Clinical attributes and treatment characteristics are associated with work productivity and activity impairment in people with severe haemophilia A

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Funding information
BioMarin Pharmaceutical, Inc.

Abstract

Introduction: Few studies have examined the real-world impact of haemophilia on daily activities and work productivity in people with severe haemophilia A (PWSHA).

Aim: To determine clinical attributes and treatment characteristics associated with impairment in daily activities and work among PWSHA using the patient-reported Work Productivity and Activity Impairment-General Health Questionnaire (WPAI-GH).

Methods: PWSHA were asked to complete the WPAI-GH as part of the Cost of Haemophilia in Europe: A Socioeconomic Survey (CHESS) study. Outcomes were determined for activity impairment (AI), absenteeism, presenteeism and overall work productivity loss (WPL). Descriptive statistics and regression analyses were used to evaluate the association between these outcomes and clinical and treatment attributes.

Results: Overall, 376 participants completed the AI element of WPAI-GH; 175 were employed and thus also reported on work impact. Mean ± standard deviation scores were as follows: AI = 34.2% ± 25.8%; absenteeism = 0.06% ± 0.2%; presenteeism = 26.8% ± 22.4%; WPL = 28.6% ± 24.0%. Increased AI and WPL were associated with high haemophilia-related morbidity, measured both as chronic pain (p < .001 for both) and joint synovitis (AI: p < .001; WPL: p = .017). In descriptive and multivariate analyses, lifelong prophylaxis was associated with reduced AI (p < .001 and p = .031, respectively); high therapy adherence was associated with reduced AI (p = .001 and p = .012, respectively) and with reduced WPL (p < .001 and p = .012, respectively).

Conclusion: The WPAI-GH identified haemophilia-related morbidity and treatment characteristics, including therapy regimen and adherence, as key attributes impacting functional impairment and work contributions of PWSHA. Early prophylactic intervention and greater adherence to therapy may lead to lower AI and WPL in PWSHA.

KEYWORDS
absenteeism, activity impairment, haemophilia, presenteeism, quality of life, work productivity, WPAI
1 | INTRODUCTION

Approximately 1 in 5000 males globally are affected by haemophilia, and haemophilia A (HA) constitutes greater than 80% of these cases. The proportion of people with severe HA (PWSHA) constitutes 35%–60% of the HA population in developed countries. More so than for mild or moderate forms of haemophilia, severe haemophilia predisposes individuals to increased risks of both trauma-related and spontaneous bleeding into joints, muscles and internal organs, leading to long-term complications including haemarthropathy, deformity, reduced mobility, and chronic pain. The combined physical and psychosocial impacts of haemophilia impair health-related quality of life (QoL), negatively affecting daily activities and employment.

People with haemophilia report difficulty finding employment and coordinating the demands of work and treatment. In a 2018 analysis of the haemophilia-specific Patient Reported Outcomes, Burdens and Experiences (PROBE) Questionnaire, a significant proportion of respondents with severe haemophilia chose to work part-time and/or opted for early retirement for health-related reasons, compared with a control population without a bleeding disorder. A post hoc analysis of eight countries in the Hemophilia Experiences, Results and Opportunities (HERO) study found that people with haemophilia who experienced mobility limitations were less likely to be employed than those who did not. In addition, 64.7% of respondent PWSHA in PROBE and 86% in HERO reported a negative impact of haemophilia and associated pain on their activities of daily living (ADL). Treatment options for HA are rapidly evolving. Prophylactic administration of factor VIII (FVIII) replacement therapy is recommended by the World Federation of Hemophilia for PWSHA to manage bleeding and preserve musculoskeletal function. However, the QoL burden due to treatment-related and clinical factors remains high.

Gene therapy has the potential to significantly improve outcomes for PWSHA, and several investigational gene therapies are in clinical development. With the potential for additional reductions in bleeding episodes in sight, attention is focusing on areas of unmet need such as improved QoL and the potential for unrestricted participation in employment and leisure activities.

The patient-reported Work Productivity and Activity Impairment Questionnaire (WPAI) quantifies activity impairment (AI) and work productivity loss (WPL)—an amalgam of absenteeism and reduced productivity—caused by the respondent’s general health (WPAI-GH) or owing to a specific health problem. Few studies are published using the WPAI in people with haemophilia. A recent study of young adult PWSHA across Europe found high WPL even with lifelong prophylaxis. In a Dutch cohort of young adults with congenital coagulation disorders (CCDs), WPL was not statistically associated with clinical characteristics, physical functioning or illness cognitions (helplessness, acceptance); AI was not evaluated. Furthermore, the clinical and treatment management options influencing AI and WPL in haemophilia remain unclear.

The real-world study, Cost of Haemophilia in Europe: A Socioeconomic Survey (CHESS), assessed the economic and psychosocial burden of severe haemophilia. The present study evaluates the clinical attributes and treatment characteristics of WPL and AI, and the associated health status of CHESS participants with PWSHA who completed the WPAI-GH.

2 | MATERIALS AND METHODS

2.1 | Study population

The CHESS study was a cross-sectional, retrospective study of adult males (age ≥18 years) with severe HA or severe haemophilia B (<1 IU/dl FVIII or factor IX [FIX] levels) across France, Germany, Italy, Spain and the UK. Data were collected between December 2014 and April 2015 and captured a retrospective 12-month period.

2.2 | Procedure

This analysis was performed on the subset of CHESS participants with severe HA, who were recruited by haematologists. After obtaining informed consent, physicians completed a web-based patient record form (PRF) describing each participant’s medical history, consultations and sociodemographic status. Participants completed a corresponding paper-based patient self-completion (PSC) Questionnaire, which included the WPAI-GH and the EuroQoL EQ-5D-3L health status measure. For this analysis, PWSHA with active FVIII inhibitors at the time of the CHESS study were excluded. The CHESS dataset, including WPAI-GH, are held under license by the University of Chester.

2.3 | Measures

2.3.1 | Sociodemographic, clinical and treatment characteristics

The EQ-5D-3L captured participants’ health across the five dimensions of mobility, self-care, usual activities, anxiety/depression and pain/discomfort, with three levels per dimension (no problems, some problems, extreme problems). To assess and compare health status between groups of patients with different levels of AI and WPL, scores were converted into a single index score for each individual based on the UK-specific value set, resulting in a score range from −0.59 to 1. Values <0 represent a health state “worse than death”, and a value of 1 is equivalent to “perfect health”.

2.3.2 | Impairment

The WPAI-GH is a 6-item instrument that assesses impairment levels in the past 7 days and is scored on 4 metrics: absenteeism (proportion of work time missed because of one’s health), presenteeism...
(proportion of work time with impaired productivity due to one's health), overall WPL (overall impairment estimate that is a combination of absenteeism and presenteeism) and AI (proportion of impairment in daily activities because of one's health). All respondents are asked to complete question relating to AI; those in full- or part-time employment also complete the work-related sections. Impairment percentages are calculated based on responses provided on a 0–10 visual analogue scale and converted to a 0%–100% score; higher numbers indicate greater impairment.

### 2.4 Data analysis

To facilitate description of the cohorts, impairment was categorised into subgroups of <10%, 10%–40% and >40% impairment. Descriptive statistics included frequencies and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. For descriptive analyses, linear model analysis of variance (ANOVA) was used to determine statistical significance for continuous variables. To facilitate comparison of results with those from previous studies, characteristics of participants reporting <10% and >40% AI or WPL were compared using Pearson’s chi-squared test.

Univariate and multivariate regression analyses for AI and WPL cohorts were performed with continuous and categorical variables using ordinary least-squares regression (OLS) in R software (v3.6.1, GNU General Public License v3). Covariates significantly associated with impairment (p < .05) in the univariate model were selected for multivariate analyses of the relationship of clinical attributes and treatment characteristics with AI and overall WPL. Multicollinearity between covariates was assessed via Pearson’s correlation coefficient prior to inclusion in the regression model. The assumptions of normality from OLS were assessed through quantile-quantile plots and through inspection of the distribution of residuals.

### 3 RESULTS

#### 3.1 Demographics, clinical attributes, treatment characteristics and impairment

In the CHESS study, 139 haematologists provided demographic and clinical information on 1285 participants. Of these, 996 were PWSHA, of which 58 had FVIII inhibitors and were excluded from the current analysis. In the final analysis, there were 376 eligible respondents who completed the AI sections, of which 175 employed participants completed work-related sections (Table 1).

In the AI and WPL cohorts, most participants were between 18–45 years of age (75.3%, AI; 81.7%, WPL); mean age was approximately 37 years (Table 1). Annual bleed event frequency was between 2–5 for approximately 50% of both cohorts. The mean ± SD number of joints affected by chronic synovitis was similar between cohorts (1.5 ± 1.5 and 1.4 ± 1.3, respectively; Figure 1). Only a minority of

| Variable | Activity impairment (n = 376) | Work productivity loss (n = 175) |
|----------|-------------------------------|----------------------------------|
| Age      |                               |                                  |
| 18–30    | 153 (40.7)                    | 60 (34.3)                        |
| 31–45    | 130 (34.6)                    | 83 (47.4)                        |
| 46–60    | 61 (16.2)                     | 26 (14.9)                        |
| 60+      | 32 (8.5)                      | 6 (3.4)                          |
| Age, mean ± SD | 37.2 ± 14.7 | 36.8 ± 11.4                     |
| BMI, mean ± SD | 24.8 ± 3.3          | 24.8 ± 2.5                       |
| Education |                               |                                  |
| Primary or less | 70 (18.6) | 31 (17.7)                       |
| Secondary | 164 (43.6)                    | 72 (41.1)                        |
| Undergraduate | 97 (25.8)  | 49 (28.0)                       |
| Postgraduate | 45 (12.0)   | 23 (13.1)                       |
| Country of survey |               |                                  |
| France    | 125 (33.2)                    | 60 (34.3)                        |
| Germany   | 76 (20.2)                     | 47 (26.9)                        |
| Italy     | 83 (22.1)                     | 3 (18.9)                         |
| Spain     | 67 (17.8)                     | 23 (13.1)                        |
| UK        | 25 (6.6)                      | 12 (6.9)                         |
| Coinfection |                               |                                  |
| Yes       | 28 (7.4)                      | 12 (6.9)                         |
| No        | 348 (92.6)                    | 163 (93.1)                       |
| Anxiety/depression |               |                                  |
| Yes       | 96 (25.5)                     | 35 (20.0)                        |
| No        | 280 (74.5)                    | 140 (80.0)                       |
| Bleed frequency |               |                                  |
| 0–1       | 105 (27.9)                    | 40 (22.9)                        |
| 2–5       | 179 (47.6)                    | 90 (51.4)                        |
| 6+        | 92 (24.5)                     | 45 (25.7)                        |
| Bleed frequency, mean ± SD | 4.2 ± 4.5 | 4.4 ± 4.51                       |
| Number of joints with chronic synovitis, mean ± SD | 1.5 ± 1.5 | 1.4 ± 1.3                        |
| Therapy regimen |               |                                  |
| Lifelong prophylaxis | 55 (14.6) | 19 (10.9)                        |
| Other     | 321 (85.4)                    | 156 (89.1)                       |
| Presence of inhibitors |               |                                  |
| Never     | 331 (88.0)                    | 151 (86.3)                       |
| Previously | 45 (12.0)   | 24 (13.7)                        |
| Therapy adherence |               |                                  |
| Low/medium | 139 (37.0)  | 65 (35.4)                        |
| High      | 237 (63.0)                    | 113 (64.6)                       |
| Pain      |                               |                                  |
| None      | 101 (26.9)                    | 50 (28.6)                        |

(Continues)
Table 1 (Continued)

| Variable         | Activity impairment (n = 376) | Work productivity loss (n = 175) |
|------------------|-------------------------------|--------------------------------|
| Mild             | 155 (41.2)                    | 77 (44.0)                       |
| Moderate         | 105 (27.9)                    | 45 (25.7)                       |
| Severe           | 15 (4.0)                      | 3 (1.7)                         |

Activity impairment category

- <10%: 115 (30.6)
- 10%-40%: 132 (35.1)
- >40%: 129 (34.3)

Mean ± SD 34.2 ± 25.8

Work productivity loss category

- <10%: 64 (36.6)
- 10%-40%: 66 (37.7)
- >40%: 45 (25.7)

Mean ± SD 28.6 ± 24.0

Absenteeism, mean ± SD 0.06 ± 0.1

Presenteeism, mean ± SD 25.1 ± 21.4

EQ-5D-3L, mean ± SD 0.73 ± 0.26 0.78 ± 0.22

EQ-5D-3L by impairment category of AI and WPL, mean ± SD

| Impairment Category | AI | WPL |
|---------------------|----|-----|
| <10%                | 0.91 ± 0.12<sup>a</sup> | 0.90 ± 0.12<sup>b</sup> |
| 10%-40%             | 0.74 ± 0.16<sup>c</sup> | 0.77 ± 0.15<sup>d</sup> |
| >40%                | 0.57 ± 0.34<sup>e</sup> | 0.63 ± 0.30<sup>f</sup> |

Data are n (%) unless otherwise indicated.
AI, activity impairment; BMI, body mass index; EQ-5D-3L, European Quality of life form 5D-3L; SD, standard deviation; WPL, work productivity loss.
<sup>a</sup>Coinfections included hepatitis B/C or HIV/AIDS.
<sup>b</sup>EQ-5D-3L scores by category of activity impairment.
<sup>c</sup>EQ-5D-3L scores by category of work productivity loss.

3.2 | Descriptive analysis of clinical attributes and treatment characteristics affecting AI and WPL

There were differences in AI and WPL by the country of survey (Supplemental Table S1). Participants in Germany reported relatively lower levels of impairment, while participants in Italy had relatively higher levels. Compared with participants with <10% AI, a significantly higher proportion of participants with AI >40% were 31–45 years old, had annual bleed frequency of 2–5 events, >1 location affected by chronic synovitis, high hospitalisation rate and experienced moderate chronic pain (p < .001, all comparisons). This category also had the lowest proportions of participants reporting lifelong prophylaxis as therapy regimen and high therapy adherence (p < .001 and p = .001, respectively). Similar trends in clinical and treatment characteristics were observed in participants with WPL >40% vs those with WPL <10%.

3.3 | Regression analysis of clinical attributes and treatment characteristics affecting AI and WPL

Supplemental Table S2 summarises the univariate regression analysis; all variables except those demonstrating nonsignificant association with AI or WPL (education level, BMI, inhibitor history, and coinfection, p ≥ .05) were included in the multivariate regression. The multivariate regression demonstrated greater AI in participants ≥61 years than those aged 18–30 years (p = .004, Table 2). Participant cohorts with non-zero levels of physician-recorded pain had increased AI as compared to those with no pain (mild pain, p = .007; moderate and severe pain, p < .001 for both). Lifelong prophylaxis had a greater association with reduced AI than other therapy regimens (p = .031), and high adherence to therapy had a greater association with reduced AI than low/medium adherence to therapy (p = .012).

High therapy adherence had a greater association with reduced WPL than low/medium adherence (p = .012). The presence of severe pain (as compared to no pain) and >1 prior bleed-related hospitalisation (as compared to no hospitalisations) were associated with higher WPL (p = .012 and 0.002, respectively). Presence of anxiety/depression was not associated with worse AI or WPL (p = .286 and .278, respectively). Interestingly, this study did not associate worse AI or WPL with a higher number of chronic synovitis locations (Table 2). In both the AI and WPL cohorts, the degree of chronic pain increased with the number of chronic synovitis locations involved (Supplemental Figure S2).
4 | DISCUSSION

Clinical and treatment characteristics driving daily AI and WPL in PWSHA are largely unknown. In these analyses presented, lifelong prophylaxis and high therapy adherence were associated with less severe AI and WPL, while greater bleeding event frequency and pain were associated with worse AI and WPL. This is the first study to demonstrate the association of clinical and treatment characteristics in PWSHA with health-related absenteeism, presenteeism and daily AI using the WPAI.

These results suggest that prevention of early morbidity through high adherence to prophylactic replacement therapy may be the best approach to minimise AI and WPL. However, most participants with moderate to high levels of AI and WPL (>10%) reported high therapy adherence. This residual burden, despite treatment adherence, could reflect a treatment challenge and an unmet need for therapies that allow for long-term improvements in daily activities and productivity. This study is limited in temporal scope, such that high AI and WPL in participants with high reported therapy adherence at the time of study could be due to the presence of persistent clinical manifestations that arose during prior periods of lower adherence and/or reduced treatment availability. Further research is needed to determine drivers of adherence and therapy uptake among individuals at different life stages and the best methods for ensuring optimal therapy use.

The relationship between clinical manifestations of severe HA and WPL has not been clearly characterised. Recently, a study by Limperg et al. suggested that WPL was not associated with clinical factors in a small cohort of young adults with CCDs.25 Contrastings findings may be due to levels of specificity around the disease being studied (HA vs any CCD), severity (severe HA vs all severities of CCD) and mean age (37 vs 24 years).22 For example, young adults with CCDs experience reduced rates of missed working time and reduced rates of work impairment when compared to WPAI outcomes assessed in adults with other chronic diseases such as axial spondyloarthritis.22,25 Of note, the present study cohort may be more biased towards the inclusion of individuals experiencing greater morbidity, joint damage and/or requiring intensive management than the cohort in Limperg et al., as suggested by the low proportion of patients on lifelong prophylaxis and method of recruitment.
Table 2: Multivariate regression of sociodemographic as well as clinical and treatment characteristics for activity impairment and work productivity loss.

| Variable                  | Activity impairment (n = 376) | Work productivity loss (n = 175) |
|---------------------------|-------------------------------|---------------------------------|
|                           | Median           | 95% CI               | p value | Median       | 95% CI               | p value |
| Age                       |                  |                      |         |              |                      |         |
| 18–30                     | Ref              |                      |         |              |                      |         |
| 31–45                     | 3.40             | -2.47 to 9.27        | .255    | 2.79         | -5.32 to 10.90       | .498    |
| 46–60                     | 4.17             | -3.12 to 11.45       | .262    | -4.08        | -14.79 to 6.63       | .453    |
| ≥61                       | 12.80            | 4.07 to 21.53        | .004*   | 8.87         | -11.14 to 28.88      | .383    |
| BMI                       |                  |                      |         |              |                      |         |
| Normal                    | Ref              |                      |         |              |                      |         |
| Overweight                | -0.65            | -5.39 to 4.09        | .787    | -3.11        | -9.89 to 3.67        | .366    |
| Obese                     | -3.30            | -15.22 to 8.61       | .586    | -3.08        | -22.15 to 15.99      | .750    |
| Underweight               | 17.82            | -6.95 to 42.59       | .158    | -            | -                  | -       |
| Country of survey         |                  |                      |         |              |                      |         |
| France                    | Ref              |                      |         |              |                      |         |
| Germany                   | -10.26           | -17.10 to -3.43      | .003*   | -4.47        | -13.17 to 4.24       | .312    |
| Italy                     | 8.20             | 1.98 to 14.41        | .010*   | 7.76         | -2.05 to 17.56       | .120    |
| Spain                     | -4.56            | -11.21 to 2.09       | .178    | -3.52        | -14.07 to 7.03       | .511    |
| UK                        | 4.96             | -4.39 to 14.32       | .297    | 13.65        | 0.02 to 27.29        | .050    |
| Anxiety/depression        |                  |                      |         |              |                      |         |
| No                        | Ref              |                      |         |              |                      |         |
| Yes                       | 2.92             | -2.45 to 8.29        | .286    | 4.62         | -3.76 to 13.01       | .278    |
| Bleed frequency           |                  |                      |         |              |                      |         |
| 0–1                       | Ref              |                      |         |              |                      |         |
| 2–5                       | 5.46             | -0.34 to 11.27       | .065    |              |                      |         |
| 6+                        | 6.42             | -0.68 to 13.52       | .076    |              |                      |         |
| Locations of chronic synovitis |                  |                      |         |              |                      |         |
| 1–None                    | Ref              |                      |         |              |                      |         |
| 2–One                     | 0.53             | -5.61 to 6.68        | .864    | 2.58         | -6.35 to 11.51       | .570    |
| 3–2 or more               | -3.68            | -10.21 to 2.85       | .269    | 4.96         | -3.72 to 13.64       | .261    |
| Therapy regimen           |                  |                      |         |              |                      |         |
| Other                     | Ref              |                      |         |              |                      |         |
| Lifelong prophylaxis      | -8.09            | -15.42 to -0.75      | .031*   | -8.48        | -20.45 to 3.48       | .163    |
| Therapy adherence         |                  |                      |         |              |                      |         |
| Low/medium                | Ref              |                      |         |              |                      |         |
| High                      | -5.94            | -10.58 to -1.30      | .012*   | -9.04        | -16.06 to -2.01      | .012*   |
| Pain                      |                  |                      |         |              |                      |         |
| None                      | Ref              |                      |         |              |                      |         |
| Mild                      | 7.78             | 2.13 to 13.42        | .007*   | 4.65         | -3.39 to 12.69       | .255    |
| Moderate                  | 18.00            | 11.41 to 24.60       | <.001*  | 5.74         | -3.90 to 15.38       | .241    |
| Severe                    | 33.04            | 20.52 to 54.57       | <.001*  | 33.67        | 7.55 to 59.80        | .012*   |
| Hospitalisation           |                  |                      |         |              |                      |         |
| None                      | Ref              |                      |         |              |                      |         |
| More than one             | 3.02             | -2.14 to 8.18        | .251    | 12.12        | 4.69 to 19.55        | .002*   |

BMI, body mass index; CI, confidence interval; N/A, not applicable; Ref, statistical reference category.

*There were no participants in this category for work productivity loss.

bN/A represents variables that were not significant in the univariate analysis and were not included in multivariate regression.

*Indicates statistical significance.
reported here. Future studies on a broader cohort should involve qualitative assessments of how differing approaches to treatment and magnitude of joint disease can impact upon workplace impairment.

It is important to note that physician-reported chronic pain, as used in this analysis, may underestimate the pain experienced by PWSHA. A level of ‘disability paradox’ arising as a result of long-term adaptation to their state of health may cause individuals to lack any recognition of poor QoL or the ability to attribute poor QoL to the associated condition, thus complicating accurate assessments of pain. Regardless of the potential to underestimate pain, in this study, high reported levels of haemophilia-related chronic pain were associated with increased AI and WPL. These correlations are similar to those observed in other chronic diseases such as osteoarthritis.

The finding that higher AI is associated with increased absenteeism and presenteeism suggests that AI and WPL may be driven by common factors. Presenteeism among PWSHA in this study (25%; mean age 37 years) was comparable to that reported in participants with osteoarthritis (24.2%; mean age 59 years), rheumatoid arthritis (28.8%; mean age 43.7 years) and axial spondyloarthritis (24.9%; median age 36.7 years). This suggests that, similar to other conditions impacting joint function, haemophilia-related morbidity greatly affects work productivity. Further exploration of the contextual work-related factors in HA—such as job type, workplace dynamics, social service provision, geographical location and their role in QoL—is much needed.

This study would likely benefit from the removal of methodological limitations around recruitment, population size and participant recall. Participants were recruited for the original CHESS study through their haematologist; individuals who consult less frequently with their treating haematologist may be underrepresented in this cohort. The study missed the population of unemployed PWSHA and those unable to seek employment due to their symptoms, since only employed respondents complete work-related sections in the WPAI-GH. It is possible that the pain reported by patients who were able to complete the assessment may differ from those who were not and may not represent pain experienced by all PWSHA. Future studies should assess if there are systematic differences in the characteristics of participants that complete the WPAI vs those who are unable to complete it.

Other limitations for this study include the absence of clear definitions for chronic synovitis and adherence, which may result in the acquisition of less precise clinical data. Additionally, the potential for subgroup analyses in this study was limited by the size of the study cohort, despite being a relatively large study of PWSHA. Similarly, limited data and informal assessment methods may have contributed to the lack of statistically significant association between factors such as anxiety/depression and AI or WPL in the multivariate regression analysis. Finally, this study design relied on participants’ abilities to accurately recall and represent retrospective behaviours and experiences; it is therefore susceptible to recall bias.

While worse EQ-5D-3L responses were associated with increasing AI and WPL levels, no correlations were drawn between EQ-5D-3L dimensions and WPAI components due to the overlap of EQ-5D dimension attributes with clinical covariates. It is unclear whether WPAI-GH succeeds in capturing all HA-specific problems that affect QoL, particularly in individuals with multiple impacting comorbidities. Nevertheless, since comorbidities were not significant drivers of reported impairment in this cohort, participant responses to the WPAI-GH are presumed attributable to their HA.

Lastly, due to the cross-sectional nature of the CHESS dataset, the analysis presented here falls short of a full validation of the psychometric properties of the WPAI in PWSHA, which would require capture and collation of responses across multiple time points. With the growing inclusion of indirect health measures as endpoints in clinical trial programs, regulatory authorities and payers should ensure that such measures and any changes observed in their values are clinically meaningful to patients. A full validation of the WPAI measure would therefore be a valuable addition to the results presented here.

5 | CONCLUSION

This study demonstrates a direct relationship between clinical morbidity and the degree of activity impairment and work productivity loss in people with severe HA. These findings support the proposal that the WPAI-GH is an effective tool for capturing degrees of impairment associated with severe HA. Both AI and WPL are significantly interrelated with pain, therapy adherence and lifelong prophylaxis. Although further work will be required to fully validate the WPAI-GH, the findings herein successfully demonstrate that the clinical attributes of HA have measurable impacts on the functional impairment and work contributions of PWSHA. With novel and investigational therapies on the horizon, an optimised approach to management of haemophilia has the potential to eliminate much of the remaining clinical burden in severe HA; the resultant improvement in QoL will be reflected in greater participation, both in the workplace and in daily activities.

ACKNOWLEDGEMENTS

Medical writing support was provided by Kathleen Pieper, PhD; Puneet Dang, PhD; Atreju Lackey, PhD; and Caroline Agrawal Gamse, PhD, of AlphaBioCom, LLC, USA; and Steve Chaplin of HCD Economics, UK. This project was funded by BioMarin Pharmaceutical, Inc.

CONFLICT OF INTERESTS

JOH has no competing interests to declare. DN has no competing interests to declare. CC, SHL and CH are employees and shareholders of BioMarin Pharmaceutical, Inc. MJ is an employee of the sponsor BioMarin Pharmaceuticals and also holds stocks and shares in the company. TB and GP are employees of HCD Economics who have received funding from BioMarin for research carried out in this work.
AUTHOR CONTRIBUTIONS
MJ and JOH designed the research study. All authors contributed substantially to the acquisition, analysis or interpretation of the data. All authors drafted the manuscript or revised it critically for important intellectual content, approved the final version and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT
De-identified individual participant data underlying these results (including text, tables, figures, and appendices) will be made available together with the clinical protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via the Publication Data Request page at www.BioMarin.com beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Approximately 1 in 5000 males globally are affected by haemophilia, which is a genetic disorder characterized by a deficiency in clotting factors such as Factor VIII (FVIII) and Factor IX (FIX). This deficiency leads to spontaneous bleeding into joints, muscles, and internal organs, posing significant challenges for affected individuals. The treatment of haemophilia involves administering factor replacement therapy to prevent or control bleeding episodes. The long-term prophylactic administration of factor VIII (FVIII) replacement therapy is recommended to reduce the frequency of bleeding episodes, improving patient quality of life (QoL) and work productivity.

### INTRODUCTION

The patient-reported Work Productivity and Activity Impairment (WPAI) questionnaire is a validated tool used to quantify productivity loss and activity impairment caused by health issues in the past 7 days. It is scored on four metrics: absenteeism (proportion of work time missed because of one's health), presenteeism, reduced productivity, and reduced work efficiency. The WPAI is a widely used measure in economic evaluations, particularly in the context of hemophilia, to assess the impact of the disorder on patients' health-related quality of life (HRQoL), employment, and productivity.

### MATERIALS AND METHODS

#### Study population

Participants were included if they were aged 18 years or older, had a diagnosis of severe haemophilia A (HA) or severe haemophilia B, and had participated in the CHESS study. The CHESS (Cohort Study of Economic and Sociodemographic Survey) was a cross-sectional study that assessed the economic and psychosocial impacts of severe haemophilia. It was conducted in five European countries: France, Germany, Italy, Spain, and the UK. The study population was recruited from haemophilia centers, and patients were eligible if they had been diagnosed with severe HA or severe haemophilia B for at least 1 year and had undergone at least one bleeding episode in the past 12 months.

#### Measures

The EQ-5D-3L measure was used to assess patients' health across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This measure assigns a health status value ranging from −0.5 to 1.0, with 1.0 representing perfect health. The WPAI-GH was used to measure activity impairment caused by general health. The WPAI-GH was calculated by multiplying the proportion of work time missed by the average daily earnings for the period of absence. Presenteeism was measured using the WPAI-PES, which quantifies productivity loss due to reduced activity while at work.

### RESULTS

Analysis of the CHESS data revealed high WPAI scores, indicating significant work productivity loss and activity impairment caused by the general health of severe HA patients. The WPAI-GH scores were found to be significantly correlated with the EQ-5D-3L scores, highlighting the importance of assessing both health-related and productivity outcomes in economic evaluations of health care interventions for severe HA.

### CONCLUSION

The CHESS study demonstrated the substantial impact of severe HA on work productivity and activity impairment. Further research is needed to explore the long-term effects of prophylactic treatment on productivity outcomes and to develop strategies to optimize care delivery for severe HA patients, thereby improving their quality of life and work productivity.

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### SUPPORTING INFORMATION

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