Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)

Sylvia von Mackensen | Olivier Catalani | Elina Asikanius | Ido Paz-Priel | Michaela Lehle | Peter Trask

Abstract

Introduction: The Haem-A-QoL is frequently utilized in haemophilia clinical trials and captures relevant aspects of disease impact. Thresholds for some domains 'Physical Health' (PH), 'Sports & Leisure' (S&L) and 'Total Score' (TS) have previously been identified to benchmark the amount of change that is meaningful to patients, but not been independently confirmed.

Aim: The objective of this analysis was to determine the clinically important responder (CIR) thresholds for these three domains.

Methods: CIR thresholds in adult persons with haemophilia A (PwHA) enrolled in HAVEN 1, 3 and 4 studies were determined for improvements from baseline to 24 weeks of emicizumab prophylaxis using anchor-based methodology with the EQ-5D-5L as the validated anchor, cumulative distribution functions (CDF) and distribution-based methodology. The results were compared with previously published thresholds.

Results: At baseline and after 24 weeks of emicizumab prophylaxis, Haem-A-QoL data from 241/258 patients were available. Concordance was observed between the Haem-A-QoL and EQ-5D-5L in patterns of improvement, deterioration or lack of change. CDF estimates of the Haem-A-QoL PH and TS grouped by response categories on the Mobility, Pain/Discomfort and Usual Activities EQ-5D-5L domains demonstrated the same pattern of responses to each scale; distribution-based estimates were 11.9 for PH, 13.9 for S&L, and 8.3 for TS.

Conclusion: Our responder thresholds are mostly consistent with those proposed by Wyrwich et al (cut-offs of −10 and −7 for PH and TS, respectively). The majority of responders to emicizumab prophylaxis had improvements greater than the previously reported 10-point reduction in PH and 7-point reduction in TS.
1 | INTRODUCTION

Haemophilia A (HA) is a congenital bleeding disorder characterized by spontaneous or traumatic bleeding particularly into joints and muscles, and potential resultant deterioration in physical function.\(^1\)\(^,\)\(^2\) Moreover, HA and complications such as factor (F)VIII inhibitor development can impact aspects of patients' health-related quality of life (HRQoL) such as social functioning (eg interactions with others, family planning), role functioning (eg ability to attend work/school) and emotional functioning.\(^3\)\(^-\)\(^8\)

Understanding the impact of the disease on persons with HA (PwHA) is critical, and characterizing the improvement in physical function from treatments that significantly reduce bleeds is of high interest. Physical function and impact on HRQoL are frequently captured in clinical trials via patient-reported outcomes (PROs), including the Haemophilia-specific Health-related Quality of Life Questionnaire for Adults (Haem-QoL-A), Hemophilia-QoL and Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL).\(^9\)\(^-\)\(^11\)

Knowing the score changes in different questionnaires that constitute a meaningful improvement is useful in order to characterize the clinical utility of an intervention.

The Haem-A-QoL is one of the most frequently utilized PROs in clinical trials for haemophilia. It has demonstrated psychometric reliability and validity, has been cross-culturally validated in more than 80 languages.\(^11\)\(^-\)\(^21\) The Haem-A-QoL ‘Physical Health’ (PH) domain is most likely to be immediately impacted by improvement in bleeds. More global effects are captured by the ‘Sports & Leisure’ (S&L) and ‘Total Score’ (TS) scales.

To determine what score improvement is meaningful, analyses have focused on the within-group individual change and less frequently, on the between-group change.\(^22\) Clinically meaningful individual-level change has been defined as a responder threshold, or more recently, as a clinically important responder (CIR) threshold.\(^23\) A clinically meaningful difference between two treatment groups has been designated a clinically important difference (CID).\(^24\)

Determining the CIR for a PRO has relied on anchor-based methodology,\(^25\) distribution-based methodology and/or triangulation of the two. Distribution-based methodology relies on an assessment of the distribution of questionnaire responses, using the standard error of measurement (SEM) or half of standard deviation (SD). Anchor-based methodology uses an ‘anchor’ (eg EQ-5D-5L), to which patients respond if they are better or worse after treatment versus baseline, as a reference to compare changes in scores on the questionnaire of interest (eg Haem-A-QoL). Santagostino et al\(^16\) published a responder threshold for the Haem-A-QoL using a distribution-based approach. They defined responders based on the SEM for each scale and the TS. For the 129 adults (17–60 years) treated prophylactically or on-demand, a reduction of 8.9, 16.4 and 6.3 points for PH, S&L and TS, respectively, was identified as the responder thresholds.\(^16\)

Wyrwich et al\(^18\) used rigorous assessments applying anchor- and distribution-based methodology, as well as triangulation of the PH, S&L and TS scales. Using the EQ-5D-3L as an anchor, the authors concluded that change scores of −10 represented the responder threshold for PH and S&L, and −7 for TS. They noted that due to the limited sample size in the analyses (n = 67 at baseline and Week 28), the results should be considered preliminary and additional haemophilia studies were needed.

Here, we employ results from adult PwHA enrolled in the HAVEN 1, 3 and 4 studies conducted as part of the emicizumab (HEMLIBRA\(^\circledR\); F. Hoffmann-La Roche Ltd) development programme.\(^26\)\(^-\)\(^28\) Emicizumab is a humanized bispecific antibody that bridges activated factor IX and X, to restore coagulation in PwHA regardless of FVIII inhibitors. Emicizumab prophylaxis is associated with lower annualized bleed rate (ABR) versus FVIII\(^29\) or bypassing agents,\(^27\) allowing for assessment of the impact of reduced ABR on HRQoL assessed by the Haem-A-QoL. Employing anchor-based methodology with EQ-5D-5L as the validated anchor, cumulative distribution functions and distribution-based methodology, we analysed the amount of change that is clinically meaningful to PwHA on three Haem-A-QoL scales (PH, S&L and TS), and compared the results with those reported by Wyrwich et al.\(^18\)

2 | MATERIALS AND METHODS

2.1 | HAVEN 1, 3 and 4 studies

HAVEN 1 (NCT02622321), 3 (NCT02847637) and 4 (NCT03020160) were global, multicentre, open-label, Phase 3 studies, which enrolled PwHA with or without FVIII inhibitors to receive subcutaneous emicizumab prophylaxis once-weekly, every 2 weeks or every 4 weeks, or no prophylaxis. This analysis utilizes data from PwHA ≥ 18 years old in all study arms for HAVEN 1 and 3, and for HAVEN 4, data from PwHA enrolled in the expansion cohort, who provided baseline PRO data. The studies’ methods were published previously.\(^26\)\(^-\)\(^28\) These HAVEN studies included the Haem-A-QoL and EQ-5D-5L to assess the impact of emicizumab on symptoms, functional limitations, treatment burden and HRQoL. All studies were approved by the institutional review board at each study site and adhered to Good Clinical Practice and informed consent guidelines.
2.2 | Measures

The Haem-A-QoL and EQ-5D-5L were completed at baseline prior to first emicizumab dose, at protocol-specified points throughout the study, and after 24 weeks of treatment. HAVEN 1, 3 and 4 study participants were included in this analysis if they completed the Haem-A-QoL and EQ-5D-5L assessments at baseline and after 24 weeks.

The Haem-A-QoL is a 46-item measure consisting of 10 scales (‘Physical Health,’ ‘Feelings,’ ‘View of Yourself,’ ‘Sport & Leisure,’ ‘Work & School,’ ‘Dealing with Haemophilia,’ ‘Treatment,’ ‘Future’, ‘Family Planning’ and ‘Partnership & Sexuality’) validated for use in individuals >18 years of age.12,13 Summation of the scales creates a ‘Total Score’. Participants respond based on their experience in the previous 4 weeks, with response options ranging from ‘Never’ (1) to ‘All of the time’ (5). In the domains ‘Sport & Leisure’, ‘Family Planning’ and ‘Work & School’, an additional ‘Not applicable’ option is available and is scored as (0). When calculating scores, any (0) is recoded as missing data and not included in the scoring. To have all responses scored in the same direction, several items were reverse scored before calculating the scale scores. Scale scores were transformed to a 0–100 scale with higher scores reflecting greater impairment or poorer HRQoL.

Health status was assessed using the EQ-5D-5L questionnaire and the EQ-5D visual analog scale (EQ-VAS) for adults/adolescents.29 The five dimensions of the EQ-5D-5L health profile assess Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression; each with five levels of severity ranging from ‘No problems’ to ‘Extreme problems’ on the day the questionnaire was completed.29-31 The five dimensions are combined into an index utility score (IUS) using the UK value set.32 Participants rated their general health using the EQ-VAS, where 0 is the worst and 100 the best imaginable health status. The EQ-5D-5L IUS and the EQ-VAS have previously been shown to be reliable and valid tools for assessing health status in PwHA with or without FVIII inhibitors.33

2.3 | Statistical analyses

2.3.1 | Anchor-based responder analyses

Data for PwHA who completed both the Haem-A-QoL and EQ-5D-5L at baseline and after 24 weeks of treatment in the HAVEN 1, 3 and 4 studies were combined and subsequently grouped according to their change from baseline to after 24 weeks of treatment in the items from the EQ-5D-5L (Pain/Discomfort, Mobility and Usual Activities). In order to reduce the number of categories, PwHA were grouped into five categories: improvement by more than one point, improvement by one point, stable, deterioration by one point and deterioration by more than one point. As several categories included a small number of PwHA, the median change score for PH, S&L and TS were used instead of the mean to eliminate the potential influence of outliers. This is consistent with the previous approach.18

Using anchor-based methodology,25,34 we examined the distribution of the change from baseline in Haem-A-QoL PH, S&L and TS using the change from baseline observed in the EQ-5D-5L Mobility, Usual Activities and Pain/Discomfort items. Graphs were used to display the three EQ-5D-5L items side by side. The x-axis depicts the change in each item of EQ-5D-5L and the y-axis depicts the median change from baseline in Haem-A-QoL, from baseline to after 24 weeks of treatment.

2.3.2 | Cumulative Distribution Functions (CDFs)

CDFs provide the full range of responses by either a treatment group or a grouping category to characterize the effect of treatment or in different subsets of PwHA. CDF curves were created on the change scores from baseline to after 24 weeks of treatment on the Haem-A-QoL scales in reference to changes in different response categories on the EQ-5D-5L Mobility, Usual Activities and Pain/Discomfort items. PwHA were grouped into four categories: improvement by more than one point, improvement by one point, stable, deterioration by one or more points.

2.3.3 | Distribution-based responder analyses

Use of half the SD of the Haem-A-QoL PH, S&L and TS scales at baseline, as well as SEM, were used to further inform the cut-offs for meaningful change identified from the anchor-based and CDF analyses. Cronbach’s alpha was derived from the combined HAVEN studies to calculate SEMs for Haem-A-QoL scales and TS.

Triangulation was conducted with the anchor-based, CDF and distribution-based analyses to determine cut-offs for within-group CIRs, and to examine the results compared to those reported previously.18

3 | RESULTS

3.1 | Patient population in HAVEN 1, 3 and 4

Descriptive baseline data of patients included in this analysis are shown in Table 1.

At baseline, 241 PwHA provided information on the Haem-A-QoL PH and TS, and 170 on the S&L scale. In all three domains (PH, S&L and TS), there was a decrease in median scores of 15–20 points (HRQoL improvement) from baseline to after 24 weeks follow-up with emicizumab prophylaxis (Table 2).

3.2 | Anchor-based responder estimates

On the EQ-5D-5L, 61 (35%), 81 (46.5%) and 40 (23%) PwHA reported no problems at baseline in Mobility, Usual Activities and
Pain/Discomfort, respectively, and this pattern continued after 24 weeks of treatment. Thirty-seven (21.3%), 30 (17.2%) and 50 (28.7%) PwHA reported slight/moderate impairments at baseline in these EQ-5D-5L domains, and this was maintained after 24 weeks of treatment. Also after 24 weeks, 106 (61%), 113 (65%) and 99 (57%) PwHA were in the unchanged category in Mobility, Usual Activities and Pain/Discomfort, respectively. There was a high number of participants with no problems at baseline on the EQ-5D-5L who, therefore, could not experience improvement.

3.2.1 | Haem-A-QoL PH

Overall, PwHA who deteriorated on the EQ-5D-5L tended to also deteriorate on the PH domain, whereas those who did not change or improved on EQ-5D-5L also improved on the PH domain (Figure 1). PwHA who did not change on any of the EQ-5D-5L domains experienced median changes of −5 to −10 points in Haem-A-QoL PH between baseline and after 24 weeks of treatment. PwHA who improved on any of the EQ-5D-5L domains over 24 weeks had a median change in Haem-A-QoL PH of −20 to −42.5 points. Few participants declined in Mobility, Pain/Discomfort and Usual Activities on the EQ-5D-5L domains over 24 weeks; these PwHA reported median changes in PH of −2.5 to 12.5 points. The results suggest that the majority of responders had improvements greater than the 10-point change in this domain described previously.18

3.2.2 | Haem-A-QoL S&L

The S&L domain had a similar pattern to that observed in PH, although there was no concordance between the responses on the two measures (Figure 2). Participants with no change on the EQ-5D-5L had median changes of −2.5 to −3.1 on the Haem-A-QoL S&L. PwHA who improved on the EQ-5D-5L showed median changes between 5 to −32.3; and those who deteriorated on the EQ-5D-5L showed a median improvement from −2.5 to −5.0. The results suggest that there was no consistent directional change among the PwHA in each anchor category.

### Table 1: Demographic characteristics at baseline

|                   | HAVEN 1 (n = 72) | HAVEN 3 (n = 142) | HAVEN 4 (n = 44) | Total (n = 258) |
|-------------------|------------------|-------------------|-----------------|----------------|
| Median age, years (range) | 38.5 (18-75)     | 39.0 (19-77)      | 42.0 (20-68)    | 39.0 (18-77)   |
| Race, n (%)       |                  |                   |                 |                |
| Asian             | 15 (20.8)        | 30 (21.1)         | 7 (15.9)        | 52 (20.2)      |
| Black or African American | 8 (11.1) | 7 (4.9)           | 1 (2.3)         | 16 (6.2)       |
| White             | 46 (63.9)        | 96 (67.6)         | 35 (79.5)       | 177 (68.6)     |
| Other a           | 3 (4.2)          | 9 (6.3)           | 1 (2.3)         | 13 (5.1)       |
| Prior bleeding events, n (%) |          |                   |                 |                |
| <9                | 30 (41.7)        | 64 (45.1)         | 30 (68.2)       | 124 (48.1)     |
| ≥9                | 42 (58.3)        | 78 (54.9)         | 14 (31.8)       | 134 (51.9)     |
| Number of target joints prior to study, mean (SD) | 1.6 (1.6) | 1.7 (1.6) | 1.8 (2.0) | 1.7 (1.7) |
| FVIII inhibitors status, n (%) | |                   |                 |                |
| With inhibitor    | 72 (100)         | 0 (0)             | 7 (15.9)        | 79 (30.6)      |
| Without inhibitors| 0 (0)            | 142 (100)         | 37 (84.1)       | 179 (69.4)     |
| Pts using coagulation product in the 24 weeks before study, n (%) | |                   |                 |                |
| aPCC              | 43 (71.7)        | 0                 | 2 (8.3)         | 45 (25.7)      |
| Recombinant FVIIa | 45 (75.0)        | 0                 | 2 (8.3)         | 47 (26.9)      |
| FVIII             | 3 (5.0)          | 90 (98.9)         | 20 (83.3)       | 113 (64.6)     |

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIIa, activated factor seven; FVIII, factor eight; SD, standard deviation.

a These characteristics include three participants from the run-in cohort who were not asked to complete the Haem-A-QoL questionnaire.

b Other includes native Hawaiian or other pacific Islander and those of unknown race.

### Table 2: Pooled Haem-A-QoL scores from HAVEN 1, 3 and 4 at baseline and after 24 weeks of emicizumab prophylaxis

| Domain                  | Baseline | 24 weeks of follow-up |
|-------------------------|----------|-----------------------|
| Physical health         |          |                       |
| Median (range)          | 45 (0—95.0) | 25 (0—95.0)          |
| [n]                     | [241]    | [181]                 |
| Sports and Leisure b    |          |                       |
| Median (range)          | 60 (0—100) | 45.0 (0—100)         |
| [n]                     | [170]    | [116]                 |
| Total score             |          |                       |
| Median (range)          | 35.0 (2.7—87.8) | 20.6 (0.6—85.7)     |
| [n]                     | [241]    | [181]                 |

b Participants could answer ‘Not applicable’ for the ‘Sports & Leisure’.

---

**Figure 1**

**Figure 2**
As with PH, PwHA who deteriorated on the EQ-5D-5L also deteriorated on the Haem-A-QoL TS and those who improved had the greatest improvement in TS (Figure 3). The majority of participants reported no change in scores on EQ-5D-5L over 24 weeks. PwHA reporting no change in the EQ-5D-5L had median changes between −6.7 and −5.7 points in TS. PwHA noting an improvement in their EQ-5D-5L over 24 weeks experienced a median change of −10.5 to −30.9 points in TS, while those noting a decline in any of the
EQ-5D-5L domains experienced a median change in TS from −7.5 to 3.6 points.

3.3 | Cumulative distribution function (CDF) estimates

CDF estimates of the Haem-A-QoL PH and TS grouped by response categories on the Mobility, Pain/Discomfort and Usual Activities EQ-5D-5L domains demonstrated the same pattern of responses for each scale, eg 100% of PwHA who improved by at least −2 points on the Pain/Discomfort domain of the EQ-5D-5L (category −2 patients) and 70% of category −1 PwHA had improvements in excess of 10-points from baseline on PH. In contrast, approximately 25% of category 1 patients (those with a deterioration in EQ-5D-5L Pain/Discomfort) had a PH score that exceeded this amount (Figure 4A). Among PwHA in the improved categories on the Pain/Discomfort domain of the EQ-5D-5L (category −2 patients) and 70% of category −1 PwHA had improvements in excess of 10-points from baseline on PH. In contrast, approximately 25% of category 1 patients (those with a deterioration in EQ-5D-5L Pain/Discomfort) had a PH score that exceeded this amount (Figure 4A).

3.4 | Distribution-based responder definition estimates

Using the half SD, the estimates for PH were 11.9, 13.9 for S&L and 8.3 for TS. Cronbach’s alpha for PH was 0.87, 0.78 for S&L and 0.92 for TS. The SEMs (based on Cronbach’s alpha) for PH, S&L and TS were 7.9, 11.7 and 4.6, respectively.

3.5 | Triangulation

For PH, the distribution-based method creates a lower CIR estimate than the anchor-based approach (−10.6 to −11.9 vs −20 to −42.5). For S&L, the estimates of −12.9 and −13.9 are within the range of 5 and 8.3 observed with the anchor-based approach. For TS, the distribution-based estimate of 8.3 is also lower than the −10.5 to −30.9 range observed with the anchor-based method. However, such a wide range precludes a definitive conclusion.
(A) Physical Health scale of the Haem-A-QoL

Cumulative proportion

Change from baseline

Change in EQ-5D-5L score

-2 (N = 10 / Median = -37.5)
-1 (N = 41 / Median = -25)
0 (N = 99 / Median = -5)
1 (N = 22 / Median = 2.5)

(B) Sports & Leisure scale of the Haem-A-QoL

Cumulative proportion

Change from baseline

Change in EQ-5D-5L score

-2 (N = 7 / Median = 5)
-1 (N = 24 / Median = -22.5)
0 (N = 56 / Median = -3.13)
1 (N = 12 / Median = -3.13)

(C) Total Score of the Haem-A-QoL

Cumulative proportion

Change from baseline

Change in EQ-5D-5L score

-2 (N = 10 / Median = -26.25)
-1 (N = 41 / Median = -17.29)
0 (N = 99 / Median = -6.1)
1 (N = 22 / Median = -3.09)
(A) Physical Health scale of the Haem-A-QoL

(B) Sports & Leisure scale of the Haem-A-QoL

(C) Total Score of the Haem-A-QoL
FIGURE 5 Cumulative distribution function estimates performed on the Haem-A-QoL Physical Health, Sports & Leisure and Total Score grouped by response categories on the Mobility EQ-5D-5L domain. Physical Health scale of the Haem-A-QoL. Vertical dotted lines at −10 denote the responder threshold identified by Wyrrich et al18 Sports & Leisure scale of the Haem-A-QoL. Vertical dotted lines at −10 denote the responder threshold identified by Wyrrich et al18 Total Score of the Haem-A-QoL. Vertical dotted lines at −7 denote the change in Total Score responder threshold identified by Wyrrich et al18.

4 | DISCUSSION

The HAVEN studies demonstrated that emicizumab provides superior bleed control in adults and adolescents,26–28 and improvements in HRQoL on the Haem-A-QoL in excess of responder thresholds identified previously by Wyrrich et al. Collectively, these studies employ one of the largest groups of PwHA to utilize anchor-based methodology, CDFs and distribution-based methodology to determine the extent of change for an individual that qualifies as a CIR on the Haem-A-QoL after 24 weeks of treatment; an endpoint that corresponds closely to the timepoints of Week 28 and Week 26 used previously in the A-Long and B-Long trials.18 The thresholds observed in the current study did not contradict those previously reported, although the results were less consistent for the S&L domain.

Use of the EQ-5D-5L allowed better differentiation of the health status of a large group of PwHA across gradations of improvement or deterioration than with the EQ-5D-3L. Our CDF curves are consistent with responder thresholds proposed by Wyrrich et al (cut-offs of −10, −10 and −7 for PH, S&L and TSs, respectively), to separate those who reported improvement in the EQ-5D-5L and subsequent improvement in the Haem-A-QoL scales most robustly for the PH and the TS. In each of the three selected HRQoL dimensions, the majority of PwHA who reported an improvement of one level on the EQ-5D-5L scored at or above the responder thresholds identified by Wyrrich et al.18

A larger range than previously reported18 was observed when using the anchor-based thresholds. In PwHA showing an improvement on the EQ-5D-5L from baseline, median improvements between 20 and 42.5 points were observed in Haem-A-QoL PH. In patients who were stable on the EQ-5D-5L, median improvements up to 10-points were observed. This analysis may be limited by a very high proportion of participants reporting no problems in Pain/Discomfort, Mobility or Usual Activities on the EQ-5D-5L. This may explain why PwHA who had stable EQ-5D-5L scores over time reported improvement on the Haem-A-QoL domains, and why the scores of the PwHA who improved were even higher than those reported by Wyrrich et al18 who utilized the EQ-5D-3L (three response options). Due to two additional response options in the EQ-5D-5L, it is unlikely that we would have seen results that were exactly concordant with previous.

The higher thresholds on the PH scale may stem from the large improvement in bleeds observed with emicizumab. This analysis includes participants with FVIII inhibitors (HAVEN 1 and 4) and those without (HAVEN 3 and 4); in contrast, Wyrrich et al included patients with both haemophilia A and B without inhibitors. Participants with FVIII inhibitors often have more bleeds on standard treatment than those without inhibitors, a resultant reduced HRQoL and larger potential for improvement.21 As patients taking emicizumab had fewer bleeds, they no longer experienced joint pain, swelling, painful movements, or difficulty walking. Indeed, the 20-point improvement on the PH scale can be considered a substantial improvement on a scale that ranges from 0 to 100. The 15-point improvement on the S&L and TS demonstrates the broad impact of treatment, affecting other aspects of HRQoL. While the CIR should be independent of treatment, the degree of improvement seen for emicizumab was numerically much larger than reported previously,18 likely contributing to the difference in observed scores. This is consistent with information from King et al25 who noted that estimates for meaningful changes may vary by anchors and datasets.

5 | CONCLUSION

This analysis demonstrated that previously identified CIR thresholds for PH and the TS were appropriate for determining meaningful changes in the Haem-A-QoL for adult PwHA; less support was provided for the S&L scale. As we did not evaluate potential CIRs for the other scales of the Haem-A-QoL, future studies should examine whether these may provide additional information and are meaningfully responsive to new treatments.

ACKNOWLEDGEMENTS

Editorial assistance for the development of this manuscript, under the direction of the authors, was provided by Rebecca A Bachmann, PhD of Gardiner-Caldwell Communications. This analysis was funded by F. Hoffmann-La Roche Ltd. Open access funding enabled and organized by ProjektDEAL.

DISCLOSURES

SvM is a consultant for F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd; OC and EA are employees of F. Hoffmann-La Roche Ltd; IP-P is an employee of Genentech, Inc; ML is an employee and shareholder of F. Hoffmann-La Roche Lt; PT is an employee and shareholder of Genentech, Inc

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, and data analysis and interpretation. All authors were involved with drafting of this article and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
(A) Physical Health scale of the Haem-A-QoL

(B) Sports & Leisure scale of the Haem-A-QoL

(C) Total Score of the Haem-A-QoL
DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivi.org/). Further details on Roche’s criteria for eligible studies are available here (https://vivi.org/members/ourmembers/). For further details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are/how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

ORCID

Sylvia von Mackensen https://orcid.org/0000-0002-5926-0478

REFERENCES

1. Morfini M, Haya S, Tagariello G, et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia. 2007;13(5):606-612.
2. Scalone L, Mantovani LG, Mannucci PM, Gringeri A, Investigators CS. Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. Haemophilia. 2006;12(2):154-162.
3. Holstein K, von Mackensen S, Bokemeyer C, Langer F. The impact of bleeding disorders on the socioeconomic status of adult patients. Haemostaseologie. 2018;38(3):150-157.
4. Booth J, Oladapo A, Walsh S, et al. Real-world comparative analysis of bleeding complications and health-related quality of life in patients with haemophilia A and haemophilia B. Haemophilia. 2018;24(5):e322-e327.
5. Buckner TW, Batt K, Quon D, et al. Assessments of pain, functional impairment, anxiety, and depression in US adults with hemophilia across patient-reported outcome instruments in the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. Eur J Haematol. 2018;100(Suppl. 1):5-13.
6. Brown TM, Lee WC, Joshi AV, Pashos CL. Health-related quality of life and productivity impact in haemophilia patients with inhibitors. Haemophilia. 2009;15(4):911-917.
7. Gringeri A, Mantovani LG, Scalone L, Mannucci PM. COCIS Study Group. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood. 2003;102(7):2358-2363.
8. Mahlangu J, Oldenburg J, Callaghan MU, et al. Health-related quality of life and health status in persons with haemophilia A with inhibitors: a prospective, multicentre, non-interventional study (NIS). Haemophilia. 2019;25(3):382-391.
9. Remor E, Arranz P, Quintana M, et al. Psychometric field study of the new haemophilia quality of life questionnaire for adults: the ‘Hemofilia-QoL’. Haemophilia. 2005;11(6):603-610.
10. Rentz A, Flood E, Atlisent C, et al. Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. Haemophilia. 2008;14(5):1023-1034.
11. von Mackensen S, Gringeri A, Ravera S, et al. Validation of the haemophilia-specific quality of life questionnaire for adult patients with haemophilia (Haem-A-QoL) [abstract 0290]. Haematologica. 2005;90(Suppl. 2):115-116.
12. von Mackensen S, Gringeri A. Quality of life in hemophilia. In: Preedy VR, Watson RR, eds. Handbooks of Disease Burdens and Quality of Life Measures. New York, NY: Springer; 2010:1895-1920. https://doi.org/10.1007/978-0-387-78665-0_112
13. von Mackensen S, Eldar-Lissai A, Auguste P, et al. Measurement properties of the Haem-A-QoL in haemophilia clinical trials. Haemophilia. 2017;23(3):383-391.
14. Ferreira AA, Leite IC, Bustamante-Teixeira MT, et al. Health-related quality of life in hemophilia: results of the Hemophilia-Specific Quality of Life Index (Haem-a-Qol) at a Brazilian blood center. Rev Bras Hematol Hemoter. 2013;35(5):314-318.
15. Salomon T, Chaves DG, Brenner S, Martins PR, Mambrini JV, Peixoto SV. Determining the health-related quality of life in individuals with haemophilia in developing economies: results from the Brazilian population. Haemophilia. 2017;23(1):42-49.
16. Santagostino E, Lentz SR, Busk AK, Regnault A, Iorio A. Assessment of the impact of treatment on quality of life of patients with haemophilia A at different ages: insights from two clinical trials on turoctocog alfa. Haemophilia. 2014;20(4):527-534.
17. von Mackensen S, Campos IG, Acquardo C, Strandberg-Larsen M. Cross-cultural adaptation and linguistic validation of age-group-specific haemophilia patient-reported outcome (PRO) instruments for patients and parents. Haemophilia. 2013;19(2):e73-83.
18. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia. 2015;21(5):578-584.
19. Mercan A, Sarper N, Inanir M, et al. Hemophilia-Specific Quality of Life Index (Haemo-Qol and Haem-A-Qol questionnaires) of children and adults: result of a single center from Turkey. Pediatr Hematol Oncol. 2010;27(6):449-461.
20. Varaklioti A, Kontodimopoulos N, Katsarou O, Niakas D. Psychometric properties of the Greek Haem-A-Qol for measuring quality of life in Greek haemophilia patients. Biomed Res Int. 2014;2014:968081.
21. Oldenburg J, Mahlangu JN, Bujan W, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study. Haemophilia. 2019;25(1):33-44.
22. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertainment the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-415.
23. Cella D, Bullinger M, Scott C, Barofsky I. Clinical Significance Consensus Meeting Group. Group vs individual approaches to understanding the clinical significance of differences or changes in quality of life. Mayo Clin Proc. 2002;77(4):384-392.
24. Coon CD, Cappelleri JC. Interpreting change in scores on patient-reported outcome instruments. Ther Innov Regul Sci. 2016;50(1):22-29.
25. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims in: 2009.
26. Mahlangu J, Oldenburg J, Paz-Priell I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379(9):811-822.
27. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
28. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
29. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
30. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.
31. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-1727.
32. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Econ*. 2018;27(1):7-22.
33. Buckner TW, Wang M, Cooper DL, Iyer NN, Kempton CL. Known-group validity of patient-reported outcome instruments and hemophilia joint health score v2.1 in US adults with hemophilia: results from the Pain, Functional Impairment, and Quality of life (P-FiQ) study. *Patient Prefer Adherence*. 2017;11:1745-1753.
34. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol*. 2003;56(5):395-407.
35. King MT, Dueck AC, Revicki DA. Can methods developed for interpreting group-level patient-reported outcome data be applied to individual patient management? *Med Care*. 2019;57(Suppl. 5):S38-S45.

How to cite this article: von Mackensen S, Catalani O, Asikanius E, Paz-Priel I, Lehle M, Trask P. Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL). *Haemophilia*. 2020;26:1019–1030. [https://doi.org/10.1111/hae.14184](https://doi.org/10.1111/hae.14184)