frequency of FVIII product ordering, and differences among countries in product use. Whether improved stability and storage influenced compliance was not addressed in this preliminary study but could be addressed in a future study.

Conclusion

Having a better understanding of patients' and caregivers' perspectives on haemophilia A treatment is important. FVIII product accessibility, usage and storage (particularly in compliance with manufacturer guidelines) are directly related to successful disease management. This real-world study adds to the existing literature and provides information on FVIII product practices and preferences that could influence treatment choices and/or adherence. Results from this study support the need for an improved FVIII product that is more convenient and accessible to patients in daily life and while travelling. In addition, flexibility

in FVIII product storage options potentially could reduce the frequency of FVIII product wastage. Finally, the use of social media sites has potential value in recruiting this population. The multimode recruitment approach used in our study provides participants with several options for accessing a web-based survey and appears to optimize recruitment, implying that this approach is a viable way of reaching patients and caregivers in this disease area.

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Author contributions

DBD designed and conducted the research study, collaborated on the analysis and interpretation of study results, and contributed to development of the manuscript. TMC analysed the data, collaborated on interpretation of the study results, and contributed to development of the manuscript. TS sponsored the study and collaborated on the study design, interpretation of the study results, and development of the manuscript. LP collaborated on the study design, interpretation of the study results and development of the manuscript. RK contributed to interpretation of the study results and to development of the manuscript.

Disclosures

DBD is an employee of RTI Health Solutions, which was contracted by Novo Nordisk to design and conduct the study. TMC is an employee of RTI Health Solutions, which was contracted by Novo Nordisk to design and conduct the study. TS was an employee of Novo Nordisk during the design and conduct of this study. LP was an employee of Novo Nordisk during the design and conduct of this study. RK stated that she had no interests which might be perceived as posing a conflict or bias.

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Appendix: Storage and shelf life of selected FVIII products.

Product	Storage and shelf life
Advate [5]	Stored refrigerated at 2°C–8°C; can be stored at room temperature (up to 30°C) for up to 6 months
Alphanate [2]	Can be refrigerated at between 2°C–8°C or stored at room temperature (up to 30°C) for up to 2 months
Helixate FS/Kogenate FS [9,3]	Stored refrigerated at 2°C–8°C, shelf life 30 months; can be stored at room temperature (25°C) for up to 12 months
Hemofil M [10]	Can be stored refrigerated at 2°C–8°C for 30 months or stored at room temperature for up to 12 months or until expiration date, whichever is earlier
Koate-DVI [11]	Should be stored under refrigeration (2°C–8°C; 36°F–46°F). Lyophilized powder can be stored for 6 months at room temperature (up to 25°C or 77°F)
Recombinate [12]	Can be refrigerated at 2°C–8°C or stored at room temperature (up to 30°C) Do not use beyond the expiration date printed on the box
Xyntha [13]	Store refrigerated at 2°C–8°C for up to 36 months from the date of manufacture until the expiration date stated on the label; if within the expiration date, may be stored at room temperature not to exceed 25°C for up to 3 months. After room temperature storage, can be returned to the refrigerator until the expiration date
Turoctocog alfa* (in development by Novo Nordisk)	May be stored at room temperature not to exceed 30°C for up to 6 months

*This information was provided by Novo Nordisk.