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ORIGINAL ARTICLE

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Quality of electronic treatment records and adherence to prophylaxis in haemophilia and von Willebrand disease: Systematic assessments from an electronic diary

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Abstract

Introduction: Haemoassist™ 2 is an electronic system designed for people with bleeding disorders and their physicians to record prophylactic infusions and treatment of bleeds. It aims to improve adherence by permitting reminders and accuracy of documentation by facilitating real-time reporting.

Aim: To assess documentation quality and adherence to prophylactic regimens in patients with haemophilia A, haemophilia B or von Willebrand disease who are using Haemoassist™ 2.

Methods: Ten centres enrolled consecutive patients, who had been using Haemoassist™ 2 for ≥ 3 months (Cohort 1, 'quality of documentation'). Of these, patients who had a specified prophylactic regimen in Haemoassist™ 2 for ≥ 3 months were eligible for inclusion in Cohort 2 ('adherence to prophylaxis').

Results: Cohort 1 comprised 796 patients (71% with severe haemophilia A; median 20.5 months of Haemoassist™ 2 use). The most common method of documentation for patients was using the mobile app; the median time between infusion and documentation was 4 hours using the app, compared with 85 hours using a web portal on a stationery device. The median total annualised number of infusions was consistent in the first and last 3 months of documentation (128; IQR: 70-184 and 120; IQR 64-176, respectively). Cohort 2 comprised 202 patients (79% severe haemophilia A; median of 13 months on prophylactic regimen in Haemoassist™ 2). The rate of adherence to prophylaxis was 83%; median deviation between planned and actual infusion time was ± 2 hours.

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Conclusion: Haemoassist™ 2 was used consistently over prolonged periods of time and allowed for precise analysis of adherence to prophylaxis.

KEYWORDS
Adherence, compliance, medication, prophylaxis, telemedicine

1 | INTRODUCTION

For patients with bleeding disorders, home administration of prophylactic and on-demand treatment is the standard of care in most European countries.[1] A comprehensive evidence base has established that prophylactic factor treatment is superior to on-demand treatment.[2-8] Real-world data indicate that this approach is effective: a large-scale longitudinal study conducted over ten years in patients with haemophilia in the United States highlighted a significant association between increased use of prophylactic therapy and decreased bleeding rates.[9] Furthermore, prophylaxis (as opposed to on-demand treatment) was found to be the only predictor of joint preservation in children with severe haemophilia A who were treated with prophylactic factor VIII concentrate.[10]

Routine administration of coagulation factor concentrates is typically performed by patients themselves or by their caregivers. Prophylactic treatment requires long-term adherence, which may become more difficult as patients transition to adulthood, when the primary responsibility for infusion passes from caregivers to teenagers and young adults themselves. Rates of adherence are reported to be highest when caregivers administer infusions and lowest among young adults aged 25-40 years old.[11]

Adherence to an agreed treatment regimen is difficult to assess in clinical studies and even more so in the real world: it can vary widely, even between patients in a single study.[12-15] Many published studies of adherence to prophylaxis in haemophilia have used subjective measures such as patient and caregiver interviews, with results being vulnerable to bias. Efforts to standardise data collection led to the development, validation and use of questionnaires such as the Validated hEmophilia-RegImen Treatment-Adherence Scale – Prophylaxis (VERITAS-Pro).[16-18] Despite use of these tools, data sets can still be affected by confounding factors, including desirability bias and different interpretations of 'adherence' by patients and physicians.[19] This problem was highlighted by a recent study that showed significant differences between subjective reporting of adherence and an objective measure, the number of returned vials of clotting factor concentrates.[19] Another consideration is that adherence is a complex phenomenon consisting of different components.[20] For example, a patient who administers the prescribed dose on the correct days, but at a different time of day each day, may not be fully adherent.[13,21] This effect can be magnified by differences in lifestyle and activity between patients and over time in the same patient, which also affect bleeding risk.

Given the above considerations, accurate, reliable documentation of treatment is a crucial part of care for people with bleeding disorders. Documentation provides essential information for physicians monitoring the efficacy of treatment plans and factor consumption. Historically, paper-based diaries have been used by patients following treatment plans at home. However, an important limitation of paper-based diaries is that they are not always to hand and so may be completed sometime after the infusion took place, with a corresponding decrease in accuracy. Use of paper systems also makes central collection of data more labour-intensive, and the time lag involved means that suboptimal treatment patterns can only be identified retrospectively.[22] A retrospective single-centre study of 79 well-managed haemophilia patients documented that infusion logs were available in just 47 (59%) patients, covering a median of 59 (range 2 - 241) months per patient during the time period from April 1982 to August 2003.[23]

Electronic infusion logs have been developed for patients with haemophilia for more than 20 years.[24-26] They were occasionally implemented in local or regional disease management programs[27] and may have the potential to improve the documentation process. Walker et al randomised 41 haemophilia patients to electronic or paper documentation and found that compliance with data submission was higher, and time intervals between infusion and receipt of data were shorter with electronic documentation.[28] An observational study showed that, after 12 months, use of the Medtep Hemophilia online platform was associated with improved adherence to prophylactic regimens, improved quality of life and stabilisation of joint health scores compared with baseline.[29] However, there are few other published studies that characterise the adoption and value of electronic diary systems in haemophilia.

Haemoassist™ 2 is an electronic documentation system for patients with haemophilia in European countries, primarily Germany and Spain. It comprises an application on a mobile phone or tablet that patients can use to record bleeding events and details of infusion. Documented information is then encrypted and stored in a central database, which can be accessed via the Internet by the treating physician, using the physician portal. Haemoassist™ 2 includes reminders and alerts for patients and physicians.[26] In one explorative study, the sequential use of paper and electronic documentation using Haemoassist™ 2 was assessed in 99 patients with haemophilia A or B. Significant improvements were reported with Haemoassist™ 2 compared with paper records in documentation of bleeding episodes, patient compliance in data reporting and record delivery.[30]

Although evidence to date supports the use of e-diaries in improving documentation of home treatment, the consistency with which such systems are used has not yet been assessed nor has the

quality of the data they provide. The objectives of this study were therefore twofold:

- To study the quality of electronic documentation in a consecutive cohort of patients with haemophilia A, haemophilia B or von Willebrand disease who were using the Haemoassist™ 2 electronic diary (Cohort 1, 'quality of documentation')
- To study adherence to prophylactic treatment in patients using Haemoassist™ 2 (Cohort 2, 'adherence to prophylaxis')

2 | METHODS

This retrospective multicentre study included consecutive patients with haemophilia A, haemophilia B or von Willebrand disease of any severity who were enrolled at 10 haemophilia care centres in Spain and Germany from January 2019. In Cohort 1, patients using the Haemoassist™ 2 electronic diary for ≥ 3 months were included. For inclusion in Cohort 2, patients were additionally required to have a prophylactic regimen that had been defined in Haemoassist™ 2 for ≥ 3 months. Patients were not aware of the study aims at the time of their treatment.

Documentation of treatment or bleeds in Haemoassist™ 2 can be done by the patient, using either the patient app on their mobile phone or by accessing the system via web browser. Physicians can access the physician portal only via web browser, in order to document infusions given in the centre, infusions required for surgery, or to document events in some cases if the patients are unable to document themselves. Regardless of user, 'entry' was defined as the recording in Haemoassist™ 2 of a bleeding event or infusion.

Quality of documentation was analysed by (i) assessing the time lapse between reported infusion time (entered by patient) and actual documentation time (electronic timestamp); (ii) comparing the annualised number of records in the first and last 3 months of use (if a patient had been using Haemoassist™ 2 for exactly 3 months, these values would be identical); and (iii) comparing the annualised number of entries (bleeding events and prophylactic infusions) to the number of similar events reported in the literature in patients with severe and non-severe haemophilia A and B. Analyses were stratified according to disease and severity of disease, duration of Haemoassist™ 2 use and type of treatment (prophylaxis, bleed treatment or subsequent treatments). All analyses were done using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Adherence to prophylactic treatment, as reported here, was defined as the ratio between documented performed infusions and planned infusions that were entered into Haemoassist™ 2 per physician recommendation. An algorithm was developed to match documented infusions with planned infusions. Any documented infusion could be assigned to just one planned infusion date. Infusions for acute bleeds or subsequent treatment(s) of previous bleeds were not included in the analysis. If two or more infusions were performed within 48 hours of the planned infusion, priority was assigned in the following order:

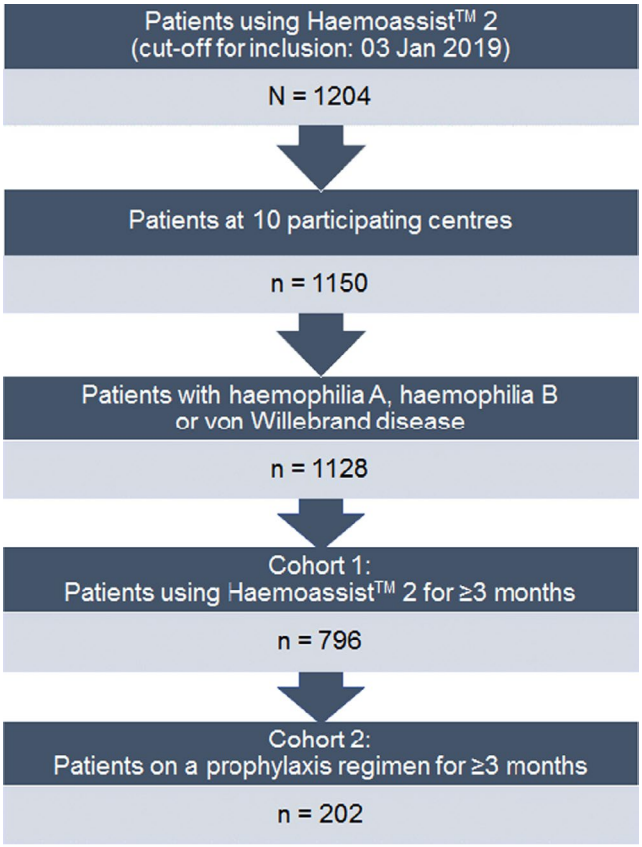

FIGURE 1 Patient screening and inclusion in Cohort 1 and Cohort 2 [Colour figure can be viewed at wileyonlinelibrary.com]

1. Calendar day of planned infusion
2. Shorter time gap
3. Infusion performed after, rather than before, the planned date and time

If no infusion was performed within 48 hours of a planned infusion, this infusion was considered as missed for the purposes of data collection. The time gap between planned and actual infusion time was also analysed.

All patients signed the Haemoassist™ 2 privacy statement. This study was approved by Hannover Medical School Ethics Committee and was conducted according to local regulations and in line with the Helsinki Declaration.

3 | RESULTS

In the overall data set, 1,204 patients were screened in 10 participating centres. As shown in Figure 1, 796 met the inclusion criteria for Cohort 1 and 202 met the inclusion criteria for Cohort 2. Of note, this feature of Haemoassist™ 2 had only been made available for a short time before this study, and so, not all patients in Cohort 1 who were undergoing prophylaxis had this defined in Haemoassist™ 2.

TABLE 1 Patient population at baseline—Cohort 1

Disease	n (%)	Age, years: mean ± SD	Prophylaxis:[a] n (%)	Duration of Haemoassist™ 2 use, months: median (IQR)
Haemophilia A				
Severe	566 (71)	29.6 ± 17.9	530 (94)	20.1 (11.0-29.1)
Moderate	55 (6.9)	33.6 ± 21.1	30 (55)	20.7 (13.7-29.8)
Mild	28 (3.5)	36.3 ± 20.6	6 (21)	14.3 (7.9-22.2)
Haemophilia B				
Severe	70 (8.8)	24.9 ± 17.2	65 (93)	23.4 (15.6-30.3)
Moderate	23 (2.9)	37.4 ± 18.4	17 (74)	19.6 (13.4-24.4)
Mild	4 (0.5)	41.0 ± 25.2	2 (50)	21.1 (14.0-26.0)
Von Willebrand disease				
All severities	50 (6.3)	30.0 ± 19.8	35 (70)	23.3 (11.0-32.4)
Total	796 (100)	30.0 ± 18.5	685 (86)	20.5 (11.4-29.3)

[a]As opposed to on-demand or mixed treatment forms.

This explains why the number of patients in Cohort 2 is slightly lower than would be expected based on Cohort 1.

3.1 | Cohort 1: Quality of documentation

In total, 796 patients met the inclusion criteria and were enrolled in this cohort (Table 1). The average age of patients in this cohort was 30 years. The majority of patients (71%) had severe haemophilia A, and 86% of all patients were using prophylactic treatment. Median duration of Haemoassist™ 2 use in this cohort was 20.5 months (IQR: 11.4-29.3).

These patients (or their physicians) recorded 195,936 infusions in total. The proportion of patients and physicians using the different methods to access Haemoassist™ 2 is shown in Table 2. The most common method of access for patients entering data was mobile phone or tablet (88% of all entries), with only 8% of entries made via patient web access. Physician entries accounted for 5% of the total number of entries, but covered 52% of patients, indicating that physicians documented infusions or bleeds for a lot of patients, but only did so rarely for each patient. This is reflected in the median number of entries per patient, which was 155 (IQR: 71-341) and 165 (IQR: 25-346) entries per patient coming from patient mobile app or web browser, respectively. In contrast, a median of 7 (IQR: 2-22) entries per patient were done by physicians.

In the largest patient subgroup (patients with severe haemophilia A, n = 566), the median number of documentations of prophylaxis infusions was 122 per year (IQR: 78-165). In the largest subgroup of patients with haemophilia B (severe haemophilia B, n = 70), the median number of documentations of prophylaxis infusions was 55 per year (IQR: 37-87). Overall, the median total annualised number of infusions was consistent during the first 3 months of documentation using Haemoassist™ 2 (128; IQR: 70-184) and the last 3 months of documentation (120; IQR: 64-176). In some subgroups, this pattern was less consistent, which may partly be attributable to the lower number of patients in subgroups with haemophilia B and von Willebrand disease (Table 3). In addition, in the haemophilia B subgroup, the median annualised number of infusions during the first 3 months of documentation was markedly higher in patients with mild haemophilia B (150; IQR: 92-190) than in patients with a severe form of the disease (74; IQR: 52-132). However, the number of patients with mild haemophilia B was very low (n = 4), and the difference is not seen in data from the last 3 months of documentation.

Finally, within each subgroup, the annualised number of infusions was reasonably similar regardless of whether patients had been using Haemoassist™ 2 for < 1 year, 1-2 years, 2-3 years or longer (Figure 2).

Comparison of the first and last 3 months of documentation shows a slight decrease in documentations made within 2 hours of infusion (50% to 44%) and a slight increase in documentations made ≥ 72 hours after infusion (20% to 29%; Figure 3A). Differences

TABLE 2 Method used to access and enter infusions into Haemoassist™ 2

Method	Number of patients: n (%)	Total number of entries: n (%)	Median number of entries per patient (IQR)
Patient mobile app	720 (90)	172,220 (88)	155 (71-341)
Patient web browser access	71 (8.9)	14,932 (7.6)	165 (25-346)
Physician web browser access	411 (52)	8,784 (4.5)	7 (2-22)
Any of the above	796 (100)[a]	195,936 (100)	158 (75-352)

[a]For some patients, >1 method of data entry is used.

TABLE 3 Annualised number of entries according to disease type and severity and over time

Disease	Severity	n	Median (IQR)				
			Prophylaxis: infusion without a bleed (may include surgery)	Initial bleed treatment: first infusion for a documented bleed	Subsequent treatments: second or further infusion for a previously documented bleed	Annualised number of entries	
						First 3 months	Last 3 months
Haemophilia A	Severe	566	122 (78-165)	2 (0-7)	0 (0-7)	144 (96-192)	144 (96-184)
	Moderate	55	45 (0-140)	5 (1-17)	1 (0-13)	80 (36-176)	100 (24-176)
	Mild	28	0 (0-0)	6 (3-9)	3 (0-13)	44 (16-120)	40 (14-86)
Haemophilia B	Severe	70	55 (37-87)	2 (0-4)	0 (0-3)	74 (52-132)	58 (48-104)
	Moderate	23	51 (0-101)	2 (0-6)	2 (0-10)	80 (32-108)	56 (36-84)
	Mild	4	15 (0-56)	13 (5-26)	5 (0-28)	150 (92-190)	60 (36-92)
Von Willebrand disease	All severities	50	67 (0-106)	6 (1-14)	0 (0-3)	94 (32-136)	104 (40-144)
Total		796	106 (50-158)	2 (0-7)	0 (0-7)	128 (70-184)	120 (64-176)

in the timeliness of documentation according to the method used to access Haemoassist™ 2 were observed. As shown in Figure 3B, the proportion of documentations made ≤ 2 hours after infusion was higher using the mobile application (47%) than with a web browser (20%). Conversely, the proportion of documentations made ≥ 72 hours after infusion was higher with a web browser (54%) than with the mobile application (26%). In all patients, the median time lapse between infusions—including prophylaxis and for bleeding events—and documentation was 4 hours using a mobile phone or tablet and 85 hours using stationary web-based documentation. Documentation of new bleeds was done more promptly than documentation of prophylactic infusions or subsequent infusions for previously reported bleeds (Figure 3C).

3.2 | Cohort 2: Adherence to prophylaxis

This cohort included 202 patients (Table 4). The average age of patients was 25 years, and the majority (79%) had severe haemophilia A. In line with the inclusion criteria for this cohort, all patients were receiving prophylactic treatment. Median duration on prophylactic regimens documented in Haemoassist™ 2 was 13 months (IQR:

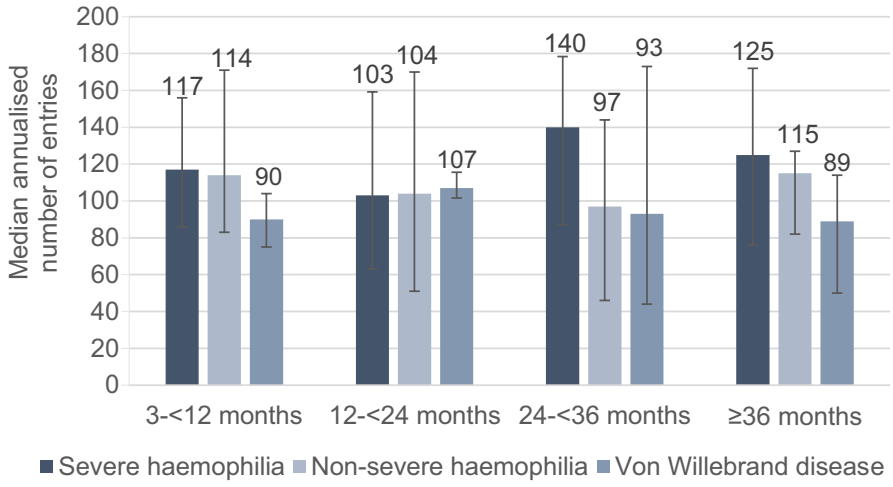

FIGURE 2 Annualised number of entries (median ± IQR) by duration of Haemoassist™ 2 use [Colour figure can be viewed at wileyonlinelibrary.com]

7.1-17.3). Median duration of Haemoassist™ 2 use in this cohort was 18 months (IQR: 12.4-27.2).

Overall, over 30,000 planned prophylactic infusions were analysed in this cohort (Table 5), and the rate of adherence to prophylaxis was 83%. Subgroups with low adherence were patients with von Willebrand disease (67%), mild haemophilia A (69%) and severe haemophilia B (71%; Table 5). Adherence was approximately stable according to time on regimen (Figure 4A), with rates of 80% at 3-6 months (n = 31), 84% at 6-12 months (n = 60) and 83% at ≥ 12 months (n = 111).

The median deviation between planned and actual infusion was ± 2 hours; this remained stable over the first 12 months of the regimen (Figure 4B). For infusions ≥ 18 months after starting on a regimen, the median time between planned infusion and actual infusion time increased slightly (Figure 4B).

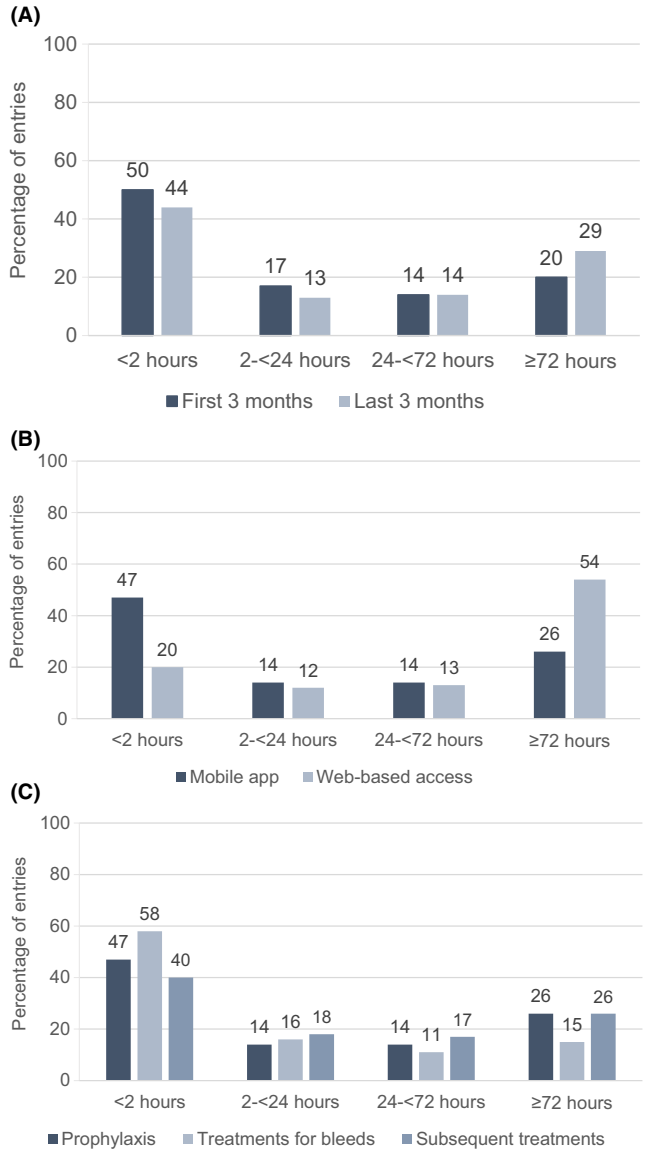

FIGURE 3 Time lapse from infusion to documentation. (A) by first vs. last 3 months of study participation; (B) by type of device used for documentation; (C) by type of treatment documented [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Our study is the first to evaluate the use of Haemoassist™ 2 in the routine care of patients with bleeding disorders. With nearly 800 patients enrolled from 10 centres in two countries (Cohort 1), it is the largest study addressing the quality of electronic records. With over 200 patients on regular prophylactic regimens (Cohort 2), it is also the largest set of data available to assess adherence to prophylaxis and allowed us to describe the phenomenon of adherence in greater granularity than before.

First, we assessed the quality of documentation that can be achieved with Haemoassist™ 2. The annualised number of infusions was consistent up to three years of system use, and the median number of annualised infusions was in line with what would be expected in this patient population, based on published literature. For example, in the largest patient subgroup (patients with severe haemophilia A), the median number of prophylaxis infusions per year was 122, which corresponds to an average of 2.3 infusions per week for every week of the year. The majority of patients with standard half-life factor VIII infuse 3 times per week or every other day, whereas patients on extended half-life factor VIII infuse twice per week or every 3 to 5 days.[31-34] In patients with severe haemophilia B, the median annualised number of prophylactic infusions was 55, which corresponds to reported median prescribed annual infusions (52, ie weekly) for patients using extended half-life FIX.[32] Our data are broadly comparable with the number of infusions in the Malmö and Utrecht protocols for haemophilia A and B, as included in the World Federation of Hemophilia treatment guidelines.[1] When considering the median annualised rates of first infusion for a treated bleed in our study, these were broadly in line with annualised bleeding rates in patients using prophylaxis for severe haemophilia in the published literature.[33-35] Although these comparisons with published literature are indirect, it is difficult to envisage a practical alternative method of assessing the robustness of documentation systems in the home care setting. Taken together, the comparisons above suggest that electronic documentation of prophylaxis and bleed treatments in Haemoassist™ 2 is complete and constant over time.

We also investigated the time interval between infusions and their electronic documentation. When a mobile phone or tablet was used, close to half of all documentations took place within two hours of the infusion itself. These documentations are easy to make and are likely to be precise, with patients logging one infusion at a time and recording the date and time of infusion as shown on the device. In contrast, about one-quarter of infusions were documented with a delay of 72 hours or more. In these cases, the timeframe between documentation and infusion implies that patients who are using regular prophylaxis are documenting more than one infusion at a time and so will have to actively enter the date and time of the infusion. This

TABLE 4 Patient population at baseline—Cohort 2

	n (%)	Age, years: mean ± SD	Duration of specified prophylactic regimen[a], months: median (IQR)	Duration of Haemoassist™ 2 use*, months: median (IQR)	Regimen: median (IQR) number of planned infusions per month
Haemophilia A					
Severe	159 (79)	25.0 ± 17.0	12.5 (6.8-16.2)	17.5 (11.9-25.4)	13.1 (8.8-13.2)
Moderate	13 (6.4)	24.0 ± 19.3	17.8 (11.5-21.5)	21.4 (17.3-31.2)	8.9 (8.7-13.1)
Mild	1 (0.5)	43.0	17.5	17.6	5.8
Haemophilia B					
Severe	15 (7.4)	17.3 ± 15.1	11.3 (7.4-17.7)	17.8 (12.2-30.5)	6.2 (4.4-8.8)
Moderate	8 (4.0)	26.6 ± 11.6	16.2 (12.9-19.6)	24.0 (22.5-29.6)	4.8 (4.4-8.7)
Mild	1 (0.5)	52.0	5.5	10.6	4.5
Von Willebrand disease					
All severities	5 (2.5)	29.4 ± 31.9	12.6 (10.0-16.5)	25.0 (12.7-30.5)	8.8 (8.8-8.8)
Total	202 (100)	24.8 ± 17.3	13.0 (7.1-17.3)	18.0 (12.4-27.2)	10.7 (8.7-13.1)

[a]Specification of a prophylactic regimen is optional in Haemoassist™ 2. Time on specified prophylactic regimen is shown.

[b]Total duration of Haemoassist™ 2 use including time on specified prophylactic regimen, but also other treatment forms and prophylaxis without specified regimen.

TABLE 5 Number of records analysed to assess adherence

Disease	Severity	Patients: n (%)	Total planned infusions: n	Planned infusions per patient per month: mean ± SD	Time gap between planned and performed infusion, hours: median (IQR)	Adherence to prophylaxis: %
Haemophilia A	Severe	159 (79)	25,040	12.2 ± 4.9	1.9 (0.6-5.9)	83
	Moderate	13 (6.4)	2,286	10.5 ± 2.6	2.1 (0.4-7.0)	86
	Mild	1 (0.5)	101	5.8	9.1 (1.4-23.0)	69
Haemophilia B	Severe	15 (7.4)	1,267	6.4 ± 2.0	3.8 (1.5-12.5)	71
	Moderate	8 (4.0)	810	5.9 ± 2.5	7.9 (2.8-12.0)	88
	Mild	1 (0.5)	25	4.5	0.7 (0.6-1.6)	100
Von Willebrand disease	All severities	5 (2.5)	535	8.2 ± 2.2	1.8 (0.4-5.6)	67
Total		202 (100)	30,064	11.2 ± 4.9	2.0 (0.7-6.7)	83

is a potential source of error that is difficult to control and probably also happens with paper documentation. We observed a clear trend that documentation using a mobile phone or tablet was done more promptly than documentation using desktop web browser access. Given the above considerations, we suggest that physicians should encourage patients to use a mobile phone or tablet for documentation and to document infusions immediately after they have been completed.

In the second part of our study, we evaluated adherence to prophylaxis based on use of the electronic diary. Our results include data on adherence to prophylaxis in patients with non-severe haemophilia, on which little has been published to date. Our approach to assessing adherence is novel and possibly more robust than questionnaire-based, self-reported adherence or counting dispensed and returned vials. We evaluated the ratio of performed over recommended prophylactic infusions, with a time tolerance of 48 hours, to provide an initial estimate of adherence. While this estimate of adherence provides more detailed information than previous approaches based on returned numbers of vials, we acknowledged that it still does not address all aspects of adherence. For example, if patients administered more prophylactic infusions than recommended in a time window, these would not have been

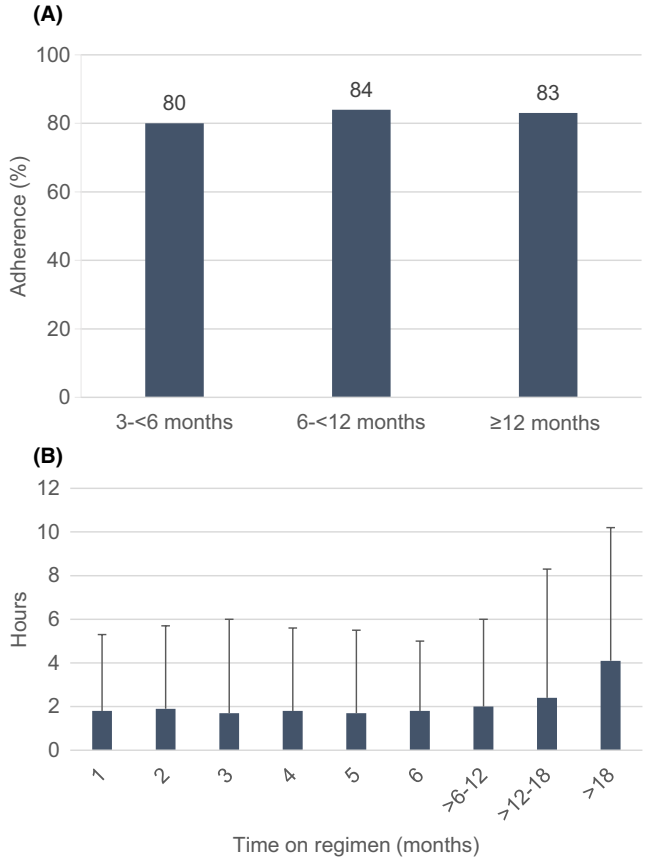

FIGURE 4 (A) Overall ratio of documented versus planned infusions, according to time on prophylaxis; (B) median time lapse between planned and documented infusion, according to time on prophylaxis. Error bars show Q3 [Colour figure can be viewed at wileyonlinelibrary.com]

counted. Without knowing the reason for such additional infusions, it is difficult to qualify them as non-adherent (overtreatment) or adequate (eg because of planned physical activity or pain sensations that were not counted as bleeds etc).

For a more specific estimate of the timeliness of adherence, we also evaluated the median elapsed time between the recommended and actual infusion timepoint. This estimate of the precision of adherence to prophylactic regimens will be particularly important when considering patients taking standard versus longer-acting factor concentrates, as delays in prophylaxis administration may have very different effects in these two groups.

Our results showed that overall, patients adhered to a defined prophylactic regimen: in total, 83% of planned infusions were documented. There was some variation in adherence across disease subgroups, which may be partly accounted for by low numbers of patients in some subgroups. Interestingly, patients with severe haemophilia A (n = 159) had a higher rate of adherence (83%) than patients with severe haemophilia B (n = 15; 71%). In both haemophilia A and B, adherence to prophylaxis was similar in patients with moderate and in patients with severe disease. Median time lapse between planned and documented infusion was consistent regardless of time on prophylaxis up to 12 months but seemed to increase slightly between 12 and 18 months, possibly highlighting a key timepoint at which physicians should engage with patients about the importance of maintaining a consistent treatment regimen. Another consideration is that the median time lapse between planned and documented infusions varied with disease and severity, with longer time lapses observed in patients with mild haemophilia A and moderate haemophilia B (although the number of patients in these groups was low). This aspect of adherence warrants more detailed study in future to clarify trends and identify patients for whom education about adherence could be improved.

Limitations of this study include the lack of control groups, for example a group of patients using paper documentation, and the impossibility of knowing what was not documented. It is also impossible to verify that documented infusions and infusion times were indeed correct, a limitation that is also expected with paper documentation. In addition, our study only included patients who had been using Haemoassist™ 2 for ≥ 3 months. This means that patients who refused to use the system or never adopted it were excluded and are difficult to evaluate in this setting. In addition, patients were not required to be ongoing active users of Haemoassist™ 2. This makes it difficult to differentiate those patients who had stopped using Haemoassist™ 2 altogether during the study from those who had mild disease and may only have used the system rarely, for example to record bleeding events. Both of these categories of patient would have been eligible for inclusion in Cohort 1. Furthermore, for those patients who stopped using Haemoassist™ 2 during the study, reasons for discontinuation could not be analysed because this information cannot currently be recorded in the system. These reasons would be an interesting subject for future data collection: they are likely to vary considerably between patients, ranging from change of clinic or therapy to change in a patient's overall health or mental status, lack or loss of adherence or even death. Finally, the study included relatively few patients with mild haemophilia or von Willebrand disease.

In general, increased use of mobile phones and tablets is likely to further improve the accuracy of real-time documentation. As use of Haemoassist™ 2 becomes increasingly widespread, it will be interesting to make comparisons of documentation quality and adherence across patient age groups, to evaluate whether using this type of system can negate the difficulties in adherence often encountered during adolescence. Patient and carer involvement and engagement are essential for the effective treatment of bleeding disorders. Our study contributes to a growing evidence base showing that engagement may be facilitated by use of electronic systems such as Haemoassist™ 2.

5 | CONCLUSION

Haemoassist™ 2 and other electronic documentation devices hold great promise for the collection of data on the efficacy and safety of haemophilia medications in the real world. This makes them a valid and important resource for national haemophilia registries. Use of

these systems can be taken further: they can facilitate analysis not only of adherence, but also of other outcomes that are important to patients, and allow us to understand how these are linked. In order to fulfil this potential, data capture in these systems should be harmonised to allow pooling of data and comparisons across countries.

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AUTHORS' CONTRIBUTIONS

AT designed and supervised the study. JR, DA and MH managed data and performed statistical analysis. All authors analysed data, critically revised the manuscript and approved it for submission.

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