Haemophilia

WILEY

Haemophilia WFH

REVIEW ARTICLE OPEN ACCESS

Systematic Literature Review of Outcomes Associated With Adherence to Haemophilia Drug Therapy

Cynthia Khanji[1] | Weyinmi Nuabor[2] | Travis Gould[1] | Hae Kyung Kim[1] | Stephanie Barrows[3] | Brittney Herbel[3] | Annete Njue[2]

[1]Pfizer Inc., New York, New York, USA | [2]Department of Market Access and Outcomes Strategy, RTI Health Solutions, Manchester, UK | [3]Department of Market Access and Outcomes Strategy, RTI Health Solutions, Ann Arbor, Michigan, USA

Correspondence: Brittney Herbel (bherbel@rti.org)

Received: 8 May 2024 | **Revised:** 16 December 2024 | **Accepted:** 6 January 2025

Funding: The study was sponsored by Pfizer Inc.

Keywords: adherence | clinical outcomes | economic outcomes | haemophilia | haemophilia drug therapy | humanistic outcomes | systematic review

ABSTRACT

Introduction: Prophylactic therapy improves clinical and quality of life (QoL) outcomes in patients with haemophilia; however, this effect could be influenced by the degree of treatment adherence. Adherence to therapy may be difficult due to the administration mode and the frequency of self-infusions. There is a need to investigate the effect of treatment adherence on clinical, humanistic and economic outcomes in a real-world setting.

Aim: A systematic literature review (SLR) was performed to describe the impact of adherence to haemophilia drug therapies on clinical, humanistic and economic outcomes.

Methods: Embase, MEDLINE and the Cochrane Library were searched for English language articles published after 22 June 2013; the search was conducted on 22 June 2023. No geographic limits were applied. Twenty articles met the inclusion criteria.

Results: The studies investigated associations between treatment adherence and bleeding, joint health, inhibitor development, pain, QoL, daily activity/work productivity (WP), cognitive function and healthcare resource use. Fifteen studies reported that better adherence to drug therapy in patients with haemophilia is associated with better outcomes, including a reduction in bleeding risk, improved joint structure and function, less chronic pain, better health-related QoL (HRQoL), lower activity impairment (AI), less school/work absenteeism, higher WP and better cognitive function. Two studies reported mixed results, with adherence being associated with some outcomes but not others. Five studies reported no association.

Conclusion: This SLR found associations between greater adherence to haemophilia drug therapies and better results on clinical, humanistic and economic outcomes, indicating that patients with haemophilia would benefit from improvements in treatments that promote adherence.

1 | Introduction

The treatment landscape for persons with haemophilia A (HA) and B (HB) (PwH) has expanded, and current options include factor replacement therapies, nonfactor therapies and gene therapies [1, 2] offering improved life expectancy for PwH similar to that of the general population [3]. Factor replacement therapies consist of intravenously administered Factor VIII (FVIII) or IX (FIX) proteins and can be used as prophylaxis or as on-demand treatment [3, 4]. Nonfactor therapies are currently administered subcutaneously for prophylaxis [1], and gene therapy is usually administered as a one-time infusion [2].

The benefits of prophylaxis therapy are well known; however, its effectiveness is dependent on adherence. Adherence is described as patients' active and voluntary involvement in their own caregiving in collaboration with their healthcare providers, with the purpose of achieving a predetermined therapeutic target [5]. In relation to haemophilia, nonadherence means not keeping to the agreed frequency or dosing of prophylactic injections [6]. Barriers to prophylaxis adherence include symptom burden, disease denial, low perceived benefits of prophylaxis, lack of knowledge, inability to recognise a bleed, lack of transition training, venous access issues [6] and challenges with self-treatment [4], which is especially challenging because it requires frequent, typically 1–3 times per week of self-infusions, depending on the type and severity of haemophilia [7].

Several validated adherence measurement tools are available for use in PwH. The validated haemophilia regimen treatment adherence scale-prophylaxis (VERITAS-Pro) measures prophylaxis adherence in PwH [8]; it comprises 24 questions on 6 subscales (time, dose, plan, remember, skip, communicate). Subscale scores range from 4 to 20, and total scores range from 24 to 120, with higher score representing poorer adherence [8]. A similar scale, the VERITAS–On-Demand (VERITAS-PRN), is used to evaluate adherence in PwH receiving on-demand treatment [9]. The recently developed Haemo-Adhaesione scale (validated in the Spanish population) comprises 25 questions grouped into 5 dimensions (illness awareness, sequelae knowledge, treatment difficulties, doctor-patient relationship and haemorrhagic process treatment); higher scores represent better adherence [10].

Treatment burden associated with the mode and frequency of administration could affect patient adherence [11] and outcomes [12]. Innovations in mode and frequency of administration are being explored in haemophilia therapies, with the promise of improving the convenience and quality of life (QoL) of PwH. It is important to improve our understanding of the impact of adherence to haemophilia therapies on outcomes.

This systematic literature review (SLR) aimed to describe the impact of adherence to haemophilia treatments on clinical, humanistic and economic outcomes. To our knowledge, no SLR of outcomes associated with adherence to haemophilia treatments has been conducted.

2 | Materials and Methods

2.1 | Search Strategy

An SLR was conducted on 22 June 2023 using Embase, MEDLINE and MEDLINE In-Process, and Cochrane Library. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Table S1 presents the MEDLINE search strategy. Searches were limited to articles published in English after 22 June 2013, with no geographic limitations. The search included terms relating to HA/HB, treatment adherence, treatment convenience, patient satisfaction or patient preference (Table S1).

2.2 | Eligibility Criteria

The population of interest was individuals with inherited HA/HB with or without inhibitors receiving any haemophilia treatment. Outcomes of interest included adherence, treatment convenience, patient satisfaction and patient preference. Observational studies (cohort, cross-sectional, case-control and other observational) were eligible for inclusion; randomised and nonrandomised clinical trials, case reports, letters and editorials were excluded. SLRs and meta-analyses were hand-searched to identify additional relevant studies.

2.3 | Screening and Data Extraction

Study selection was performed in two phases: at level 1 screening, titles and abstracts of studies identified from the electronic databases were reviewed independently by two researchers (B.H. and W.N.) to determine eligibility; at level 2 screening, full texts of studies selected at level 1 were obtained and independently reviewed for eligibility by the same two researchers. At each screening stage, where there was disagreement about study relevance, consensus was reached with a senior researcher (A.N.). The inclusion and exclusion processes were documented, including the completion of a PRISMA flowchart.

Data extraction tables were developed in Microsoft Word. Data were extracted from full-text articles by one researcher and quality checked by a second researcher not involved with the extraction. Extracted data included country, study design, year of study, adherence assessment method, population (number of patients, haemophilia type, disease severity, age, sex, treatment) and adherence outcomes (including adherence scores or proportion of adherent patients).

3 | Results

A total of 722 titles and abstracts from the database search were manually screened. After level 1 screening, 198 articles progressed to level 2 screening, where 135 articles were selected for inclusion.

Studies reporting an association between adherence and outcomes presented in this article were part of a larger SLR that also identified studies presenting data on outcomes associated with convenience of, satisfaction with, and adherence to haemophilia drug therapies (results for these other outcomes are not reported here). After further screening of the 135 articles, 115 articles that reported outcomes associated with convenience and satisfaction were excluded and 20 were identified that reported an association between adherence and outcomes (Figure 1).

Of the 20 included studies, 12 were conducted in patients with HA/HB [14–25] and 7 in patients with HA [26–32]. One study did not report type of haemophilia [33]. Studies were conducted in Europe ($n = 11$) [14, 22–25, 27, 29–33], East Asia ($n = 4$) [15, 16, 20, 26], North America ($n = 2$) [19, 28], Africa ($n = 2$) [18, 21] and an international setting ($n = 1$) [17]. Although eight studies [15, 17, 19, 20, 23, 25, 31, 33] did not state type of therapy, it appears that factor replacement therapy was used in all of them.

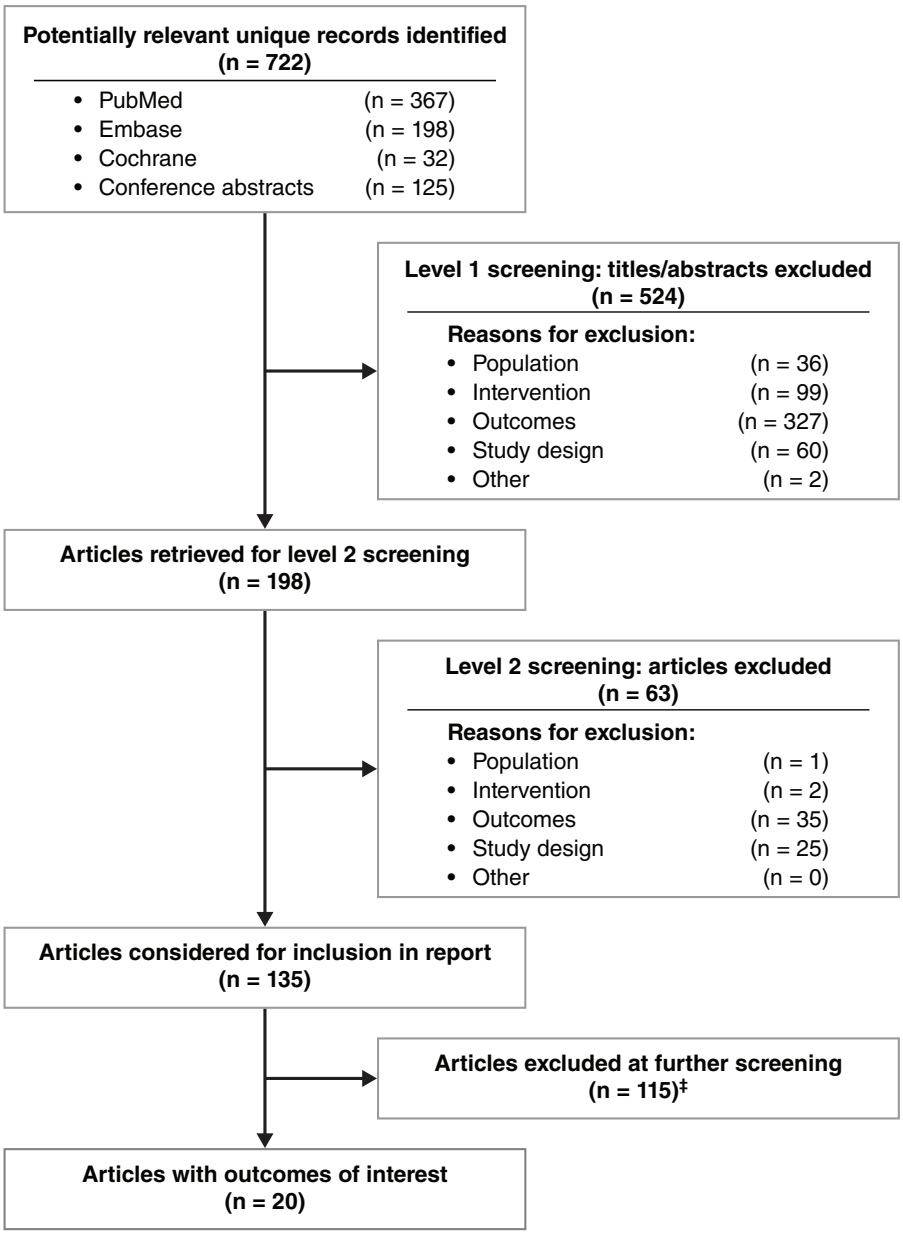

FIGURE 1 | Study selection process flow diagram (adapted from Page et al. [13]). ‡ The studies reporting an association between adherence and outcomes presented in this article were part of a larger SLR that also identified studies presenting data on the outcomes associated with convenience of, satisfaction with, and adherence to haemophilia drug therapies. The results for these other outcomes are not reported here and are planned for future publication; hence, a further 115 articles were excluded. SLR indicates systematic literature review.

Methods used to measure adherence included VERITAS-Pro (10 studies) [14–17, 19–21, 25, 26, 33], self-reported questionnaires (3 studies) [23, 31, 32], logbooks and/or interviews (2 studies) [18, 28], pharmacy records (2 studies) [22, 30], adherence index (1 study) [29], vial counting (1 study) [27] and physician reports (1 study) [24]. Table 1 presents additional study details; Table 2 presents results on the associations between treatment adherence and bleeding, joint health, pain, QoL, activity impairment (AI), work productivity (WP), cognitive function and healthcare resource utilisation (HRU).

Among the included studies, 15 reported an association between adherence and improvements in some of the outcomes of interest [14–20, 24–29, 31, 32]. Five studies showed no association between adherence and improved outcomes [21–23, 30, 33]. Two studies reported mixed results, with adherence being associated with some outcomes but not others [15, 17].

3.1 | Bleeding

Seven studies reported increased bleeding with poor adherence [17, 18, 20, 27–29, 32] (Table 2). The Canadian Haemophilia Prophylaxis Study assessed adherence to standard half-life (SHL) FVIII concentrate prophylaxis using infusion and bleeding logs in 56 boys with severe HA over a 15-year follow-up period. In that study, a 10% increase in the absolute adherence rate over any 12-week period was associated with a 15% reduction in bleeding

TABLE 1 | Study characteristics.

Study	Country/ region	Study design	Brief description of population	Adherence measure
Zhao et al. [26]	China	Single-centre, cross-sectional study	31 patients with severe HA	Adherence was measured using the VERITAS-Pro. The subscale score range was 4–20 points, with the highest score representing the poorest adherence.
Zanon et al. [27]	Italy	Prospective study	42 patients with severe HA; 13 were children (31%), 9 (21.4%) were adolescents and 20 (47.6%) were adults	Adherence to therapy was evaluated by comparing the number of empty vials of octocog alfa returned with the number of those prescribed. Adherent = 75%–100% empty vials returned; nonadherent ≤75% empty vials returned.
Bago et al. [14]	Croatia and Slovenia	Cross-sectional, multicentre study	82 patients with severe or moderate HA or HB	The implementation phase of adherence was evaluated with the self-reported VERITAS-Pro instrument. Total scores range from 24 to 120 points, and higher scores indicate poorer reported adherence. Cut-off for nonadherence is 57 points, meaning a score 57 and above was considered nonadherent.
Cheung et al. [15]	Hong Kong	Qualitative study	56 patients with HA or HB; 42 were adults and 14 were paediatric	Adherence to treatment was evaluated using the VERITAS-Pro. Higher scores indicate poorer reported adherence. Cut-off for nonadherence is 57 points, meaning a score 57 and above was considered significantly nonadherent.
Cheung et al. [16]	Hong Kong	Cross-sectional, multicentre study	42 patients with HA or HB; 11 were aged <18 years, 22 were aged 18–<40 years, 9 were aged >40 years	Adherence was evaluated using the VERITAS-Pro questionnaire. Total scores range from 24 (most adherent) to 120 points (least adherent).
Dover et al. [28]	Canada	Single-arm, multicentre, prospective study	56 young boys (aged 12–30 months at the time of enrolment) with severe HA	From 1997 to 2013, information on adherence was collected from each subject's factor infusion and bleeding logs. Adherence to the prescribed prophylaxis regimen was calculated weekly. If the subject completed all their infusions per their prescribed step on the protocol, they were considered adherent. No participant could have an adherence rate >100% since infusions given beyond the number required were not included.
García-Dasí et al. [29]	Spain	Cross-sectional, observational study	78 children and adolescents (aged 6–20 years) with severe HA	The adherence index was used to quantify adherence. The adherence index was assessed by the units administered divided by the units prescribed, then multiplied by 100. A calculation was done to find the difference between this value and the perfect percentage of adhesion (100%). The result was determined by the difference in percentage points the patient moves away from the perfect percentage of adhesion.
Krishnan et al. [17]	US, Canada, and Australia	Qualitative study	55 adult men with HA or HB and 55 parents of boys aged <18 years with HA or HB	Adherence was measured using the VERITAS-Pro. Total scores range from 24 (most adherent) to 120 points (least adherent). Using the 57-point cut-off as the minimum for nonadherence in the original validation study, adherence was also dichotomised. Rather than coarse adherence/nonadherence dichotomy, the VERITAS-Pro scores were used as a constant because this constant allows for testing the relationship between degree of adherence and outcomes, and the cut-off score has not been validated or used in a patient population.

(Continues)

TABLE 1 | (Continued)

Study	Country/ region	Study design	Brief description of population	Adherence measure
Lambert et al. [18]	West Africa	Prospective study	25 boys with HA or HB	Data recorded in the logbooks and data collected through interviews with the parents at the time of visits were used to assess adherence.
McLaughlin et al. [19]	US	Qualitative study	80 adolescents and young adults with moderate or severe HA or HB	Adherence was assessed using the VERITAS-Pro and VERITAS-PRN. Total scores range from 24 (most adherent) to 120 points (least adherent). To assess the relationship between adherence and chronic pain for prophylactic and on-demand treatment simultaneously, VERITAS-Pro and VERITAS-PRN responses were combined into 1 category.
Meijón-Ortigueira et al. [30]	Spain	Retrospective study	60 patients with severe HA	Computerised records of the pharmacy department were used to calculate adherence. To be considered adherent, patients needed to take ≥85% of the prescribed doses (ratio of the number of doses administered to the prescribed doses).
Mokhtar et al. [20]	Malaysia	Cross-sectional study	103 patients with severe HA or HB	Adherence was assessed using the VERITAS-Pro. Nonadherence was defined as a total cut-off score of >57.
Nwagha et al. [21]	Nigeria	Cross-sectional, multicentre study	42 patients with HA or HB	Adherence was measured using the VERITAS-Pro. Total scores range from 24 to 120 points. Subscale scores range from 4 to 20 (lower scores indicating higher level of adherence). Adherence was defined as the total of all subscales <61, and nonadherence was defined as the total of all subscales >61.
O'Hara et al. [31]	France, Germany, Italy, Spain, and UK	Cross-sectional, retrospective study	376 adult males with severe HA	Adherence was measured by the patient self-completion questionnaire.
Pérez-Robles et al. [22]	Spain	Retrospective, observational study	52 male patients with HA or HB	Objective adherence was measured through pharmacy dispensing records. Objective adherence was calculated as a percentage and adherence was categorised as adherence ≥75% (adherent patients) and adherence <75% (nonadherent patients). Subjective adherence was measured with an ad hoc questionnaire which also included four questions from the Morisky-Green-Levine test. Patients could categorise their perceived adherence as poor, fair, or good. A NO to the four questions is considered as adherent and a YES to one or more questions is considered as nonadherent.
Schrijvers et al. [23]	The Netherlands	Prospective, multicentre study	241 patients with HA or HB; 73 children aged 2–11 years and 168 aged 12–77 years	Adherence was measured with a semistructured questionnaire. Patients were classified, as adherent: missing <15% infusions, <10% dose changes (IU) and <30% deviation in time; sub-optimally adherent: missing 15%–25% infusions, <25% dose changes or >30% deviation in time; nonadherent: missing >25% infusions or >25% dose changes.
Shaikh et al. [24]	France, Germany, Italy, Spain, and UK	Predictive model	514 patients with severe HA or HB	Adherence was measured by the physician (low, moderate, or high).

(Continues)

TABLE 1 | (Continued)

Study	Country/ region	Study design	Brief description of population	Adherence measure
Torres-Ortuño et al. [25]	Spain	Multicentre, cross-sectional descriptive study	23 patients with severe haemophilia, who follow prophylactic treatment, 21 type-A patients and 2 type-B patients	Adherence was assessed using VERITAS-Pro. Adherence ≤62 points, and nonadherents >62 points on VERITAS-Pro.
van Os et al. [33]	England and Wales	Observational study	91 patients with severe haemophilia	Adherence was assessed with VERITAS-Pro and scores on each VERITAS-Pro subscale ranged from 4 to 20, with higher scores indicating worse adherence. Patients were dichotomised into adherent and nonadherent groups, with a score of ≥51 indicating nonadherence.
Zupan et al. [32]	Slovenia	Observational study	63 patients with HA	Adherence was measured using a self-administered, paper-based survey with questions on compliance. If a respondent reported they missed, forgot, or delayed their scheduled doses at any point in the past, they were referred to as noncompliant.

Abbreviations: HA = haemophilia A, HB = haemophilia B, IU = international unit, UK = United Kingdom, US = United States, VERITAS-PRN = validated haemophilia regimen treatment adherence scale–on-demand, VERITAS-Pro = validated haemophilia regimen treatment adherence scale-prophylaxis.

rate [28]. Krishnan et al. [17] evaluated the relationship between prophylaxis adherence and health outcomes in 55 adults and 55 caregivers of children with moderate or severe HA/HB in Australia, Canada and the United States. Although the study reported no association between adherence and bleeding in children, a higher VERITAS-Pro score (indicating poorer adherence) was associated with more target joint bleeds in the prior year (regression coefficients = 0.055) and more breakthrough bleeds (regression coefficients = 0.047) among adults [17]. Lambert et al. [18] investigated adherence based on logbook records and interviews in 25 young boys with HA/HB who were treated with extended half-life (EHL) FVIII and FIX prophylaxis in Ivory Coast. A significant difference in annualised bleeding rate (ABR) for spontaneous joint bleeds was observed at the end of the follow-up period and at enrolment for those experiencing adherence issues versus those without adherence issues. Mokhtar et al. [20] explored the effect of adherence to prophylaxis using the VERITAS-Pro questionnaire in 103 adults with severe HA and HB attending a haemophilia clinic in Malaysia; the mean ABR of adherent patients (3.91) was significantly lower than that of nonadherent patients (7.67) [20].

Three studies reported no significant associations between adherence and bleeding [21–23]. In Spain, Pérez-Robles et al. [22] assessed the association between adherence (measured with pharmacy records) to prophylaxis with clotting factor concentrate and bleeding episodes in 52 patients with HA/HB. Approximately 63% of patients in the adherent group and 79% in the nonadherent group reported no bleeding episodes/year (nonsignificant differences) [22]. Although there was no significant association between the rate of objective adherence and the number of bleeding episodes, two patients in the nonadherent group and none in the adherent group reported three bleeding episodes/year [22]. In the Netherlands, semistructured interviews about adherence to prophylaxis were conducted with 241 patients or parents of a child with HA/HB [23]. In adolescent/adult patients, adherence levels showed no association with bleeding frequencies, with median joint bleeds/year of 1.7 for adherent adults, 1.2 for suboptimally adherent individuals and 1.0 for nonadherent individuals (nonsignificant differences) [23]. However, there was more joint bleeding in nonadherent children and similar joint bleeding in suboptimally adherent and adherent children [23]. Nwagha et al. [21] measured prophylaxis adherence using the VERITAS-Pro questionnaire and found that the difference between the mean ABR (8.12 vs. 7.59) and the mean number of target joints (2.57 vs. 2) between the adherent and nonadherent groups, respectively, was not statistically significant.

One study involving 91 adolescents and young people with severe haemophilia in England and Wales reported that nonadherent patients had significantly fewer bleeds than adherent patients (mean difference, −2.71) [33].

3.2 | Joint Health

Two studies showed that patients with high prophylaxis adherence had better joint structure and function [26, 27] (Table 2). Zhao et al. [26] investigated the association between joint health and adherence to on-demand or prophylactic FVIII replacement therapy in 31 children and adults with severe HA in China. Joint structure was examined with the haemophilia joint health score (HJHS), and joint function was examined with the Haemophilia Early Arthropathy Detection with UltraSound in China (HEAD-US-C) scale, with higher scores on both scales indicating worse joint health. The correlation coefficient (r) between VERITAS-Pro score and HEAD-US-C or HJHS was 0.49 and 0.64, respectively, indicating that better adherence was beneficial for joint health [26]. In Italy, prophylaxis adherence was measured by counting the empty medication vials for 42 children and adults with severe

TABLE 2 | Outcomes related to adherence.

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
Zhao et al. [26] China	Patients with severe HA who received prophylaxis ($n = 17$) Age, median (range), years: 22 (4–41)	Severe, 31 (100)	FVIII replacement therapy: On demand: 14 (45) Intermittent prophylaxis: 13 (42) Continuous prophylaxis: 4 (13)	Mean VERITAS-Pro scale scores (higher scores represented poorer adherence): Time: 11.2 Dose: 8.9 Plan: 8.3 Remember: 10.2 Skip: 9.0 Communicate: 12.1	■ VERITAS-Pro scores were positively correlated with both HEAD-US-C ($r = 0.49$; $p = 0.046$) and HJHS scores ($r = 0.64$; $p = 0.005$) - Indicates better adherence to prophylaxis was favourable for joint protection
Zanon et al. [27] Italy	Patients with severe HA ($N = 40$) Age, years: NR	Severe, 40 (100)	Octocog alfa: Prophylaxis: 40 (100)	Level of adherence, *n* (%): None: 4 (10) Minimal: 4 (10) Low: 4 (10) Medium: 9 (22.5) High: 19 (47.5)	■ 32 of 40 patients (80%) adhered to prophylactic regimen (95% CI, 66.1%–93.9%) – In all patient groups, adherence was significantly similar ■ Adherence by age groups, % (95% CI): – Children, 83.3 (60.2–106.4) – Adolescents, 77.8 (47–108.6) – Adults, 78.9 (58.3–99.6) ■ Adherent patients: – 50% had at least 1 bleeding episode in the year before enrolment; this percentage dropped during the 3 years of the study ■ Number of the total target joints declined for adherent patients from a baseline of 19 to a final value of 13, whilst remaining stable in the nonadherent group ($n = 9$) ■ Mean HJHS score (lower scores represent better joint status) decreased in the 'adherent' patients from 2.3 (SD, 3.2) to 0.1 (SD, 0.4) ■ Mean no. of school/workdays lost: – Adherent patients (from 3.4 [SD, 6.8] to 0.2 [SD, 0.9]) – Nonadherent patients (8.5 [SD, 12.6] to 2.8 [SD, 4.0]) ■ Physical activity: highly adherent patients did more sports and engaged in more physical activities with a medium impact on joints vs. patients with no or low adherence

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
	Children with severe HA ($n = 12$) Age, years: NR	Severe, 12 (100)	Octocog alfa: Prophylaxis: 12 (100)	Level of adherence, *n* (%): None: 1 (8.3) Minimal: 2 (16.7) Low: 1 (8.3) Medium: 3 (25) High: 5 (41.7)	
	Adolescents with severe HA ($n = 9$) Age, years: NR	Severe, 9 (100)	Octocog alfa: Prophylaxis: 9 (100)	Level of adherence, *n* (%): None: 1 (11.1) Minimal: 0 Low: 1 (11.1) Medium: 3 (33.3) High: 4 (44.4)	
Adults with severe HA ($n = 19$) Age, years: NR	Severe, 19 (100)	Octocog alfa: Prophylaxis: 19 (100)	Level of adherence, *n* (%): None: 2 (10.5) Minimal: 2 (10.5) Low: 2 (10.5) Medium: 3 (15.8) High: 10 (52.6)		
Bago et al. [14] Croatia and Slovenia	Patients with severe or moderate HA ($n = 70$) or HB ($n = 12$) Age, median (range), years: 44.50 (18–73)	Severe, 77 (94)	Factor VIII and Factor IX prophylaxis: Prophylactic: 82 (100)	Mean reported VERITAS-Pro adherence score: 42 Adherent: 83%	■ Medication nonadherence was associated with poorer health: – Bodily Pain domain: ($r = -0.24$; $p = 0.033$) – MCS ($r = -0.26$; $p = 0.019$) ■ Bodily Pain and Social Functioning domains and MCS: – Medication adherence was notably associated with better HRQoL – Mental Health domain: adherence was $p = 0.059$. ■ After controlling for important demographic, socioeconomic, and clinical variables, SF-36v2 scores indicated that medication adherence was a significant predictor of HRQoL.

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
Cheung et al. [15] Hong Kong	Adults with HA or HB ($n = 42$) Age, mean (SD) [range], years: 37.2 (14.5) [17.5–68.4]	Mild, 4 (9.5) Moderate, 14 (33.4) Severe, 22 (52.3)	Prophylaxis an on demand: 26 (61.9) On demand: 15 (35.7) Note: therapy not reported	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence): Overall: 63.7 (13.8) Time: 10.9 (3.9) Dose: 9.2 (3.5) Plan: 8.7 (3.3) Remember: 10.0 (4.1) Skip: 10.0 (4.3) Communicate: 14.8 (3.3)	■ Skipping prophylactic treatment: – Worse self-perception: ($r = 0.32$; $p = 0.044$) – Worse functioning in sports and leisure: ($r = 0.31$; $p = 0.033$) ■ Adherence score was not significantly associated with the HRQoL scores. – All patients: unstandardised coefficient, 0.15 (95% CI, −0.19 to 0.50) ■ Adult patients: 0.21 (95% CI, −0.13 to 0.54)
	Paediatric patients with HA or HB ($n = 14$) Age, mean (SD) [range], years: 10.0 (2.8) [5.2–15.1]	Mild, 0 (0) Moderate, 2 (14.3) Severe, 11 (75.6)	Prophylaxis + on demand: 12 (85.7) On demand: 2 (14.3) Note: therapy not reported	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence): Overall: 43.3 (10.2) Time: 6.4 (3.1) Dose: 8.1 (1.8) Plan: 8.7 (3.1) Remember: 5.3 (1.9) Skip: 5.2 (1.3) Communicate: 9.6 (4.5)	
Cheung et al. [16] Hong Kong	Adults (>40 years) with HA or HB ($n = 9$) Age, median (IQR), years: 55.2 (50.9–56.8)	Mild, 3 (33.3) Moderate, 2 (22.2) Severe, 4 (44.5)	On demand: 4 (44.4) Prophylaxis: 5 (55.6) Plasma-derived factor concentrates: 5 (55.6) Bypassing agents: 0	Nonadherence median (IQR): 65 (54–76.5) (VERITAS-Pro)	■ For patients receiving prophylactic treatment (71.4%), medication adherence was significantly correlated with: – Attention: ($p = 0.024$) – Cognitive flexibility: ($p = 0.037$)
	Young adults (18 to <40 years) with HA or HB ($n = 22$) Age, median (IQR), years: 33.0 (26.4–36.9)	Mild, 4 (18.2) Moderate, 5 (22.7) Severe, 13 (59.1)	On demand: 7 (31.8) Prophylaxis:15 (68.2) Plasma-derived factor concentrates: 13 (59.1) Bypassing agents: 2 (9.1)	Nonadherence median (IQR): 61 (53–67) (VERITAS-Pro)	
	Paediatrics (<18 years) with HA or HB ($n = 11$) Age, median (IQR), years: 15.6 (13.4–16.6)	Mild, 1 (9.1) Moderate, 1 (9.1) Severe, 9 (81.8)	On demand: 1 (9.1) Prophylaxis: 10 (91.9) Plasma-derived factor concentrates: 10 (91.9) Bypassing agents: 0	Nonadherence median (IQR): 47 (45–57) (VERITAS-Pro)	

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
Dover et al. [28] Canada	Young boys with severe HA ($n = 56$) Age, median age at enrolment (ROV), years: 1.63 (1–2.5)	Severe, 56 (100)	Prophylaxis with an SHL rFVIII concentrate: 56 (100)	Overall median (ROV) adherence with prophylaxis: 85.7% (37.4%–99.8%) weeks per patient Overall median (ROV) adherence with enhanced episodic therapy protocol: 47.1% (0%–100%) per patient	■ Over any 12-week period: - 10% Increase in the absolute adherence rate corresponded with a 15% reduction in bleeding rate (HR, 0.85; 95% CI, 0.81–0.90)
García-Dasí et al. [29] Spain	Children and adolescents with severe HA ($n = 78$) Age, mean (SD), years: 11.9 (3.9)	Severe, 78 (100)	FVIII prophylaxis: Primary prophylaxis regimen: 26 (33.3)	AAI range (mean, SD): −64.4 to 66.7 (−3.08, 14.4) Infra-adherents,[a] *n* (%): 26 (33.3) Adherents,[b] *n* (%): 41 (52.6) Over adherents,[c] *n* (%): 11 (14.1)	■ Among AAI and the Feelings, Views, Family, Sport and School, Coping, and Treatment subscales – Significant correlation: $p < 0.05$ ■ Number of bleeding episodes in the adherent group (mean, 1.4) and infra-adherents (mean, 4.5) – Significant difference: $p < 0.010$
Krishnan et al. [17] US, Canada, and Australia	Adults with HA or HB ($n = 55$) Age, years: NR	Severe, 53 (96.4) Moderate, 2 (3.6)	Prophylactic treatment: Mean (SD) recommended infusions/week in HA: 2.9 (1.2) Note: therapy not reported	VERITAS-Pro mean (SD) adherence score: 50.8 (13.0) Nonadherence to prophylaxis (VERITAS-Pro < 57), *n* (%): Adherent: 41 (74.5) Nonadherent: 14 (25.5)	■ Adults with HA or HB: - Worse adherence (higher VERITAS-Pro scores) was associated with more breakthrough bleeds (B = 0.047; $p < 0.01$) - More target joint bleeds in the prior year (B = 0.055; $p < 0.01$) - No correlation was observed among adherence and other bleeding-related outcomes or HRQoL outcomes in adults (all *p* values >0.05)
	Paediatrics with HA or HB ($n = 55$) Age, years: NR	Severe, 54 (98.2) Moderate, 1 (1.8)	Prophylactic treatment: Mean (SD) recommended infusions/week in HA: 3.0 (1.0) Note: therapy not reported	VERITAS-Pro mean (SD) adherence score: 39.6 (11.7) Nonadherence to prophylaxis (VERITAS-Pro <57), *n* (%): Adherent: 51 (92.7) Nonadherent: 4 (7.3)	■ Paediatric patients: - Worse adherence associated with more days of work or school missed due to bleeding ($B = 0.072$; $p < 0.01$) - Worse adherence corresponded with the PHS score, indicating worse physical QoL ($B = -0.372$; $p < 0.05$)
Lambert et al. [18] Côte d'Ivoire	Boys with HA ($n = 21$) or HB ($n = 4$) Age, mean (SD), years: 5.6 (2.5)	Severe, 24 (96) Moderate, 1 (4)	Prophylaxis with EHL Fc-rFVIII and Fc-rFIX: Primary prophylaxis: 5 (20) Secondary prophylaxis: 20 (80)	Adherence, *n* (%): 7 (29)	■ Experiencing adherence issues or not: – Wilcoxon tests showed a notable difference on the ASJBR between T2 (at the end of the follow-up period)-2 (months before T2) and T0 (inclusion) ($p = 0.0063$)

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
McLaughlin et al. [19] US	Adolescents and young adults with HA or HB ($n = 80$) Age, years: 13–17 years ($n = 41$) 18–25 years ($n = 39$)	Severe, 73 (91) Moderate, 7 (9)	On demand: 11 (14) Prophylaxis: 69 (86) Note: therapy not reported	Mean (SD) VERITAS-Pro ($n = 69$): 49.6 (12.9) Mean (SD) VERITAS-PRN ($n = 11$): 51.0 (11.6)	■ High chronic pain level: - Higher (worse adherence) combined VERITAS-Pro and VERITAS-PRN scores (53.1 [SD, 12.0] vs. 48.0 [SD, 12.8]; $p = 0.08$) ■ Low levels of self-reported chronic pain: - $p < 0.05$ ■ Prophylactic patients: - Mean VERITAS-Pro scores for those with high chronic pain were higher (worse adherence) compared with those who reported low chronic pain (53.6 [SD, 12.3] vs. 47.4 [SD, 12.9]; $p = 0.05$) ■ Logistic regression showed: - For each 10-point decrease (i.e., increase in adherence) in the combined VERITAS (Pro and PRN) and VERITAS-Pro scores, there was a 35% (OR = 0.65; 95% CI = 0.44–0.96; $p = 0.03$) and 39% (OR = 0.61; 95% CI = 0.39–0.96; $p = 0.03$) decrease in the likelihood of having high chronic pain, respectively
Meijón-Ortigueira et al. [30] Spain	Patients with severe HA ($n = 64$) Age, mean (SD), years: 10.7 (5.5)	Severe, 64 (100)	SHL-FVIII products prophylaxis: Plasma-derived FVIII concentrates, %: Patients with joint involvement ($n = 14$): 28.6% Recombinant FVIII concentrates prophylaxis, %: Patients without joint involvement ($n = 46$): 100% Patients with joint involvement ($n = 14$): 71.4% Switch to EHL FVIII products prophylaxis, *n* (%): Patients without joint involvement ($n = 46$): 14 (30.4%) Patients with joint involvement ($n = 14$): 1 (7.1%)	Adherence, % (IQR): Patients without joint involvement ($n = 46$): 96% (87–102) Patients with joint involvement ($n = 14$): 88% (80–101)	■ Considered adherent: - Patients needed to take ≥85% of the prescribed doses (ratio of the number of doses administered to the prescribed doses) ■ 15 cases were switched from SHL recombinant FVIII to EHL FVIII concentrates, 9 due to the increase in ABR over the previous year and the degree of physical activity performed, and 6 to aid adherence by reducing the number of annual infusions - Adherence was ≥ 85%, with no statistically significant differences ($p = 0.167$)

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
Mokhtar et al. [20] Malaysia	Patients with severe HA or HB ($n = 103$) Age, mean (SD), years: 33.13 (11.91)	Severe, 103 (100)	Prophylaxis: 103 (100) Note: therapy not reported	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence) pre-HMTAC: Total score: 48.01 (13.684) Time: 6.66 (2.936) Dose: 7.47 (3.497) Plan: 7.26 (2.364) Remember: 8.58 (3.756) Skip: 8.52 (4.728) Communicate: 9.51 (4.051) Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence) post-HMTAC: Total score: 38.03 (9.848) Time: 5.52 (1.846) Dose: 5.10 (1.866) Plan: 6.29 (2.243) Remember: 7.00 (2.853) Skip: 5.91 (2.716) Communicate: 8.20 (3.510)	■ Post-HMTAC: - Notable difference in the mean ABR between the adherent (94.2%) and nonadherent patients (5.8%) - Mean bleeding rate of the adherent patients (3.91; SD, 3.989) was remarkably lower than the nonadherent group (7.67; SD, 7.367; $p = 0.005$). ■ Dose and Remember subscales: - Significant relationships between adherence with ABR, with p values of 0.025 and 0.018, respectively
Nwagha et al. [21] Nigeria	Patients with HA or HB ($n = 42$) Age, mean (SD), years: 9.8 (6.3) Range, 1–30 years	Moderate, 37 (88) Severe, 5 (12)	EHL products: Prophylaxis: 42 (100)	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence): Total score: 37.35 (9.08) Time: 0.78 (0.17) Dose: 5.12 (1.68) Plan: 8.68 (3.23) Remember: 5.62 (1.94) Skip: 6.50 (2.53) Communicate: 0.67 (0.13)	■ Difference between the mean ABR (8.12 vs. 7.59; mean difference: 1.09) and the mean number of target joints (2.57 vs. 2; mean difference: 1.29) between the adherent versus nonadherent groups - Not statistically significant, p values of 0.90 and 0.31, respectively ■ Pearson's correlation was used to test the association between self-reported adherence and ABR - No statistically significant associations with subscales between the groups with the exception of Skip in the nonadherent group, with a significantly high positive correlation coefficient of 0.94 and a p value of 0.018

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
O'Hara et al. [31] France, Germany, Italy, Spain, and UK	Adult males with severe HA (*n* = 376) Age, mean (SD), years: 37.2 (14.7)	Severe, 376 (100)	Lifelong prophylaxis: 55 (14.6) Other: 321 (85.4) Note: therapy not reported	Low/medium *n* (%): 139 (37.0) High *n* (%): 237 (63.0)	■ High adherence had more substantial association with: - Reduced AI than low/medium adherence to therapy (p = 0.012) - Reduced WPL than low/medium adherence (p = 0.012) ■ Compared with low or medium adherence to therapy, high adherence to therapy was correlated with: - Reduced AI (median, −5.94; 95% CI, −10.58 to −1.30; p = 0.012) - Reduced WPL (median, −9.04; 95% CI, −16.06 to −2.01; p = 0.012)
Pérez-Robles et al. [22] Spain	Male patients with HA or HB (*n* = 52) Age, mean (SD), years: 17.56 (4.2)	Severe, 46 (88.5) Moderate, 5 (9.6) Mild, 1 (1.9)	Clotting factor concentrate: Prophylaxis primary: 10 (19.2) Prophylaxis secondary: 42 (80.8)	Average adherence (SD): 85.72 (23.76%) Mean adherence ≥100% (SD): 113.4 (16.97) Adherence rate ≥75%, *n* (%): 38 (73.1) Objective adherence <75%, *n* (%): 14 (26.9)	■ No significant association was observed between the adherence rate and the number of bleeding episodes in any site ■ For patients with an adherence rate ≥75%, 24, 9, 5 and 0 patients had 0, 1, 2 and 3 bleeding episodes per year, respectively ■ For patients with an adherence rate <75%, 11, 1, 0 and 2 patients had 0, 1, 2 and 3 bleeding episodes per year, respectively ■ Of the 2 patients who suffered hemarthrosis, adherence was <50%
Schrijvers et al. [23] The Netherlands	Paediatric (parent reported) patients with HA or HB (*n* = 73) Age, median (IQR), years: 8.4 (6.2–10.5) Range: 2–11 years	Severe, 70 (96)	Prophylaxis: 73 (100) Note: therapy not reported	Adherent, *n* (%): 48 (66) Suboptimally adherent, *n* (%): 21 (29) Nonadherent, *n* (%): 4 (5)	■ Adherent and suboptimally adherent children: - Joint bleeding was similar (p = 0.7) ■ According to adherence level: - Target joints in children were rare and similar (p = 0.2) ■ Across adherence levels: - CFC was similar (mean CFC, 124–134×103 iu/year) ■ Patients with lower adherence: - CFC was significantly lower: annual CFC declined from 212 to 150 × 103 IU/year (p < 0.01)
	Patients with HA or HB (*n* = 168) Age, median (IQR), years: 29.9 (17.1–49.8) Range, 12–77 years	Severe, 160 (95)	Prophylaxis: 168 (100) Note: therapy not reported	Adherent, *n* (%): 72 (43) Suboptimally adherent, *n* (%): 62 (37) Nonadherent, *n* (%): 34 (20)	

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
Shaikh et al. [24] Europe	Patients with severe HA or HB ($n = 514$) Age, mean (SD), years: 37.5 (15.0)	Severe, 514 (100)	SHL treatment: Prophylaxis from diagnosis: 73 (14) Prophylaxis previously on demand: 240 (47) Always been on demand: 113 (22) Moved to on demand: 88 (17)	Low/medium, *n* (%): 202 (39) High, *n* (%): 312 (61)	■ EQ-5D scores were higher for patients with high overall treatment adherence (vs. low/medium) ■ High vs. low/medium adherence was associated with a 0.06 increment in EQ-5D utility score
Torres-Ortuño et al. [25] Spain	Patients with severe haemophilia ($n = 23$) Age, mean (SD), years: 31.96 (11.81)	Severe, 21 (91) Moderate, 2 (9)	Prophylaxis: 23 (100) Note: therapy not reported	≤62 points (adherent) on VERITAS-Pro = 10 (43.5%) >62 points (nonadherent) on VERITAS-Pro = 13 (56.5%)	■ A greater number of hemarthrosis episodes were presented in the most nonadherent patients ■ Patients who were the most nonadherent perceived greater cyclicity regarding the disease (ES = −0.83) ■ Adherent patients showed a higher QoL in terms of: - Pain (ES = 0.85) - Vitality (ES = 0.78) - Physical Health (ES = 0.80) - Emotional Functioning (ES = 0.88) - Better overall health ($p < 0.01$) ■ Behaviour was more hypochondriac toward the disease ($p < 0.05$), even though they considered themselves to have fewer medication side effects ($p < 0.05$)
van Os et al. [33] England and Wales	Adherent patients with severe haemophilia ($n = 64$) Age, mean (SD), years: 19.00 (4.22)	Severe, 64 (100)	Prophylaxis: 64 (100) Note: therapy not reported	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence): Log Timing: 6.14 (1.41) Log Planning: 6.22 (1.49) Remembering: 7.28 (2.27) Log Skipping: 5.01 (1.35) Communicating: 12.07 (4.14) Sum: 37.87 (7.24)	■ Mean (SD) clinical data: - Pain severity (previous 4 weeks, $n = 62$): 2.94 (1.41) - Impact of pain (previous 4 weeks, $n = 64$): 2.16 (1.25) - Log total bleeds (previous 6 months, $n = 60$): 3.34 (2.70) - Log hospital visits (previous 6 months, $n = 49$): 2.82 (2.62)

(Continues)

TABLE 2 | (Continued)

Study	Population	Disease severity, *n* (%)	Therapy, *n* (%)	Treatment adherence	Outcomes related to adherence
	Nonadherent patients with severe haemophilia ($n = 14$) Age, mean (SD), years: 18.94 (3.75)	Severe, 14 (100)	Prophylaxis: 14 (100) Note: therapy not reported	Mean (SD) VERITAS-Pro scale scores (higher scores represented poorer adherence): Log Timing: 12.06 (1.32) Log Planning: 10.16 (1.39) Remembering: 12.38 (2.59) Log Skipping: 7.06 (1.56) Communicating: 15.26 (2.65) Sum: 58.50 (5.60)	■ Mean (SD) clinical data: - Pain severity (previous 4 weeks, $n = 13$): 3.15 (1.73) - Impact of pain (previous 4 weeks, $n = 13$): 2.46 (1.71) - Log total bleeds (previous 6 months, $n = 14$): 1.41 (1.79); (mean difference −2.71, $t_{74} = -3.593$, $p = 0.001$) - Log hospital visits (previous 6 months, $n = 11$): 1.95 (1.95); (mean difference −0.507, $t_{64} = -2.235$, $p = 0.034$)
Zupan et al. [32] Slovenia	Patients with HA ($n = 63$) Age, years: *n* (%) ≤11: 3 (4.8) 12–18: 1 (1.6) 19–30: 6 (9.5) 31–40: 10 (15.9) 41–0: 8 (12.7) 51–60: 19 (30.2) ≥61: 16 (25.4)	Mild, 11 (17.5) Moderate, 9 (14.3) Severe, 43 (68.3)	FVIII prophylaxis: 45 (71.4) FVIII on demand: 16 (25.4)	56 Of the 63 respondents answered the questions about compliance. Of those 56 patients, almost half (26 [46.4%]) reported that they had missed, forgotten, or delayed their scheduled doses at some point in the past.	■ Adherence affected bleeding frequency: - Nonadherent patients, higher number of bleeds within the last 12 months (mean, 5.9 [median, 4.0]) - Adherent patients (mean, 4.6 [median, 3.0]) - More than half of the 45 patients on prophylaxis (24 [53.3%]) reported being nonadherent at some point during treatment - Nonadherent patients had a higher mean or median number of bleeds than adherent patients

Abbreviations: AAI = absolute adherence index, ABR = annualised bleeding rate, AI = activity impairment, ASJBR = annual spontaneous joint bleeding rate, CFC = clotting factor consumption, CI = confidence interval, EHL = extended half-life, ES = effect size, Fc-rFIX = Fc fusion protein-recombinant factor, FVIII = Factor VIII, HA = haemophilia A, HB = haemophilia B, HEAD-US-C = haemophilia early arthropathy detection with ultraSound in China, HJHS = haemophilia joint health score, HMTAC = haemophilia medication therapy adherence clinic, HR = hazard ratio, HRQoL = health-related quality of life, IQR = interquartile range, IU = international unit, MCS = mental component summary, NR = not reported, OR = odds ratio, PHS = physical health summary, QoL = quality of life, rFVIII = recombinant FVIII, ROV = range of values, SD = standard deviation, SF-36v2 = 36-item short form health survey, version 2, SHL = standard half-life, US = United States, UK = United Kingdom, VERITAS = validated haemophilia regimen treatment adherence scale, VERITAS-PRN = validated haemophilia regimen treatment adherence scale –on-demand, VERITAS-pro = validated haemophilia regimen treatment adherence scale-prophylaxis, WPL = work productivity loss.

[a]Adherents were patients who were administered as prescribed.

[b]Infra-adherents were patients who were administered less than prescribed.

[c]Over adherents were patients who were administered more than prescribed.

HA [27]. The mean HJHS score decreased from 2.3 to 0.1 in adherent patients; low number of clinical assessments prevented score comparisons in nonadherent patients [27].

One study reported that adherence rate was not significantly different between patients without and with joint involvement [30]. Meijón-Ortigueira et al. [30] retrospectively analysed adherence to prophylactic SHL and EHL concentrates in 60 patients with severe HA without inhibitors. Joint involvement was defined as an HJHS or HEAD-US score of ≥1. Approximately 23.3% of patients had joint involvement ($n = 14$), and 76.7% had no joint involvement ($n = 46$). Adherence was ≥85% in both groups with no statistically significant differences [30].

3.3 | Pain

One study showed that better treatment adherence was associated with a significantly lower likelihood of having high chronic pain levels [19], whereas 1 study showed no relationship between adherence and pain [33] (Table 2). In the US, a cross-sectional study involving adolescents and young adults with moderate or severe HA/HB reported that, compared with patients with low chronic pain, those with high chronic pain had higher mean VERITAS-Pro scores (47.4 vs. 53.6), indicating worse adherence. For each 10-point decrease (i.e., increase in adherence) in the VERITAS-Pro and combined VERITAS (Pro and PRN) scores, there was a 39% and 35% decrease in odds of experiencing high chronic pain, respectively. However, van Os et al. [33] noted that pain severity and impact were not significantly different in adherent and nonadherent adolescents and young adults with severe haemophilia (VERITAS-Pro scores).

3.4 | QoL

Four studies reported that treatment adherence was a significant predictor of better health-related QoL (HRQoL) [14, 24, 25, 29] (Table 2). Bago et al. [14] investigated the relationship between prophylaxis adherence (measured with the VERITAS questionnaire) and HRQoL (measured with the 36-item Short Form Health Survey, version 2 questionnaire) in adult males with moderate or severe HA/HB in Croatia and Slovenia. Adherence was significantly associated with better HRQoL, especially for body pain (standardised beta coefficient [β] = −0.27) and social functioning domains ($\beta = -0.26$) and mental component summary ($\beta = -0.22$) [14]. In Spain, García-Dasí et al. [29] investigated adherence to FVIII prophylaxis using an adherence index in 78 children and adolescents with severe HA; QoL was measured using the Haemophilia-Specific QoL Assessment Instrument for Children and Adolescents (Haemo-QoL) and the version for adults (Haemo-QoL-A). Significant differences in mean QoL scores were observed between suboptimally adherent and adherent patients (74.1 vs. 81.2), but not between over-adherent (received more than prescribed) and adherent patients (80.6 vs. 81.2). Similarly, parents of adherent patients had the highest QoL score (80.1), followed by parents of over-adherent patients (76.8); parents of suboptimally adherent patients had the lowest score (72.3) [29].

Two studies found no association between adherence and HRQoL [15, 17]. Cheung et al. [15] investigated the association between HRQoL and treatment adherence, measured with VERITAS-Pro, in 38 patients (26 adults, 12 children) with moderate or severe HA/HB in Hong Kong. The HRQoL of children and adults was measured using Haemo-QoL short form and Haemo-QoL-A, respectively. The unstandardised coefficient was 0.15 in all patients and 0.21 in adult patients only, indicating no significant association between HRQoL and adherence [15]. Similarly, Krishnan et al. [17] found no relationship between adherence and HRQoL in adults. Nonetheless, both studies reported an association between poor adherence to prophylaxis with worse physical health or worse functioning in sports and leisure [15, 17].

3.5 | AI and WPL

Five studies reported that higher treatment adherence was associated with lower AI or WPL [15, 17, 27, 29, 31] (Table 2). In 376 adults with severe HA, O'Hara et al. [31] examined the factors linked with AI and WPL using the WP and AI-General Health Questionnaire and measured adherence using a self-reported questionnaire. Compared with low or medium adherence to therapy, high adherence was correlated with reduced AI and reduced WPL ($p = 0.012$ both). Similarly, lower adherence was associated with poorer physical health status and more school absenteeism among children [17]. Cheung et al. [15] noted that among patients receiving prophylactic treatment, those who reported skipping their treatment tended to have worse functioning in sports and leisure ($r = 0.31$).

3.6 | Cognitive Function

Among patients receiving prophylactic treatment, better adherence was associated with better cognitive function [16] (Table 2). Cheung et al. [16] investigated factors associated with neurocognitive outcomes in 42 patients with HA/HB in Hong Kong and evaluated adherence using the VERITAS-Pro questionnaire. Adherence was positively correlated with cognitive flexibility (unstandardised point estimate = 0.28), indicating that better adherence was associated with better cognitive function [16].

3.7 | HRU

One study investigating the link between adherence and HRU was identified, which found that nonadherent adolescents and young adults with severe haemophilia ($n = 14$) had significantly fewer hospital visits compared with adherent patients ($n = 64$; mean difference: −0.507) [33] (Table 2).

4 | Discussion

We identified 15/20 studies that reported that better adherence to treatment among PwH was associated with better outcomes, including a reduction in bleeding risk, improved joint structure and function, less chronic pain, better HRQoL, lower AI, less school/work absenteeism, higher WP and better cognitive function.

Of the 20 included studies, 7 reported no association between adherence and bleeding [21–23], HRQoL [15, 17], joint

involvement [30] and pain [33]. One study reported better outcomes (bleeding and HRU) in nonadherent patients [33]. Nwagha et al. [21] assessed adherence using VERITAS-Pro and reported no difference in dosing subscale score between nonadherent and adherent groups, suggesting that nonadherent participants received the recommended dose of infusions despite altering their dose timing, skipping infusions, or failing to stock infusions. Furthermore, most participants on prophylaxis received EHL products, but details of the exact product were not reported. These factors could have affected the association between ABR and prophylaxis adherence [21]. Although two studies found no association between adherence and HRQoL, they both reported that poor adherence to prophylaxis was correlated with worse physical health or worse functioning in sports and leisure [15, 17]. Krishnan et al. [17] further demonstrated that poorer adherence to prophylactic treatment as assessed by the VERITAS-Pro is particularly related to more bleeding episodes among adults, who reported lower levels of adherence than children. The frequency of regression-estimated bleeds/year among adults more than doubled from <6 at the 25th percentile VERITAS-Pro score (lower score indicates greater adherence) to ~12 at the 75th percentile score, implying that a significant number of bleeding episodes among adults could be eliminated through increased adherence.

There are several potential explanations for the difference in results across the extracted studies, including issues with adherence measures and outcomes reporting. Ten of the identified studies used the VERITAS-Pro scale; one of these studies used VERITAS-Pro and VERITAS-PRN [19]; and none of the studies used the Haemo-Adhaesione scale. Other methods used to measure adherence included pharmacy records ($n = 2$), nonvalidated questionnaires or interview with patients and parents ($n = 5$), and comparison of prescribed dosage with actual quantity of factor used ($n = 1$). Interestingly, the two studies that assessed adherence using pharmacy records reported no association between adherence and outcomes [22, 30]. Pharmacy records usually provide no information on the time or dose of infusion and offer no clear evaluation of prophylaxis or additional clotting factors for the treatment of bleeding [23]. Schrijvers et al. [23] assessed adherence using a nonvalidated short questionnaire developed by participating nurses, which could be prone to recall bias or inaccurate recording. van Os et al. [33] measured adherence using the VERITAS-Pro scale but did not use the scale's dosing subscale, and therefore the cut-off score was different from that used in other included studies. The questionnaire had not been validated in the United Kingdom at the time of use; this may explain the large numbers of missing data, as the more personalised and flexible way in which UK patients manage their treatment was not reflected [33]. It may also explain why this was the only study that reported better health outcomes in nonadherent compared with adherent patients.

Use of bleeding logs is the standard method for measuring bleeding in haemophilia studies. As this is a self-reported measure, it could be prone to underreporting. Less adherent patients may be more relaxed and less likely to interpret symptoms as bleeds and not report them, whereas more adherent patients may be more attentive to bleeding episodes and symptoms and report them frequently [33]. The nonadherent patients in the study by Schrijvers et al. [23] reported lower bleeding frequency (reporting bias), and Pérez-Robles et al. [22] noted that the number of bleeding episodes reported by patients was generally low. The lower frequency of reported outcomes might make it difficult to demonstrate a significant association between adherence and clinical outcomes.

Additional possible explanations for the different results could be the short follow-up period and the assessment of adherence at a single timepoint in some studies. Pérez-Robles et al. [22] assessed adherence objectively, using dispensing records from 1 year and subjectively using questionnaires completed at a single timepoint during study enrolment, whilst Schrijvers et al. [23] measured adherence at one timepoint. Similarly, van Os et al. [33] obtained clinical outcomes during the 6 months preceding the study start, whereas adherence was assessed during the last month before the study start date. It is possible that patients who experienced frequent and/or severe bleeds in the months preceding the study start were motivated to improve their adherence with the intention of reducing the bleeding risk, thereby leading to better adherence scores in the last month before the study start date. Also, levels of patient adherence could fluctuate over time [23], thereby making it important to conduct repeated assessments of adherence.

Treatment adherence is a multifaceted problem that is not fully understood. Several types of adherence barriers are linked to the treatment, condition, patient, socioeconomic factors and healthcare system [11]. Factors related to patients include patient's age, disease severity and bleeding frequency. For example, switching to self-infusion or moving away from home is associated with less adherence in young adults transitioning from paediatric to adult care [4]. Treatment-related factors include dosage frequency, drug form, dosage amount, drug preparation time and administration route [11]. Patients with difficult venous access have tended to give up on infusions if their first or second attempt was unsuccessful, and patients have identified the time-intensive nature of prophylaxis regimen as an adherence barrier [6, 11]. Development of new therapies that decrease dosing frequency or provide an easier administration route whilst maintaining efficacy may potentially help improve patient acceptance and adherence to prophylaxis by reducing the treatment burden. Indeed, evidence suggests that adherence improves when dosing frequency decreases, both with weekly versus daily dosing in osteoporosis [34], diabetes [35, 36], multiple sclerosis [37], growth hormone deficiency [38] and chronic disease in general [39].

Considering dosing frequency, one might expect improved adherence with EHL relative to SHL factor products. However, current real-world evidence is lacking to confirm improved adherence with EHL products. Iorio et al. [40] reported better (but still suboptimal) real-world adherence with EHL recombinant FIX Fc fusion protein compared with conventional recombinant FIX products and that improved adherence was correlated with statistically significant mean ABR reductions. The improved real-world adherence could be because patients regularly met the prescribed number of infusions/week and were infused on scheduled days [40]. In an analysis of a record-based survey in the US and Europe, the proportion of fully adherent patients (none of the last 10 doses missed per physician assessment) was similar for patients on SHL and EHL products (FVIII: 72% vs.

75%; FIX: 68% vs. 73%) [41]. The mean number of missed doses was comparable in the SHL and EHL FIX groups in the US (SHL: 0.8 vs. EHL: 0.5) and in Europe (SHL: 0.5 vs. EHL: 0.1) [41]. A recent observational study reported that SHL users were more likely to be adherent to treatment than EHL users (adherence rate: 72.0% vs. 47.4%, $p = 0.06$) [42].

Regarding the administration route, a review of 65 studies compared different injection routes of several drugs and found that subcutaneous administration was mostly favoured over intravenous administration in terms of patient preference or experience and efficacy [43]. This is in line with a previous SLR on patient preference that showed that patients prefer the subcutaneous over the intravenous route [44]. There is paucity of evidence on whether patients with haemophilia using subcutaneous nonfactor therapy show improved adherence compared with those on factor replacement therapy. A real-world study published in 2022 analysed adherence and 1-year persistence to emicizumab prophylaxis administered subcutaneously using two secondary claims databases (IQVIA PharMetrics Plus [P+], $n = 184$; and IBM MarketScan, $n = 105$) [45]. Adherence to emicizumab was high, with a mean proportion of days covered of 90% for IBM and 87% for P+, and most patients (IBM: 92%; P+: 87%) were persistent with emicizumab prophylaxis after 1 year. Additionally, adherence and persistence were high regardless of inhibitor status [45].

The findings of this study hold relevant implications for healthcare professionals and patients. Given the value of prophylaxis in improving outcomes (e.g., reduced bleeding and joint damage and improved QoL) and the importance of adherence to treatment in achieving these outcomes, it is essential to work with and educate patients and caregivers of children with haemophilia to ensure that they understand their treatment and the significant role they play in its efficacy. Effective haemophilia treatment is a function of good management by a healthcare professional and the willingness of the patient to adhere to treatment. Haemophilia is a lifelong disease, and for patients on prophylaxis receiving repeated treatment, continued adherence is critical for improved long-term outcomes, allowing patients to experience a QoL similar to that of their peers without haemophilia.

The strength of this SLR is the use of systematic processes to identify and summarise recent studies on the relationship between adherence and health outcomes using real-world evidence. Limitations are related to the real-world nature of the studies, which include the heterogeneity of the patient population (i.e., haemophilia type, age of patients, geographic variation and haemophilia severity), treatment regimen, management practices and the method by which adherence and outcomes were defined and reported across the included studies. The heterogeneity across studies precluded combining the results for meta-analysis. Also, the quality assessment of individual papers was not planned due to the assumed heterogeneity of the individual study designs. This review did not assess factors associated with nonadherence or potential strategies to address these factors. It is possible that this SLR's results may not be applicable to nonfactor therapies because the review did not identify studies on nonfactor therapies; included studies generally evaluated the effect of adherence to factor replacement therapies. Studies evaluating the effect of adherence to nonfactor therapies are needed.

5 | Conclusions

This SLR shows that high adherence to haemophilia treatment is generally associated with reduced bleeding rates, pain and school/work absenteeism as well as with improved joint health and QoL for patients with HA/HB. Although the relationships between adherence and specific outcomes varied across studies, the relationships between greater adherence and better outcomes indicate that patients would benefit from treatments that improve adherence. The development of newer innovative drugs such as products administered subcutaneously or therapies that will require lower frequency of infusions could improve adherence to treatment and thereby have a positive impact on patients' outcomes.

Author Contributions

Weyinmi Nuabor, Brittney Herbel, Stephanie Barrows and Annete Njue performed the research, analysed the data and wrote the paper. All authors designed the research study.

Acknowledgements

The support provided by Jonathan Pattishall and John Forbes of RTI Health Solutions, funded by Pfizer, consisted solely of manuscript formatting and editing support, and no contribution was made to editorial content. The authors thank Lisa Wilcox of Pfizer Inc. as a non-author contributor for providing feedback on the manuscript.

Disclosure

RTI Health Solutions performed the SLR and drafted the manuscript. All Pfizer authors contributed to the critical review and revision of the manuscript. All authors granted approval for the submission of the manuscript.

Ethics Statement

Ethical approval was not required for this study because it is a review of previously conducted studies and did not include humans or animals.

Conflicts of Interest

Cynthia Khanji, Travis Gould and Hae Kyung Kim are employees of Pfizer Inc. Weyinmi Nuabor, Annete Njue, Stephanie Barrows and Brittney Herbel are employees of RTI Health Solutions, which received financial support from Pfizer Inc. in connection with the development of this manuscript.

Data Availability Statement

Published journal articles were used to obtain data for this systematic review and are available in the public domain.

References

1. M. C. Ozelo and G. G. Yamaguti-Hayakawa, "Impact of Novel Hemophilia Therapies Around the World," *Research and Practice in Thrombosis and Haemostasis* 6, no. 3 (2022): e12695.

2. W. Miesbach, R. Klamroth, J. Oldenburg, and A. Tiede, "Gene Therapy for Hemophilia—Opportunities and Risks," *Deutsches Ärzteblatt International* 119 (2022): 887–894, https://doi.org/10.3238/arztebl.m2022.0353.

3. L. Aledort, P. M. Mannucci, W. Schramm, and M. Tarantino, "Factor VIII Replacement Is Still the Standard of Care in Haemophilia A," *Blood Transfusion* 17, no. 6 (2019): 479.

4. A. Srivastava, E. Santagostino, A. Dougall, et al., "WFH Guidelines for the Management of Hemophilia, 3rd Edition," *Haemophilia* 26, no. Suppl. 6 (2020): 1–158, https://doi.org/10.1111/hae.14046.

5. R. Núñez, M. T. Álvarez-Román, S. Bonanad, et al., "The Limitations and Unmet Needs of the Five Cornerstones to Guarantee Lifelong Optimization of Prophylaxis in Hemophilia Patients," *TH open: companion journal to thrombosis and haemostasis* 6, no. 04 (2022): e365–e377.

6. S. Van Os, N. Troop, N. Ryder, and D. Hart, "Adherence to Prophylaxis in Adolescents and Young Adults With Severe Haemophilia A, a Qualitative Study With Patients," *Health Psychology and Behavioral Medicine* 6, no. 1 (2018): 277–300.

7. G. Lee Mortensen, A. M. Strand, and L. Almén, "Adherence to Prophylactic Haemophilic Treatment in Young Patients Transitioning to Adult Care: A Qualitative Review," *Haemophilia* 24, no. 6 (2018): 862–872.

8. N. Duncan, W. Kronenberger, C. Roberson, and A. Shapiro, "VERITAS-Pro: A New Measure of Adherence to Prophylactic Regimens in Haemophilia," *Haemophilia* 16, no. 2 (2010): 247–255, https://doi.org/10.1111/j.1365-2516.2009.02129.x.

9. N. A. Duncan, W. G. Kronenberger, C. P. Roberson, and A. D. Shapiro, "VERITAS-PRN: A New Measure of Adherence to Episodic Treatment Regimens in Haemophilia," *Haemophilia* 16, no. 1 (2010): 47–53, https://doi.org/10.1111/j.1365-2516.2009.02094.x.

10. A. Torres-Ortuno, R. Cuesta-Barriuso, J. Nieto-Munuera, A. Castiello-Munuera, M. Moreno-Moreno, and J. A. Lopez-Pina, "Haemo-Adhaesione: A New Measure of Adherence for Adolescent and Adult Patients With Haemophilia," *Patient Preference and Adherence* 14 (2020): 455–465, https://doi.org/10.2147/PPA.S233601.

11. C. D. Thornburg and N. A. Duncan, "Treatment Adherence in Hemophilia," *Patient Preference and Adherence* 11 (2017): 1677–1686.

12. S. Von Mackensen, W. Kalnins, J. Krucker, et al., "Haemophilia Patients' unmet Needs and Their Expectations of the New Extended Half-Life Factor Concentrates," *Haemophilia* 23, no. 4 (2017): 566–574.

13. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *British Medical Journal* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

14. M. Bago, A. Butkovic, I. Preloznik Zupan, et al., "Association Between Reported Medication Adherence and Health-Related Quality of Life in Adult Patients With Haemophilia," *International Journal of Clinical Pharmacy* 43, no. 6 (2021): 1500–1507, https://doi.org/10.1007/s11096-021-01270-x.

15. Y. T. Cheung, P. H. Lam, H. H. W. Lam, et al., "Treatment Adherence and Health-Related Quality of Life in Patients With Hemophilia in Hong Kong," *International Journal of Environmental Research and Public Health* 19, no. 11 (2022): 6496, https://doi.org/10.3390/ijerph19116496.

16. Y. T. Cheung, C. T. Ma, H. H. W. Lam, et al., "Clinical, Neuroimaging, and Behavioural Risk Factors for Neurocognitive Impairment in Chinese Patients With Haemophilia: A Multicentre Study," *Haemophilia* 29, no. 4 (2023): 1074–1086, https://doi.org/10.1111/hae.14816.

17. S. Krishnan, J. Vietri, R. Furlan, and N. Duncan, "Adherence to Prophylaxis Is Associated With Better Outcomes in Moderate and Severe Haemophilia: Results of a Patient Survey," *Haemophilia* 21, no. 1 (2015): 64–70, https://doi.org/10.1111/hae.12533.

18. C. Lambert, N. Meité, I. Sanogo, S. Lobet, and C. Hermans, "Feasibility and Outcomes of Low-Dose and Low-Frequency Prophylaxis With Recombinant Extended Half-Life Products (Fc-rFVIII and Fc-rFIX) in Ivorian Children With Hemophilia: Two-Year Experience in the Setting of World Federation of Haemophilia Humanitarian Aid Programme," *Haemophilia* 27, no. 1 (2021): 33–40, https://doi.org/10.1111/hae.14216.

19. J. M. McLaughlin, M. L. Witkop, A. Lambing, T. L. Anderson, J. Munn, and B. Tortella, "Better Adherence to Prescribed Treatment Regimen Is Related to Less Chronic Pain Among Adolescents and Young Adults With Moderate or Severe Haemophilia," *Haemophilia* 20, no. 4 (2014): 506–512, https://doi.org/10.1111/hae.12360.

20. F. M. Mokhtar, J. Sathar, and H. Z. Huri, "Medication Adherence for Haemophilia Patients: Outcome of Prophylaxis Treatment Intervention," *Healthcare (Basel)* 9, no. 12 (2021): 1702, https://doi.org/10.3390/healthcare9121702.

21. T. U. Nwagha, H. C. Okoye, S. Yuguda, et al., "Adherence to Prophylaxis and Bleeding Outcome: A Multicenter Nigerian Study," *PLoS ONE* 18, no. 2 (2023): e0264600, https://doi.org/10.1371/journal.pone.0264600.

22. T. Pérez-Robles, J. A. Romero-Garrido, E. C. Rodriguez-Merchan, and A. Herrero-Ambrosio, "Objective Quantification of Adherence to Prophylaxis in Haemophilia Patients Aged 12 to 25 Years and Its Potential Association With Bleeding Episodes," *Thrombosis Research* 143 (2016): 22–27, https://doi.org/10.1016/j.thromres.2016.04.015.

23. L. H. Schrijvers, M. Beijlevelt-van der Zande, M. Peters, et al., "Adherence to Prophylaxis and Bleeding Outcome in Haemophilia: A Multicentre Study," *British Journal of Haematology* 174, no. 3 (2016): 454–460, https://doi.org/10.1111/bjh.14072.

24. A. Shaikh, G. Pedra, M. Cawson, and C. Wiseman, "Examining the Impact of Haemophilia Treatment on Health-Related Quality of Life," *Haemophilia* 28, no. 5 (2022): 796–805, https://doi.org/10.1111/hae.14583.

25. A. Torres-Ortuño, R. Cuesta-Barriuso, J. Nieto-Munuera, P. Galindo-Piñana, and J. A. López-Pina, "The Behaviour and Perception of Illness: Modulating Variables of Adherence in Patients With Haemophilia," *Vox Sanguinis* 113, no. 6 (2018): 577–583, https://doi.org/10.1111/vox.12669.

26. L. Zhao, H. Yang, Y. Li, et al., "Joint Status and Related Risk Factors in Patients With Severe Hemophilia A: A Single-Center Cross-Sectional Study," *Hematology (Amsterdam, Netherlands)* 27, no. 1 (2022): 80–87, https://doi.org/10.1080/16078454.2021.2019892.

27. E. Zanon, A. Tagliaferri, S. Pasca, et al., "Physical Activity Improved by Adherence to Prophylaxis in an Italian Population of Children, Adolescents and Adults With Severe Haemophilia A: The SHAPE Study," *Blood Transfusion* 18, no. 2 (2020): 152–158, https://doi.org/10.2450/2019.0040-19.

28. S. Dover, V. S. Blanchette, D. Wrathall, et al., "Hemophilia Prophylaxis Adherence and Bleeding Using a Tailored, Frequency-Escalated Approach: The Canadian Hemophilia Primary Prophylaxis Study," *Research and Practice in Thrombosis and Haemostasis* 4, no. 2 (2020): 318–325, https://doi.org/10.1002/rth2.12301.

29. M. García-Dasí, J. A. Aznar, V. Jiménez-Yuste, et al., "Adherence to Prophylaxis and Quality of Life in Children and Adolescents With Severe Haemophilia A," *Haemophilia* 21, no. 4 (2015): 458–464, https://doi.org/10.1111/hae.12618.

30. M. D. M. Meijón-Ortigueira, M. T. Álvarez-Román, H. De La Corte Rodríguez, N. Butta Coll, and V. Jiménez-Yuste, "Long-Term Impact of Primary Prophylaxis on Joint Status in Patients With Severe Hemophilia A," *Research and Practice in Thrombosis and Haemostasis* 7, no. 1 (2023): 100005, https://doi.org/10.1016/j.rpth.2022.100005.

31. J. O'Hara, D. Noone, M. Jain, et al., "Clinical Attributes and Treatment Characteristics Are Associated With Work Productivity and Activity Impairment in People With Severe Haemophilia A," *Haemophilia* 27, no. 6 (2021): 938–946, https://doi.org/10.1111/hae.14302.

32. I. P. Zupan, K. Rener, and S. A. Doma, "Treatment Satisfaction and Limitations in Haemophilia A, With a Focus on Factor VIII Product Storage Conditions: Patients' perspectives and Challenges," *Drugs and Therapy Perspectives* 39, no. 2 (2023): 71–80, https://doi.org/10.1007/s40267-022-00967-x.

33. S. B. van Os, N. A. Troop, K. R. Sullivan, and D. P. Hart, "Adherence to Prophylaxis in Adolescents and Young Adults With Severe Haemophilia: A Quantitative Study With Patients," *PLoS ONE* 12, no. 1 (2017): e0169880, https://doi.org/10.1371/journal.pone.0169880.

34. R. R. Recker, R. Gallagher, and P. E. MacCosbe, "Effect of Dosing Frequency on Bisphosphonate Medication Adherence in a Large

Longitudinal Cohort of Women," *Mayo Clinic Proceedings* 80, no. 7 (2005): 856–861, https://doi.org/10.4065/80.7.856.

35. W. H. Polonsky, R. Arora, M. Faurby, J. Fernandes, and A. Liebl, "Higher Rates of Persistence and Adherence in Patients With Type 2 Diabetes Initiating Once-Weekly vs Daily Injectable Glucagon-Like Peptide-1 Receptor Agonists in US Clinical Practice (STAY Study)," *Diabetes Therapy* 13, no. 1 (2022): 175–187, https://doi.org/10.1007/s13300-021-01189-6.

36. S. Suzuki, T. Oura, M. Takeuchi, and K. S. Boye, "Evaluation of the Impact of Once Weekly Dulaglutide on Patient-Reported Outcomes in Japanese Patients With Type 2 Diabetes: Comparisons With Liraglutide, Insulin Glargine, and Placebo in Two Randomized Studies," *Health and Quality of Life Outcomes [Electronic Resource]* 15, no. 1 (2017): 123, https://doi.org/10.1186/s12955-017-0696-7.

37. G. Cutter, A. Veneziano, A. Grinspan, et al., "Higher Satisfaction and Adherence With Glatiramer Acetate 40 mg/mL TIW vs 20 mg/mL QD in RRMS," *Multiple Sclerosis and Related Disorders* 33 (2019): 13–21, https://doi.org/10.1016/j.msard.2019.04.036.

38. G. Johannsson, U. Feldt-Rasmussen, I. H. Håkonsson, et al., "Safety and Convenience of Once-Weekly Somapacitan in Adult GH Deficiency: A 26-Week Randomized, Controlled Trial," *European Journal of Endocrinology* 178, no. 5 (2018): 491–499, https://doi.org/10.1530/eje-17-1073.

39. S. D. Saini, P. Schoenfeld, K. Kaulback, and M. C. Dubinsky, "Effect of Medication Dosing Frequency on Adherence in Chronic Diseases," *American Journal of Managed Care* 15, no. 6 (2009): e22–e33.

40. A. Iorio, S. Krishnan, K. J. Myrén, et al., "Continuous Prophylaxis With Recombinant Factor IX Fc Fusion Protein and Conventional Recombinant Factor IX Products: Comparisons of Efficacy and Weekly Factor Consumption," *Journal of Medical Economics* 20, no. 4 (2017): 337–344, https://doi.org/10.1080/13696998.2016.1265973.

41. A. Chhabra, D. Spurden, P. F. Fogarty, et al., "Real-World Outcomes Associated With Standard Half-Life and Extended Half-Life Factor Replacement Products for Treatment of Haemophilia A and B," *Blood Coagulation & Fibrinolysis* 31, no. 3 (2020): 186–192, https://doi.org/10.1097/mbc.0000000000000885.

42. D. Q. Tran Jr, M. M. Ullman, B. Riske, et al., "Adherence to Clotting Factor Treatment and Association With Bleeding and Health-Related Quality of Life in Persons With Hemophilia," *Blood* 142 (2023): 7334, https://doi.org/10.1182/blood-2023-187387.

43. J. F. Jin, L. L. Zhu, M. Chen, et al., "The Optimal Choice of Medication Administration Route Regarding Intravenous, Intramuscular, and Subcutaneous Injection," *Patient Prefer Adherence* 9 (2015): 923–942, https://doi.org/10.2147/ppa.S87271.

44. K. L. Stoner, H. Harder, L. J. Fallowfield, and V. A. Jenkins, "Intravenous versus Subcutaneous Drug Administration. Which Do Patients Prefer? A Systematic Review," *Patient* 8 (2014): 145–153, https://doi.org/10.1007/s40271-014-0075-y.

45. R. Khairnar, C. Meyer, R. Schuldt, et al., "Real-World Persistence With and Adherence to Emicizumab Prophylaxis in People With Hemophilia A – Results From Two Secondary Claims Database Analyses," *Haemophilia* 28, no. Suppl. 3 (2022): 70, https://doi.org/10.1111/hae.14537.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.