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ORIGINAL ARTICLE

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Natural history study of factor IX deficiency with focus on treatment and complications (B-Natural)

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Abstract

Introduction: Haemophilia B (HB) is less well studied than haemophilia A (HA); despite similarities between the two inherited bleeding disorders, important differences remain that require further research.

Aim: B-Natural is a multi-centre, prospective, observational study of HB, designed to increase understanding of clinical manifestations, treatment, quality-of-life (QoL), inhibitor development, immune tolerance induction (ITI) outcome, renal function and create a biorepository for future investigations.

Methods: Participants include sibling pairs/groups without a current/history of inhibitors and singletons or siblings with a current/history of inhibitors followed for six months. Demographics, medical, social history and treatment were recorded. A physical examination including joint range of motion (ROM) was performed; QoL was assessed. Samples were collected for *F9* gene mutation, HLA typing, non-inhibitory antibodies and renal function testing.

Results: Twenty-four centres enrolled 224 individuals from 107 families including 29 with current/history of inhibitors. Of these, 68, 30.4%, had severe (<1% FIX level of normal); 114, 50.9%, moderate (1%-5%); and 42, 18.8%, mild (>5-<40%) disease. At enrolment, 53.1% had 50 + exposure days to exogenous FIX. Comparison of joint scores showed significant ($P < .05$) differences between those with severe (with/without inhibitors), and those with moderate/mild disease. The majority with severe disease, 80.0% with current/history of inhibitors and 64.3% of those without, were treated with prophylaxis.

Conclusion: B-Natural provides data supporting an increased understanding of HB and its impact throughout life. The need for optimal disease control to normalize physical and psychosocial outcomes is underscored, and further analyses will contribute to an increased understanding of critical issues in HB.

KEYWORDS
factor IX deficiency, FIX inhibitors, haemophilia B, joint range-of-motion, quality-of-life, treatment

1 | INTRODUCTION

Haemophilia B (HB), factor IX (FIX) deficiency, is the second most common type of haemophilia, occurring in about one in 25 000 male births. This disease is less well studied than haemophilia A (HA). While there are several similarities between the two, including types of bleeding events—primarily haemarthroses—and inhibitor development, there are important differences as well. These include the frequency of occurrence, variation in the distribution of severities,[1-3] predominance of types of gene mutations, factors associated with inhibitor development, ability to achieve tolerance with immune tolerance induction (ITI) and risk of ITI-associated sequelae.

While the incidence of inhibitors among those with severe HA is approximately 25%-30%, it is closer to 5% in severe HB[4-6] and up to 10% in one recent study.[7] While incidence is lower, inhibitors are associated with increased frequency of anaphylactoid reactions [8,9] and, based upon small series, less successful outcome of ITI.[9]

Major bleeding sites in both HA and HB include joints and muscles, haematuria, mucocutaneous bleeding and intracranial haemorrhage. There are no consistent data to support a difference in the bleeding phenotype of patients with HA and HB.

The Factor IX Treatment Network was formed to investigate the treatment, outcomes, and complications of HB and provide an improved understanding of the disease.[10] To shed more light on the clinical manifestations of HB, the Network initiated the B-Natural study, in which two groups of subjects with FIX deficiency are examined—those with a current or history of inhibitors to FIX, and groups of two or more affected siblings, with or without inhibitors. Enrolment of siblings permits within-family examination of clinical outcomes to document the degree of concordance with minimized variation of relevant genetic factors. The primary objective was to characterize the study group in terms of medical history, patterns of bleeding, care, quality of life (QoL) and complications including the development of inhibitory antibodies to FIX, allergy, renal and joint disease. The current manuscript addresses the design and methods

of B-Natural and provides a description of the participants and an overview of their treatment, joint status and QoL.

2 | METHODS

2.1 | Design and eligibility

B-Natural is a multi-centre, prospective, observational study. Subjects were eligible to participate if they had FIX deficiency and were part of an affected sibling pair/group; and/or had a current or history of inhibitor, defined as > 0.6 Bethesda units (BU). Participants were followed for six months with in-person visits at enrolment and study termination. Tests to determine eligibility (inhibitor, clotting factor level) were performed in the local laboratories. Blood and urine samples were collected for central laboratory typing of *F9* gene mutation (if not already determined) and HLA, non-inhibitory antibody and renal function testing, and repository storage for future haemophilia-related studies.

2.2 | Clinical and demographic characteristics

Demographics, including date of birth, race/ethnicity, a medical and social history, and a haemophilia-related history were obtained. In addition to severity of FIX deficiency (mild = >5% - <40%; moderate = 1-5; severe = <1% FIX level of normal), factors related to early treatment and product use were recorded. If the participant had a history of an inhibitor, information including characteristics of the inhibitor was collected. Data were collected to describe the use of ITI and overall success. A brief physical examination was performed including weight and height, from which body mass index (BMI) was calculated (kg/m^2).

2.3 | Joint assessment

Range-of-motion (ROM) for elbows, knees, and ankles was assessed by qualified staff trained in joint measurement. A four-point scale was used: 0 = No loss of total full range of motion (FROM); 1 = Loss of < 10% of total FROM; 2 = Loss of 10-33⅓% of total FROM; 3 = Loss of > 33⅓% of total FROM. This method was chosen primarily for feasibility and the belief that each centre would be able to reliably provide the measurements. A composite score was calculated by summing the FROM scores for each joint, ranging from 0, no loss of FROM in any joint evaluated, to 18, loss of > 33⅓ in all joints.

2.4 | Health-related quality of life

The EQ-5D instruments[11] were used to measure health-related QoL at study entry. The EQ-5D-5L *Self-given* health questionnaire was used for participants 16 + years of age, the EQ-5D-5L *Proxy* version was completed by a caregiver for those 4-8 years, and the EQ-5D-Y *Youth* version for those 8-16 years of age.

2.5 | Statistical methods

All statistical analyses were performed in the R language.[12] Descriptive statistics including means (standard deviations) and medians [25th percentile, 75th percentile] were used. Relationships between continuous variables were examined with linear regression and Pearson correlation coefficients.

The procedures followed were approved by the ethical committees in each participating centre. B-Natural is registered at ClinicalTrials.gov (NCT02502409).

3 | RESULTS

3.1 | Clinical and demographic characteristics

Twenty-four centres participated, 16 in North America, seven in Europe and one in Asia. From the population under care at participating centres, a total of 392 potential subjects were identified. Two hundred and twenty-four individuals ranging in age from 1 to 73 from 107 families were enrolled between January 2016 and February 2018:167 (74.6%), median age 12.8, in North America; 38 (17.0%), median age 18.4, in Europe; and 19 (8.5%), median age 13.7, in Asia. Data collection covered the period January 2015 through November 2018. The mean centre enrolment rate was 78.8%, the median 53.2% [25th, 75th percentiles: 40.0%, 83.6%]. Figure 1 and Table 1 show the distribution and characteristics of families and participants across severity and inhibitor status. Of the 224 individuals enrolled, 68 (30.4%) had severe FIX deficiency, 114 (50.9%) moderate and 42 (18.8%) mild. Twenty-nine had a current or history of an inhibitor. Twenty-one families contained members with mixed severities: severe and moderate (N = 4 families), and moderate and mild (N = 17 families). Three families contained siblings discordant for inhibitor status. By the time of the first visit, 53.1% of participants had 50 + exposure days to FIX replacement therapy, 93.1% of those with inhibitors and 47.2% of those without.

All subjects with inhibitors had severe disease. Of the 29, 13 had peak titres ≤ 5 Bethesda Units (BU), 13 had peak titres > 5 BU, and for three the peak titre was unknown. Twenty-two underwent one or more courses of ITI. Eleven of these were deemed successfully tolerized by the investigator at the conclusion of B-Natural follow-up.

3.2 | Haemophilia treatment in the year prior to enrolment

Of the 224 subjects enrolled, 196 (87.5%) were able to report the treatment burden defined by the estimated number of infusions of

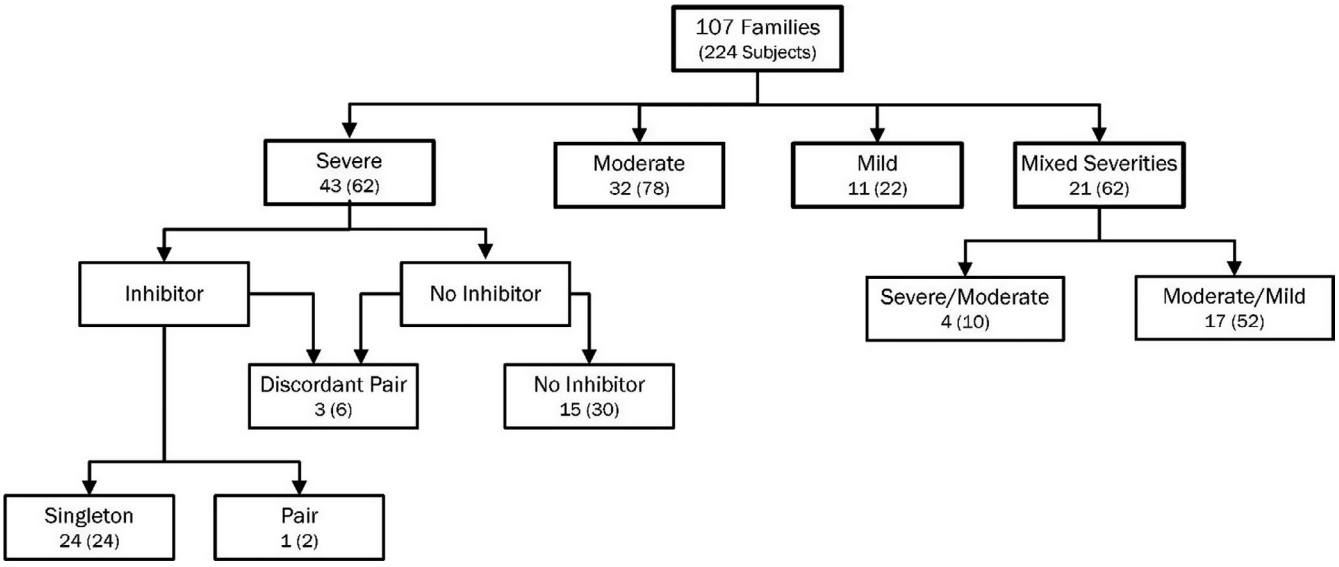

FIGURE 1 Distribution of families and individual participants across severity of factor IX deficiency. The number of families in each category is shown with the number of individuals in each group in parentheses

TABLE 1 Characteristics of study participants by severity group[a]

	Inhibitor	No Inhibitor			
	N = 29	Severe (<1%) N = 39	Moderate (1%-5%) N = 114	Mild (>5%) N = 42	N
Age	16.5 [8.08; 31.9]	15.4 [11.0; 32.3]	13.3 [8.58;20.3]	12.1 [7.65; 20.8]	224
	23.3 (20.5)	22.6 (16.9)	16.9 (12.5)	17.1 (14.1)	224
Age group:					224
<6	5 (17.2%)	3 (7.69%)	14 (12.3%)	7 (16.7%)	
6-17	10 (34.5%)	19 (48.7%)	63 (55.3%)	23 (54.8%)	
18-49	11 (37.9%)	13 (33.3%)	34 (29.8%)	11 (26.2%)	
50+	3 (10.3%)	4 (10.3%)	3 (2.63%)	1 (2.38%)	
Gender:					224
Female	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (9.52%)	
Male	29 (100%)	39 (100%)	114 (100%)	38 (90.5%)	
Ethnicity:					224
Asian	0 (0.00%)	7 (17.9%)	13 (11.4%)	0 (0.00%)	
Black	5 (17.2%)	8 (20.5%)	2 (1.75%)	0 (0.00%)	
Hispanic	1 (3.45%)	0 (0.00%)	2 (1.75%)	2 (4.76%)	
White	22 (75.9%)	24 (61.5%)	96 (84.2%)	40 (95.2%)	
Other	1 (3.45%)	0 (0.00%)	1 (0.88%)	0 (0.00%)	
BMI (kg/m^2)	21.9 [17.8;25.6]	19.9 [16.6;27.9]	20.0 [16.0;23.6]	20.4 [16.5;25.4]	223
	23.7 (7.85)	22.4 (7.60)	20.8 (5.97)	21.4 (6.18)	223

[a]Continuous variable statistics are displayed as: median [25th percentile, 75th percentile] and mean (standard deviation) in two separate rows. Categorical variable statistics are displayed as frequency counts (per cents).

replacement products or bypassing agents used in the prior year. Forty-nine (25%) reported no infusions. The mean and median numbers of infusions by inhibitor status and severity are shown in Table 2.

The majority of subjects with severe FIX deficiency, 80.0% among those with a current or history of inhibitors and 64.3% of those without, were treated with prophylaxis (Table 3). Excluding one centre with a lower level of resourcing, the proportion among those without inhibitors increased to 75.0% (data not shown). The types of replacement product(s) used are shown in Table 4. Type of product(s) varied by region and subjects might have been exposed to more than one type of product or received no infusions during

TABLE 2 Estimated number of infusions of replacement products or bypassing agents in the year prior to enrolment[a]

	Inhibitor	No Inhibitor			
	N = 25	Severe (<1%) N = 28	Moderate (1%-5%) N = 104	Mild (>5%) N = 39	N
No. infusions	180 [115;200]	51.0 [19.5;104]	3.00 [0.00;11.0]	1.00 [0.00;3.00]	196
	184 (145)	57.0 (45.3)	12.3 (24.8)	4.54 (9.58)	196

[a]Continuous variable statistics are displayed as: median [25th percentile, 75th percentile] and mean (standard deviation) in two separate rows.

TABLE 3 Treatment in the year prior to enrolment among subjects with non-missing number of infusions[a]

	Inhibitor	No inhibitor			N
	N = 25	Severe (<1%) N = 28	Moderate (1%-5%) N = 104	Mild (>5%) N = 39	196
Treatment:					
On-demand	5 (20.0%)	10 (35.7%)	95 (91.3%)	39 (100.0%)	
Prophylaxis	20 (80.0%)	18 (64.3%)	9 (8.7%)	0 (0.0%)	

[a]Categorical variable statistics are displayed as frequency counts (per cents).

TABLE 4 Type of treatment in year prior to enrolment[a]

	Inhibitor	No inhibitor			N
	N = 25	Severe (<1%) N = 28	Moderate (1%-5%) N = 104	Mild (>5%) N = 39	196
1. Plasma/prothrombin complex concentrates/whole blood	0 (0.00%)	4 (14.3%)	7 (6.73%)	0 (0.00%)	
2. Plasma derived: non-monoclonal antibody purified	2 (8.00%)	3 (10.7%)	2 (1.92%)	0 (0.00%)	
3. Plasma derived: monoclonal antibody purified	5 (20.0%)	1 (3.57%)	1 (0.96%)	0 (0.00%)	
4. Recombinant: standard half-life molecule	14 (56.0%)	13 (46.4%)	63 (60.6%)	19 (48.7%)	
5. Recombinant: extended half-life molecule	1 (4.00%)	10 (35.7%)	8 (7.69%)	2 (5.13%)	
6. Other[b]	5 (20.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	

[a]Subjects with non-missing estimated number of infusions in the year prior to enrolment. Categorical variable statistics are displayed as frequency counts (per cents). Subjects may have received more than one type of product in the year prior to enrolment or received no infusions during the period.

[b]rFVIIa and FEIBA

the period. In the North American centres, recombinant standard half-life products were used by 63.2% of subjects, recombinant extended half-life products by 9.7%, plasma-derived monoclonal purified products by 2.6%, non-monoclonal purified products by 0.6% and bypassing agents by 2.6%. In European centres, the percentages were 36.7%, 20.0%, 10.0%, 20.0% and 3.3%, respectively. The difference in type of product used (plasma derived vs. recombinant) between North America and Europe is largely explained by participant age. Use of recombinant products was significantly related to younger age in both geographic areas and subjects enrolled in North America were significantly younger than those in Europe. In the Asian centre, plasma/prothrombin complex concentrates and whole blood were used exclusively.

3.3 | Joint assessment

Table 5 presents the distribution of FROM of each joint and a composite score. In Figure 2, a comparison of the linear regression slopes of FROM composite score over age shows significant ($P < .05$) differences between the groups with severe deficiency (with or without inhibitor) and those with moderate or mild disease.

3.4 | Quality-of-life

Figure 3 combines data from the three versions of the EQ-5D instrument to show the proportions of individuals reporting problems in each of the dimensions by severity group. Fifteen participants were too young (<4 years of age) to have been assessed.

3.5 | Early treatment

Participants with severe haemophilia (with or without inhibitors) were more likely to begin treatment within the first year of life, whereas onset of treatment for those with moderate or mild disease most commonly occurred between one and five years of age. Across

TABLE 5 Joint assessment: loss of total free range of motion (FROM)[a]

	Inhibitor	No Inhibitor			
	N = 29	Severe (<1%) N = 39	Moderate (1%-5%) N = 114	Mild (>5%) N = 42	N
Left ankle					224
No loss	15 (51.7%)	26 (66.7%)	90 (78.9%)	40 (95.2%)	
Loss of < 10%	3 (10.3%)	5 (12.8%)	9 (7.89%)	1 (2.38%)	
Loss of 10%-33.3%	2 (6.90%)	2 (5.13%)	13 (11.4%)	0 (0.00%)	
Loss of > 33.3	7 (24.1%)	6 (15.4%)	1 (0.88%)	0 (0.00%)	
Not assessed	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Right ankle					224
No loss	13 (44.8%)	26 (66.7%)	87 (76.3%)	40 (95.2%)	
Loss of < 10%	1 (3.45%)	2 (5.13%)	11 (9.65%)	1 (2.38%)	
Loss of 10%-33.3%	5 (17.2%)	6 (15.4%)	13 (11.4%)	0 (0.00%)	
Loss of > 33.3%	7 (24.1%)	5 (12.8%)	1 (0.88%)	0 (0.00%)	
Not assessed	2 (6.90%)	0 (0.00%)	1 (0.88%)	0 (0.00%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Left knee					224
No loss	17 (58.6%)	29 (74.4%)	99 (86.8%)	39 (92.9%)	
Loss of < 10%	0 (0.00%)	0 (0.00%)	7 (6.14%)	2 (4.76%)	
Loss of 10%-33.3%	4 (13.8%)	6 (15.4%)	6 (5.26%)	0 (0.00%)	
Loss of > 33.3%	6 (20.7%)	4 (10.3%)	1 (0.88%)	0 (0.00%)	
Not assessed	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Right knee					224
No loss	14 (48.3%)	26 (66.7%)	100 (87.7%)	38 (90.5%)	
Loss of < 10%	3 (10.3%)	0 (0.00%)	6 (5.26%)	2 (4.76%)	
Loss of 10%-33.3%	2 (6.90%)	6 (15.4%)	6 (5.26%)	0 (0.00%)	
Loss of > 33.3%	7 (24.1%)	7 (17.9%)	1 (0.88%)	0 (0.00%)	
Not assessed	2 (6.90%)	0 (0.00%)	0 (0.00%)	1 (2.38%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Left elbow					224
No loss	13 (44.8%)	31 (79.5%)	95 (83.3%)	41 (97.6%)	
Loss of < 10%	2 (6.90%)	2 (5.13%)	14 (12.3%)	0 (0.00%)	
Loss of 10%-33.3%	8 (27.6%)	5 (12.8%)	4 (3.51%)	0 (0.00%)	
Loss of > 33.3%	4 (13.8%)	1 (2.56%)	0 (0.00%)	0 (0.00%)	
Not assessed	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Right elbow					224
No loss	16 (55.2%)	31 (79.5%)	96 (84.2%)	40 (95.2%)	
Loss of < 10%	3 (10.3%)	2 (5.13%)	14 (12.3%)	0 (0.00%)	
Loss of 10%-33.3%	1 (3.45%)	3 (7.69%)	1 (0.88%)	1 (2.38%)	
Loss of > 33.3%	7 (24.1%)	3 (7.69%)	1 (0.88%)	0 (0.00%)	
Not assessed	1 (3.45%)	0 (0.00%)	1 (0.88%)	0 (0.00%)	
'Missing'	1 (3.45%)	0 (0.00%)	1 (0.88%)	1 (2.38%)	
Range of motion: composite score[b]	3.00 [0.00;12.0]	0.00 [0.00;5.00]	0.00 [0.00;2.00]	0.00 [0.00;0.00]	216
	6.35 (7.01)	3.72 (5.37)	1.46 (2.46)	0.20 (0.88)	216

[a]Continuous variable statistics are displayed as: median [25th percentile, 75th percentile] and mean (standard deviation) in two separate rows. Categorical variable statistics are displayed as frequency counts (per cents).

[b]Composite scores include subjects with non-missing data for all joints.

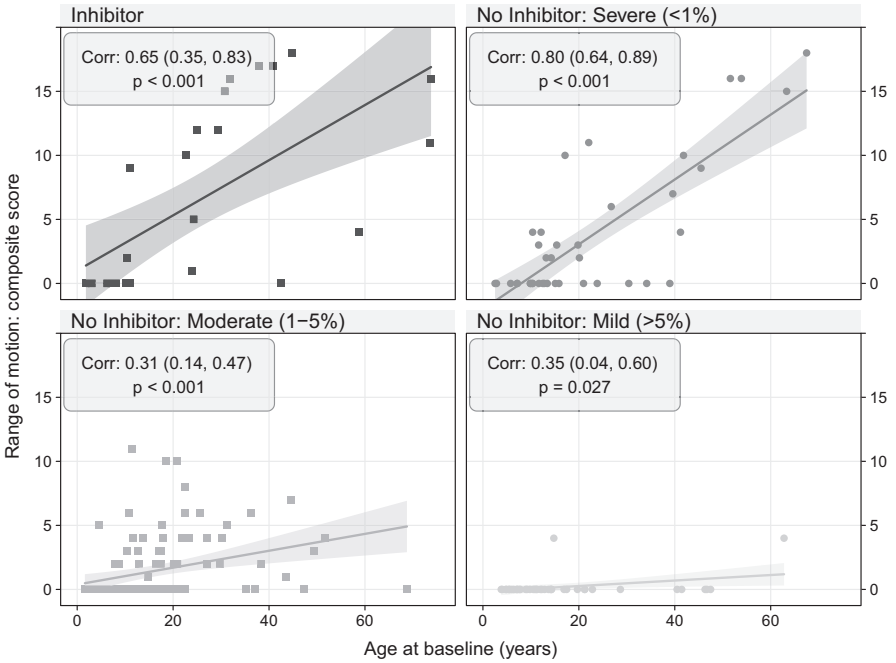

FIGURE 2 Joint composite score by haemophilia severity and inhibitor group. A panel for each of the groups of interest shows the linear regression line and confidence interval or range of motion composite score by age at baseline. In each panel, the Pearson correlation coefficient, an indicator of the strength of the linear association, its 95% confidence interval and *p*-values are shown

all severity groups, a bleeding episode was the most common reason for the first exposure (72.8%). The presence of illness or infection at first exposure was infrequent (5.4%).

Prior to inhibitor development or in the first 50 exposure days, greater than 50% of all groups received on-demand treatment—those with severe disease were somewhat more likely to be treated with prophylaxis, alone or in combination with on-demand, 34.5% (participants with inhibitors) and 48.7% (without inhibitors). Type of product varied by geographic location. In the United States, recombinant standard half-life products were used by 85.6% of subjects. In Europe, the most commonly used concentrates were plasma-derived non-monoclonal (42.1%) and recombinant standard half-life products (39.5%). In Asia, plasma/prothrombin complex concentrates and whole blood were used exclusively.

4 | DISCUSSION

The B-Natural study was designed to obtain an in-depth description of contemporary aspects of HB, including contributing factors to inhibitor development, ITI use and outcome and associated sequelae. The study groups of most investigations related to haemophilia natural history and outcomes include a majority of individuals with HA, and hence, our understanding of the similarities and differences in HB has lagged. Some studies, but not all, indicate a milder bleeding phenotype in HB compared to HA with a less severe HB phenotype for each level of severity measured by number of reported bleeding episodes, limitations in joint ROM, hospitalizations and orthopaedic interventions.[13-19] Both genetic and molecular mechanisms have been implicated as causative factors for this potential difference in clinical/phenotypic manifestations, but the findings have not been consistent and require further evaluation.[16]

The B-Natural study included 24 centres representing the United States, EU and one in Asia, with 224 individuals from 107 families and collected medical history, bleeding patterns, QoL and complications. B-Natural participants closely mirror the distribution of severity reported in HB, but the number/percentage of moderately deficient patients was enriched as the two US centres with the highest enrolment have large populations of Old Order Amish with HB (data not shown). These individuals have a unifying founder mutation (*F9* c.1025C > T [p.Thr342Met]) that predicts moderate factor IX deficiency. The enrichment of these patients provides an opportunity to improve the breadth of analysis in this category. Further, inclusion of siblings permits a comparison of phenotypic expression of disease within families, contributing more information. Interestingly, 21 families contained members with differing severities of HB. The reason for this is not clear, but may be due, in part, to assay discordance, which has been observed in individuals with the same mutation. The *F9* c.1025C > T mutation has been reported 128 times in the European Association for Haemophilia and Allied Disorders (EAHAD) Coagulation Factor Databases, www.dbs.eahad.org, with levels ranging from < 1% to 16%.[18,20] This also occurs in HA, where, for example, the *F8* c.2167G > A (p.Ala723Thr) mutation, reported 144 times in the EAHAD variant database, has levels ranging from < 1 to 20%. In addition, there is known variability in assay sensitivity across laboratories, when results are performed in separate runs, based upon the source of substrate, as well as a variety of pre-analytic variables.

Individuals with a current or history of inhibitors, 29 of 224 participants (12.9%), all with severe FIX deficiency, were purposely

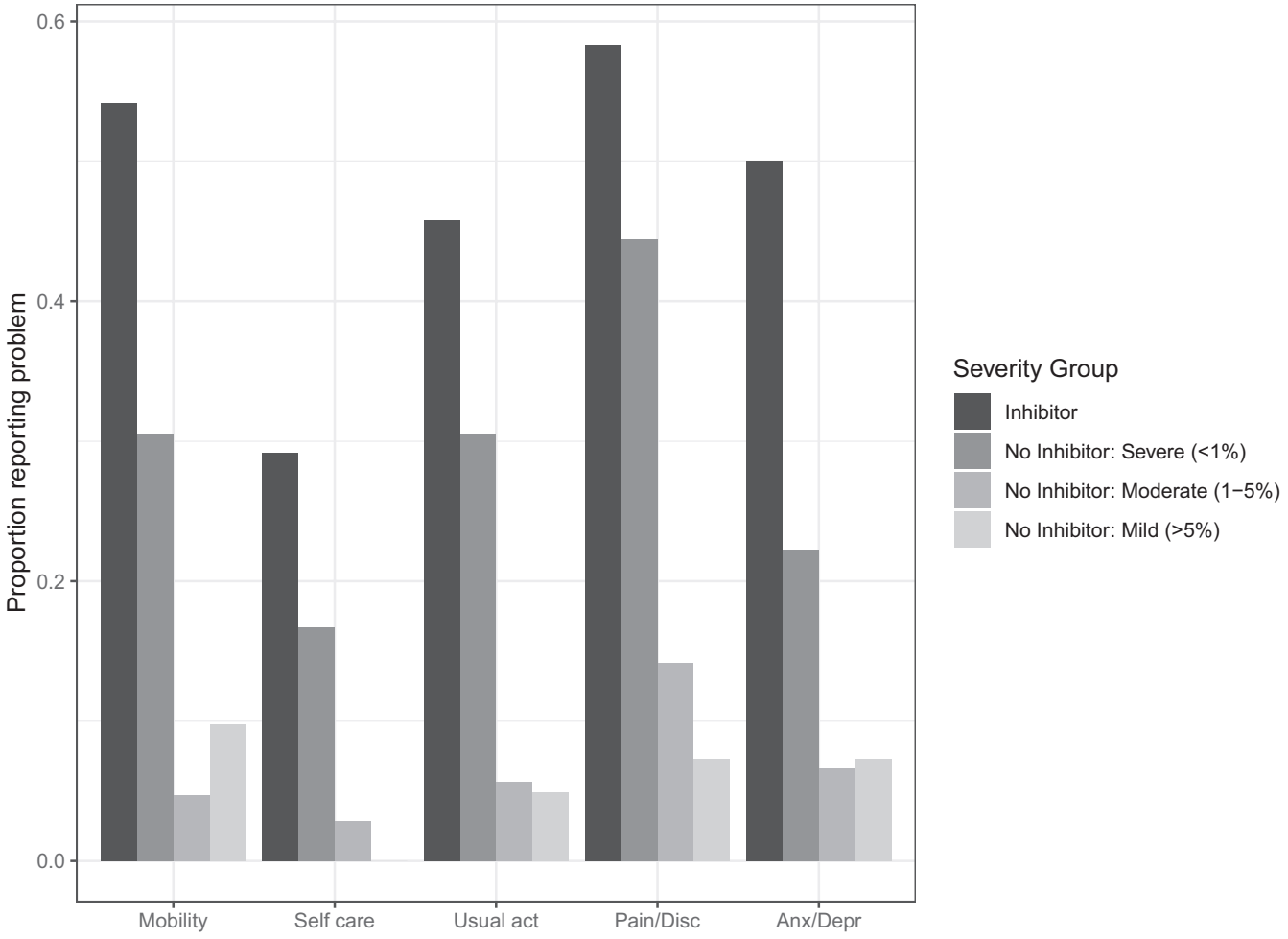

FIGURE 3 Proportion of subjects reporting problems in EQ-5D subscales by haemophilia severity and inhibitor status group

enriched in this study, allowing evaluation of contributors to this complication associated with unique manifestations and outcomes compared to HA. The cohort with inhibitors is relatively small; a complete description and analysis of this group will be reported separately.

The participants in B-Natural spanned a wide age range (median 13.6 years, range 1-73 years) and included 144 (64.3%) participants < 18 years of age. Importantly, at the time of enrolment, 53.1% of the participants had achieved 50 + exposure days overall, most commonly in the severe deficient patients > 6 years of age. Taken together, the data collected in B-Natural provide a comprehensive overview of HB as they span a wide age range, represent all levels of deficiency and racial/ethnic diversity from centres from across the United States, EU and parts of Asia.

Factors impacting the number of infusions administered in the year prior to enrolment (Table 2) include presence or history of an inhibitor and level of severity with a median/mean higher in the severe group followed by the moderate and then mild categories, as expected and similar to those for HA. However, the number of infusions is, overall, less compared to that expected in HA with severe disease without an inhibitor.[21] This may be multifactorial, impacted by the per cent of the population treated with prophylaxis (64.3%) and the longer half-life of FIX concentrates, both standard and extended half-life, as compared to HA. Together, these result in a need for fewer infusions for bleeding resolution in FIX deficiency compared to FVIII, as well as fewer bleeding events experienced. Prior to inhibitor development or in the first 50 exposure days, 34.5% of participants with inhibitors and 48.7% of those with severe deficiency, but without inhibitors, were treated with prophylaxis. Given published guidelines for severe haemophilia, it appears that the standard of instituting prophylaxis, either primary (before the age of three and before the first or second large joint bleed) or secondary (after two or more large joint bleeds but before the onset of chronic arthropathy)[22] has not been uniformly applied to children with severe HB.

The comparison of the linear regression slopes of the joint composite score indicates significant ($P < .5$) differences between the group with severe deficiency and those with moderate or mild disease over time. These data support the occurrence of cumulative damage due to haemarthroses—clinical or subclinical. The smaller per cent treated with prophylaxis in severe disease may result from the perception that it may not be required in HB due to the decreased number of bleeding episodes experienced,[16,18,19] that prophylaxis, when applied, is either provided after damage has occurred or is insufficient to adequately suppress all bleeding episodes, or

that local health economies prohibit prophylaxis. It is documented that prophylaxis is less utilized in under- or poorly resourced health economies yet the vast majority of centres participating in B-Natural represent well-supported facilities where prophylaxis is widely available; prophylaxis in patients with severe deficiency and without inhibitors was provided in 64.3% overall, and 75.0% when one centre with a lower level of resourcing was excluded.

Soucie, et al, 2004,[16] reported the predicted percentage of range of motion limitation over time and included subjects with FVIII and IX deficiency in the analysis [16]; overall, fewer bleeding episodes were reported and less ROM limitation was observed in persons with HB compared to HA.[16] Taken together, the B-Natural and other studies demonstrate that arthropathy will occur over time in severe HB even in the presence of fewer bleeding episodes per year compared to HA. Although more costly, prophylaxis has been proven to protect joints and prevent arthropathy in HA[23]; its more uniform application in severe HB is warranted and should be considered in all patients.

B-Natural utilized the EQ-5D instruments as a measure of health-related QoL.[11] Subjects with severe haemophilia, both with and without an inhibitor, had poorer outcomes for mobility, self-care, usual activity and pain/discomfort compared to those with moderate or mild disease. Those with inhibitors reported a higher level of anxiety/depression than the other groups, emphasizing the importance of optimizing the prevention and management of this complication.

B-Natural QoL data reveal the significant impact of HB on the affected population and underscore the need for optimal disease control to normalize physical and psychosocial outcomes.

This study has limitations. The degree to which subjects are representative of patients cared for at participating sites is not known, although a majority of those identified as eligible were enrolled and, for example, we observed an enrichment of subjects with moderate HB as a result of centre bias. Classification of severity was performed at the local centre, not centralized, which may jeopardize accuracy. Further, a substantial portion of data collection was retrospective and comparison with aspects of HA is based on literature and not on controls matched for age, severity and geographic distribution. Given the aims of the B-Natural study, however, these limitations will not likely jeopardize future studies in a substantive way.

Ultimately, as haemophilia is costly to treat, if health resource funding is utilized and less than desired outcomes achieved, treatment regimens must be re-evaluated. There are clear similarities in the expression of both HA and HB including the types of bleeding events experienced. Due to the similarities and rarity of these bleeding disorders, they have, however, often been grouped together in studies that evaluate impact and outcomes.

As early as 1959, it was suggested by Quick[24] that individuals with HB may bleed less frequently than those with HA. In the final analysis, however, the frequency of bleeding between these two forms of haemophilia may be less important than the resultant physical and psychosocial implications of bleeding. As an understanding of the need for a higher residual level of FVIII than originally proposed to suppress risk of bleeding in HA has emerged,[25] we may need to re-evaluate HB in light of not just the frequency of bleeding but the sequelae of these events that accumulate over time. B-Natural provides important data to support an increased understanding of the natural history of HB and its impact throughout life.

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AUTHOR CONTRIBUTIONS

JA, EB and ADS conceptualized and designed the study, acquired, analysed and interpreted the data, drafted and finalized the manuscript. MVR, MB, YLA, MDT, KH, SC, RL, CT, MC, CM, EF, CLK, CB, AC, JO, SK, CK, PK, SA, UMR, RK and MW acquired the data, reviewed and participated in the critical review and final approval of the version to be submitted. SL designed the study and participated in critical review and final approval. SD and PL analysed and interpreted the data, drafted and finalized the manuscript.

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