

Evaluation of a pre-filled diluent syringe (MixPro[®]) among patient/carer users and nurses

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Management of haemophilia involves on-demand or prophylactic intravenous administration of recombinant or plasma-derived replacement clotting factors or bypassing agents. These products are provided as lyophilised powder and diluent, which need to be mixed to produce a solution for infusion. While this process has previously involved multiple time-consuming steps, several reconstitution systems are now available to make mixing easier and more convenient. This study aimed to investigate experience of use and perceptions of the Novo Nordisk MixPro[®] mixing device among patients and carers using activated recombinant factor VII (rFVIIa) or recombinant factor VIII (rFVIII) with MixPro, and nurse specialists who were either familiar or unfamiliar with MixPro. Nurses were asked to simulate the preparation of an inactive solution using MixPro. Semi-structured interviews were used to gain insight into participants' opinions of mixing systems in general and their

perceptions of MixPro. Likert scales were used to rate the performance of MixPro against predefined characteristics of mixing systems, and the importance of the predefined characteristics to the design of a mixing system. Patients/carers and unfamiliar nurses identified low contamination risk when mixing as the most important characteristic of a mixing system; the most important criterion for familiar nurses was confidence that patients/carers could prepare the system correctly. MixPro was perceived to perform very well overall, particularly in parameters identified as most important. It was described as being user-friendly, simple and quick; its compactness and portability were highlighted as advantages for storage and travel. The main disadvantages reported related to its small components. The majority of nurses said that they were highly likely to recommend MixPro to their patients.

Keywords: *Haemophilia, Recombinant factor VIIa, Recombinant factor VIII, Reconstitution device, Reconstitution system*

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Haemophilia A and B are recessive, X-linked inherited bleeding disorders, characterised by a deficiency or absence of factor VIII (FVIII) or factor IX (FIX) clotting factors, respectively^[1-2]. Both forms are associated with bleeding into muscles and joints, and based on residual factor levels are classified as mild (>5% to <40% of normal), moderate (1–5% of normal) or severe (<1% of normal)^[3-4].

Priorities for the health and quality of life of patients with haemophilia include prevention of bleeding and joint damage, as well as prompt management of bleeding episodes^[3]. Treatment modalities include on-demand and prophylactic

intravenous administration of recombinant or plasma-derived replacement factor. On-demand therapy aims to re-establish haemostatic control in the event of a bleed to reduce bleeding complications and preserve musculoskeletal function^[5-6]. Prophylaxis is recommended to prevent bleeding and musculoskeletal damage^[3].

A major challenge in the management of haemophilia is the development of anti-FVIII or FIX alloantibodies (inhibitors) in some patients. These reduce the efficacy of factor replacement therapies through the neutralisation of factor activity^[7].

The management of haemophilia is time-consuming. It can be challenging for patients and carers, who may have work and school commitments, to incorporate a prophylactic regimen into a busy schedule^[8]. Inadequate treatment, which may be caused by poor adherence, can lead to poorer outcomes in patients with haemophilia, including spontaneous bleeding and joint damage^[3,9]. Poor adherence can be caused by a number of factors, but lack of time and inconvenience of treatment have been identified as primary barriers for prophylaxis and early treatment of bleeds^[8,10,11].

At present, recombinant factor concentrates and recombinant bypassing agents are provided as lyophilised powder and diluent, which can require multiple time and/or labour-intensive steps to prepare a solution for infusion (depending on the product)^[9,12]. It is imperative that reconstitution systems encourage optimal treatment adherence by being convenient for patients and carers in daily life. Most patients learn to self-infuse at a young age, but require the assistance of carers prior to becoming completely independent^[11,13,14]. Nevertheless, treatment challenges remain for a number of patients. The elderly, for example, may require assistance from carers because of physical or cognitive limitations, such as fatigue, arthropathy or memory loss^[15].

MixPro[®] (Novo Nordisk) is a reconstitution device comprising a syringe pre-filled with diluent, a vial adaptor and a plunger rod, supplied with a vial containing activated recombinant factor VII (rFVIIa) or recombinant FVIII (rFVIII) powder (respectively Novo Nordisk NovoSeven[®] and NovoEight[®])^[16,17]. The MixPro system replaces the original rFVIIa reconstitution system, which requires two vials (powder and diluent) and additional steps for reconstitution. In 2014, Novo Nordisk conducted quantitative research in Italy, Spain and United States to assess preference – and reasons for preference – between the newer MixPro system

and the original reconstitution system, to help improve the design of new delivery systems^[18]. The study was conducted among adult patients with haemophilia and carers of children with haemophilia who had no prior experience with rFVIIa, MixPro or the original reconstitution system (i.e. were non-users). The results of the study favoured use of MixPro over the original reconstitution system, as it was perceived as being quick, easy to use, convenient and portable.

The aim of the study reported here was to investigate experience of use and perceptions of MixPro among patients and carers already using either rFVIIa or rFVIII with MixPro, and nurse specialists who were either familiar or unfamiliar with MixPro.

METHODS

Participants

Adults (≥ 18 years old) and adolescents/children (< 18 years old) with haemophilia A or B and carers of children with haemophilia A or B were eligible for inclusion in the study if they were currently using rFVIIa or rFVIII with MixPro, had used MixPro to reconstitute factor at least once, and infused factor at home. Nurses were eligible if they had ≥ 2 years' experience in the long-term treatment and management of patients with haemophilia, had personally treated or managed ≥ 10 patients with haemophilia A or haemophilia with inhibitors in the previous 12 months, and were responsible for educating patients on systems used to mix factors for ≥ 1 year. Approximately 50% of the nurses were to be familiar with MixPro and to have personally managed ≥ 1 patient using this system in the previous 12 months; approximately 50% were to be unfamiliar with MixPro. Participants were recruited in France, Germany, Italy, the United Kingdom (UK) and the United States (US).

Research design

Pilot interviews were conducted in the United Kingdom with one patient, two carers and three nurses who were all familiar with MixPro. The 20-minute face-to-face sessions involved a quantitative questionnaire-based semi-structured interview, and were followed by a 15-minute debrief. Based on the pilot interviews, the questions, assessment parameters and interviewer/interviewee instructions were refined and validated. Personal experience gained by the study co-ordinator was used to brief interviewers in other countries.

The main study interviews also lasted approximately 20 minutes, and were quantitative, questionnaire-based and semi-structured. Interviews with patients with

haemophilia and carers were conducted by telephone, while those with haemophilia nurses were conducted face-to-face at a central location (US) or their place of work (Europe).

The sequence of assessments completed by the study participants during the interviews is detailed in Figure 1. Initially, nurses were asked to use MixPro to simulate the preparation of an inactive solution (ie without factor product) for infusion using the instructions provided. Patients and carers had their own MixPro device with them for reference only, and were not required to reconstitute factor. The interview questionnaires explored the advantages and disadvantages of MixPro; current perceptions of the performance of MixPro against each of 18/19 predefined characteristics of mixing systems; word association with MixPro; the extent to which MixPro addresses unmet needs; the likelihood of recommending MixPro (nurses only); and perceptions of MixPro based on first use (patients and carers only). The interviewees were also asked to rank the importance of predefined characteristics of mixing systems in general and treatment settings (home vs away, prophylaxis vs on-demand therapy).

Data analysis

A “win-loss” table was compiled, showing the frequency with which each parameter in the “characteristics of mixing systems” ranking task was classified as more important than any of the other parameters. These data were entered into a scaling algorithm to calculate an importance score for each parameter, with higher scores indicating greater importance. The importance score was linear; for example, a score of 20 would be twice as important or desired as a score of 10.

The perceived performance of MixPro was based on the percentage of respondents selecting one of the top two ratings (6 or 7) on the seven-point Likert scale for each parameter (ie where 1 = does not describe the mixing system at all, and 7 = completely describes the mixing system).

RESULTS

Participants

The study was conducted between 3 November 2015 and 9 March 2016. 84 participants were recruited, including 26 patients, 19 carers and 39 nurses (20 familiar and 19 unfamiliar with MixPro). The mean age

Figure 1. Sequence of assessments in the interview questionnaire

Review of MixPro

Nurses: Read instructions provided and used MixPro to simulate the preparation of an inactive solution for infusion
Patients/carers: Had their own MixPro device in front of them for reference only

Exploration of advantages and disadvantages of MixPro (spontaneous comments) and assessment of current perceptions of MixPro using a self-completion sheet

Current perceptions: Participants were asked to rate the performance of MixPro against each of 18/19 predefined characteristics of mixing systems using a seven-point Likert scale (1 = does not describe mixing system at all; 7 = completely describes mixing system)

Word association with MixPro

Participants were asked to state which of a predefined list of words they most associated with the MixPro device; up to eight words could be selected

Nurses: addressing unmet needs and recommending MixPro

Extent to which MixPro addresses unmet needs of mixing systems and the likelihood of them recommending MixPro. Assessment of each was rated on a seven-point Likert scale (1 = does not meet needs at all/not at all likely to recommend; 7 = meets needs completely/extremely likely to recommend)

Patients/carers: perceptions of first-time use of MixPro

Evaluation of MixPro using a self-completion sheet based on the first time they used MixPro. Participants were asked to rate the performance of MixPro against each of 18/19 predefined characteristics of mixing systems using a seven-point Likert scale (1 = does not describe mixing system at all; 7 = completely describes mixing system)

Ranking task: importance of characteristics of mixing systems

Participants were asked to rank 18/19 predefined parameters in order of importance using a seven-point Likert scale (1 = not important; 7 = very important)

Confirmation of “settings” (infusion at home versus away from home/prophylaxis versus on-demand) where the top-ranked parameters are important

Table 1A. Sample demographics of patients and carers

PARAMETER	TOTAL (N=45)	PATIENT (N=26)	CARED FOR (N=19)	US (N=9)	FRANCE (N=10)	GERMANY (N=8)	ITALY (N=10)	UK (N=8)
Mean age, years	25	37*	9	23	30	32	17	25
Mean length of time on MixPro®, months	14	15	12	15	13	10	7	26
Type of haemophilia, %								
A (no inhibitors)	16	23*	5	33	40	0	0	0
A (with inhibitors)	73	62	89**	56	50	88	100	75
B (with inhibitors)	11	15	5	11	10	13	0	25
Treatment type, %								
On-demand	42	50	32	11	90	38	20	50
Prophylaxis	58	50	68	89	10	63	80	50
Infusion method, %								
PICC	2	4	0	0	10	0	0	0
Port-a-Cath	31	15	53	44	0	63	20	38
Peripheral vein with butterfly needle	67	81*	47	56	90	38	80	63
USE OF ORIGINAL RECONSTITUTION SYSTEM FOR rFVIIa AS WELL AS MixPro®, %								
	TOTAL (N=25)	PATIENT (N=13)	CARED FOR (N=12)	US (N=6)	FRANCE (N=7)	GERMANY (N=4)	ITALY (N=0)	UK (N=8)
Yes	76	100*	50	50	100	100	-	63
No	24	0	50**	50	0	0	-	38

Superscript symbol denotes statistically significant result at 90% level: *patient data higher than 'cared for' data; **'cared for' data higher than patient data

PICC: peripherally inserted central catheter

rFVIIa: recombinant activated factor VIIa

Table 1B. Sample demographics of nurses

PARAMETER	TOTAL (N=39)	FAMILIAR WITH MixPro® (N=20)	UNFAMILIAR WITH MixPro® (N=19)	US (N=12)	FRANCE (N=7)	GERMANY (N=6)	ITALY (N=8)	UK (N=6)
Mean number of years involved in treatment/management of patients with haemophilia	11	12	9	11	13	10	10	10
Patient caseloads in last 12 months, mean number of patients								
Haemophilia A (without inhibitors)	51	77*	24	68	89	15	21	50
Haemophilia B (without inhibitors)	20	33*	7	31	35	3	9	14
Haemophilia with inhibitors	9	12*	7	10	10	4	15	5
Involvement in treatment decisions or routinely recommending factor products, %								
Yes	58	71	44**	67	0	-†	0	50
No	42	29	56**	33	100	-†	100	50

*Denotes statistically significant result at 90% level: familiar nurse data higher than unfamiliar nurse data

**Unfamiliar, n=16

†Question not asked in Germany

of patients was 37 years (range: 16–69 years; see Table 1A). All but one of the participants was adult (≥ 18 years old); in Germany, one patient aged 16 years who had personally used MixPro participated in the interview. The average ages of children who were looked after by carers was 9 years (range: <1 –17 years).

The majority (89%) of patients had haemophilia A and most had inhibitors (84% of patients with haemophilia A/B). Two thirds of children were receiving prophylaxis, while adult patients were evenly split between on-demand and prophylactic treatment. The mean length of time that MixPro had been used was 15 months ($n=26$) and 12 months ($n=19$) in the patient and cared-for groups respectively. Across specific countries, this equated to: UK ($n=8$), 26 months, US ($n=9$), 15 months; France ($n=10$), 13 months; Germany ($n=8$), 10 months; Italy ($n=10$), 7 months. Of the 25 participants receiving rFVIIa with MixPro, 44% had used it in the previous week or more frequently, and 28% had used it in the previous month or more frequently.

Nurses who were familiar with MixPro had been involved in the treatment of patients with haemophilia for longer than those who were unfamiliar with the system (mean, 12 vs 9 years), and had therefore spent longer educating patients on mixing systems. Furthermore, nurses who were familiar with MixPro had significantly larger caseloads of patients with haemophilia A and B, including those with inhibitors,

than nurses who were not familiar with the system. Of nurses who were familiar with MixPro, 71% were involved in treatment decisions or routinely recommended factor products, compared with 44% of nurses who were not familiar with the system, with notable differences between countries.

Rating of characteristics of mixing systems

Respondents were asked to rank 18–19 characteristics in order of importance to the design of mixing systems (Figure 2). “Low contamination risk when mixing” was rated as the most important for patients and carers, with carers placing particular emphasis on this parameter (importance scores: 11.9 and 24.8 for patients and carers, respectively – Figure 2A). Other important factors for patients and carers were confidence in preparing the system for injection correctly, and ease of assessing whether the factor had dissolved in the powder vial.

Low contamination risk when mixing was also very important for nurses, particularly those who were unfamiliar with MixPro, who rated it as the most important parameter (importance scores: familiar 11.4, unfamiliar 29.2 – Figure 2B). Having confidence that patients and carers could prepare the system for injection correctly was the primary concern for nurses who were familiar with MixPro, and was also important for nurses who were unfamiliar with the

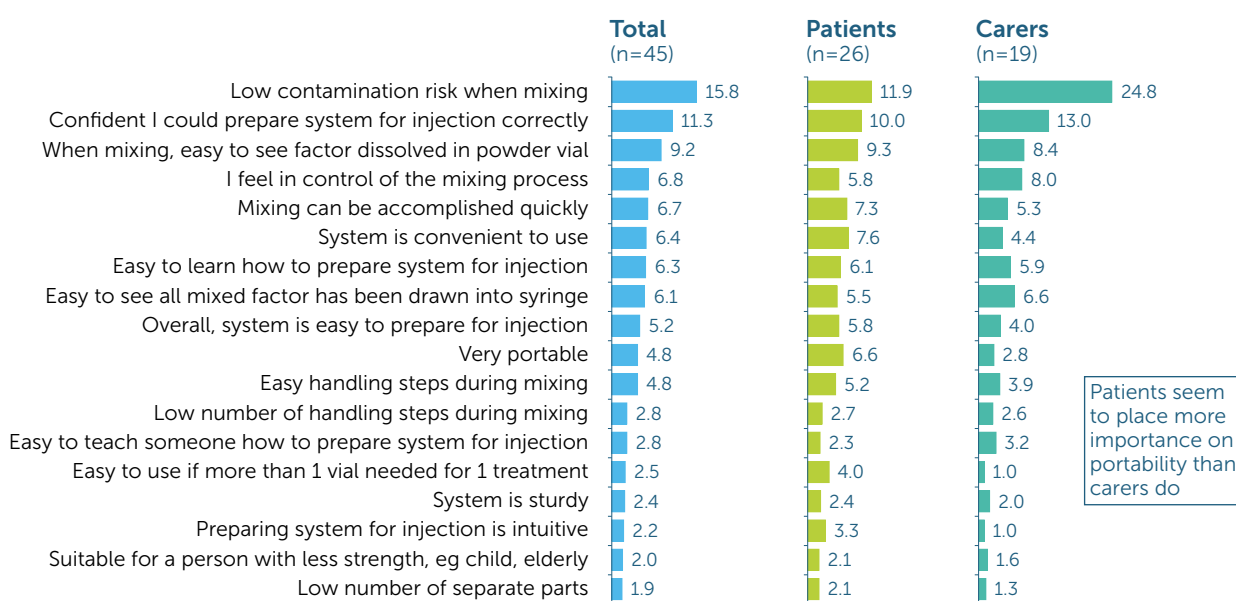


Figure 2A. Scores and ranking of 18 predefined characteristics of mixing systems by patients and carers. An influencing factor may be that 53% of carers administer product through a Port-a-Cath versus 15% of patients

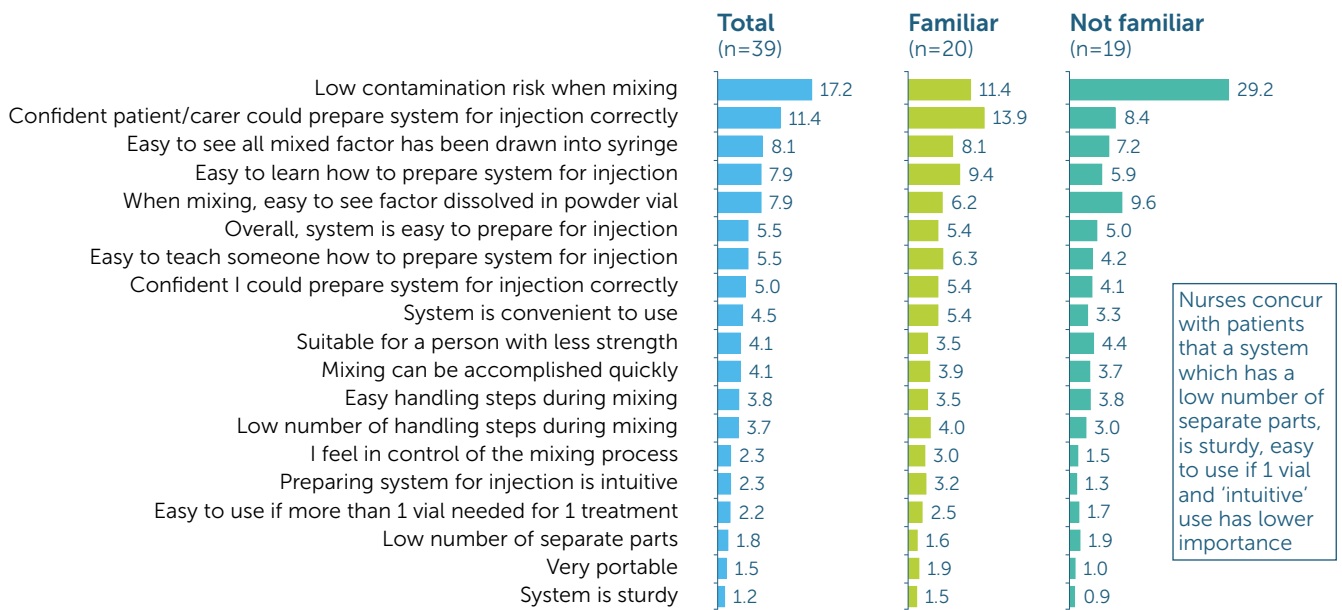


Figure 2B. Scores and ranking of 18 predefined characteristics of mixing systems by nurses. Having confidence that patients and carers can prepare the system for injection correctly is the primary concern for nurses familiar with MixPro

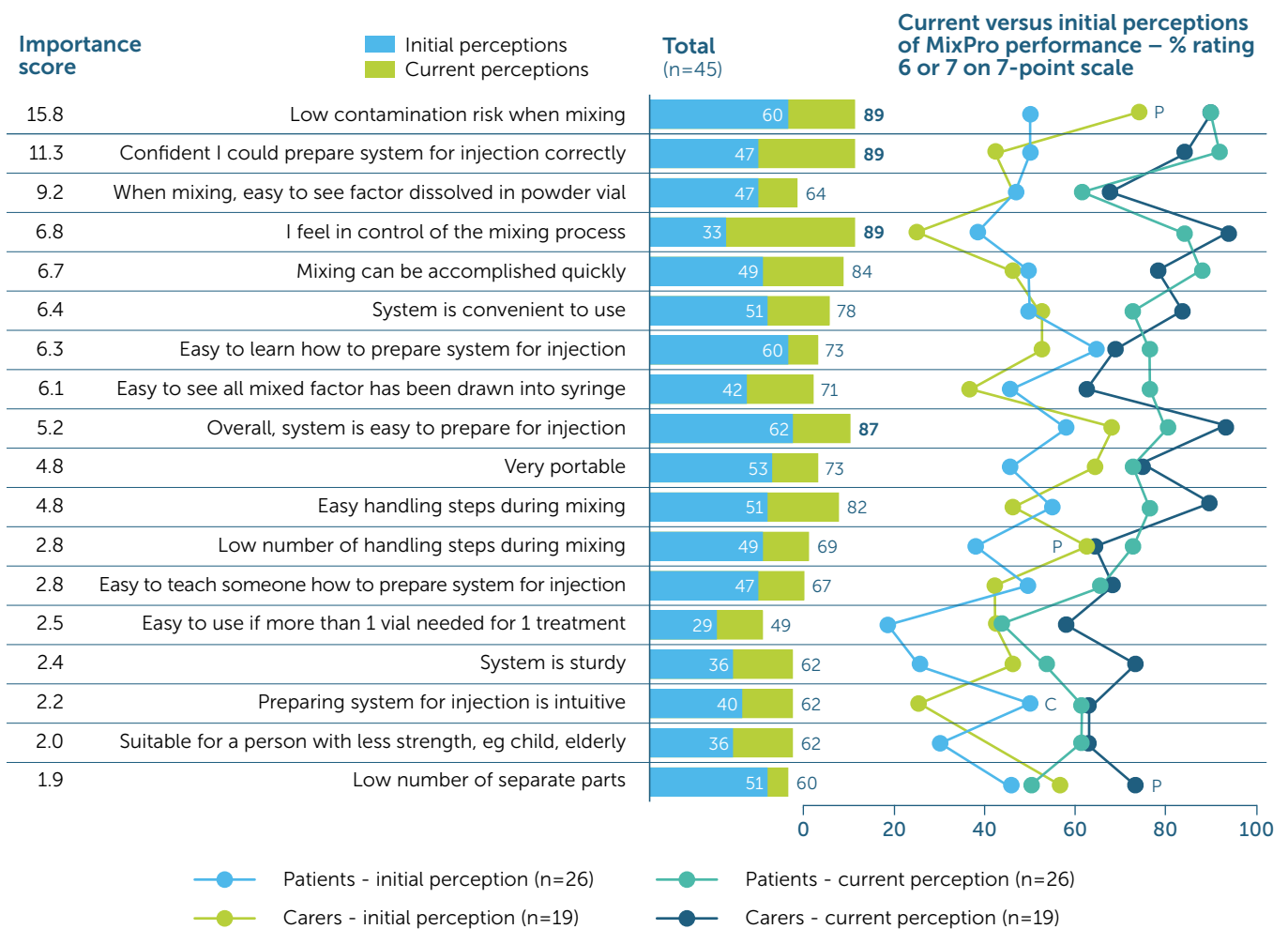
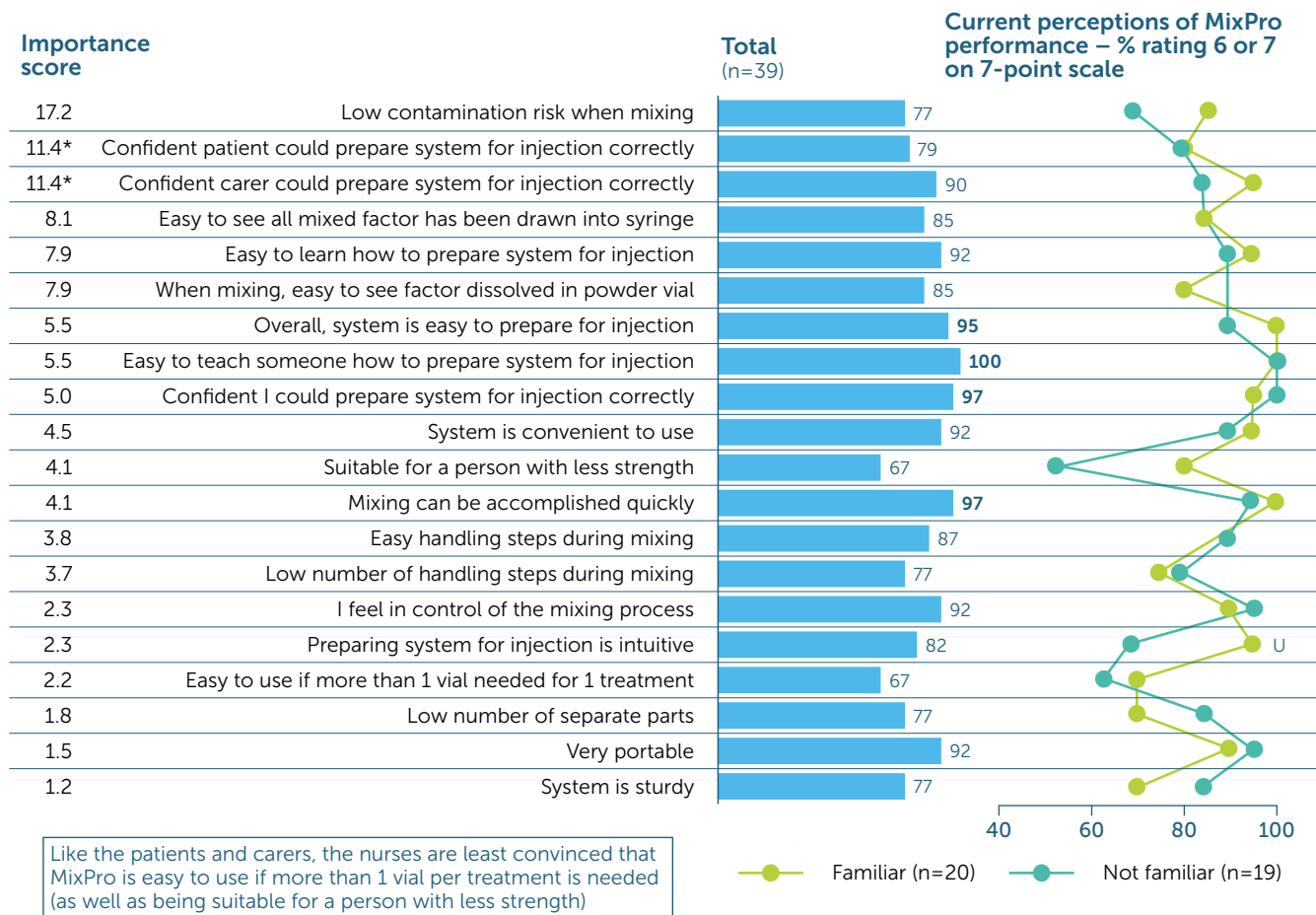


Figure 3A. Patient and carer assessment of the perceived performance of MixPro versus the importance of each parameter. Results that are statistically significant at the 90% level are indicated by letters C (where patient result is higher versus carers) and P (where carer result is higher versus patients). Patients and carers clearly become much more confident, in control and faster regarding the mixing process after initial usage



Like the patients and carers, the nurses are least convinced that MixPro is easy to use if more than 1 vial per treatment is needed (as well as being suitable for a person with less strength)

Figure 3B. Nurses' assessment of the perceived performance of MixPro versus the importance of each parameter. Results that are statistically significant at the 90% level are indicated by letter U (where familiar nurses result is higher versus unfamiliar nurses). Nurses are clearly confident in their ability to mix correctly, and believe MixPro to be quick and easy to teach
* "Patient/carers" working combined for performance ranking

system (importance scores: familiar 13.9, unfamiliar 8.4). Other important criteria for nurses included ease of learning how to prepare the system for injection, ease of assessing whether the factor had dissolved in the powder vial and ease of viewing whether all mixed factor had been drawn into the syringe. When nurses were asked the open-ended question "How, if at all, could the currently available systems for mixing factor products be improved? Why do you say that?", 49% spontaneously mentioned that they would like mixing systems to have fewer steps so that they are easier to use.

EVALUATION OF MixPro®

Perceived performance

Patients' and carers' current perception of MixPro was that it performed very well overall, including in areas deemed most important (low contamination risk when mixing; ease of preparation; confidence that the system could be prepared correctly for injection; feeling in control of the mixing process –

see Figure 3A). The highest mean performance scores for patients and carers were for feeling in control of the mixing process, confidence that the system could be prepared correctly for injection and ease of preparation (data not shown).

In general, the performance of MixPro was rated lowest ($\leq 62\%$ scoring 6 or 7 on the Likert scale) for parameters considered to be of lower importance (Figure 3A). The system performed least well on ease of use when needing more than one vial per treatment, low number of separate parts, suitability for a person with less strength, sturdiness of the system and the system being intuitive.

Comparison of current versus initial perceptions of MixPro showed that patients and carers became much more confident and felt more in control of the mixing process, as well as mixing more quickly after initial usage. Nevertheless, there was no change in the assigned score for carers between current and initial perceptions of the low number of handling steps during mixing.

Nurses tended to assign higher performance scores than patients and carers to MixPro, including that system preparation for injection was easy to learn (scores of 6 or 7: nurses 92%; patients/carers 73% – see Figure 3B). Nurses were confident in their ability to mix correctly and considered that MixPro was quick to use and easy to teach. Similar to patients and carers, nurses provided lower performance scores for ease of use when needing more than one vial per treatment, and suitability for a person with less strength.

Advantages and disadvantages

The advantages and disadvantages of MixPro reported spontaneously by respondents are presented in Table 2. For patients and carers, the main advantage of MixPro was its ease of use, followed by a low risk of contamination/infection when mixing, and portability (Table 2A). Nurses also considered MixPro to be easy, intuitive and quick to use, with a low risk of contamination/infection when mixing (Table 2B). Both

patients/carers and nurses considered the system to be compact for storage or travel.

In terms of disadvantages of MixPro, 16% of patients and carers mentioned that the vial was too small to see or handle easily, and 13% noted that preparation was still required (several parts/two-part syringe/complicated at first – Table 2A). Nurses believed that the main disadvantages of the system related to its small components (vial, vial adaptor and plunger), the fact that the plunger is not pre-attached, and difficulty in removing the plastic caps (syringe and vial adaptor caps) (Table 2B). Comments included concern that those with arthritis, poor dexterity or poor vision may find these aspects problematic.

Importance of top-ranking parameters in different settings

Patients and carers considered portability to be particularly advantageous when infusing away from home. This group also considered portability and ease of use when learning how to mix as particularly important when preparing an

Table 2A. Advantages and disadvantages of MixPro as perceived by patients and carers

% SPONTANEOUS MENTIONS	TOTAL (N=45)	PATIENTS (N=26)	CARERS (N=19)
Advantages			
Ease of use (fewer steps/pre-filled syringe/quick to administer/fewer errors)	96	96	95
Hygienic/sterile – low risk of contamination/infection (advantageous for Port-a-Cath)	47	38	58
Ease of transport/portable/can take everywhere/on holidays (as small/compact packaging/no refrigeration needed/immediate treatment/can do more activities)	33	35	32
Reassuring/increased peace of mind	13	4	26*
Able to self-administer (increased independence/autonomy)	11	15	5
Disadvantages			
Vial too small to see/handle easily (cannot see if powder dissolved/all solution has been drawn up/afraid of breaking at first/especially if arthritis)	16	15	16
Preparation still required (several parts/two-part syringe/complicated at first)	13	12	16
No large syringe for high doses, such as 3000 units, >10mg, multiple vials	9	15**	–
Not the easiest/quickest on market (Pfizer, all-in-one including needle, pen style)	7	12**	–
More boxes/waste	4	8	–
Cumbersome/takes up more space during transport	4	8	–
Cost/have to pay extra due to high price	4	4	5
Requires assistance from caregiver	4	4	5
May touch edge when attaching plunger to syringe/difficult to tell if attached properly	2	–	5
Vial made of glass – worried about dropping and glass in solution	2	4	–
1mL dose – risk of losing mixed-up solution if not careful	2	–	5
Mixed solution remains clear – have I remembered to mix the entire dose?	2	4	–
No disadvantages	33	23	47*

Superscript symbol denotes statistically significant result at 90% level:
*carer data higher than patient data; **patient data higher than carer data

Table 2B. Advantages and disadvantages of MixPro as perceived by nurses

% SPONTANEOUS MENTIONS	TOTAL (N=39)	FAMILIAR WITH MixPro® (N=20)	UNFAMILIAR WITH MixPro® (N=19)
Advantages			
Easy/intuitive/less steps/quick to use or to teach to use	85	85	84
More sterile/low risk of contamination (less handling/single vial/closed system/cap on vial adaptor)	33	25	42
Needle-less system (lower risk of needle stick injury/safe/easy disposal/no need for sharps box)	28	25	32
Not bulky/small/fewer parts (easier to store/for travel)	23	20	26
Low risk of error (few parts/easy steps)	15	20	11
Powder easily dissolved/mixes easily	10	15	5
Ease of disposal (less waste/saves costs)	8	5	11
No need to change syringe for injection	8	10	5
Pre-filled syringe (can draw immediately)	8	15*	–
Increased autonomy for patients (and reduces work in hospitals)	5	5	5
Smaller injection volume (no foam/with correct syringe size)	5	5	5
Syringe compatible with IV/PICC/butterfly	5	10	–
Vial adaptor grips well on to vial	3	–	5
Disadvantages			
Components (such as vial, vial adaptor, plunger base) too small for nurses/patients with large hands/arthritis/poor dexterity/poor vision	15	20	11
Plunger not attached (not intuitive where to put it/one extra step/may not attach properly/risk of contamination)	15	15	16
Difficult to remove plastic caps (syringe cap/vial adaptor cap)	13	–	26**
Vial adaptors are cheap/flimsy/do not fit properly/spike risk of bending	10	15	5
Air bubbles are still a concern	5	5	5
Syringe is not suitable for large doses/multiple vials	5	5	5
Increased cost (syringes/solvents cheaper in big packages)	5	5	5
Unable to see clearly that powder is fully dissolved due to label	5	5	5
Syringe not compatible with central lines	5	5	5
Still risk of contamination (need to disinfect vial/may touch syringe tip)	5	5	5
Not suitable for those with Port-a-Cath – need sterile 10mL syringe	3	5	0
Still too many steps: pre-attached vial adaptors already exist	3	5	0
Vial adapter not attached	3	0	5
Risk of loss of vacuum seal so cannot draw out product	3	5	0
None/no disadvantages	28	25	32

Superscript symbol denotes statistically significant result at 90% level: *familiar nurse data higher than unfamiliar nurse data;

**unfamiliar nurse data higher than familiar nurse data

IV: intravenous

PICC: peripherally inserted central catheter

infusion to treat a bleed. Nurses considered speed of mixing to be particularly important when treating a bleed.

Word association

Patients and carers associated MixPro most often with being user-friendly (76% of patients/carers),

easy (64%), simple (64%), quick (64%), hygienic/sanitary (62%), and convenient (60%). Words with negative connotations were selected by relatively few patients and carers (eg fiddly, 16%; fragile, 11%; bulky, 7%; complicated, 7%; impractical/awkward/difficult, each ≤4%).

Nurses associated MixPro most often with being user-friendly (72%), quick (69%), simple (64%), portable (62%), safe (56%), and easy (54%). Relatively few nurses selected words with negative connotations (eg too small, 10%; fiddly, 8%; fragile, 8%; impractical/awkward, each 3%).

Unmet needs and recommending MixPro

Examples of unmet needs of mixing systems reported by nurses included simplification by reducing the number of steps in the mixing procedure, a pre-assembled system to avoid contamination, components that are easy to handle, and reduced size and packaging of the kit. Nurses considered that the system addressed unmet needs of mixing systems reasonably well. Using a seven-point Likert scale (1 = does not meet needs at all, 7 = meets needs completely), 66% of nurses gave a rating of 6 or 7 (mean score 5.4), with similar observations for nurses who were familiar with MixPro (63% rating 6 or 7; mean score 5.4) and for nurses who were unfamiliar with the device (69% rating 6 or 7; mean score 5.5). MixPro addressed the desire for fewer steps in the mixing process, ease of use, and a needle-less system. Examples of reasons given for why the system did not meet unmet needs included the potential need for multiple syringes per injection and the non-integral plunger.

When nurses were asked how likely they would be to recommend MixPro to their patients with haemophilia, the majority reported that they were highly likely to recommend the device (79% rated 6 or 7 on a seven-point Likert scale, where 1 = not at all likely, and 7 = extremely likely; mean score 6.2). Nurses who were unfamiliar with MixPro were particularly likely to recommend it to their patients (6 or 7 rating: unfamiliar nurses, 89%, mean score 6.3; familiar nurses, 70%, mean score 6.2).

Discussion

Overall, MixPro was perceived favourably by patients/carers and nurses, who most associated the system with being user-friendly, simple and quick.

When ranking characteristics of mixing systems, patients and carers identified low contamination risk when mixing as most important, with carers placing greater emphasis on this parameter than patients. An influencing factor in this observation may be that 53% of carers administered factor through a Port-a-Cath, compared with just 15% of patients self-administering in that way. Nurses also ranked low contamination risk when mixing most highly, although this may also have included their

consideration of the risk in patients using a Port-a-Cath, rather than when reconstituting replacement factor products themselves. Nurses unfamiliar with MixPro placed particular emphasis on low contamination risk when mixing, which might reflect a lack of experience in reconstituting and administering replacement factors. Notably, having confidence that patients and carers could prepare the system correctly was the primary concern for nurses who were familiar with MixPro.

The higher performance scores for MixPro provided by nurses versus patients and carers suggested that the nurses were confident in their ability to mix correctly and believed that MixPro was quick to use and easy to teach. The performance scores of patients and carers indicated that they became much more confident, felt more in control, and completed mixing more quickly after initial usage.

Unmet needs of mixing systems identified by nurses included a reduced number of steps, a pre-assembled system, components that are easy to handle, and reduced size and packaging. Overall, nurses considered that MixPro addressed the unmet needs of mixing systems reasonably well and were highly likely to recommend the device to their patients. The main disadvantages of MixPro reported by participants related to its small components.

The study has a number of strengths. The multinational design of the study confers confidence that the findings could be generalisable to the wider haemophilia community in the developed world. The inclusion of patients with different types of haemophilia, receiving factor VII or factor VIII replacement therapy, using a variety of infusion methods, as well as nurses who were familiar and unfamiliar with MixPro, provided a wide cross-section of experience, thereby ensuring that the study was comprehensive and allowed expression of a wide range of opinions.

In the previous survey of patient and caregiver perceptions of MixPro, comparing MixPro against the original reconstitution system for rFVIIa and rFVIII, low contamination risk when mixing with MixPro was also considered of key importance, and the low number of handling steps was highlighted as an advantage^[18]. Specific guidance on how to correctly handle MixPro to minimise contamination risk is provided with every infusion pack.

The results of our study in patients and carers already using MixPro, and nurses familiar or unfamiliar with MixPro, further support the quick, easy to use, convenient and portable nature of the system

highlighted in the previous survey in patients and carers with no prior experience of MixPro^[18]. Furthermore, MixPro addressed the desire for fewer steps in using mixing systems.

Although not widely used, pre-filled syringes offer a number of advantages, including ease of administration, convenience for healthcare professionals, patients, and carers (particularly in emergency situations and home use), improved dose accuracy, increased assurance of sterility, and reduction of medication errors^[20,21]. Other very similar mixing devices incorporating pre-filled syringes have been launched, and a limitation of the present study was that it did not compare MixPro with any other device.

Few adolescents or children participated in this study – of five eligible patients aged between 12 and 17 years, only one (aged 16 years) participated – meaning that the views of this part of the haemophilia population were not obtained. Surveys have been conducted previously in children with haemophilia^[13,22], showing that it is feasible to include them and seek their opinions about their healthcare. A study of a similar device (ReFacto Rapid Reconstitution™) in children with haemophilia showed that they found using the device quicker and more convenient than the conventional reconstitution method^[22].

A potential limitation of the questionnaire flow in the present study was that patients/carers and nurses were asked to evaluate MixPro performance prior to being asked to rank the importance of characteristics of mixing systems. This could have potentially biased their responses relating to mixing systems in general. The use of rFVIIa and rFVIII as prophylaxis or on-demand treatment (dependent on severity of haemophilia) varied across the countries surveyed. Whether MixPro with rFVIIa or rFVIII was used prophylactically (prophylaxis is not indicated for rFVIIa) or on-demand would have had an impact on the frequency of use, and this could have influenced the survey results. Furthermore, MixPro with rFVIII was not available in the United Kingdom when this study was conducted.

Although patients/carers and nurses from several countries were included, data collected in the United States and Western Europe may not be applicable to less developed countries with differing healthcare practices. It is notable that patient samples from Germany, Italy and the United Kingdom included only patients with haemophilia with inhibitors. The impact of this on the findings of the study is unknown, as the responses were not analysed according to the type of haemophilia

or the presence/absence of inhibitors. The nurse recruitment criteria (≥ 2 years' experience in haemophilia and having treated ≥ 10 patients with inhibitors over the previous year) limited the type of nurse involved, and likely excluded nurses with experience who may have expressed other views. It might have been valuable to have included general ward nurses with very limited access or no access to giving replacement factor therapy, and who would have had minimal knowledge of any reconstitution devices.

In future research, it would be interesting to investigate whether there are important geographical variations in perceptions of MixPro and mixing systems in general between developed and less developed countries that may be influenced by differing healthcare practices and cultures. Future surveys should also include a higher proportion of children with haemophilia and device-naïve nursing staff, who could provide valuable input. In addition, studies should investigate possible differences in perceptions of MixPro between patients and carers with a family history of haemophilia and potential past exposure to different delivery systems versus totally device-naïve patients and carers. Studies could also include medical staff other than nurses who administer MixPro to ascertain if they are able to use the system and to compare their survey responses to those of patient/carers and nursing staff.

Feedback from users is an important part of the design process for reconstitution systems^[18], and a number of surveys of patients' perceptions of different reconstitution systems have been published^[9,12,22-24]. If a patient finds a system easy to use and they like it, they are more likely to be compliant with their recommended treatment regimen^[9].

In conclusion, as this study in patient/carer users of MixPro and nurse specialists who were familiar or unfamiliar with MixPro showed that the system was perceived favourably, it is likely that using MixPro couple improve treatment compliance in other patients.

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