

REVIEW ARTICLE

Measuring patient-reported outcomes in haemophilia clinical research

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Summary. Patient-reported outcome (PRO) measures have been used to assess quality of life and health state preferences from the patient's perspective. However, they have not been fully utilized in haemophilia clinical practice and research. A series of meetings were convened to review and document the state of the art in PROs relevant to haemophilia. Experts developed a process for selection of measures and identified published measures of health-related quality of life (HRQoL) relevant to patients with haemophilia. These were synthesized and reviewed. Patient preference measures were

also identified and reviewed. Although the majority of measures were developed for and validated in adults, several measures were identified for use in paediatric populations. This paper recommends an approach to the selection of PROs for application in haemophilia clinical research and practice and identifies several potential measures relevant for application in haemophilia clinical research and practice.

Keywords: factor VIII, haemophilia, health status, primary prophylaxis, quality of life, utility

Introduction

Joint damage from bleeding episodes is a major cause of disability in patients with haemophilia. The long-term consequences of joint bleeds are a concern for patients, families and providers. Hence, avoidance of bleeding episodes is a major treatment goal. Clinical measures that assess changes in joint status over time have been a focus for haemophilia researchers, with an aim to establish international standards and facilitate cross-study comparisons. However, clinical measures alone fail to adequately characterize the burden of disease on patients.

The introduction of the science of health-related quality of life (HRQoL) into the clinical realm of haemophilia research has resulted in a portfolio of patient-reported outcome (PRO) measures to docu-

ment patients' perspectives on the impact of the disease and its treatment. The usefulness of these measures is demonstrated by the increasing integration of PRO measures into haemophilia clinical research [1–3]. Even more importantly, integration of PRO measures into economic analyses is needed to elucidate the value of different treatment regimens (e.g. prophylactic care). However, the heterogeneity of the measures used has impeded the ability to compare data across studies.

The purpose of this paper was to educate clinicians on the science of measuring PROs in clinical practice and research, by providing an overview of these concepts and identifying high-quality measures for both adults and children.

The foci of haemophilia research include: the discovery of novel treatments, innovations to enhance efficacy or simplify the mode of administration of current treatments, and strategies to optimize treatment regimens and cost-effectiveness. The primary endpoints for most of these studies are clinical measures, such as bleeding frequency or joint damage. Yet, an equally important measure of effectiveness in

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these studies might stem from the patients' perspectives which are measured by PROs. PROs for this use can be divided into three general categories; (i) generic HRQoL measures, (ii) disease-specific HRQoL measures and (iii) patient preference measures (PPMs). PRO measures also differ in their application across age categories (e.g. paediatric populations) and cultures (international vs. single-country focus).

The selection of PRO measures should consider the specific objectives of the research study or goals of the clinical programme. The expertise required to match the objectives to the best measure may reside outside of the clinical domain of most haemophilia researchers and clinicians. In particular, it is necessary to set standard definitions and provide references for physicians and researchers who may be unfamiliar with HRQoL research or less familiar with the constructs relevant to patients with haemophilia. Consistent use of measures that are sensitive and specific to factors important to patients with haemophilia may also be useful to influence policy, facilitate global comparisons and to assist in clinical decision-making.

Core concepts in HRQoL

The inclusion of the term 'health-related quality of life' in medical research reflects the need to address patients' perspectives of their health conditions and treatments. Conceptually, HRQoL has been defined as 'reflecting a person's valuation of goals, expectations and aspirations with regard to different areas of life' [4]. More specifically, HRQoL has been viewed as the subjective perception of well being and function in different life-domains, namely concerning physical, social, emotional, mental and everyday-life role performance [5].

Generic HRQoL measures are designed to be applicable to persons with a variety of health conditions, including the general population where most subjects have no serious health condition. Such measures enable comparisons to be made across diagnostic groups, but sometimes lack the sensitivity to detect subtle changes over time that are important in clinical research. Disease-specific measures are developed specifically for one defined population, and hence focus on the most relevant health issues for that group, enhancing sensitivity to change at the expense of comparability (e.g. a measure that is valid to measure HRQoL among diabetics may not be valid for asthmatics). In addition, their measurement properties are specific to the purpose for which the measure was developed [6]. Measures developed to discriminate between diagnostic groups may not be

sufficiently reliable to detect changes over time, to treatment within a clinical sample or to predict future outcomes. Thus, both the purpose and the population must be considered by the clinician or researcher when selecting the most appropriate measure for their specific study.

Health-related quality of life measures are generally developed through a multi-step process, in which the patient is in the foreground. Patient input during the development of a HRQoL measure is imperative, as the goal of the questionnaire is to document the impact of the disease on the patient's life, from the patient's perspective [7]. Feinstein *et al.* emphasizes that the assessment of well-being and functioning must be guided by the patient's view in concert with the clinical expertise of those working in the field [8]. The process is sometimes referred to as the clinimetric approach. Using this approach, measure development may begin with an in-depth literature review to develop a conceptual model of the clinical description and symptomatic manifestations of the disease. The model then illustrates the physical, social and psychological impact of the disease. The different areas (or domains) in which illness or disease may impact HRQoL are then presented to focus groups of clinicians and patients to determine if all of the relevant domains have been identified. Domains are then rank-ordered in terms of importance to patients and the impact on their daily lives. Next, individual items are developed to document the patients' perceptions of each domain. Once items are matched to each of the domains, the draft questionnaire is administered to a small sample of patients. Several patients are interviewed (cognitive debriefing) to determine if perceived interpretation of the item from the patient's perspective is consistent with the intended content from the development process and to ascertain the degree of relevance of the item. The revised measure is then administered to a larger subset of patients.

All measures must undergo rigorous statistical testing, also referred to as 'psychometric testing', to assess their quality in terms of measurement properties. The measure is scored and psychometric testing is completed to assess the reliability, validity and responsiveness (sensitivity to change) of the measure. At this stage, the number of items may also be decreased to minimize the burden on patients. Demonstration of these rigorous criteria is essential for PROs to be included in a US label claim and similar criterion are being developed by the European Agency for the Evaluation of Medicinal Products (EMA) [7,9].

Patient preference measurements

Patient preferences are numeric measures that represent the value placed on a particular health state [10]. The number reflects how much risk that individual would be willing to take in exchange for a specific improvement in this health state and provide standardized metrics to compare different PROs across various diseases. PPMs may be elicited either directly or indirectly. In direct measurement, participants value the health state [11]. Currently, three different approaches are used to assess preferences directly: standard gamble (risk that an individual is willing to take for a given probability of being cured from a prespecified health state), time trade-off (TTO) (the number of years that a person would be willing to give up in order to receive a treatment that returns him/her to perfect health compared with a prespecified health state) and category rating (a scale ranging from 0 to 10 with anchors at worst and best health states to rank the prespecified health state). The value received from these three approaches is then assigned to the prespecified health state. Indirect measurement involves using a health status measure where the preferences have been assigned independent of the study, preferably by community-based judges. The values generated may differ depending on the measurement method used and whose values are applied – those of the individual vs. those of society [12–15].

Patient preference measurements are valuable for economic analyses of alternative treatments for a particular disease (i.e. prophylaxis) and are used in the economic models utilized by many health technology assessment agencies to provide information for funding decisions for current and new therapies. Some countries currently approve reimbursement for prophylactical care (e.g. Canada, Germany), others have variability in approving this treatment regimen (e.g. US depending on individual insurer restrictions), and others do not provide this care (e.g. India). Especially, relevant to haemophilia is measuring the impact of prophylaxis on HRQoL and incorporating these measures into cost-effectiveness analyses.

Materials and methods

A group of PRO experts met three times during 2005–2007 and participated in interim conference calls as part of the International Prophylaxis Study Group (IPSG). The purpose of these series of meetings was to identify the best PROs measures for use in haemophilia research.

The group identified available measures of direct relevance to haemophilia and reviewed them accord-

ing to *a priori* defined criteria. Specifically, the IPSG group developed the literature synthesis, set standards of reliability and validity for inclusion of measures in the review, and discussed recommendations for PRO measures that would be most useful in haemophilia research.

The first step in the review process was to identify generic QoL measures, haemophilia-specific QoL's measure and PPMs. Next, the working group documented whether the measure had been used in adult-only, paediatric-only or combined adult and paediatric patient groups.

To be included in the list of recommended measures, literature reporting acceptable levels of reliability and validity needed to be identified. Evidence of responsiveness and number of languages were also evaluated, however these were not essential for inclusion in the recommended list.

Reliability was defined as 'the stability or reproducibility of measures of the same concept over time or across methods of gathering data' [16]. To be included in the recommendations, the summary scores should have an intra-class correlation coefficient >0.80. In the absence of this information, internal consistency coefficient (Cronbach's alpha) >0.8 was accepted.

Validity is defined as the degree to which the measure's scores agree with an external standard or an *a priori* hypothesis. Demonstration of validity conveys that the full meaning of the concept they the measure was intended to address is expressed [16]. Content validity is a qualitative assessment that the measure captures the breadth of way that haemophilia may impact a patient's QoL. The acceptable cut-off for criterion validity which assesses how well the items within each scale measure a similar concept, was accepted with a correlation of 0.60 or greater for each individual item with the overall scale [17]. Construct validity required a statistically significant association ($P < 0.05$) of scale scores with related categorical concepts (e.g. severity of disease) or a correlation with other scale scores (e.g. another HRQoL measure) of at least 0.60 [15]. Responsiveness was defined as the measure's sensitivity to changes in health status. Assessment of responsiveness was not a necessary criterion for inclusion.

Results

This review resulted in the identification of nine generic, seven targeted measures of HRQoL and three generic and one targeted measure of PPM. Measures were pertinent to both adults as well as children. Several reviews of HRQoL measures

relevant to haemophilia researchers have been published and are included in the results presented in this article.

PRO assessment in haemophilia

Generic and haemophilia-specific quality of life measures for adults *Generic measures for adults.* Generic measures to assess HRQoL in adults have been developed over the past 20 years, many of which are appropriate for the haemophilia population. These include the Sickness Impact Profile, Nottingham Health Profile, the General Health Perception Questionnaire, the SF-36 and the WHO Quality of Life measure [1,2,18–21]. As haemophilia is a relatively rare disease, multinational patient recruitment is frequently necessary to accumulate a sufficient number of patients to complete the psychometric analysis of these measures. A review of the literature showed that the SF-36 Health Survey, as well as its short version, the SF-12, have been most widely used to assess quality of life in adult haemophilia [20].

Haemophilia-specific measures for adults. The development of targeted measures for haemophilia is comparatively recent. At the time of this current review five haemophilia-specific measures were identified, where as none were identified in a similar review only 5 years earlier [1]. The current measures include the Haemofilia-QoL [22], the Hemolotain-Qol [2], the Haem-A-QoL [23,24] the Qual-Hemo [25] and the HAEMO-QOL-A [26,27] questionnaires for adults. The Hemofilia-Qol was developed in Spain and is only validated in Spanish [28], while the Qual-Hemo was developed in France and is currently being psychometrically tested. The Haem-A-QoL was originally developed in Italy and consists of 41 items compiled from focus groups of patients with haemophilia in different countries. The Haem-A-QoL is validated for Germany, UK and Hungary and linguistically validated for several additional languages.

Generic and haemophilia-specific HRQoL measures for children *Generic measures for children.* In terms of children's quality of life assessment, parent-report has been originally obtained more frequently than children's self-report. The Child Health Questionnaire by Landgraf was developed from an adult measure, the SF-36, and is predominantly a parent report of their perception of the child's HRQoL [29]. However, efforts have recently been directed towards developing and testing scales measuring quality of life from the child's (as well as parents') perspective

and in different age groups [30]. The Health Utilities Index (HUI) is unique in that it was developed first for children, specifically as a PRO measure for those with low birth-weight, and the adult version was developed secondarily [31]. Scoring of this measure yields both a general HRQoL score, as well as a preference score. Some researchers prefer to use only the preference score, as the breadth of concepts are narrow compared with other general HRQoL measures. Several internationally available generic measures such as the PedsQL [18,54], or the KINDL [33,35] questionnaires are currently available for completion by child- or parent-report. The PedsQL has previously been used in haemophilia research [32].

Haemophilia-specific measures for children. Two of the first measures for children with haemophilia were developed concurrently: the Haemo-QoL [33] and the Canadian Haemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT) [32]. However, only the latter directly included children's views.

The initial development of the Haemo-QoL questionnaire used clinical expert consensus on relevant dimensions of children's quality of life. This input was used to construct a parental reported quality of life measure for children and a self-report measure for children. Statements were then modified for three age groups (4–7, 8–12, 13–16 years) of children. The age-specific measures were pilot tested, also using cognitive debriefing for applicability of these questions, and then field tested in over 300 haemophilic children in six European countries [34]. Psychometric analysis revealed good internal consistency both for the interview-based form in small children (21 items), the self-report in children age 8–12 (68 items) as well as in adolescents 13–16 years (71 items). A short form with 16 items (4–7 years) and 35 items (8–16 years) was developed which is also available as a self-report [34]. The 35-item instrument has been used in children up to the age of 18. An index version with eight items was constructed for children and parents spanning all age groups [35].

The CHO-KLAT was developed initially in Canada and a single cross-age version was sought specifically to facilitate longitudinal follow-up research. The priority was given to children in the development of the CHO-KLAT to ensure that the measure reflected their experiences and could be used directly by them. The CHO-KLAT was originally developed from an item bank of 228 items generated from focus groups [36]. A revised version of 79 items was validated in 52 children. This measure is currently used in children 4–18 years of age in five

languages (English, French, Spanish, Dutch and German) and is available in parent- and self-report forms.

Other measures for the targeted assessment of quality of life in haemophilic children have been published. For example, Manco-Johnson and colleagues developed and tested a parent-report measure to assess the HRQoL of very young children between the age of 2 and 6 years [37]. Some of the other more recent measures in young haemophilia patients however still have to undergo psychometric testing.

Patient preference measures

Generic PPMs for adults and children. To date, the reliability and validity of preference scores generated from various PPM methods are not well understood. The HUI is a generic PPM that has been used in both paediatric and adult populations, although its use in haemophilia populations has been limited [38].

In an effort to begin to assess HRQoL and patient preferences in patients with haemophilia A and B, Miners *et al.* utilized the SF-36 and the EQ-5D [39]. The EQ-5D is a generic utility questionnaire that measures five attributes: mobility, self-care, usual activity, pain/discomfort and anxiety/depression [40]. The authors found that individuals with severe haemophilia have reduced levels of HRQoL compared with (i) individuals with moderate or mild forms of the disease and (ii) with the UK male normative population.

Haemophilia-specific PPMs for adults and children. Wasserman *et al.* [41] developed and validated a disease-specific utility measure that directly measured patient preferences for nine unique haemophilia health states. Health states ranged from mild to severe and included common morbidities experienced by persons with haemophilia. Visual analogue scale (VAS) and the standard gamble (SG) methods were both used to assess patient preferences. The authors found statistically significant differences for all nine health states combined between paediatric and adult participants ($P = 0.045$) as well as differences between adult and paediatric group preferences for the individual mild, severe (episodic treatment) and severe (prophylactical treatment) health states. These results indicated that age can influence patients' preferences regarding their state of health.

Research so far has demonstrated that both generic and disease-specific measures can be used to reliably measure different aspects of HRQoL in haemophilia. However, given the complex nature of the disease, its unique characteristics and the co-morbidities associ-

ated with it, there is a need for multi-attribute preference measurements. To date, no preference measure integrating two or more health states (multi-attribute) has been developed specifically for this population.

Choosing PRO measures for haemophilia research

The choice of measures in a given study depends on the study population as well as the research question. The measures should fit the patient population in terms of the dimensions of quality of life covered (which might be different between populations depending on their age, clinical characteristics and nationality). A decision about who should be the primary respondent to quality of life questions is imperative: should it be the patient, the parent, the relative or a member of the medical staff? We recommend self-report whenever possible. In addition, clinical characteristics of the patient such as inhibitor status or concomitant HIV, as well as type of treatment and treatment regimen (on-demand vs. prophylaxis) should be considered.

For clinical trials, as well as other types of research studies, the pertinent question in PRO research is 'what are the relevant domains in terms of the specific aims of the study and who is the appropriate population to assess?' Will children be integrated into the trial? For all ages, the measure needs to address domains that are relevant to the study population (e.g. severity of haemophilia) and the mode of administration of the therapeutic entity (e.g. dosage, frequency of treatment, method of treatment delivery and treatment history). Standards set by local health authorities, health technology agencies and funders should also be considered in the selection.

If young children are included in the trial, added characteristics in selecting a HRQoL measure include their developmental stage, as well as the treatment setting (administration in clinic, parent administration, use of a central venous access device, etc.). If unable to self-report (e.g. at age 4) is the proxy-respondent an acceptable surrogate? Research on correlation between mothers' and children's reports shows variations in the degree of concordance between responses within mother-child dyads. For instance, in the CHO-KLAT measure, there is a high correlation in physical function scores between mother and child [32,36], while other measures demonstrate poor correlation. The emerging picture is complex and does not easily allow determination that one mode of report may be substituted by the other. The working group recommends that both the

parent's and child's reports are included in the trial design when feasible.

Controlled, randomized clinical trials include PRO measures such as HRQoL as primary, secondary or tertiary endpoints. If the measure will be used as a primary endpoint, criteria for selecting the measure should include psychometric evidence from other trials in the same or similar population. Estimates of the sample size necessary to detect changes over time and differences between groups should be utilized.

If the research is multinational, it is important that the measure has been translated, cross culturally validated and psychometrically tested in the relevant contexts. This is true for the recently developed quality of life measures in haemophilia, both for children and adults, and it is also true for a range of other generic and targeted measures. Longitudinal designs need to consider the implications of age-specific versions including methods to translate scores between versions and to compare responses within and among children.

These selection criteria also apply to other haemophilia research. A number of cross-sectional studies appear in the literature which utilize quality of life measures to better understand the impact of haemophilia on patients in specific cultural settings [42,43] or in specific disease-conditions [44] complications such as HIV, hepatitis, and inhibitors [45] or impact of events, such as intracranial bleeds [46] and arthropathy [3]. The ability to compare results of observational and clinical research across countries will facilitate the ability to assess the impact of haemophilia on patients, payers and societies as well as the benefits and risks of various treatment approaches. This information is vital in planning for the future care of patients with haemophilia.

Integrating PPM and HRQoL in patient-reported outcomes assessment

Patient preference measures for varying health states are important components of a clinical trial from both an economic and an outcomes perspective. Measures such as the HUI and EQ-5D are available in a number of translations and are commonly used in multinational trials, to facilitate comparisons of the baseline characteristics of subjects, as well as the efficacy of the drug within and among countries [47,48]. These results are also associated with the likelihood of seeking care, the type of treatment selected, selection of provider specialty and compliance with care [49].

Along with individual and environmental characteristics, preferences shape an individual's perception

of his/her general health. For example, high utilization of health care services is associated with poorer self-reported health status [50]. As patient preferences are related to an individual's perception of health status, it is not surprising that initial investigation has supported the existence of a relationship between health state preferences and patient health-seeking behaviour. For instance, Patrick *et al.* [13] demonstrated that prescriptions for psychotropic medications for patients with anxiety were related to patient self-assessment of the desirability of their current state. The association between patient preferences and treatment decisions of patients with haemophilia has not been explored and is it not yet known how severity of haemophilia, treatment of haemophilia and patient preferences might be related.

Patient preferences are most commonly integrated into clinical trials for use in cost-effectiveness analyses that are submitted to health technology assessment agencies, such as National Institute for Clinical Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH) for reimbursement decisions. The PPMs serve as a part of the denominator term to assess the incremental cost effectiveness ratio, reported as costs per quality-adjusted life-year (QALY). A separate working group of the IPSPG has assessed methods for economic valuation in haemophilia research. Cost evaluation, together with PPMs, provide the tools for reimbursement decisions for both new and existing therapies [7].

Several investigators have developed methods to report a single, generic utility value from HRQoL measures when patient preferences are not directly measured in a study. This method is particularly useful in economic analyses. Currently, there are several quality of life measures methods that may be used to derive utility values from HRQoL questionnaires. These methods report an equation that can be used to 'map' the responses from a generic HRQoL questionnaire to a utility value. These indirect utility measures include the SF-6D, derived from the SF-36 Health survey [51], as well as the Quality of Well-Being Scale [52]. To date, there is only one haemophilia-specific PPM [41]. The development of an algorithm to estimate a targeted PPM from haemophilia-specific HRQoL measures can be useful for multinational economic analyses.

Discussion

General and disease-specific measures are available to assess HRQoL and patient preferences in adults

and children with haemophilia. Choosing between those two types of measures can pose a challenge. Using multiple and varied measures in different research and clinical settings for haemophilia results in a lack of comparable PROs necessary to translate information across studies. Introducing method complexity into an emerging research area, such as haemophilia quality of life, can indeed be counter-productive. Alternatively, comparison of measures is often necessary to determine those approaches that are psychometrically sound and serve the intended study purpose and are feasible within study budgets. Original source references are provided to assist readers in selecting appropriate PRO.

One strategy to achieve optimal information on measurement performance in haemophilia would be to use core sets of measures across studies. Based on the current literature synthesis, this core set of measures would include the SF-36 Health Survey as an adult generic measure and the PedsQoL as a generic measure for paediatric populations of age two and above. The SF-36 has been shown to be reliable and valid in haemophilia populations, and provides both disease-specific and general scores as a comparator for study results [53]. The scores for the PedsQoL can be compared across age ranges and can also be compared with the SF-36 physical composite and mental composite scores, which makes it useful for longitudinal studies, as well as research which includes both adult and paediatric populations [54]. The EQ-5D is often included as the PPM in international trials. There are a number of translations available and the measure takes little additional time for subjects to complete. We recommend its use in future haemophilia research. As the HUI is one of the few PPMs validated in children, it is recommended for research that includes paediatrics when the EQ-5D cannot be used. Research that includes both paediatrics and adults might also utilize the HUI to provide comparability of scores across different age groups. Inclusion of Wasserman's tool [41] will provide disease-specific preference scores as well.

The development of haemophilia-specific measures is still evolving. At this point in time, we would recommend the CHO-KLAT for haemophilia-related paediatric research in North America¹, while in Europe the Haemo-QoL is available in many languages. For adults, there are three international questionnaires: (i) the HAEMOQOL-A, which was developed in the US, Spain and Germany, (ii) the

Haem-A-QoL developed in Italy and linguistically validated in 19 additional languages and (iii) the Hemolatin-QoL, which was developed in South America (Spanish, Portuguese). International psychometric evaluation is still ongoing for these instruments. Costs for including these measures may vary by location of the project, institutional affiliation of the principle investigator and the intended use of the results. Use of generic measures often requires a fee, while costs for disease-specific measures are more likely to be minimal.

The development and assessment of PPM in haemophilia research has received little attention. It is important to have robust tools to measure PPM in haemophilia research as these measures document the degree of improvement in HRQoL from a given treatment. Generic PPM have only been utilized in a few studies and little work has been done to assess the reliability and validity of these measures.

An important emphasis for future haemophilia research is the validation of PPM 'mapping' algorithms (e.g. EQ-5D). There are a number of datasets, which incorporate generic or disease-specific (or both) HRQoL measures. Mapping algorithms would provide a useful tool to utilize existing data. These data can be used to estimate patient preferences and thus facilitate economic evaluations of new and existing treatments and treatment approaches such as prophylaxis.

Paediatric PRO assessment can pose several challenges. Wasserman *et al.* were able to ascertain disease-specific preferences for haemophilia-specific paediatric health states [41]. A limitation of this study was that parents served as proxies for children aged 14 and below because the health states were considered too difficult for them to comprehend. A study done by Bullinger *et al.* on quality of life in children and families with bleeding disorders showed that parents' and children's assessments of HRQoL differed with regard to social and emotional aspects of HRQoL [55]. Sung *et al.* assessed utility-based measures in children [56]. In this study, families of children admitted for cancer chemotherapy and those attending rheumatology, haemophilia and bone marrow transplantation clinics were given the SG, VAS, TTO and HUI mark 2/3 (HUI2 and HUI3). The authors found that parents and children rate HRQoL similarly according to the SG, but parents rate HRQoL significantly worse using the TTO and HUI2.

Another concern regarding PPM is that the stability of health state preferences over time has not been extensively studied. The relationship between changes in clinical status and changes in patient preferences is not well understood [11].

¹The CHO-KLAT has been cross-culturally validated in Dutch, French, German, Spanish and UK English.

Conclusion

As resources in health care become increasingly constrained, the pressure to demonstrate an empirical foundation to support treatment choices increases. Payers are assessing new and existing therapies on the basis of demonstrated efficacy from prospective clinical trials and comparative effectiveness derived directly from observational research. This informed decision-making is very much dependent on the existence of relevant and comparable or compatible clinical and observational data specific treatment scenarios such as starting Port-A-Caths in young children, identifying the best prophylaxis strategy, changing treatment strategies in later life, or patient compliance are examples of haemophilia care delivery that would greatly benefit from PRO evaluation. These measures should be incorporated as much as possible into haemophilia research in order to augment the data upon which to base the best choice of treatment strategies. Translating these data into economic terms will provide exceedingly useful information for decision makers who must approve reimbursement for costly haemophilia treatments including prophylactical care.

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References

- 1 Szende A, Schramm W, Flood E *et al.* Health-related quality of life assessment in adult haemophilia patients: a systematic review and evaluation of instruments. *Haemophilia* 2003; **9**: 678–87.
- 2 Remor E, Young N, VonMackensen S, Lopatina E. Disease-specific quality-of-life measurement tools for haemophilia patients. *Haemophilia* 2004; **10**(Suppl. 4): 30–4.
- 3 Fischer K, Bom Jvd, Mauser-Bunschoten E, Roosendaal G, Berg HM. Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters. *Haemophilia* 2005; **11**: 43–8.
- 4 Szabo S, on behalf of the World Health Organization Quality of Life (WHOQOL) assessment instrument. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 355–62.
- 5 Bullinger M. Quality of life-definition, conceptualization and implications – a methodologists view. *Thero Surg* 1991; **6**: 143–9.
- 6 Bowling A. *Measuring Disease: A Review of Disease-Specific Quality of Life Measurement Scales*, 2nd edn. Buckingham: Open University Press, 2001.
- 7 Revicki D, Gnanasakthy A, Weinfurt K. Documenting the rationale and psychometric characteristics of patient reported outcomes for labelling and promotional claims: the PRO evidence dossier. *Qual Life Res* 2007; **16**: 717–23.
- 8 Feinstein A. Multiterm “instruments” versus Virginia Apgar’s principles of clinimetrics. *Arch Inter Med* 1999; **159**: 125–8.
- 9 Apolone G, Carli GD, Brunetti M, Garattini S. Health-related quality of life (HR-QOL) and regulatory issues. An assessment of the European Agency for the Evaluation of Medicinal Products (EMA) recommendations on the use of HR-QOL measures in drug approval. *Pharmacoeconomics* 2001; **19**: 187–95.
- 10 Torrance G. Measurement of health state utilities for economic appraisal. *J Health Econ* 1986; **5**: 1–30.
- 11 Bennett K, Torrance G. Measuring health state preferences and utilities: rating scale, time trade-off, and standard gamble techniques. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 253–65.

- 12 Lohr K, Aaronson N, Burnam M, Patrick D, Perrin E, Robers J. Evaluating quality-of-life and health status instruments: development of scientific review criteria. *Clin Ther* 1996; **18**: 979–92.
- 13 Patrick D, Mathias S, Elkin E, Fifer S, Buesching D. Health state preferences of persons with anxiety. *Int J Technol Assess Health Care* 1998; **14**: 357–71.
- 14 Gold M, Franks P, McCoy K, Fryback D. Towards a consistency in cost-utility analyses: using national measures to create condition-specific values. *Med Care* 1998; **36**: 778–92.
- 15 Torrance G. Social preferences for health states: an economic evaluation of three measurement techniques. *Socioecon Plann Sci* 1976; **10**: 129–36.
- 16 Aday L. *Designing and Conducting Health Surveys*, 2nd edn. San Francisco: Jossey-Bass Inc., 1996.
- 17 Streiner D, Norman G. *Health Measurement Scales: A Practical Guide to Their Development and Use*, 2nd edn. New York: Oxford University Press, 1998.
- 18 Beeton K. Evaluation of outcome of care in patients with haemophilia. *Haemophilia* 2002; **8**: 428–34.
- 19 De KP, Heijnen L, Van MN. Clinimetric instruments to assess functional health status in patients with haemophilia: a literature review. *Haemophilia* 2002; **8**: 419–27.
- 20 Fischer K, van der Bom J, van den Berg H. Health-related quality of life as outcome parameter in haemophilia treatment. *Haemophilia* 2003; **9**(Suppl. 1): 75–81.
- 21 von MS. Quality of life and sports activities in patients with haemophilia. *Haemophilia* 2007; **13**(Suppl. 2): 38–43.
- 22 Arranz P, Remor E, Quintana M *et al.* Development of a new disease-specific quality-of-life questionnaire to adults living with haemophilia. *Haemophilia* 2004; **10**: 376–82.
- 23 von MS, Gringeri A, Santoni L *et al.* Development and pilot testing of a disease-specific quality of life questionnaire for adult patients with haemophilia (Haem-A-QoL). *Blood* 2004; **104**: 2214.
- 24 Gringeri A, Mantovani L, von MS. Quality of life assessment in clinical practice in haemophilia treatment. *Haemophilia* 2006; **12**(Suppl. 3): 1–8.
- 25 Guerois C, Lambert T, Peynet J, Fressinaud E, Chambost H, Trudeau E. Assessment of quality of life in hemophilia population: validation of the QUAL-HEMO, a French haemophilia age-group specific quality of life questionnaire. *Haemophilia* 2006; **12**(Suppl. 2): 121–5 (abstract number P0804).
- 26 Flood E, Szende A, Rentz A *et al.* Health-related quality of life in adults with hemophilia: the patient perspective. *J Thromb Haemost* 2003; **1**(Suppl. 1): 25 (abstract number P0657).
- 27 Rentz A, Flood E, Altisent 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**: 1023–34.
- 28 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**: 603–10.
- 29 Landgraf J, Maunse E, Speechley K *et al.* Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. *Qual Life Res* 1998; **7**: 433–45.
- 30 Ravens-Sieberer U, Erhart M, Wille N, Wetzel R, Nickel J, Bullinger M. Generic health-related quality of life assessment in children and adolescents: methodological considerations. *Pharmacoeconomics* 2006; **24**: 1198–220.
- 31 Torrance G, Boyle M, Horwood S. Application of multi-attribute utility theory to measure social preference for health states. *Oper Res* 1982; **30**: 1043–69.
- 32 Young N, Bradley C, Wakefield C, Barnard D, Blanchette V, McCusker P. How well does the Canadian Haemophilia Outcomes-Kids’ Life Assessment Tool (CHO-KLAT) measure the quality of life of boys with haemophilia. *Pediatr Blood Cancer* 2006; **47**: 305–11.
- 33 Bullinger M, von MS, Fischer K *et al.* Pilot testing of the ‘Haemo-QoL’ quality of life questionnaire for haemophiliac children in six European countries. *Haemophilia* 2002; **8**(Suppl. 2): 47–54.
- 34 VonMackensen S, Bullinger M, Haemo-QoL Group. Development and testing of an instrument to assess the Quality of Life of Children with Haemophilia in Europe (Haemo-QoL). *Haemophilia* 2004; **10**(Suppl. 1): 17–25.
- 35 Pollak E, Mühlhan H, von MS, Bullinger M, H-QG. The Haemo-QoL Index: developing a short measure for health-related quality of life assessment in children and adolescents with haemophilia. *Haemophilia* 2006; **12**: 384–92.
- 36 Young N, Bradley C, Blanchette V *et al.* Development of a health-related quality of life measure for boys with haemophilia: the Canadian Haemophilia Outcomes – Kids Life Assessment Tool (CHO-KLAT). *Haemophilia* 2004; **10**(Suppl. 1): 34–43.
- 37 Manco-Johnson M, Morrissey-Harding G, Edelman-Lewis B, Oster G, Larson P. Development and validation of a measure of disease-specific quality of life in young children with haemophilia. *Haemophilia* 2004; **10**: 34–41.
- 38 Feeny D, Torrance G, Furlong W. Health utilities index. In: Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd edn. Philadelphia: Lippincott-Raven, 1996: 239–52.
- 39 Miners A, Sabin C, Tolley K, Jenkinson C, Kind P, Lee C. Assessing health-related quality-of-life in individuals with haemophilia. *Haemophilia* 1999; **5**: 378–85.
- 40 Brooks R, Group E. EuroQol: the current state of play. *Health Policy* 1996; **37**: 53–72.
- 41 Wasserman J, Aday L, Begley C, Ahn C, Lairson D. Measuring health state preferences for haemophilia: development of a disease-specific utility instrument. *Haemophilia* 2005; **11**: 49–57.

- 42 Barr R, Saleh M, Furlong W *et al.* Health status and health-related quality of life associated with haemophilia. *Am J Hematol* 2002; 71: 152–60.
- 43 Wang T, Zhang L, Li H, Zhao H, Yang R. Assessing health-related quality-of-life in individuals with haemophilia in China. *Haemophilia* 2004; 10: 370–5.
- 44 Barr R, Sek J, Horsman J *et al.* Health status and health-related quality of life associated with von Willebrand disease. *Am J Hematol* 2003; 73: 108–14.
- 45 Gringeri A, Mantovani L, Scalone L, Mannucci P, Group. CS. Cost of care and quality of life for patients with haemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; 102: 2358–63.
- 46 Revel-Vilk S, Golomb M, Achonu C *et al.* Effect of intracranial bleeds on the health and quality of life of boys with haemophilia. *J Peds* 2004; 144: 490–5.
- 47 Torrance G, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. Health utilities index. *Pharmacoeconomics* 1995; 7: 503–20.
- 48 Larners L. The transformation of utilities for health states worse than death: consequences for the estimation of EQ-5D value sets. *Med Care* 2007; 45: 238–44.
- 49 Coons S, Rao S, Keininger D, Hays R. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000; 17: 13–35.
- 50 Gold M, Siegel J, Russell L, Weinstein M. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996.
- 51 Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 health survey. *J Clin Epidemiol* 1998; 51: 1115–28.
- 52 Fryback D, Lawrence W, Martin P, Klein R, Klein B. Predicting quality of well-being scores from the SF-36: results from the Beaver Dam Health Outcomes Study. *Med Dec Making* 1997; 17: 1–9.
- 53 Walsh M, Macgregor D, Stuckless S, Barrett B, Kawaja M, Scully M-F. Health-related quality of life in a cohort of adult patients with mild hemophilia A. *J Thromb Haemost* 2008; 6: 755–61.
- 54 Varni J, Burwinkle T, Seid M. The PedsQL as a pediatric patient-reported outcome: reliability and validity of the PedsQL measurement model in 25,000 children. *Expert Rev Pharmacoecon Outcomes Res* 2005; 5: 705–19.
- 55 Bullinger M, von MS, Haemo-QoL G. Quality of life in children and families with bleeding disorders. *J Pediatr Hematol Oncol* 2003; 25: S64–7.
- 56 Sung L, Young N, Greenberg M *et al.* Health related quality of life (HRQL) scores reported from parents and their children with chronic illness differed depending on utility elicitation method. *J Clin Epidemiol* 2004; 57: 1161–6.