

# Quality of life assessment in haemophilia

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**Summary.** Quality of life (QoL) is a recent focus of research in haemophilia. It can be defined – in analogy to the World Health Organization (WHO) definition of health – as patient-perceived wellbeing and function in terms of physical, emotional, mental, social and behavioural life domains. The paper describes conceptual, methodological and practical foundations of QoL research in adults and children at an international level. It then proceeds to review the QoL literature in the field of haemophilia. With regard to assessment of QoL in haemophilia patients, both generic and very recently targeted instruments have been applied. Recent publications have focused

on describing QoL in adults, showing specific impairments in terms of physical function (arthropathy) and mental wellbeing (HIV infection) as well as focusing on the cost–benefit (QoL) ratio of haemophilia care. In paediatric haemophilia, research has suggested the beneficial QoL outcomes with prophylaxis and stressed the role of the family for patients' wellbeing and function. QoL research is a relevant area for haemophilia research which should be pursued further.

**Keywords:** quality of life, assessment, children, adults, cross-cultural

## Introduction

Within medical research, the need to assess patient-based outcomes has increased during recent years [1]. In accordance with the World Health Organization (WHO) definition of health, outcomes have been identified which include the personal experience of the patient, i.e. the person concerned in terms of his/her condition and its treatment. Classical outcomes such as indicators of morbidity, symptomatology and mortality have increasingly been complemented by patient-based criteria, which include the patient's view of his condition and its care. These outcomes have been identified in the WHO definition of health, which includes not only the mere absence of infirmity but also physical, mental and social wellbeing. Health-related quality of life (HRQoL) has, since then, been introduced into medicine as a relevant parameter [2].

HRQoL can be seen as a subjective representation of health, including the above-mentioned physical, mental and social, but also emotional and everyday life dimensions in terms of wellbeing and function

from the patient's perspective [3]. Several definitions of QoL have been provided, ranging from operational to more philosophical approaches, such as the definition of the WHO viewing QoL as 'individuals' perceptions of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectation standards and concerns' (World Health Organization Quality of Life Assessment (WHOQoL) Group [4]). More operational definitions of QoL have acknowledged that it is 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. Many publications focus on these components of QoL as well as the fact that HRQoL is influenced both by disease and treatment but also by personal characteristics such as coping or internal locus of control and by living conditions including, for example, access to care and financial status [5].

Different QoL models have been proposed to describe the theoretical concept underlying the QoL field. These theoretical models range from social comparison approaches (maintaining that an individual's QoL is judged within a social reference system) to homeostasis models (indicating that QoL is ideally a minimal gap between expectations and their fulfilment). While debates are still ongoing about the appropriate conceptual framework of

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HRQoL research (and the relationship between QoL and other indicators of wellbeing such as happiness, satisfaction, positive emotions or mood), the operational model of QoL has gained most acceptance. This is because it describes clearly how components of the QoL construct can be identified and measured [6].

In parallel to the more theoretical discussions about models and conceptions of QoL, which were conducted mainly during the 1970s, the development of QoL assessment instruments began from the mid-1980s. Although interviews and individualized approaches had been available, more recently QoL measures have been developed in the form of questionnaires to be completed by the patients themselves [7]. These questionnaires have been constructed according to the psychometric approach, which requires that instruments for each relevant QoL domain should contain a number of questions (items) which should represent the construct in a reliable, valid and sensitive way. In psychometric test theory, reliability refers to the repeatability or internal consistency of the measure, validity refers to the conceptual fit between the items and the theoretical model and/or the convergence between instruments assessing the same construct; sensitivity refers to the ability of the instrument to measure changes over time, due to treatment or intervention. Test theory provides mathematical and statistical tools to examine the reliability, validity and sensitivity of a given measure [8].

From the 1980s onwards, several instruments to assess QoL were developed. First came the so-called generic measures which assess HRQoL independently of the actual health condition. They are therefore applicable to patients both with and without a chronic health condition. More recently, disease-specific measures which are targeted towards assessing QoL with regard to specific health conditions were developed. Most of the QoL measures are self-reported [9,10]. However, some, especially in the paediatric area, are rated by other people (e.g. parents, physicians). While multidimensional measures assess different dimensions of QoL representing the original construct, several measures assess only one dimension of HRQoL, either in the form of an index or as a summary measure. Among the generic measures are the SF-36 health survey ([10] and the WHOQoL questionnaire [11]); other generic measures have been described in overviews and publications [9,10]. Among the disease-specific measures is the European Organization for Research and Treatment of Cancer (EORTC) questionnaire for cancer patients [12].

By now most of these measures are available in different languages, due to an increased attention to international and cross-cultural QoL assessment. Interest in cross-culturally useable measures comes from epidemiological studies (health surveys) [13] in which the QoL of the population is to be compared not only within but also across different countries and also for outcome assessment in the form of randomized clinical trials which, especially in rare conditions, are conducted with patients from different countries. Also quality assurance programmes and health-economic evaluations tend to include internationally available measures. A prerequisite for using measures across cultures is to ensure cross-cultural comparability. This includes functional equivalence (similarity of items in cross-cultural meaning), operational equivalence (comparability of procedures used to obtain information), scale equivalence (individuals responding similarly to similar items) and metric equivalence (individuals ordered or measured in a cross-culturally comparable way).

In international research, different strategies to obtain cross-culturally useable measures have been employed [14]. First is the *sequential* approach in which an instrument originating in one country is translated from the original language to another (e.g. this was performed with the SF-36 health survey). A *parallel* strategy includes a common identification of dimensions which are relevant across cultures. This makes use of established scales from each specific culture to measure commonly agreed-upon domains of QoL (the EORTC Questionnaire is an example of this procedure). A *simultaneous* approach includes national identification of dimensions and domains, wording of items and consensus on items to be used across cultures (this approach was used by the WHOQoL Group).

In international HRQoL research four steps are important to derive a measure. The first is *instrument development*, the second is *translation*, the third is *psychometric testing* (reliability, validity, responsiveness) and the fourth is *norming*. These four steps may not follow sequentially but can also be iterated in that, e.g. retranslation might be necessary after psychometric testing.

With regard to instrument development, this includes the generation of items mainly by focus groups which include patients who are asked about their perception of their condition, the problems and impairments associated with them as well as the resources employed to cope with the situation. A further phase is item formulation, which is followed by pretesting with cognitive debriefing items, i.e.

interviewing respondents about how items were understood. After review, items are then assembled in a pilot questionnaire which is sampled in one language and then translated into other languages.

The translation step includes translating the original via forward translation into the target language and then retranslating in backward translation into the original language. It has been recommended that two independent translators are used for each of the steps (forward and backward) and that quality ratings are included to assess the difficulty of the translation of original and the quality of the forward as well as the backward translations. Comparison of the retranslated version with the original is an important task in order to ensure that the conceptual content has been retained. An additional procedural step includes the international harmonization of translations, which pertains to discussing in a multilingual group of experts the translation of one item into these respective languages and comparing these national translations with each other.

Concerning psychometric testing, the application of the measure in a sample of at least 50–100 patients per country is necessary in order to obtain preliminary information about the reliability, validity and responsiveness of the measure (in a longitudinal study). For reliability, test–retest reliability or internal consistency (Cronbach's alpha) of items belonging to one dimension (or subscale) are examined. For validity, the factorial structure, both via factor analysis and structural equation modelling of the questionnaire, may be tested. Discriminant and convergent validity approaches can also be used, which include comparing the instrument with another instrument measuring similar concepts (convergent) or differentiating subgroups of patients with clinically known differences in symptomatology (discriminant validity). Responsiveness pertains to a known change in clinical status. It can be tested only longitudinally, in that the measure is applied before and after an intervention, ideally in a randomized clinical trial in which a control group is available [15].

Norming is important, especially for generic measures, and performed by applying the measure to a nationally representative sample of the population, so that reference data can be used to interpret results of clinical and non-clinical populations. Non-representative data can be assembled from study populations.

Several working groups exist that have addressed these issues of cross-cultural instrument development. These have produced both guidelines and methodologies, as well as results using these instruments in cross-cultural testing [8].

Examples of cross-cultural QoL assessment in adults include the International Quality of Life Assessment (IQOLA) Project, which used the SF-36 health survey in several countries, as well as adult publications of the WHOQoL project [10,11]. While these former projects concern adults, the paediatric area has only recently received attention.

### Assessing QoL in children and adolescents

One of the problems of QoL research in children is the question of whether the dimensions of QoL used in adults also apply to children, from which age the self-report of children is possible, and what role is played by parents' reports of children's wellbeing [16].

Compared to the literature in adults, QoL research in children is still rare. Although papers on the subjective perception of health and illness in children are available, instruments to assess QoL have only recently begun to be developed. A recent review shows that although internationally several measurement instruments to assess QoL in children are available both in generic as well as disease-specific terms, few of them meet the criteria of cross-cultural applicability [17]. The WHO has issued guidelines according to which instruments should be developed for children. These include that QoL assessment instruments for children should be related developmentally to the age of respondents, should be child-centred, should include both positive and negative aspects of the health condition being studied, should be short, concise and practicable (see [17]). Historically, QoL in children was represented by the parents' view. However, recent research has shown that children's and parents' ratings are not identical and that the difference may vary according to the health condition under study. Depending on the condition, parents can tend to either over- or underrate children's wellbeing. Such diversion can also exist among dimensions within the same questionnaire [18].

Research so far suggests a divergence of parents' and children's ratings, suggesting that parents' ratings do not constitute proxy measures of children's QoL but that their ratings should be used as an independent source of information [16]. With regard to dimensions of QoL valid for children, it is increasingly clear that the social dimension in children is of specific importance and should be subdivided, containing aspects of family, friends and other people, and that the self-concept needs to be addressed more specifically. In addition, the age-relatedness of measures is due to the fact that during

the developmental phases, children's concerns and relevant dimensions change dramatically from early childhood to adolescence, where aspects of peer relationships, future and intimacy become important [17].

To date, several instruments are available to assess HRQoL in children either in terms of generic or disease-specific aspects. Most of these measures exist in only one language or have been tested in only one country. Several instruments, however, have been translated and tested in different languages. Among these are the generic KINDL-questionnaire [18] or the Child Health questionnaire (CHQ) [19] and several disease-specific questionnaires (e.g. in asthma). However, no study has been conducted so far to develop and test simultaneously a QoL measure for children. This is currently addressed within the DISABKIDS Project, in which a chronic-generic measure as well as disease-specific modules are constructed for children in several European countries [20]. The project, which involves children with chronic conditions (namely asthma, epilepsy, cerebral palsy, cystic fibrosis, diabetes and rheumatoid arthritis), has worked along the international instrument development guidelines described above, namely using separate focus groups involving either children (of the same age and, if feasible, gender) or parents or caregivers to generate the items, using specific procedures for item writing, testing the items using cognitive debriefing, using a pilot test to modify the test version and using a field test to examine psychometrically the chronic generic QoL module of the DISABKIDS questionnaire as well as the specific supplements.

## An overview of the haemophilia literature

### *Research in adults*

Within the haemophilia literature, one of the first groups of authors to mention the role of QoL assessment was Rosendahl *et al.* in 1990 [21], who had mailed questionnaires to 935 Dutch haemophilia patients and showed that they did not differ from the general population with respect to their own QoL. More recently, a group of haemophilia experts has conducted a large clinical study on the clinical outcomes and resource utilization associated with haemophilia care using the SF-36 health survey and finding QoL differences between prophylactic and on-demand factor replacement in European haemophilia patients [22]. In another study, the Arthritis Impact Scale (AIMS) was used to assess QoL in 31 patients with haemophilia in the Netherlands, show-

ing that the relationship between the AIMS and the Sickness Impact Profile (SIM) was low, although both are reliable and valid measures [23]. One of the largest studies assessing health-related QoL in individuals with haemophilia was published by Miners *et al.* [24], who studied the QoL of 249 individuals with severe, moderate and mild haemophilia using the SF-36 and the EuroQoL questionnaire. They found that individuals with severe haemophilia recorded poor levels of QoL and suggested that early primary prophylaxis to increase QoL in severe haemophilia patients is necessary.

Again using the SF-36, a study in 150 Finnish patients with bleeding disorders showed that QoL reflected the clinical severity of the patients [25]. In 2000 an epidemiological study of French patients with severe haemophilia ( $n = 116$ ) was published. In this study the SF-36 was used, and it was shown that physical function and social relation were acceptable; however, QoL scores in pain in the SF-36 were low, showing general invalidity [26]. In a Spanish study, Aznar and colleagues [27] reported on the QoL of 70 patients related to orthopaedic status, and found QoL to be negatively affected by severe orthopaedic impairment via haemophilia. In a Canadian survey of mild, moderate and severe haemophiliacs the Health Utility Index (HUI) marks 2 and 3 was used. It was found that the burden of morbidity was greater in haemophiliacs than in the general population and was associated linearly with severity of haemophilia [28]. Most recently, authors have addressed the functional health status of haemophiliacs. One group developed a measure of self-care: the Haemophilia Utilization Study Group (HUG) functional status measure to describe functional health in 336 patients [29].

Most treatment-related studies are not randomized, but assess patients' QoL at some time-point after treatment. This was employed, for example, to assess QoL after arthroplasty [30] or in comparison of haemophilia patients with patients with Anderson Fabry disease using the SF-36, the EuroQoL and RFD-specific questionnaires [31]. A Japanese working group [32] assessed QoL in factor VIII/IX inhibitor patients, comparing them to non-inhibitor haemophilia patients ( $n = 136$ ), showing a higher cost of treatment and QoL for haemophiliacs with factor VII inhibitors.

A relatively substantial group of papers, however, addresses psychosocial issues in haemophilia in relation to HIV [33–38]. In these studies different outcome measures were used, ranging from the Karnofsky scale to more standard psychological measures of coping and adaptation. Recently De Kleijne

*et al.* [39] criticized the World Federation of Haemophilia's scoring system as addressing primarily bodily functions and structures, rather than the whole area of functional health. In a review of the literature clinimetric instruments were identified according to the International Classification of Functional Disability and Health. The authors assessed the psychometric properties of the 34 clinimetric instruments, and found that 17 addressed functions, 13 activities and four participation. The authors advocate the development of new clinimetric instruments to also assess more comprehensively the impairments of health status in psychosocial dimensions; recently relationships between health-economics and QoL have been studied [40]. Measures included for health-related QoL are the SF-36, health-economic assessments include the Standard Gamble technique [41] and the use of Quality Adjusted Life Years (QALYs) [31]. Within large European health-economics study groups, pilot and field study results were reported with regard to health-economically relevant data which were related to QoL outcomes [42,43].

An Italian study assessed QoL and utility in patients with haemophilia using both the SF-36 and haemophilia-related questionnaires in 56 haemophiliacs. The study group found low scale values in general health perceptions and higher scale values in social functioning. Severity significantly influenced both EQ-5D and SF-36 scores and both measures were found to be related [44].

#### *Research in children*

With regard to children, in 1996 the issue of QoL was studied in 26 children by Liesner *et al.* [45]. However, only from 2000 onwards have more studies have addressed the issue. In these studies, QoL has been addressed, but rarely measured using standard questionnaires (e.g. [46,47]). Among the instruments used have been the generic CHQ in a study with six children [48] and questionnaires concerning activities of daily living (ADL) [49]. Several authors have addressed the QoL assessment in children with haemophilia and advocated the development and use of QoL measures in this area. Fischer *et al.* [50] performed a multicentre study in Sweden and the Netherlands comparing the effects of two prophylactic treatment regimens in 128 patients with haemophilia, including QoL aspects. They found that clinical scores and QoL were high in both prophylactic groups, but they also pointed out that in spite of short-term improvement, arthropathy in later life might not be affected. One of the more

comprehensive assessments of children with haemophilia included a study on academic achievement in 140 children, which also included QoL measures [51]. Using the CHQ, the authors found that children with fewer bleeds have higher physical functioning scores in the CHQ and that the physical functioning score of groups of children with fewer bleeding episodes was similar to the general population. In addition, physical symptom scales were related positively to reading achievement, advocating the use of their comprehensive care programmes for the benefit of both individuals and society. While in the children's area QoL was assessed with *ad hoc*-developed questions or generic instruments, the development of the Haemo-QoL questionnaire was one of the first attempts to generate a targeted instrument for QoL assessment in haemophiliac children [52,53]. The Haemo-QoL project included centres from six European countries, active in developing a pilot test version of the Haemo-QoL questionnaire [54], which was included in a field test. Using focus groups with experts in the field of haemophilia (clinicians, nurses) several dimensions of HRQoL of children with haemophilia were identified. Three age-group versions were developed, one relating to children between 4 and 7 years, the second relating to children from 8 to 12 years and the third version for 13–16-year-old adolescents. Recently the psychometric structure of the questionnaire was tested in a cross-sectional study in six countries, involving 339 children from 20 centres, which showed acceptable psychometric properties for the three age-group versions as well as the accompanying parent forms (see [53], this issue). More work on QoL assessment in haemophilic children is under way, one example being the Canadian haemophilia-specific questionnaire, the Canadian Haemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT), as can be seen from Young *et al.* [55] in this issue.

#### **Discussion and outlook**

A review of the haemophilia literature shows that QoL has only recently been addressed. Available research can be subdivided broadly into research with adults and with paediatric patients, and in studies on the national and international level. Most prevalent are cross-sectional studies with adult haemophilia patients, in which generic QoL measures such as the SF-36 have been included to represent HRQoL. One example of an international study was published by Royal *et al.* [22], who used the SF-36 to assess HRQoL of haemophilia patients treated in the European

Union, focusing both on wellbeing and function as well as on health-economic indicators. In the children's QoL area, such research is just beginning. Only recently have studies appeared in which QoL of children has been addressed, one of which also includes the construction and testing of a haemophilia-specific QoL instrument [52,53]. Recently several groups have addressed the issue of QoL assessment in children and have proposed measurement instruments. Even more recently such disease-specific instruments have been constructed for adults.

Concerning the development of an adult haemophilia questionnaire following comparable methodology, an instrument was developed in three countries (Germany, Spain and the United States). Again using focus-group interviews, adult haemophilia patients were questioned with regard to their specific concerns, which included a wide range of issues from physical impact to social impact of the condition. The measure is under development and first field-test results are expected shortly.

The most recent study is a large international European study on clinical health-economic and QoL outcomes in haemophilia treatment (ESCHQoL project). This study is funded by the European Commission in the 5th framework programme and includes a total of 22 European countries participating in a prospective study designed to measure outcomes in haemophilia on the basis of structured characteristics of care in Europe [56]. The study, which includes baseline data collection, a 6-month patient diary and retesting after 6 months, will include both parents and children, as well as adults. Adults as well as children from 4 years onwards and their parents will be included. In patients aged 4–7 years, both children's interviews as well as parent forms will be used. For the older children, aged 8–12 years, both self-report and parent report will be used as well as in adolescents 13–16 years old. In this study approximately 2040 patients, both adults and children, will be asked to participate. The aim is to identify relevant clinical QoL and health-economic outcomes in haemophilia care in Europe in order to understand the situation better and to make recommendations for improvement.

An important aspect will be to differentiate patients with different clinical characteristics of haemophilia and different treatment histories, in order to identify factors associated with positive vs. negative outcome in haemophilia. Especially important is the role of on-demand vs. prophylactic treatment in patients, not only concerning their actual treatment regimen but also their treatment history. Consequently, gathering clinical data and

grouping patients into relevant clinical clusters will be one of the important tasks of this project.

The second task will be to collect detailed information related to the healthcare consumption of haemophilia patients within the 6-month observation period and to relate this to known information about the structure of haemophilia care in the European Union. Considering the high costs associated with haemophilia treatment, this project has a strong health-economic background. The reason for this is to advocate neither an increased nor a reduced use of factor in haemophilic patients, but to identify prognostic information for optimal use of comprehensive care. The project includes four phases; the first is an instrument development phase in which available instruments will be reviewed and, if accepted, included in both pilot and field tests, followed by statistical analysis and reporting phases. Specific comprehensive care centres will be involved, with the aim of including the patients' sample as completely as possible.

The review of the literature shows that no randomized clinical trials in haemophilia patients exist in which QoL measures are used. In addition the older QoL assessments, both in the adult and children's areas, tended to work with *ad hoc*-developed measures not specific to QoL, or merely included implied QoL information. Only recently have standard generic questionnaires (such as the SF-36 and EQ-5D in the adult area) appeared. Information about such measures is forthcoming. International aspects are rarely studied. In the few international studies the SF-36 was used as a generic measure. In the children's area, comparable international work has been conducted only recently within the Haemo-QoL study group, although the CHQ has been recommended as a generic instrument with normative data. However, no study has been published in the haemophilia area in which the CHQ was applied across different groups or countries. International development of haemophilia-specific measures for QoL, both for adults as well as children, are necessary in order to make available methodologically sound assessment instruments that are relevant to patients and assess a major outcome—health-related QoL.

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