Haemophilia (2004), **10,** (Suppl. 4), 30–34

Disease-specific quality-of-life measurement tools for haemophilia patients

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Summary. The purpose of this paper is to summarize the state of the art in measuring quality of life in haemophila populations. The paper reviews the measures recently included in haemophila trials in the published literature. It also summarizes the development of four new disease-specific measures of health-related quality of life. Two of these were developed for children (the Haemo-QoL and the CHO-KLAT), and two for adults (the Hemofilia-QoL and the Hemolatin-QoL). These new measures show promise for use in clinical trials. Further research is in progress to complete the psychometric testing and cross-cultural validation.

Keywords: adults, assessment, children, haemophilia, quality of life

Introduction

Assessing the outcome of treatment is an essential component of evaluating practice. One important outcome for the evaluation of haemophilia care is health-related quality of life (HRQoL), defined as a multidimensional construct pertaining to the physical, emotional, mental, social and behavioural components of wellbeing and function as perceived by the patients and/or observers [1]. HRQoL is not only influenced by disease and its treatment, but also by personal characteristics such as coping, internal locus of control, living conditions and socioeconomic status.

Literature review indicates increasing use of HRQoL measures as outcomes in haemophilia treatment [2,3]. It is particularly important to have different options available to measure this construct that match the needs of health professionals and researchers. General guidelines that direct healthcare professionals in the selection of well-developed and validated questionnaires to assess the relevant aspects of quality of life (QoL) have been described by Bullinger and Mackensen [4]. For an adequate assessment of HRQoL, validated questionnaires are necessary. In general, generic questionnaires are used in other clinical trials, which allow a comparison with patients of other chronic diseases or the general population. By contrast, only disease-specific measures can give a detailed pattern of specific symptoms and impairment related to a specific disease such as haemophilia.

Until now, disease-specific measures to assess QoL for individuals with haemophilia were not available. The advantage of disease-specific measures for QoL lies in the fact that the content of these instruments are more appropriate for haemophilia patients, because they address relevant issues related to haemophilia. Therefore, these questionnaires are expected to be more sensitive to clinically significant changes.

This paper will review the latest advances and availability of disease-specific measures for the assessment of QoL in people living with haemophilia. Characteristics and applications of these instruments will be described and future applications will be discussed.

Quality-of-life assessment in haemophilia

Several studies that address QoL issues in people living with haemophilia have been published since 1990, most of which employed generic measures for the assessment of QoL. Table 1 presents an overview of these studies in chronological order.

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Table 1. Studies assessing HRQoL with generic and disease-specific measures in haemophilia

Year	Authors	Country	Participants	Sample (*n*)	Measure
Generic					
1990	Rosendaal *et al.* [5]	Netherlands	Adults	935	*Ad hoc* questionnaire
1996	Szucs *et al.* [6]	Germany	Adults	50	SF-36, UQ
1999	Miners *et al.* [7]	England	Adults	99	SF-36, EQ-5D
1999	Miners *et al.* [8]	England	Adults	249	SF-36, EQ-5D
2000	Aznar *et al.* [9]	Spain	Adults	70	SF-36
2000	Brewin *et al.* [10]	Australia	Children	6	CHQ-CF/PF, EQ-5D
2000	Khair [11]	England	Children	30	MMQoL
2000	Sek *et al.* [12]	Canada	Adults	129	HUI
2000	Molho *et al.* [13]	France	Adults	11	SF-12
2000	Schick *et al.* [14]	Switzerland	Adults	116	SF-36
2001	Solovieva [15]	Finland	Adults	150	SF-36
2001	Ekert *et al.* [16]	Australia	Adolescents	6	CHQ-CF/PF, EQ-5D
2001	Trippoli *et al.* [17]	Italy	Adults	56	SF-36, EQ-5D
2001	Schoenmakers *et al.* [18]	Netherlands	Children	39	CHAQ
2002	Royal *et al.* [19]	European countries	Adults	1033	SF-36
2003	Gringeri *et al.* [20]	Italy	Adults	52	SF-36, EQ-5D
Specific					
2000	Bullinger *et al.* [21]	6 European countries	C/A and P	58*	Haemo-QoL
2004	von Mackensen *et al.* [22]	6 European countries	C/A and P	339	Haemo-QoL
2004	Young *et al.* [24]	Canada	C/A and P	52†	CHO-KLAT
2004	Arranz *et al.* [23]	Spain	Adults	73† 35*	Hemofilia-QoL
2004	Remor *et al.* [25]	8 Lat-Am countries	Adults	50†	Hemolatin-QoL

*Pilot testing, psychometric; †Development study. CHAQ, Children's Health Assessment Questionnaire; CHO-KLAT, Canadian Haemophilia Outcomes – Kids Life Assessment Tool; CHQ-CF/PF, Child Health Questionnaire-Children's form/Parents' form; EQ-5D, Euroqol EQ-5D; Haemo-QoL, Haemophilia Quality-of-life questionnaire; Hemofilia-QoL, Adults Haemophilia Quality of Life questionnaire; Hemolatin-QoL, Adults Haemophilia Quality of Life questionnaire; HUI, Health Utilities Index; MMQoL, Manchester Minneapolis QoL Index; SF-36/SF-12, Medical Outcomes Study-Short Form 36/Short Form 12; UQ, Utility Questionnaire; Lat-Am; Latin-American; C/A and P; children or adolescents and their parents.

Until recently, the most widely used instruments to assess QoL in haemophilia research were the generic measures, such as SF-36 (Medical Outcomes Study) or EQ-5D (EuroQoL) questionnaires for adults, and the Child Health Questionnaire for children (see Table 1). However, a few studies have warned of possible limitations in these generic instruments for tapping specific concerns of haemophilia patients [3,21]. In order to improve the assessment of HRQoL in people with haemophilia, and following the tendency in other medical fields, different international working groups started the development of disease-specific measures to assess QoL in people living with haemophilia in Europe [21–23], North America [24] and Latin America [25].

These new recent measures for children [Haemo-QoL and the Canadian Hemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT)] and adults (Hemofilia-QoL and Hemolatin-QoL) were specially developed and validated for the adequate assessment of HRQoL in people living with haemophilia. The lower part of Table 1 summarizes the first research efforts to develop disease-specific measures to assess QoL in haemophilia patients.

The subsequent sections describe the development of these instruments.

Quality-of-life assessment measures for children with haemophilia

Development and testing of the Haemo-QoL

A literature review was conducted in 1999 that identified 14 publications with the keywords 'quality of life', 'haemophilia' and 'children'. Only a few studies used a questionnaire assessing quality of life. No disease-specific questionnaire for children with haemophilia was available. This led to the development of a disease-specific QoL questionnaire for children and adolescents with haemophilia (Haemo-QoL).

The Haemo-QoL was recently field-tested in six European countries (Germany, Italy, France, Spain, Netherlands, and the UK) involving 339 children from 20 centres [22]. The Haemo-QoL is a self-report questionnaire for children. It has three versions for different age groups: version I for children 4–7 years of age (21 items), version II for children

8–12 years of age (64 items) and version III for children 13–16 years of age (77 items), as well as a version for parent report. The versions consist of 9–11 subscales, depending on the age group. The psychometric structure of the questionnaire showed acceptable psychometric properties for the three age-group versions and for the accompanying parent forms [22]. HRQoL was shown to be satisfactory: young children were negatively affected only in the areas 'family' and 'treatment', whereas older children had higher impairments in the social areas, such as 'perceived support' and 'friends'. The Haemo-QoL questionnaire also showed that the initial burden induced by prophylaxis in younger children is compensated by improvements in HRQoL in older children, as indicated by impaired scores in the dimension 'feeling' in smaller children and improved scores in the dimension 'school & sport' in older children [26]. Using psychosocial determinants of QoL such as coping, locus of control, life satisfaction and social support, it was apparent that QoL measures not only clinical but also psychosocial characteristics [27].

The Haemo-QoL full version is now available for children of three age groups and their parents and is ready for use in clinical research.

Development and testing of the Canadian Haemophilia Outcomes – Kids Life Assessment Tool

The CHO-KLAT is a 35-item disease-specific measure of QoL that was developed using childcentred methods [24]. Its development began in 1999 [28], and was concurrent with the development of the Haemo-QoL. The CHO-KLAT is unique in that it included children in the item-generation phase, and prioritized the values of children during the item-reduction process.

Items for the CHO-KLAT were derived from generic measures and the haemophilia literature. Five discussion groups and six focus groups (three of which were exclusively made up of children) were conducted to generate additional items. This resulted in a pool of 228 items. The pool was reduced to 79 items based on the values children assigned to the items, and later to a pool of 35 items based on the psychometric properties of the items.

The value of the childcentred approach to measure development using a three-step process was then assessed: (i) the items retained in the final 35-item version of the CHO-KLAT were reviewed to determine whether children had generated unique items that would not have been identified through traditional methods; (ii) a sample of 10 children were asked to explain their understanding of the items and choice of responses to determine if children were able to understand all the items; and (iii) data from 52 child–parent dyads were analysed to determine child–parent concordance. Data collected 2 weeks later was analysed to assess test–retest reliability of child self-report.

The results showed that children are able to play an important role in the development of measures and their use. Specifically, children generated unique items and suggested important wording modifications that were not identified by other sources. Their input contributed to the CHO-KLAT's strong psychometric properties. Cognitive debriefing confirmed that children understood the questions and were capable of self-report. However, there were some inconsistencies in the use of the 'Not Applicable' response option, both by children and by parents. The concordance between children's self-report and the parents' report was substantial (greater than 0.6), as were the repeated measures intraclass correlation coefficients for children and parents.

In summary, this study found that children provided a unique perspective on QoL that was not represented by others. They understood and answered questions in a way that was consistent with their parents and was stable over time. The CHO-KLAT is a childcentred measure that shows promise for use in clinical trials. Minor modifications are now being made to determine if the consistency can be further enhanced by making the N/A responses more specific. The relationship between the CHO-KLAT and the Haemo-QoL will also be examined.

Quality-of-life assessment measures for adults with haemophilia

Development and testing of the Hemofilia-QoL

A haemophilia-specific health-related quality of life questionnaire (Hemofilia-QoL) was developed to assess quality of life in adults with haemophilia. The questionnaire was developed using patient-centred methods. In total, 73 interviews with haemophilia patients ($n = 47$) and healthcare professionals ($n = 26$) were performed to generate the items included in the questionnaire. Generation of items was performed by content analysis to identify categories (domains) and synthesized the issues that emerged from the interviews into items.

Ratings from haemophilia experts ($n = 12$) were used to address item comprehension, relevance to haemophilia and to organize items into domains. Expert judgements on the items formulated were

used to screen items for review or potential omission. This step was followed by psychometric testing in a sample of 35 patients. Preliminary psychometric testing of the revised questionnaire version, which contains eight domains (physical health, physical role, joint damage, pain, treatment satisfaction, emotional role, mental health, social support), showed acceptable reliability ($\alpha = 0.94$ for the Hemofilia-QoL total score) and adequate convergent validity with the SF-36 Health Survey [23].

Development and testing of the Hemolatin-QoL

The Hemolatin-QoL (Spanish and Portuguese versions) is a cross-cultural measure developed in Latin America using patient-centred methods [25]. It has been developed in a multinational Latin American working group (the Hemolatin-QoL Group), in cooperation with haemophilia treatment centres and national haemophilia organizations in eight Latin-American countries (Argentina, Brazil, Colombia, Cuba, Guatemala, Panama, Uruguay and Venezuela; 10 centres involved). Five adults with haemophilia per centre ($n = 50$) were interviewed. A common list of guiding questions was used for all interviews. The questions asked what issues participants believed were relevant to their quality of life as a person with haemophilia. The interviews were transcribed, subjected to content analysis, and synthesized into potential items for the new questionnaire. The items were organized into domains regarding their content. The item-generation process was carried out by bilingual Spanish–Portuguese experts to ensure the language equivalence of the questionnaire.

To address the content and face validity, the preliminary version of the instrument was sent to haemophilia experts ($n = 10$) and patients ($n = 10$), and each completed a standardized evaluation form to assess the comprehensiveness and relevance to haemophilia, and provided suggestions to delete or rephrase the items. Experts' and patients also rated whether the item was assigned to the correct domain. The result is a high-quality, disease-specific, preliminary 47-item questionnaire for adults. Psychometric evaluation is currently in progress within several Latin-American countries.

Conclusions

In the last 4 years haemophilia-specific questionnaires to assess QoL have been developed around the world. This is an important step forward in haemophilia outcomes measurement research. However, further efforts are necessary to examine the psychometric characteristics of these measures, and to generate expected scores and confidence intervals from representative samples. In addition, we need to validate cross-culturally appropriate versions of haemophilia-specific questionnaires for children and adults all over the world. Such measures will cover the areas of HRQoL that are most important to patients with haemophilia (e.g. physical functioning, social functioning, emotional wellbeing, satisfaction of care, treatment satisfaction, impairments and healthcare needs, and perceived health).

QoL assessment should be included in all clinical evaluations of treatment options, from product-licensing studies to gene-therapy trials, as one of the main outcomes. Finally, health-related QoL questionnaires should be part of the medical armamentarium for the global assessment and care of patients with haemophilia.

Acknowledgements

Funding for the development of the CHO-KLAT was provided by The Canadian Haemophilia Society, the Association of Haemophilia Clinical Directors of Canada, and Aventis-Behring. Funding for the development of the Haemo-QoL was provided by Bayer. Funding for the development of the Hemofilia-QoL was provided by Baxter, SL, Spain. Funding for the development of the Hemolatin-QoL was provided by Centro de Estudios para América Latina–UAM–BSCH.

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