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ORIGINAL ARTICLE *Inhibitors*

Health-related quality of life in haemophilia patients with inhibitors and their caregivers

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Summary. Data on the health-related quality of life (HRQoL) of congenital haemophilia patients with inhibitors (CHwI) and their caregivers are limited. To understand the association between patient demographics/clinical characteristics with HRQoL among CHwI patients and caregivers, a survey was developed to assess HRQoL with haemophilia-specific QoL questionnaires (HAEMO-QoL/HAEM-A-QoL). In the cross-sectional study, paper-pencil questionnaires were mailed to 261 US CHwI patients/caregivers in July 2010. Descriptive analyses were performed to characterize HRQoL by age and to identify drivers of impairment, from both patient/caregiver perspectives. HRQoL scores were transformed on a scale of 0–100, with higher scores indicating higher impairment in HRQoL. Ninety-seven respondents completed the HRQoL assessment. HRQoL impairment was higher in adult patients. In children ages 8–16 years, mean HAEMO-QoL total score was 33.8 (SD = 15.5), and 35.0 (SD = 16.1) in children ages 4–7 years; for adult patients the mean HAEM-A-QoL total score was 42.2 (SD = 14.8). Adults reported highest impairment in the 'sports/leisure' subscale (Mean = 62.5, SD = 18.7), whereas patients 8–16 years reported highest impairment in the 'physical health' subscale (Mean = 50.8, SD = 30.5).Caregivers of patients ages 4–7 years reported greatest impairment within the 'family' subscale (Mean = 55.6, SD = 19.4). Caregivers were "considerably/very much" bothered by their child's inhibitors and reported higher QoL impairment for their child than parents who were not bothered. Within ChwI patients, HRQoL impairments increased with age and existed across a range of physical/psychosocial domains. In addition, caregiver burden also affected the perceived HRQoL of paediatric CHwI patients. Additional research is considered necessary to further understand the support caregivers need while caring for children with CHwI.

Keywords: caregivers, haemophilia, HAEMO-QoL, inhibitors, quality of life

Introduction

Congenital haemophilia is a chronic, X-linked recessive bleeding disorder which impairs coagulation. The disorder is rare, affecting between approximately 1 in 5000–10 000 males born in the United States [1]. There are two categories of congenital haemophilia: haemophilia A, which represents nearly 85% of cases, and haemophilia B [2]. Patients with haemophilia A are deficient of clotting factor VIII, whereas those with haemophilia B are deficient of factor IX [3]. Both haemophilia A and B are characterized by excessive bleeding [4–6]. This bleeding most typically occurs in joints and can eventually result in joint degradation, severe pain and arthropathy [7]. Severity of haemophilia is dependent upon the measured activity of clotting factor, and is classified as mild (5–30% of normal clotting factor activity), moderate (1–5% of normal) or severe (<1% of normal) [8].

Standard treatment of haemophilia involves the use of routine replacement therapy for those with a severe deficiency, known as primary prophylaxis, or on-demand factor replacement therapy for those with a mild-to-moderate phenotype. However, up to one-third of severe haemophilia A and 3–5% of severe haemophilia B patients develop alloantibodies, known as inhibitors, which neutralize the coagulant effects of

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replacement therapy, therefore requiring a shift in treatment to agents that can bypass FVIII or FIX [9,10]. Those with haemophilia and inhibitors often experience serious complications, including recurrent or persistent events of muscle, joint and deep tissue bleeding [11].

Although recent advances in the treatment of haemophilia with inhibitors have resulted in improved outcomes, pain and disability related to the disorder as well as impaired health-related quality of life (HRQoL) remain a challenge [12]. Although there is data available on the HRQoL of haemophilia patients, information on the HRQoL of haemophilia patients with inhibitors is limited [13–15]. There have been some studies that have identified a connection between inhibitor development and the reduction in HRQoL. An Italian study of haemophilia patients with inhibitors observed HRQoL specific to physical health domains as compared with the general population [12]. Similarly, orthopaedic status has been linked and determined to be associated with HRQoL [16].

In addition to the HRQoL of haemophilia patients with inhibitors, there are some studies that demonstrate that parents can be less able to cope with their children's haemophilia than the children themselves [17]. However, there remains limited data available on the caregiver's role in haemophilia treatment; understanding the potential link between caregiver burden and patient HRQoL could prove useful in assisting practitioners and associated patient care algorithms, particularly those for haemophilia patients with inhibitors. As new pipeline products in this therapeutic area are introduced, their ability to address any HRQoL issues that uniquely impact this patient population is paramount.

As such, a US-based patient/caregiver survey was launched to understand the association between patient/caregiver demographics and clinical characteristics with HRQoL among congenital haemophilia patients with inhibitors.

Materials and methods

Study material

The survey instrument was a 20-page single-assessment, paper-pencil, exploratory survey that included validated instruments such as the disease-specific HAEMO-QoL (parent proxy versions of haemophilia children aged 4–16 years) and HAEM-A-QoL (patients >17 years of age), and was complimented by the following topics: (i) demographic characteristics; (ii) haemophilia profile (including self-reported titre level categorized as high or low and current treatment regimen); (iii) knowledge and attitudes relating to preventive care; (iv) history of joint-related surgical treatment; and (v) general HRQoL, measured by the EQ-5D [18]. Data gaps in the literature were learned by a systematic literature review. The search was conducted in PubMed and applied established limits, including: (i) studies published in the past 10 years; (ii) human study; and (iii) English language. The literature review focused on treatment guidelines and outcomes for congenital haemophilia inhibitor patients, treatment burden from the patient/caregiver perspectives, and health-related quality of life (HRQoL) in the inhibitor population. Finally, the questionnaire content was checked by two independent haemophilia specialists.

This study focuses on disease-specific HRQoL issues, as measured by the paediatric age-specific version of HAEMO-QoL and the adult HAEM-A-QoL version. Both instruments, validated in haemophilia, contain questions related to different domains of HRQoL [19,20]. The paediatric HAEMO-QoL assesses 8 to 12 dimensions according to age-group versions (8, 10 and 12 dimensions respectively) of HRQoL ('physical health', 'feelings', 'attitudes', 'family', 'friends', 'perceived support', 'other persons', 'sports and school', 'dealing with the disease', 'treatment', 'future', 'relationships'). Age-related proxy versions of the HAEMO-QoL instrument were administered to parents of haemophilia children (caregivers of patients 4–7 years, 8–12 years and 13–16 years). The adult HAEM-A-QoL consists of 46 items pertaining to 10 dimensions ('physical health', 'feelings', 'view', 'sport and leisure time', 'work and school', 'dealing', 'treatment', 'future', 'family planning', 'relationship') and a total score. The HAEM-A-QoL has a core instrument with 27 shared items with the paediatric HAEMO-QoL that allows a comparison between HRQoL of adults and children.

HRQoL subscale scores are generated for respondents who complete the minimum required number of questions within each section. A total HRQoL score is then generated. Scores within each subscale and overall are reported on a scale from 0 to 100, with higher scores suggesting greater impairment in HRQoL (although no threshold has been established to date). Results for the 8–12 years and 13–16 years groups are pooled, but the remaining age groups are not pooled due to differences in subscale content. In addition, the HAEMO-QoL provides the opportunity for caregivers to share their experience with the disease and its treatment, in the form of qualitative open-ended questions.

Study cohort

The target sample was haemophilia patients with inhibitors (and caregiver proxies) and was identified through their attendance at recent educational summits on this topic. The paper-pencil questionnaire was mailed to 261 inhibitor patients and caregivers during July 2010, for immediate return. Households that did not respond to the initial mailing within 3 weeks received a duplicate packet. Households that returned

a completed survey and informed consent document were paid $100 USD for their time dedicated to complete the survey.

All respondents had to satisfy certain inclusion criteria to be considered in the study data set. Patients (or caregivers/parents of minors less than 18 years of age) had to: (i) provide evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study; (ii) be identified as a patient or caregiver/parent of a minor patient with haemophilia and inhibitors; and (iii) be able to speak, write, and understand both verbal and written English. Patients were excluded from the study if they had non-eligible diagnoses. Ethics approval for the study was granted by Western Institutional Review Board.

Statistical analysis

Health-related quality of life subscale scores and total scores were stratified by variables of interest, such as age and caregiver burden. For categorical measures, statistical significance was determined using chi-squared test, and the distribution of subjects across the categories of each variable was described using cross-tabulation analysis. For continuous measures, statistical significance was determined using *t*-test and Wilcoxon rank-sum test (where appropriate). Descriptive statistics included the mean, median and standard deviation, collectively providing an interpretation of the distributional characteristics of the data. Statistical significance was set at $P < 0.05$ where sample size permitted. Missing data were excluded from significance testing. Caregivers were required to respond for patients' ages 4–16 years (HAEMO-QoL), but could respond for patients of any age; for four adult patients responses were given by caregivers. All analyses were performed using SAS version 9.1 software (SAS, Cary, NC, USA).

Results

Response rate

In total, 117 caregivers/patients, of 261 recruited subjects, returned a completed questionnaire (44.8%). Twenty-four patients (9.2%) were not reached due to incorrect addresses and 16 patients (6.1%) no longer had inhibitors. Of the 117 patients, 14 were excluded due to: lack of an informed consent document ($N = 2$); ineligible diagnoses ($N = 12$). Of the remaining 103 subjects who met the study inclusion criteria (response rate of 39.5%), 97 provided responses to the HRQoL instruments and thus served as the sample size for our subsequent analyses (Fig. 1).

Patient characteristics

More than half of the respondents (58%) were caregivers (Table 1). Overall, patients had a mean age of 20.5 years (SD = 16.3). The majority of the patients (53.6%) were less than 16 years of age with a mean age of 8.8 years (SD = 4.1). Eighty-nine per cent of patients had haemophilia A. High titre inhibitors requiring bypassing agents were predominant among all the patients (70.1%). Sixty-nine per cent of patients had received or were receiving immune tolerance induction (ITI) therapy in an effort to eradicate inhibitors.

The majority of patients were covered by private health insurance policies or received state-funded care (i.e. Medicaid). About half of the samples' insurance policies (51%) did not contain a lifetime cap (a policy in which an insurance company agrees to pay up to a certain dollar amount to total haemophilia or health care costs over a lifetime, but no more beyond that). However, of patients with a lifetime cap, all reported that they were either concerned about reaching the lifetime cap or have already reached it.

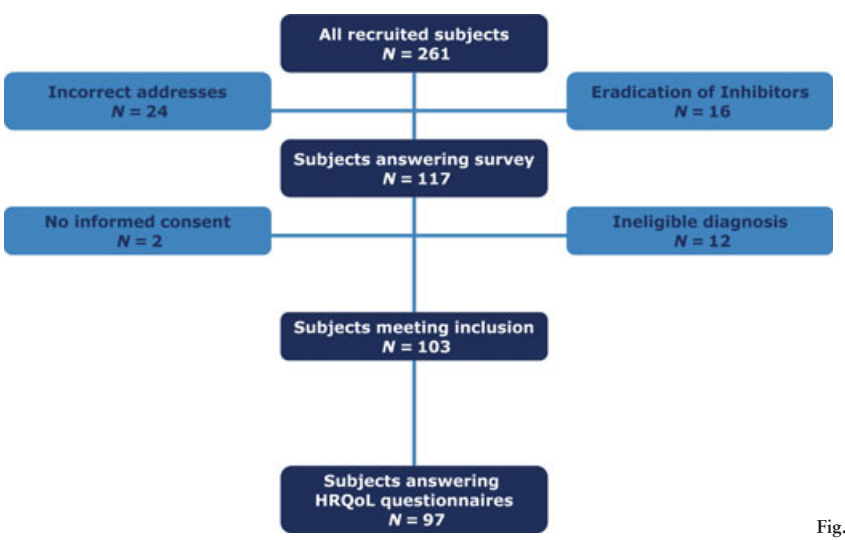

Fig. 1. Disposition of recruited subjects.

Table 1. Patient demographic and clinical characteristics ($N = 97$).

Characteristic	Value
Respondent type	*N* (%)
Patients	41 (42.3%)
Caregivers	56 (57.7%)
Patient age	Mean (SD)
Overall	20.5 (16.3)
4 to 16 years	8.8 (4.1)
17+ years	34.1 (14.9)
Patient age group	*N* (%)
4 to 16 years	52 (53.6%)
17 to 24 years	15 (15.5%)
25 to 44 years	20 (20.6%)
45 to 64 years	8 (8.3%)
65+ years	2 (2.1%)
Type of haemophilia	*N* (%)
Haemophilia A	86 (88.7%)
Haemophilia B	11 (11.3%)
Inhibitor level	*N* (%)
High titre	68 (70.1%)
Low titre	29 (29.9%)
Treatment type*	*N* (%)
On-demand	41 (42.3%)
Prophylaxis	41 (42.3%)
Episodic prophylaxis†	30 (30.9%)
Insurance type‡	*N* (%)
Private insurance	52 (53.6%)
Medicaid	44 (45.4%)
Medicare	11 (11.3%)
No insurance	2 (2.1%)

Results were categorized by authors.
*Respondents could select more than one treatment type.
†Patient takes treatments before specific activities.
‡Respondents could select more than one insurance type.

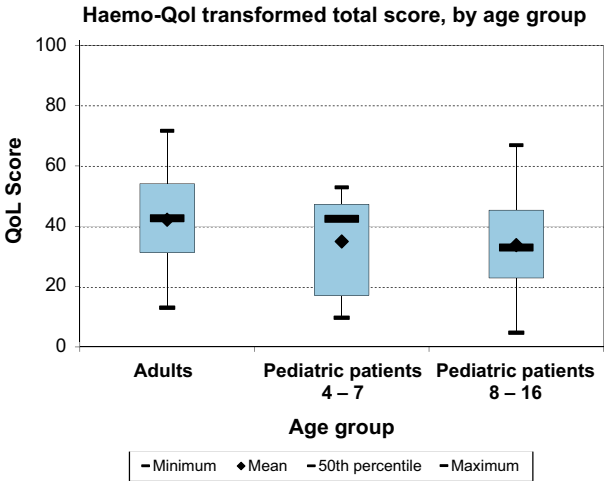

Fig. 2. Health-related quality of life impairment and relationship with patient age*.

Patient quality of life and relationship with age

For those patients currently receiving preventive treatment (defined as taking bypassing agents regularly or prior to strenuous/high risk activity to prevent bleeding), there appears to be a relationship between the level of HRQoL impairment and age (Fig. 2). Mean impairment scores were similar in the paediatric populations (M = 35.0 for ages 4–7 years and M = 33.8 for 8–16 years) but were higher in the adult population (M = 42.2). Despite the mean scores for both the adult and paediatric 4–7 age group differing, the median scores were similar.

The HRQoL domains that have the highest impairment by age group were examined at a descriptive level (Table 2). For the 4–7-year-old age group, family (M = 55.6), treatment (M = 39.3) and friends (M = 38.1) drove the HRQoL impairment, whereas for the 8–16-year-old age group, physical health (M = 50.8), sports and school (M = 42.1) and perceived support (M = 40.1) were the greatest contributors. From the 'adult perspective', 'sports and leisure' (M = 62.5), 'physical health' (M = 58.8) and 'future' (M = 50.5) were the most impacted HRQoL domains.

Caregiver burden and quality of life

The relationship between caregivers' burden and the HRQoL impairment reported for the child/patient was further explored. Caregivers of paediatric patients were asked to report how much they were bothered by their child's haemophilia on a 5-point Likert scale ('not at all'/'a little'/'moderately'/'considerably'/'very much'). As such, caregivers who reported being bothered by their child's haemophilia reported higher HRQoL impairment for their child (Table 3). For paediatric patients aged 4–7 years, caregivers who were 'moderately'/'considerably'/'very much' bothered by their child's haemophilia reported a mean HRQoL score of 38.2 as compared to 28.5 for those caregivers 'not at all'/'a little' bothered by their child's condition (not evaluated for statistical significance due to sample size). A statistically significant difference was identified for caregivers of paediatric patients aged 8–16 years. Within this age group, caregivers 'moderately'/'considerably'/'very much' bothered by their child's haemophilia reported a mean HRQoL score of 41.1 as compared to 24.9 for those caregivers 'not at all'/'a little' bothered by the disease. A statistically significant difference was noted for the domains of 'family' ($P = <0.01$) and 'friends' ($P = 0.03$) within the 4–7-year-old group, whereas 'family' ($P = 0.02$), 'treatment' ($P = 0.03$), 'relationships' ($P = 0.05$) and 'dealing with haemophilia' ($P = 0.05$) significantly contributed to the difference between caregivers in the 8–16-year-old group.

Caregiver burden and the disease of haemophilia

Caring for a patient with haemophilia with inhibitors presents unique challenges to caregivers. Caregivers were asked what bothers them about their child's haemophilia – the most frequently reported problems were emotional stress associated with the disease, financial burden, problems associated with treatment

Table 2. Health-related quality of life impairment by age.

	Paediatric subjects						Adult subjects		
	Ages 4–7			Ages 8–16			Ages ≥ 17		
Domains*	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Total score	12	35.0	16.1	20	33.8	15.5	28	42.2	14.8
Physical health	15	32.9	21.9	22	50.8	30.5	45	58.8	24.7
Feeling	17	30.4	27.2	17	37.7	26.5	45	40.6	21.1
View of yourself	23	10.9	24.5	21	30.4	20.0	45	48.4	17.8
Family	15	55.6	19.4	16	27.8	15.3	–	–	–
Friends	21	38.1	36.8	23	38.0	19.9	–	–	–
Perceived support	–	–	–	23	40.1	23.6	–	–	–
Other people	17	27.2	28.7	19	23.3	19.6	–	–	–
Sports and school/leisure	12	25.0	32.6	26	42.1	20.8	43	62.5	18.7
Work and school	–	–	–	–	–	–	38	34.5	21.9
Dealing with haemophilia	–	–	–	25	24.4	14.4	45	25.9	20.1
Treatment	14	39.3	26.8	24	29.9	19.4	45	36.9	17.0
Future†	–	–	–	12	37.7	21.1	45	50.5	21.5
Relationships†	–	–	–	11	23.9	27.6	43	23.5	27.2
Family planning	–	–	–	–	–	–	34	27.8	29.4

Higher scores indicate greater impairment.
*Domains differ by age group.
†Domains only exist in the adolescent 13–16 years version but not in the 8–12 years version.

Table 3. Patient/child quality of life impairment according to caregiver's burden.

	How much are you bothered by your son's haemophilia?												
	Paediatric patients 4–7 years old							Paediatric patients 8–16 years old						
	Not at all/A little			Moderately/Considerably/Very much				Not at all/A little			Moderately/Considerably/Very much			
Domains*	*N*	Mean	SD	*N*	Mean	SD	*P*-value	*N*	Mean	SD	*N*	Mean	SD	*P*-value
Total score	4	28.5	19.7	8	38.2	14.3	†	9	24.9	14.5	11	41.1	12.6	0.02
Physical health	6	24.7	20.7	9	38.4	22.1	0.26	11	40.2	34.2	11	61.4	23.2	0.10
Feeling	6	26.4	25.0	11	32.6	29.2	0.72	6	24.3	35.4	11	45.0	18.2	0.07
View of yourself	10	3.8	11.9	13	16.3	30.4	0.25	10	25.8	24.1	11	34.6	15.5	0.19
Family	6	39.9	21.4	9	66.0	8.3	<0.01	8	20.2	11.5	8	35.5	15.4	0.02
Friends	10	20.0	25.8	11	54.5	38.4	0.03	11	33.5	15.7	12	42.0	23.0	0.39
Perceived support								11	33.7	15.8	12	46.0	28.5	0.44
Other people	6	16.7	25.8	11	33.0	29.7	0.31	7	11.9	10.5	12	29.9	20.9	0.07
Sports & school	8	14.6	15.9	4	45.8	49.3	†	12	37.2	22.0	14	46.2	19.7	0.21
Dealing with Haemophilia								12	18.3	14.2	13	30.0	12.6	0.05
Treatment	6	47.9	30.0	8	32.8	24.0	0.26	10	19.0	13.7	14	37.7	19.5	0.03
Future								7	27.7	17.3	5	51.7	19.0	0.14
Relationships								6	8.3	20.4	5	42.5	24.4	0.05

Higher scores indicate greater impairment.
*Domains differ by age groups.
†Cell sizes <5 were not evaluated for statistical significance, *t*-test otherwise.

administration and difficulty dealing with the pain their child is going through (Fig. 3).

Discussion

Haemophilia patients with inhibitors experience more bleeding episodes per month than haemophilia patients without inhibitors [12]. As such, inhibitor patients require high management to provide a satisfactory HRQoL [20]. Impacted HRQoL domains are self-esteem, friends, school activities, physical health and perceived health [14]. Our survey highlights the important role that the presence of inhibitors and its associated treatment has on the HRQoL of both haemophilia patients with inhibitors as well as their caregivers. In the Brown study, it was demonstrated that younger age, lower physical HRQoL (PCS), more haemorrhages and surgery were associated with less patient productivity and missing days; caregivers experienced a mean of 19.1 missed days annually [21].

The drivers of HRQoL impairments vary greatly among different age groups; domains may change over time due to changing priorities, lifestyle and potential complications associated with disease progression. Within the paediatric population, 'family', 'friends' and 'treatment' drive HRQoL impairment in the earliest years. This is a difficult time period for caregivers as they cope and help their children to cope with the psychosocial outcomes of a demanding disease. During adolescence, 'physical health', 'sports and school'

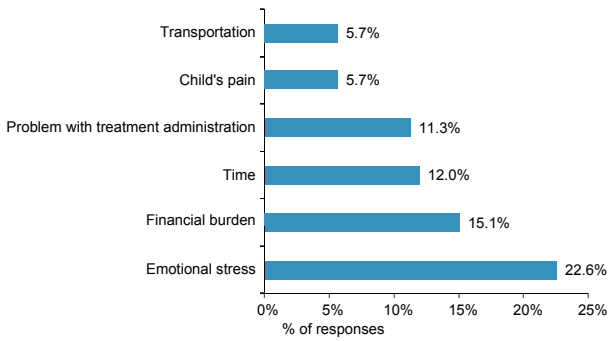

Fig. 3. Caregiver-reported burden related to caring for a child with haemophilia. There were 150 unique responses. Multiple responses were permitted. Open-ended responses were coded and categorized by themes.

and 'perceived support' stand out as the top drivers of HRQoL impairment. Caregivers may perceive support as a challenge at this stage as their child becomes more independent and plays a larger role in the care of their disease. By adulthood, 'sports and leisure', 'physical health' and the 'future' were the dominating HRQoL domains. While there remains no single modality for dealing with the various challenges experienced by haemophilia patients with inhibitors, overall goals of any treatment should be to improve HRQoL [22] for both the patient and their caregivers.

Our survey results have shown the role and associated burden of the caregiver. Hae'mophilia's impact on the caregivers' HRQoL should become more of a consideration in treatment choices and planning. Research has indicated that greater emphasis should be placed on education and patients' psychological needs, to enable inhibitor patients to cope more effectively with their disease [23,24]. However, clinicians should also consider the caregivers' burden when they create individualized disease management plans for their patients. Although there is evidence that while one of the benefits of home care for haemophilia is improved HRQoL, it requires a substantial commitment [25]. Our survey results highlight the fact that time, treatment administration and the patient's pain are areas of caregiver burden requiring further investigation. Clinicians (both physicians and nurses) as well as the community at large may all play a role in offering a more comprehensive support system to caregivers, in addition to focused educational efforts and infusion training.

Study limitations

Although this study provides valuable insight into the HRQoL of haemophilia patients with inhibitors and their caregivers, there are some limitations that warrant mention. Although our response rate was comparable with other paper-pencil surveys administered via mail [26,27] and the small sample constitutes a substantive sample of this limited patient population, small samples in general lend themselves to potential response bias. All patients/caregivers contacted, participated in educational summits specific to this topic, requiring travel to the summit site. Thus, the sample may reflect a more motivated and less disabled, patient/caregiver population. In addition, our questionnaire was written in English-only, lending itself to participation and responses from such an audience.

Patient demographics were only collected for patients, not caregivers, limiting our ability for additional stratification by variables of interest. It is also important to note that HRQoL for most of the paediatric population was measured by caregivers as a proxy, which may underestimate the actual HRQoL experienced by patients themselves. Therefore, the study would have benefitted from a comparison of self-reported HRQoL with proxy rating of HRQoL. Unfortunately, this was deemed difficult to implement as the method of administration prohibited reliable assessment of the actual respondent type.

Conclusion

Among haemophilia patients with inhibitors, health-related quality of life impairment increases with age. In addition, caregiver burden also affects the perceived HRQoL of paediatric haemophilia patients with inhibitors. There is a need for additional research with caregivers to further investigate the support, if any, they are receiving while caring for their children. This level of support, in turn, could have implications for the patients' HRQoL, as these survey results have suggested.

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Author's contribution

MD, AP and WCL conducted the literature search and developed the overall survey and statistical analysis plan. TW, DC and NH developed the study design and interpreted results. TW additionally contributed to the analysis plan. SvM previously developed and validated the haemophilia-specific HRQoL instruments used in this study and also contributed to interpretation of results. AP conducted all statistical analyses and also developed the analysis plan. All authors contributed to the writing and revision of the manuscript.

Disclosures

This study was sponsored by Novo Nordisk. MD, AP and WCL are employees of IMS Health who were paid consultants to Novo Nordisk in connection with the development of this article. TW, NH and DC are employees of Novo Nordisk. SvM has received a honorarium from Novo Nordisk for the interpretation of study results and contribution to writing this paper. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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