*Clinical Psychology and Psychotherapy*
*Clin. Psychol. Psychother.* **15,** 164–172 (2008)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/cpp.569

# *Psycho-Social Determinants of Quality of Life in Children and Adolescents with Haemophilia—A Cross-Cultural Approach*

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**Quality of life (QoL) of children with chronic conditions has received increasing attention in recent years. While frequent paediatric health conditions and life-threatening conditions are in the foreground, QoL of children with rare diseases such as haemophilia is scarce. While haemophilia-specific instruments to assess QoL in children have been developed, cross-cultural comparison of QoL and its determinants has not been addressed so far. QoL and potential psychosocial determinants such as coping were assessed in 298 paediatric haemophilia patients from six European countries demonstrating significant differences in QoL between countries. Results indicated that psychosocial predictors varied across countries, although life satisfaction and social support explained the highest proportion of variance and, moreover, superseded clinical characteristics. These findings suggest that intervention programmes should be geared towards enhancing psychosocial resources in children and adolescents with haemophilia. Copyright © 2008 John Wiley & Sons, Ltd.**

## INTRODUCTION

The quality of life (QoL) of children with chronic conditions has received increasing attention in recent years. Although the number of articles and papers related to children's QoL still is much lower than research on adult's QoL, there has been a constant increase in the publications listed in the Medline-System (Ravens-Sieberer et al., 2006). However, while frequent paediatric health conditions such as asthma or life-threatening conditions such as leukaemia are in the foreground, the QoL of young people with rare diseases has been largely neglected. Evaluating treatments in these conditions often implies including patients from different nations not only for sample size reasons, but also to compare treatment results across countries. This international orientation of paediatric research requires a clarification of the theoretical, methodological and practical foundations of cross-cultural QoL assessment (Bullinger, Schmidt, Petersen, & Ravens-Sieberer, 2006).

Cross-cultural issues have been addressed in QoL research in terms of understanding cultural diversity in the QoL concept, in terms of developing cross-culturally applicable assessment instruments, and in terms of comparing QoL across countries (Anderson, Aaronson, & Wilkin, 1993). Since QoL measures are increasingly used internationally, assessment instruments have to be available in different languages and for different cultural backgrounds. Thus, QoL research is conceptually, methodologically and practically confronted with the necessity to incorporate the concept of culture

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and language into its measurement approach. As concerns such concepts, two different views compete. While some authors maintain that QoL can only be assessed within specific cultures and are therefore highly sceptical about any attempt towards unification in terms of concepts, measurements and applications, another group of authors support the notion of cultural universality, usually on a higher abstraction level. However, it is also acknowledged that measures can be purposefully designed to be more or less sensitive to cross-cultural differences (Schmidt & Bullinger, 2007).

To address cross-cultural variation, instruments can be translated from one language to another (sequential approach), assembled from available instruments from different countries (parallel approach), or constructed across countries and cultures from the beginning (simultaneous approach) (Bullinger, 1997). Independent of the source of the items, cross-cultural instrument work has to deal with the item development phase, the translation phase, the psychometric testing phase, as well as the norming phase of an instrument. Guidelines have been published that govern these four steps mostly related not only to translation issues but also to the psychometric testing of such measures (Anderson, Aaronson, Leplège, & Wilkin, 1996; Bullinger, Anderson, Cella, & Aaronson, 1993; Streiner & Norman, 1998).

The last decades have brought increasing experiences in constructing and also in developing and testing QoL measures cross-culturally. Most of the work concerns not only generic measures, but also disease-specific measures have undergone similar processes, mainly in terms of sequentially translating available disease-specific measures into different languages. As regards translation, the recommendation includes to have at least one forward and one backward translation as well as cross-cultural harmonization of those translations (Aquadro, Jambon, Ellis, & Marquis, 1996).

One specific problem in cross-cultural psychometric testing for reliability, validity and responsiveness is whether it should be done consecutively for each culture involved or whether the data set should be merged and pooled to then examine cultural variance from the total item pool. As regards norming, representative samples or reference groups for different languages and cultures have to be recruited.

In spite of the intensive work and publication in the cross-cultural QoL area, researchers are mostly involved measuring QoL in adults. Only few studies exist in which QoL measures for young people (children and adolescents) were constructed cross-culturally in a simultaneous way (Bullinger et al., 2006). Examples are the KIDSCREEN generic instrument for population surveys of young people (Ravens-Sieberer et al., 2001), the DISABKIDS chronic generic measure for young people with disabilities (Schmidt et al., 2006), and the disease-specific HAEMO-QoL measure for children and adolescents with haemophilia (Bullinger et al., 2002) or the CHO-KLAT (Young et al., 2004).

Haemophilia is a chronic health condition, which is genetically transmitted and which affects mainly male subjects. Being a rare congenital bleeding disorder it is characterized by spontaneous and post-traumatic bleeding events due to missing blood-clotting factors (Lee, Berntorp, & Hoots, 2004). The major goal in treating patients with haemophilia is to reduce bleeding rate and, consequently, mortality and joint damage in order to prevent future disability. Treatment is based on replacement with the missing clotting factor when bleed occurs (on-demand treatment) or regularly and continuously (prophylactic treatment). The availability of factor concentrates has largely expanded the length and the quality of the lives of these patients. Early diagnosis is required to provide factor replacement therapy timely in children (Santagostino, Gringeri, & Mannucci, 2002) from the first bleeding event onwards, which most of the time—depending on the severity of the disease—occur within the first life year (Liesner, Khair, & Hann, 1996). Dependent on the economic situation of a specific country and their treatment guidelines, administration includes different treatment modalities and dosage of factor concentrate. Provision of factor concentrates, especially prophylactic treatment, is cost-intensive and few countries around the world are able to provide this service to their patients.

In addition, the health condition as well as the treatment may impact not only on patients' physical but also on the mental and the social well-being. This focus on well-being and functioning has recently been introduced into medicine under the heading of health-related QoL (Fischer, Van der Bom, Mauser-Bunschoten, Roosendaal, & van den Berg, 2005; Revel-Vilk et al., 2004).

QoL research in this patient population has focused on the description of psychosocial concomitants of the condition (Miners et al., 1999; Trippoli et al., 2001), and only very recently concerned patient-based outcome criteria as the QoL of children with haemophilia (Bullinger & von Mackensen, 2004; Fischer, van der Bom, & van



**DOI**: 10.1002/cpp

den Berg, 2003; Remor, Young, Von Mackensen, & Lopatina, 2004). While this research is related to a description of health-related QoL in terms of well-being and function as perceived by the patients themselves or their parents, virtually no information is available about the factors potentially influencing QoL of children (Canclini, Zanon, & Girolami, 2004; Bullinger, von Mackensen, & HAEMO-QoL Group, 2003). In addition, since haemophilia is present worldwide, albeit with a low prevalence, cross-cultural assessment of haemophilia is important.

For children with haemophilia, comprehensive QoL assessment is as necessary as are attempts to understand the composition of QoL and its determinants, which may include social support, coping and life satisfaction. Such knowledge is important for academic and clinical reasons, e.g., to identify intervention approaches. Should, for example, coping or social support be an important determinant of QoL, enhancement of these factors may contribute to an improved QoL in the patient.

The present paper addresses cross-cultural differences in QoL and the role of psychosocial factors in a large multi-centre international study on children and adolescents with haemophilia in Europe (von Mackensen et al., 2004a). The primary objective of this study was to assess and describe the QoL of haemophilic children in different European countries, and an ancillary goal was to better understand the factors contributing to QoL in this patient population, within and across specific countries. The objectives of the present paper are to describe the QoL characteristics of children and adolescents with haemophilia across countries, and to identify the contribution of psychosocial factors to QoL relative to socio-demographic and clinical factors.

## METHODS

Within the cross-sectional HAEMO-QoL Project (www.hamoqol.org), children and adolescents fulfilling the inclusion criteria age from 4 to 17 years, severe haemophilia A or B, without infections (hepatitis, HIV) and without inhibitor history were recruited from Haemophilia Comprehensive Care Centres (HCCC) from six European countries (France, Germany, Italy, the Netherlands, Spain, the UK). In each participating centre (see acknowledgements), patients and their parents were informed about the study purpose and were asked to participate in the study by their haemophilia specialist. Patients who were willing to participate, fulfilled the inclusion criteria and whose parents gave their informed consent were enrolled in the study. A total of 19 centres participated and recruited a total of 339 patients and their parents (von Mackensen et al., 2004). Children from three age groups were included in this study, namely, young children (age group I: 4–7 years), schoolchildren (age group II: 8–12 years) and adolescents (age group III: 13–16 years). Depending on the age group children received either an interview (young children) or filled in a questionnaire by themselves (older children) containing a generic (KINDL-R; Ravens-Sieberer & Bullinger, 1998; Bullinger, von Mackensen, & Kirchberger, 1994) as well as a disease-specific QoL questionnaire for children (HAEMO-QoL; Bullinger et al., 2002; von Mackensen, Bullinger, & the HAEMO-QoL Group, 2004).

The KINDL-R is a generic 24-item self-report instrument assessing six dimensions of QoL developed in German language, which has been sequentially translated as well as psychometrically tested in many languages. The HAEMO-QoL is a self-report measure for haemophilic children, consisting of 21–77 items which cover 9–11 domains, depending on the age group. The HAEMO-QoL was developed simultaneously according to the guidelines for cross-cultural questionnaire development. To explain the variance of QoL ratings, instruments addressing psychosocial correlates were included as well. These measures were selected for their focus on coping (Kidcope; Spirito, Stark, & Williams, 1988), on internal/external locus of control (KKG; Lohaus & Schmitt, 1989), on life satisfaction (FLZ; Henrich, Herschbach, & von Rad, 1992) and on social support (SSS; Sherbourne & Stewart, 1991). If not available as children's versions, instruments have been adapted for children from existing versions for adults (KKG, FLZ, SSS). Children's parents also filled in questionnaires relating to their view of their children's QoL and their own QoL. Clinical data were collected within the HCCCs by trained staff using patient documentation forms. The data were centrally checked, inputted and statistically analysed.

After plausibility checking, statistical analysis was performed to obtain descriptive statistics on item and scale level. Correlational analyses was then conducted to examine the relationship between QoL and clinical, socio-demographic as well as psychosocial variables (predictors). Multiple stepwise regression was used to examine the impact of predictors on patients' QoL (criterion). Since very young children did not fill in additional questionnaires about psychosocial data, only children from



**DOI**: 10.1002/cpp

age groups II (8–12) and III (13–16) were included in the present study. All statistical analysis was performed using the SPSS statistical system.

## RESULTS

A total of 339 children as well as their parents participated in the study. The number of centres differed between countries as did the number of patients included per country. More than 60 patients were recruited in 4 countries, and most patients were recruited in France. The recruitment activity of centres differed within and across countries (see Table 1).

### *Sample Description*

Of the 339 patients, only 298 patients between the age of 8 and 16 years were included in this analysis. Table 2 gives an overview over specific sociodemographic characteristics of children across countries. The mean age for the children was about 10 years, children in the Netherlands being slightly older (*Mean* = 12.48, standard deviation [*SD*] = 2.4 years). About half of the children had one sibling, and children without siblings were most frequent in Italy (30.8%) and least frequent in the UK (5.3%). Since the school systems over the countries are not fully comparable, different school types were categorized in 'grammar school', 'middle school', 'high school' and 'other school'. For example, in Spain, 'colegio privado' (18.1%) and 'colegio publico' (12.5%), were considered as 'high school'. Also, 4.5% of the children in the UK reporting to be in a 'private school' were considered as 'high school' students as well.

Since in the Netherlands and the UK only around 20 patients participated, these two countries were not included in the country comparison. Calculations of country differences (via $chi^2$-test) was performed comparing four of the countries: Germany, Italy, France and Spain.

As regards clinical characteristics, differences between countries were found (see Table 3). In Germany, children had significantly fewer major bleeds ($M = 4.15$, $SD = 6.11$) in comparison to Italy ($M = 12.56$, $SD = 21.54$). Significant differences were shown between the countries for the number of major bleeds ($F = 4.215$; $p < 0.006$). Level of factor activity ($chi^2 = 0.0001$), number of joint bleeds ($chi^2 = 0.0001$), number of bleeds other than joints ($chi^2 = 0.012$) and orthopaedic surgery ($chi^2 = 0.001$) differed between countries. Germany was the country with the highest percentage of prophylactic treatment (93.2%); differences in prophylactic versus on-demand treatment were highly significant between countries ($chi^2 = 0.0001$).

Table 1. Number of patients recruited per country and centre

| Countries | Centre | Collected | Σ |
|---|---|---|---|
| Germany | Bremen | 26 | 60 |
| | Leipzig | 14 | |
| | Hannover | 12 | |
| | Munich | 8 | |
| Italy | Florence | 11 | 70 |
| | Milan | 41 | |
| | Turin | 18 | |
| UK | London | 22 | 22 |
| France | Nantes | 12 | 86 |
| | Caen | 10 | |
| | Tours | 15 | |
| | Paris | 29 | |
| | Marseille | 15 | |
| | Brest | 5 | |
| Spain | Valencia | 17 | 76 |
| | Zaragozza | 10 | |
| | Sevilla | 14 | |
| | Madrid | 35 | |
| The Netherlands | Amsterdam | 6 | 25 |
| | Utrecht | 19 | |
| Total | | | 339 |

### *Differences between Countries in QoL*

QoL was assessed with the disease-specific HAEMO-QoL questionnaire, with high values indicating a high impairment in QoL. Analysis of mean and standard deviations across countries was performed for the scales of the HAEMO-QoL (scales were transformed from 0–100 in order to be comparable). Results revealed that countries varied considerably with regard to the score distribution (see Table 4). Most impairments were found in France ($M = 25.93$, $SD = 7.6$), followed by Spain ($M = 22.49$, $SD = 11.17$); less impairments were reported by children in Germany ($M = 19.26$, $SD = 8.2$) and Italy ($M = 21.95$, $SD = 10.2$). Significant differences were shown between the countries in almost all subscales as well for the total HAEMO-QoL score ($F = 3.178$, $p < 0.026$).



**DOI**: 10.1002/cpp

Table 2. Children's socio-demographic characteristics over the countries

| Characteristics | | Germany ($n$ = 59) | Italy ($n$ = 70) | France ($n$ = 73) | Spain ($n$ = 77) | The Netherlands ($n$ = 25) | UK ($n$ = 22) |
|---|---|---|---|---|---|---|---|
| Age | *Mean* (*SD*) | 9.78 (3.6) | 9.91 (3.9) | 10.26 (3.8) | 9.41 (3.5) | 12.48 (2.4) | 9.09 (3.3) |
| Number of siblings | 0 | 22.0% | 30.8% | 13.6% | 18.3% | 8.0% | 5.3% |
| | 1 | 50.8% | 43.1% | 50.0% | 53.5% | 52.0% | 63.2% |
| | 2 | 18.6% | 13.8% | 22.7% | 16.9% | 20.0% | 10.5% |
| | 3 | 3.4% | 7.7% | 9.1% | 5.6% | 12.0% | 5.3% |
| | ≥4 | 5.1% | 4.6% | 4.5% | 5.6% | 8.0% | 15.8% |
| Schooling | Grammar | 21.7% | 17.1% | 22.1% | 8.3% | 16.7% | 13.6% |
| | Middle | 23.8% | 34.2% | 32.5% | 25.0% | 16.7% | 27.1% |
| | High school | 6.7% | 5.7% | 2.6% | 30.6% | 33.4% | 13.5% |
| | Other school | 8.3% | 4.3% | 1.3% | 1.4% | – | 13.5% |

Table 3. Clinical status across countries (*M*, *SD* and percentages)

| | | Germany | Italy | France | Spain |
|---|---|---|---|---|---|
| Number of major bleeds | *M* (*SD*) | 4.15 (6.11) | 12.56 (21.54) | 9.37 (11.98) | 6.28 (10.14) |
| Age of first bleeding episode | Months *M* (*SD*) | 11.82 (15.42) | 10.52 (7.85) | 9.63 (8.82) | 12.96 (17.09) |
| Age of first joint bleeding episode | Months *M* (*SD*) | 25.52 (21.28) | 21.27 (15.45) | 28.56 (18.14) | 29.70 (18.58) |
| Type of haemophilia | A | 86.0% | 82.1% | 89.9% | 89.2% |
| | B | 14.0% | 17.9% | 10.1% | 10.8% |
| Level factor activity | <1% | 96.6% | 91.0% | 91.4% | 65.3% |
| | ≥1% | 3.4% | 9.0% | 8.6% | 34.7% |
| Number of joint bleedings | 0 | 45.8% | 17.9% | 24.1% | 28.8% |
| | <5 | 43.8% | 37.5% | 56.9% | 50.0% |
| | 5–10 | 6.3% | 16.1% | 13.8% | 10.6% |
| | >10 | 4.2% | 28.6% | 5.2% | 10.6% |
| Number of bleedings other than joints | 0 | 44.4% | 39.5% | 28.0% | 42.3% |
| | <5 | 42.2% | 39.5% | 32.0% | 32.7% |
| | 5–10 | 13.3% | 7.0% | 10.0% | 15.4% |
| | >10 | – | 14.0% | 30.0% | 9.6% |
| Joint impairments | Yes | 19.0% | 9.1% | 16.2% | 9.3% |
| Chronic pain | Yes | 5.1% | 3.0% | 2.9% | 4.0% |
| Orthopaedic surgery | Yes | 1.7% | 3.0% | 18.6% | 5.3% |
| Treatment mode | Prophylactic ($n$ = 217) | 93.2% | 56.7% | 50.0% | 62.7% |
| | On-demand ($n$ = 101) | 6.8% | 43.3% | 50.0% | 37.3% |

### *Variance of QoL Ratings*

In the next step, multiple stepwise regression was used to identify for each country the contribution of each of a selected number of variables on children's QoL. These predictor variables included coping, locus of control, life satisfaction and social support. In addition, two clinical variables were included, namely treatment modality (on-demand versus prophylactic) and symptoms (number of major bleedings). The regression analysis was performed separately for each country, but combined for children from 8 to 16 years, i.e., in age group II and III (see Table 5).

Results showed that life satisfaction impacted on QoL in three of four countries. In Italy, 61% of the



**DOI**: 10.1002/cpp

Table 4. Score distribution across countries (*M*, *SD*)

| (Range 0–100) | Germany | Italy | France | Spain | *F*-value, *p*-value |
|---|---|---|---|---|---|
| Physical health | 13.25 (19.9) | 20.75 (17.6) | 15.53 (14.3) | 17.45 (15.9) | n.s. |
| Feeling | 9.19 (11.4) | 11.72 (17.0) | 10.36 (13.0) | 10.53 (15.1) | n.s. |
| View | 13.67 (13.3) | 14.91 (17.1) | 23.43 (15.6) | 15.79 (17.2) | $F = 3.398$, $p < 0.019$ |
| Family | 14.69 (16.7) | 18.73 (17.0) | 16.89 (15.2) | 29.51 (21.5) | $F = 6.097$, $p < 0.001$ |
| Friend | 45.47 (30.3) | 45.43 (24.7) | 55.71 (23.4) | 37.09 (27.0) | $F = 3.839$, $p < 0.011$ |
| Perceived support | 45.16 (24.9) | 52.13 (26.8) | 59.92 (21.4) | 46.25 (23.3) | $F = 3.499$, $p < 0.017$ |
| Others | 12.19 (13.5) | 11.31 (16.2) | 11.96 (12.5) | 11.32 (17.7) | n.s. |
| School | 17.48 (13.8) | 22.45 (18.1) | 36.38 (18.9) | 25.71 (19.9) | $F = 8.543$, $p < 0.000$ |
| Dealing | 32.77 (20.4) | 37.68 (21.0) | 29.76 (19.2) | 29.49 (22.3) | n.s. |
| Treatment | 20.81 (16.3) | 17.56 (14.4) | 25.31 (16.2) | 20.85 (16.0) | n.s. |
| Total | 19.26 (8.2) | 21.95 (10.2) | 25.93 (7.6) | 22.49 (11.2) | $F = 3.178$, $p < 0.026$ |

Table 5. Regression analysis for the different countries (HAEMO-QoL)*

| | Germany | | Italy | | France | | Spain | |
|---|---|---|---|---|---|---|---|---|
| | beta | *p* | beta | *p* | beta | *p* | beta | *p* |
| Coping | – | – | – | – | – | – | – | – |
| Locus of control | – | – | – | – | – | – | – | – |
| Life satisfaction | –0.350 | 0.035 | –0.722 | 0.000 | –0.776 | 0.001 | – | – |
| Social support | 0.393 | 0.033 | – | – | – | – | – | – |
| On-demand | – | – | – | – | – | – | – | – |
| Number of major bleed | – | – | 0.232 | 0.077 | – | – | – | – |
| $R^2$ | 34.7% | | 61.2% | | 29.4% | | 9.7% | |

*Intercepts not shown.

variance of QoL impairments could be explained by reduced life satisfaction and a high number of major bleedings. In Germany, social support was associated with QoL ratings, suggesting that high social support was experienced by children with low QoL. By contrast, in Spain, only the intercept, but none of the determinants had a significant impact on the QoL of young people with haemophilia (see Table 5).

Similar results were found for the generic QoL instrument (KINDL-R), where the explained variance of QoL ranged from 26% to 48% in the respective countries.

## DISCUSSION

It is well known from epidemiology and clinical research that psychosocial and cultural factors exert an influence on patients' QoL and that the cultural background plays an important role (Schmidt & Bullinger, 2007). Psychosocial factors affecting QoL include coping, social support and locus of control (Ravens-Sieberer, Wille, Bettge, & Erhart, 2007). They relate to both resources as well as strains, which may enhance or limit patients' QoL. However, most of the available studies deal with adults, and the type and operationalization of these concepts differ, so that comparison of results is difficult. A meta-analytic review is further hampered by the fact that these factors have been assessed in different types of diseases so that variation is not only derived from the methods of assessment, but also the diversity in health conditions (Bullinger, 1991). Nevertheless, it has been shown that the proportion of variance explained by psychosocial factors is not only statistically significant but also clinically relevant. Moreover, these studies have shown that psychosocial factors may supersede clinical characteristics which usually explain less in QoL outcome than expected (Masthoff et al., 2007).

Health-related QoL has been acknowledged as an important outcome criterion in haemophilia (Beeton, 2002; Gringeri, Mantovani, & von Mackensen, 2006), and disease-specific measures have been developed for adults (e.g., Haem-A-QoL; von Mackensen et al., 2004b; von Mackensen, Gringeri, Ravera, & the HAEM-A-QoL Group, 2005) and children (e.g., Manco-Johnson, Morrissey-Harding, Edelman-Lewis, Oster, &



**DOI**: 10.1002/cpp

Larson, 2004; CHO-KLAT; Young et al., 2004). However, only few papers have addressed the question, which factors might positively or negatively impact on the QoL of children with haemophilia and how might this differ between countries. It can be expected that characteristics of the health condition and its treatment (severity of haemophilia, number of bleeding events, inhibitor status as well as type of treatment: prophylactic versus on demand) are important predictors, which are also dependent on the health care system and specific characteristics of a given country (Royal et al., 2002). The QoL of children, however, is not limited to these clinical characteristics, but also includes psychosocial predictors.

In the present study, the role of clinical and psychosocial predictors of QoL in children and adolescents with haemophilia was examined across countries. The distribution of QoL indicators (HAEMO-QoL) showed a variation across countries. Furthermore, these results showed that psychosocial predictors in contrast to clinical variables contribute highly to the explained variance, differing across countries. In a longitudinal study of 600 children with asthma, obesity and atopic dermatitis, life satisfaction as well as social support had the strongest impact on health-related QoL (Bullinger & Ravens-Sieberer, 2006). Similarly, social support was correlated with QoL in a European population survey in children and adolescents (von Rueden, Gosch, Rajmil, Bisegger, & Ravens-Sieberer, 2006). It is important to know that of the psychosocial predictors, life satisfaction has the strongest impact, and that psychosocial predictors were superior to clinical predictors in terms of explained variance in QoL. The results are important for identifying potential possibilities to intervene in children and adolescents with haemophilia. Deficits in resources such as social support may contribute to a low QoL. Interventions to increase social support may be an important treatment option. Although this study was cross-sectional in nature, it suggests innovative approaches to enhance QoL in young people with haemophilia. Longitudinal studies are needed in the future to substantiate the postulated relationships between psychosocial factors and QoL and to appropriately evaluate interventions oriented towards these determinants.

## ACKNOWLEDGEMENTS

We would like to give special thanks to all children and adolescents and their parents who took their time to fill in the questionnaires. We would like to acknowledge all participating centres of the Haemo-QoL Study Group for their precious contribution to the study, collecting all clinical and psychosocial data (Pilar Arranz, Hospital La Paz, Madrid, Spain; Günther Auerswald, Zentralkrankenhaus, Bremen, Germany; José Aznar, Hospital Universitario La Fe, Valencia, Spain; Marijke van den Berg, Academisch Ziekenhuid Utrecht, the Netherlands; Annie Borel-Derlon, Centre de l'Hémophilie, Caen, France; Hervé Chambost, Centre de l'Hémophilie, Marseille, France; Edith Fressinaud, Centre de l'Hémophilie, Nantes, France; R. Perez Garrido, University Hospital Virgen del Rocio, Sevilla, Spain; Alessandro Gringeri, IRCCS Maggiore Hospital and University of Milan, Milan, Italy; Claude Guerois, Centre de l'Hémophilie, Chambray Lés Tours, France; Kate Khair, Great Ormond Street Hospital for Children NHS Trust, London, UK; Karin Kurnik, v. Haunerische Kinderklinik, München, Germany; Harald Lenk, Klinik für Kindermedizin, Universität Leipzig, Germany; Giovanni Longo, Centro Emofilia, Firenze, Italy; Felix Lucia, Servicio de Hematologia, Zaragoza, Spain; Laura Perugini, Ospedale Infantile 'Regina Margherita', Torino, Italy; Marijolein Peters, Academish Medish Centrum, Amsterdam, the Netherlands; Eduardo Remor, Hospital La Paz, Madrid, Spain; Chantal Rothschild, Centre de l'Hémophilie, Hopital Necker, Paris, France; Marc Trossaert, Centre de l'Hémophilie, Nantes, France; Monique Vicariot, Centre de traitement de l'hémophilie, CHU de Brest, France; Cornelia Wermes, Pädiatrische Hämatologie und Onkologie, Medizinische Hochschule Hannover, Germany).

The Haemo-QoL study was sponsored by an unrestricted educational grant by Bayer HealthCare.

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