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REVIEW ARTICLE

Outcome measures in haemophilia: a systematic review

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Abstract

Haemophilia A and B are hereditary X-linked disorders due to deficiency (or absence) of coagulation factor VIII or IX, respectively. Bleeding risk is related to the severity of factor deficiency. Repeated joint bleeding can lead to a severe haemophilic arthropathy resulting in disabilities. Outcome measurements in persons with haemophilia (PWH) have been limited to laboratory evaluation (factor VIII or IX levels) and clinical outcomes (such as bleeding frequency), morbidity (for example linked with arthropathy) and mortality. Due to the new standard of care of PWH, there is a need to consider other outcome measures, such as the early detection and quantification of joint disease, health-related quality of life (QoL) and economic or cost–utility analyses. To investigate this, we performed a 10-yr systematic overview of outcome measures in haemophilia. Only clinical trials including at least 20 patients with haemophilia A or B were included. To facilitate the search strategy, eight issues of outcome measures were selected: physical scores, imaging technique scores, functional scores, QoL measurement, mortality, bleeding frequency, cost and outcome and bone mineral density. The results of these will be discussed. Clearly defined outcomes in haemophilia care are important for many reasons, to evaluate new treatments, to justify treatment strategies, to allow a good follow-up, to perform studies and to allocate resources. The use of such scoring systems is clearly recommended by experts in haemophilia care. However, most centres do not perform such scores outside clinical trials due to reasons such as lack of time and resources.

Key words haemophilia; outcomes measures; scores; bleeding frequency; quality of life measurement; bone mineral density

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Haemophilia A and B are hereditary X-linked disorders due to deficiency (or absence) of coagulation factor VIII or IX, respectively. Bleeding risk is related to the severity of factor deficiency. Repeated joint bleeding (haemarthrosis) can lead to a severe haemophilic arthropathy resulting in disabilities. Nowadays, the availability of recombinant factor VIII and factor IX concentrates has changed the care of persons with haemophilia (PWH). The efficacy of such treatment has been shown in many observational studies. However, the cost of such treatment is very high.

Outcome measurements in PWH have been limited to laboratory evaluation (factor VIII or IX levels) and clinical outcomes (such as bleeding frequency), morbidity (for example linked with arthropathy) and mortality. Due to the new standard of care of PWH, there is a need to consider other outcome measures, such as the early detection and quantification of joint disease (by physical criteria or imaging techniques), health-related quality of life (HRQoL) and economic or cost–utility analyses. It is of utmost importance to show that treatment of PWH, which is expensive, is justified. Several outcomes have been proposed with sometimes different items for each of them. Some are either difficult to perform or very expensive. Only a few have been clearly assessed. In this manuscript, a 10-yr systematic overview of outcome measures in haemophilia was performed.

Methods

Criteria for selecting studies

A systematic literature review in the field of outcome measures in haemophilia was performed. Studies that assigned comparison of different brands or types of clotting factor concentrates were excluded from the review process. Only clinical trials including at least 20 patients with haemophilia A or B were included. To facilitate the search strategy, eight issues of outcome measures were selected: physical scores, imaging technique scores, functional scores, QoL measurement, mortality, bleeding frequency, cost and outcome, and bone mineral density (BMD).

Literature search

The search strategy was designed based on the questions and the inclusion criteria. The search was performed in PubMed and included literature published from 1 January 2000 through 31 December 2011. Only articles in English were selected. The search terms for the eight items were the following:

1. Physical scores: haemophilia A, joints, score.
2. Imaging technique scores: magnetic resonance imaging (MRI)/methods, haemophilia A/diagnosis, haemophilia A/ultrasonography, haemophilia B/ultrasonography.
3. Functional scores: 'functional independence score in haemophilia' or 'haemophilia activities list'.
4. Quality of life measurement: haemophilia, QoL.
5. Mortality: haemophilia A/mortality, haemophilia B/mortality.
6. Bleeding frequency: haemophilia A, haemophilia B, FVIII, FIX, treatment outcome.
7. Economic data/cost and outcome: haemophilia A, haemophilia B, arthroplasty/replacement, analyses/costs.
8. Bone mineral density: haemophilia, BMD.

Results

Physical scores

Two main physical scores have been described: the World Federation of Haemophilia Physical Examination Score (WFH Physical Examination Score also called Gilbert Score) (1) and the Haemophilia Joint Health Score (HJHS) (2). These two scores are able to adequately discriminate severe, moderate and mild haemophilia as well as PWH on prophylaxis or not. However, the correlation with the bleeding rate is not very strong.

The Gilbert score provides a total score (higher score being worse) and joint-specific scores. It takes quite a long time to complete (30–45 min) and exists in three languages (English, Swedish and Dutch). It needs no special equipment (only a goniometer and a tape measure) but involves training. However, its reliability has not been tested. It is not very sensitive and is especially useful in PWHs with established arthropathy. Furthermore, it is not well adapted for patients on prophylaxis with low joint damage (relatively insensitive to mild joint changes) but has some interest in severely affected patients, for example, in countries with limited access to factor replacement therapy. It has been tested on children in North America and Europe with mild, moderate and severe haemophilia A and B, both with and without prophylaxis, but has not really been validated.

The HJHS exists in three versions and has an excellent reliability (3). It takes quite a long time to do (45–60 min) but needs no special equipment (goniometer, stairs). It involves training. The range of motion measurements should be interpreted according to reference values and their age-related variations (4). It is available in four languages (English, Swedish, Dutch and Chinese Mandarin). The new version of the score (HJHS 2.1) provides a total score (maximum = 124, the higher being the worst), joint-specific scores and a global gait score that is a recent improvement. It is more sensitive than the Gilbert score and is sensitive enough to detect early signs of joint damage. Therefore, it can be used for monitoring joint change over time even in PWH on prophylaxis. It has been tested on children in North America and Europe (usually on prophylaxis with mild joint impairment) and in Chinese boys with moderate-to-severe arthropathy (5–7). It has been validated in its first version (8) as well as in children (9). It has not yet been adequately studied in adults, PWH with severe joint disease or in children aged <4 yr old. HJHS correlates quite well to WFH score (but is 63–97% more efficient for the discrimination of known groups) and has a quite good correlation with cumulative number of haemarthroses. Furthermore, it seems to correlate highly with radiographic damage (10). Details of studies cited in this section are displayed in Table 1.

Imaging technique scores

Radiological imaging is used to diagnose, objectively evaluate, monitor and perform a staging of complications of haemophilia, especially arthropathy due to recurrent joint bleeding. The main imaging techniques evaluated in PWH are conventional radiography (X-ray), MRI and ultrasonography (US).

X-ray, to analyse bone lesions, has been used for many years to evaluate joint damage in PWH. It is useful to monitor advanced stages but insensitive for early changes of haemophilic arthropathy involving soft tissues or first steps of cartilage destruction. Two main classification systems have been proposed for grading the haemophilic arthropathy: the Arnold–Hilgartner system (progressive scale, simple and easy to use) and the Pettersson's score (additive scale, more

Table 1 Physical scores

References, country	Study design	Population characteristics number	Intervention	Outcome measures	Results
Saulyte Trakymiene *et al.*, Lithuania (5)	Cross-sectional study	20 patients with severe haemophilia A or B, episodically treated, mean age 11.5 yr (range 10–17); subdivided in two groups: 4–9, 10–17 yr	Musculoskeletal status measured by Haemophilia Joint Health Score (HJHS)	Musculoskeletal outcome	Significantly ($P = 0.0002$) higher HJHS in the older (31.5, SD 12.8) compared with the younger group (11.6, SD 6.5)
Groen *et al.*, European and North American Centres (6)	Prospective multicentre study	226 boys (mean age 10.8 yr, SD 3.8), 68% severe haemophilia (of whom 91% on prophylaxis); two European and three North American Centres	Measurement of HJHS and functional ability (Childhood Health Assessment Questionnaire CHAQ)	Correlation between CHAQ, HJHS, cumulative number of haemarthrosis (CNH) and age	Strong correlation of CNH and HJHS ($\rho = 0.51$), weak correlation of HJHS and CHAQ ($\rho = -0.19$), nor correlation between age and CHAQ
Groen *et al.*, The Netherlands (7)	Cross-sectional study	47 boys with haemophilia (age 8–18 yr; mean 12.5, SD 2.5)	Measurement of HJHS, physical activity (modifiable activity questionnaire, MAQ) and aerobic fitness (peak oxygen uptake)	Associations between MAQ, HJHS and aerobic fitness	Peak oxygen uptake lower in boys with haemophilia compared with healthy boys ($P = 0.03$), no correlation between HJHS, MAQ and aerobic fitness
Feldmann *et al.*, Canada (9)	Multicentre cohort study	226 boys with mild (17% of whom 3% on prophylaxis), moderate (15% of whom 24 on prophylaxis) and severe haemophilia (78% of whom 93% on prophylaxis); five centres	HJHS scored by trained physiotherapists, World Federation of Haemophilia physical examination scale (WHF) determined by physicians at each site	HJHS in comparison with World Federation of Haemophilia (WFH) score, overall arthropathy impact and severity of haemophilia	HJHS correlates moderately with WFH score and overall arthropathy impact (both $rs = 0.42$, $P < 0.0001$). HJHS more efficient to differentiate severe from mild and moderate haemophilia

difficult to perform) (11–13). Both scores have good intra- and interobserver variability and demonstrate a quite good correlation in the presence of absence or huge joint changes but poor agreement in cases of mild or moderate arthropathy (14).

MRI has many advantages compared with X-ray, including a better visualisation of soft tissue and cartilage changes and the absence of ionising radiation. MRI is considered as the method of choice for the detection of early joint damages, for staging and follow-up. It has a good reliability (15, 16). However, MRI is expensive, not easily available and requires sedation in young children. Two MRI scores have been proposed: the Denver MRI score, simple but does not allow a good discrimination between different degrees of cartilage lesions (17), and the European MRI score (18) that allows a better evaluation of soft-tissue and osteochondral changes, but is more complex than the Denver scale. Several other MRI grading systems have been proposed, making it very difficult to compare results of different centres. A compatible MRI scale has been developed by the International Prophylaxis Study Group (IPSG) to standardise the MRI interpretation (19). This score combines a progressive scale and an additive scale, seems to be highly reproducible and has a low correlation with clinical parameters but does not allow discrimination between mild and moderate/severe disease (18–21).

US imaging is mainly dedicated to examination of soft tissues but also cartilage interfaces. There is a good correlation between US score and number of bleeding (22). It has several advantages such as absence of irradiation, accessibility and possibility of dynamic examination. The main disadvantage of this technique is its operator dependence and the lack of standardisation of imaging scales. Protocols have been proposed or are under development (23, 24).

Other imaging techniques have been used such as computer tomography, scintigraphy and positive emission tomography but seem to have limited use in the follow-up of haemophilic arthropathy. Additional information on studies cited in this section is shown in Table 2.

Functional scores

Two main functional scores have been developed and evaluated: the Functional Independence Score in Haemophilia (FISH) and the Haemophilia Activities List (HAL).

The FISH is an objective performance-based instrument whose aim is to measure the functional ability of a person with haemophilia (25). It can be used to evaluate change in functional independence over time. It takes into consideration daily-life activities that could be affected by haemophilia (such as eating, dressing, etc), which are graded (from 1 to 4, maximum possible score being 32) according to the amount of assistance required to perform the activity. It is not designed to assess challenging activities and does not consider other activities such as education or employment. With some experience, it can be completed in 15 min and does not need special training. It can be used in persons of different linguistic abilities. It was developed and validated in a group of patients who have significant arthropathy and is therefore more useful in adolescents and adult patients who have not used prophylaxis. It is not sensitive enough for the detection of early change but is a good option for developing countries. The FISH showed a quite good correlation with other functional ability tests such as the Stanford Health Assessment Questionnaire (HAQ) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) (25, 26) as well as the Canadian Occupational Performance Measure (COPM) (27). It has high internal consistency and an excellent reliability. A good correlation was found between musculoskeletal function assessed by FISH and depressed mood (28).

The HAL is a self-assessment questionnaire designed to quantify (evaluate and monitor) self-perceived functional abilities of adult patients (29). It contains 42 multiple choice questions in seven domains: lying/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks, leisure activities and sports. The HAL was developed in Dutch but is also available in English, German, Swedish, Bengali, Hindi, Kannada, Tamil and Telegu. Its main disadvantage is the lack of sensitivity and the fact that it is language dependent. It needs approximately 10 min to be completed and requires no special training. The HAL has not been tested for reliability and sensitivity to detect clinical changes. The convergent validity was good when compared to the Dutch Arthritis Impact Measurement Scale 2 (AIMS) and the Impact on Participation and Autonomy questionnaire (IPA) (30, 31). The construct validity of the HAL was generally lower when compared to functional tests (30). Test–retest reliability has not been assessed. The ability of the HAL to detect clinically important changes over time has yet to be established.

The Paediatric Haemophilia Activities List (PedHAL) was developed to measure the impact of haemophilia on self-perceived functional abilities in children (32). The current version (0.11) consists of 53 items in the same seven domains as the adult one. A parent version (for children aged 4–8 yr) and a child version (for children and adolescents aged 8–18 yr) were constructed with some minor linguistic differences. The PedHAL has been developed in Dutch but Canadian English, Canadian French and Romanian translations are currently being studied. The time to complete is about 15 min for both the child and parent versions. Most subscales showed moderate associations with joint examination and moderate-to-good associations with the physical function subscale of the Childhood Health Assessment Questionnaire (CHQ–50) (32). The overall utility has to be determined with future studies. More information on studies cited in this section is shown in Table 3.

Table 2 Imaging techniques scores

References, country	Study design	Population characteristics number	Intervention	Outcome measures	Results
Doria *et al.*, Canada and Europe (15)	Multicentre cohort study	43 (96%) boys with haemophilia A, 2 (4%) with haemophilia B; ages ranging from 4 to 16 yr (mean 11)	MR images of knees (n = 22) and ankles (n = 23) were read blinded. Number of previous joint bleeds and severity of haemophilia were the reference standards for imaging assessment	Reliability and construct validity of the compatible magnetic resonance imaging (MRI) scoring system [progressive (P) and additive (A) scale] for the evaluation of haemophilic knees and ankles	High inter- and intrareader intraclass correlation of P (0.91 and 0.94) and A (0.81 und 0.92). Discrimination of disease severity similar for A- and P-scales (mild, P = 0.23; severe P = 0.05)
Lundin *et al.*, USA and Canada (16)	Cross-sectional multicentre study	39 ankle joints in 28 haemophilic boys	Magnetic resonance imaging (MRI), scoring of results according to the Denver (DS) and the (new) European scoring (ES) scheme by two independent radiologists	Reproducibility of readings	Good or moderate intraobserver agreement; interobserver agreement poorer (unweighted kappa 0.56/0.38 DS and 0.51/0.42, 0.54/0.56, 0.71/0.35 and 0.34/0.29 for components of ES)
Nuss *et al.*, USA (17)	Prospective single-centre study	21 joints with recurrent haemorrhage in 21 persons with haemophilia	Radiosynoviorthesis was administered to 21 joints. Self-report of haemorrhage history, World Federation of Haemophilia orthopaedic joint and pain scales, X-ray, and MRI joints pre- and postradiosynoviorthesis	Correlation of MRI findings an clinical outcome	MRI findings prior to procedure not predictive for outcome
Lundin *et al.*, Sweden (18)	Prospective single-centre study	56 ankle joints in 38 haemophilic boys	Magnetic resonance imaging (MRI), classification of results according to the Denver and the European scoring scheme	Comparison of MRI scores and correlation with the number of joint bleeds and the orthopaedic joint score	Strong correlation between the MRI scoring methods [correlation coefficient (CC) 0.8–0.95 ($P < 0.001$)]; weak correlation between MRI scores and clinical data (CC 0.32–0.39, $P < 0.01$)
Melchiorre *et al.*, Italy (22)	Prospective single-centre study	62 patients with haemophilia A or B; 20 healthy subjects and 20 patients with rheumatoid arthritis as controls	Power Doppler ultrasound (PDUS) on knee (US score), ankle and elbow joints; X-rays in 61/62 patients (Petterson's score, PXS) and clinical evaluation	Capacity of ultrasonography in detecting bleeding and joint damage in haemophilic arthropathy	Significant correlation between US score and PXS for bone remodelling (Spearman's ρ CC = 0.429, $P < 0.01$) and for osteophytes (SRCC = 0.440, $P < 0.01$), very significant correlation between US score and number of bleeding (SRCC = 0.375, $P < 0.01$)

Table 3 Functional scores

References, country	Study design	Population characteristics number	Intervention	Outcome measures	Results
Poonnoose *et al.*, India (25)	Cross-sectional single-centre study	35 patients over 10 yr old and with at least three major bleeds per year	Scoring for clinical [World Federation of Haemophilia (WFH) score] and radiological changes (Pettersson's score) and for functional independence [Stanford Health Assessment Questionnaire (HAQ) and Functional Independence Score in Haemophilia (FISH)]	Correlation of FISH score with other scoring systems	Modest correlation of FISH with WFH score ($r = -0.68$) and Pettersson's score ($r = -0.44$), good correlation with HAQ ($r = -0.90$). FISH had better internal consistency than HAQ
Poonnoose *et al.*, India (26)	Cross-sectional single-centre study	63 patients with severe haemophilia over 7 yr old	Assessment of FISH, WFH score, Pettersson's score, Stanford Health Assessment Questionnaire (HAQ), West. Ontario and McMaster Osteoarthritis Index (WOMAC)	Psychometric properties of FISH	Good internal consistency of FISH. Moderate correlation with WFH score ($r = -0.61$) and Pettersson's score ($r = -0.38$). Good correlation with HAQ ($r = -0.75$) and WOMAC ($r = -0.66$)
Padankatti *et al.*, India (27)	Cross-sectional single-centre study	67 patients with haemophilia (aged 10–55)	Canadian Occupational Performance Measure (COPM) was assessed, and data were compared with FISH	Utility of COPM in evaluating the musculoskeletal functional status of patients with haemophilia	Good correlation between COPM and FISH on all domains: self-care ($r = 0.772$), productivity ($r = 0.758$) and leisure ($r = 0.818$). In 78% of responses on COPM concordance between the performance and satisfaction scores
Hassan *et al.*, Egypt (28)	Cross-sectional single-centre study	50 adolescent haemophilia A patients	Assessment of musculoskeletal function by FISH and mood status by Beck Depression Inventory-Short Form (BDI-SF)	Correlation of musculoskeletal function and depressed mood	32% of patients were not depressed, 36% had a mild depression, 22% a moderate depression and 10% a severe depression. Highly significant correlation between FISH and BDI-SF ($P < 0.001$)
van Genderen *et al.*, The Netherlands (30)	Cross-sectional single-centre study	127 patients with severe haemophilia	Assessment of Haemophilia Activities List (HAL), Dutch Arthritis Impact Measurement Scale 2, and Impact on Participation and Autonomy questionnaire	Finalisation of HAL and assessment of convergent and construct validity, and internal consistency	High internal consistency of the seven domains of HAL ($\alpha = 0.61$–0.96), good convergent validity ($r = 0.47$–0.84), and lower construct validity ($r = 0.23$–0.77)
Brodin *et al.*, Sweden (31)	Cross-sectional multicentre study	225 patients with severe or moderate haemophilia A or B, three centres; 39% filled out the questionnaire	Assessment of HAL (Swedish version), Swedish Arthritis Impact Measurement 2 (AIMS 2), and Impact on Participation and Autonomy (IPA)	Validation of HAL in Sweden	High internal consistency (α 0.98–0.71), excellent correlation between HAL sum score and AIMS 2 ($r = 0.84$, $P < 0.01$), IPA indoors ($r = 0.83$, $P < 0.01$), and IPA outdoors ($r = 0.89$, $P < 0.01$)
Groen *et al.*, The Netherlands (32)	Cross-sectional single-centre study	32 children with haemophilia	Assessment of HAL (version for children, pedhal), Childhood Health Assessment questionnaire and Activity Scale for Kids	Adapt pedhal to children from the age of 4	Moderate associations of pedhal subscales with joint examination ($\rho = 0.42.0$–63) and moderate-to-good associations with physical function subscale of CHQ-50 ($\rho = 0.48$–0.74)

Table 4 Quality of life

References	Study design	Population characteristics number	Intervention	Outcome measures	Results
Scalone *et al.* (37)	Cross-sectional multicentre study	50 adult patients with haemophilia and inhibitors; 11 centres	Clinical assessment and assessment of Euro-Quality of Life (QoL) (EQ-5D) and Short Form-36 (SF-36)	Health-related QoL (HRQoL) in haemophilia patients with inhibitors	Significant correlation of EQ-5D ($P < 0.001$) and SF-36 ($P < 0.01$) with orthopaedic joint score. HRQoL in inhibitory patients is impaired by orthopaedic status and not by other aspects
Royal *et al.* (38)	Cross-sectional multicentre study, international	1033 haemophilia patients, 16 European centres	Assessment of SF-36	QoL differences between patients with prophylactic and on-demand factor replacement therapy	Patients on prophylaxis significant less bodily pain, better general health, higher physical functioning, mental health and social functioning dimensions
Rentz *et al.* (40)	Prospective cohort study	221 patients with haemophilia	Haemophilia-specific health-related QoL questionnaire for adults (HAEMO-QoL-A), SF-36 and Health Assessment Questionnaire-Functional Disability Index (HAQ-FDI) at baseline and after 4 wk	Validation of HAEMO-QoL-A	Good internal consistency of HAEMO-QoL-A (α 0.75–0.95), intraclass coefficients >0.80. Good correlation of HAEMO-QoL-A with SF-36 (0.13–0.87) and HAQ-FDI (−0.14 to −0.69)
Gringeri *et al.* (41)	Prospective cohort study	52 patients with haemophilia with high-responding inhibitors	Longitudinal observation (18 months), questionnaires for QoL filled out	Evaluation of cost of care and QoL	Average monthly cost 18 000€. No difference of QoL compared with patients with severe haemophilia without inhibitors
Bullinger *et al.* (42)	Cross-sectional multicentre study, international	58 children with haemophilia, 57 parents	Haemo-QoL filled out by patients and parents, collection of medical data	Pilot testing of Haemo-QoL	Acceptable reliability and validity
von Mackensen *et al.* (44)	Cross-sectional multicentre study, international	339 children from 20 centres with haemophilia, six countries	Assessment of Haemo-QoL questionnaire in children and their parents	Validation of Haemo-QoL for children	Haemo-QoL had acceptable internal consistency, retest reliability, and discriminant and convergent validity
Gringeri *et al.* (46)	Cross-sectional multicentre study, international	318 children with haemophilia (85.5% A), aged 4–16 yr, no inhibitors	Assessment of health-related QoL (HRQoL) by haemophilia-specific QoL questionnaire (Haemo-QoL), collection of clinical information	Health status and health care and impact of QoL in children	HRQoL satisfactory. Young children mainly impaired in dimensions 'family' and 'treatment', older children in social dimensions (perceived support and friends)

Quality of life measurement

QoL is now accepted as an outcome criterion in medicine and in decision analysis models. The aim is to evaluate the patient's perspective of well-being and the impact of haemophilia treatments on QoL. Several clinical trials include QoL assessment in their protocols. In some countries, improvement of QoL is used to determine reimbursement for drugs. For example, in the UK, the National Institute for Clinical Excellence (NICE) recommends that health benefits should be valued in terms of gains in quality-adjusted life years (QALYS) (33).

Many scores have been described to evaluate QoL: some are non-specific for haemophilia (such as EQ–5D, SF–36 and SF–12), and others have been developed specifically for PWH, the most frequently used being Haemo–QoL (for adults and children) and the Children Haemophilia Outcome (CHO)–Kids Assessment Tool (KLAT) (for children).

Non-specific QoL scores are very useful to compare QoL in patients with different diseases. For example, NICE recommends the EQ–5D, which is a simple measure of health outcomes, including only five short questions and three levels (about mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, the main disadvantage is that it was developed in healthy people who were asked to imagine a poor health state (34). It is designed for self-completion by respondents and takes only a few minutes to complete.

The most widely used generic questionnaire is the SF–36 consisting of 36 items divided in eight scaled scores (35). SF–12 is a shorter form of SF–36 (36). A significant correlation of EQ–5D and SF–36 was found with orthopaedic joint score (37). According to the SF–36, QoL was better in patients on prophylaxis than in patients receiving on-demand treatment (38).

In some circumstances, a haemophilia-specific tool may be more useful. The adult Haemo–QoL, developed in Spain, is the only validated disease-specific haemophilia-related QoL instrument (39). It includes 36 questions. HAEMO–QoL–A had a good internal consistency, and a good correlation was demonstrated between HAEMO–QoL–A and SF–36 (40). Trials were also performed in PWH with high-responding inhibitors showing no difference of QoL compared with patients with severe haemophilia without inhibitors (41).

For children, two versions of the Haemo–QoL have been developed: the original version (including 21–77 questions, depending on age) and a shorter version called the Haemo–QoL index (including only eight questions) (42, 43). It is available in six languages (English, French, Italian, German, Dutch and Spanish). A pilot testing of the child Haemo–QoL showed an acceptable reliability and validity (42). It was then tested in six European countries where it showed showing satisfactory results in terms of reliability, convergent validity and discriminant validity (44). Another score dedicated to children was developed in Canada; the CHO–KLAT includes 35 questions (45). Versions appropriate for three different age groups (4–7, 8–12 and 13–16 yr) were constructed. Another study showed that HRQoL was satisfactory in children (high level of health status and HRQoL that is better in haemophilic adolescents on prophylaxis) but found some differences according to the age of the children. Indeed, young children were mainly impaired in 'family' and 'treatment' dimensions, and older children were mainly impaired in the so-called social dimensions (46). More information on the referenced studies is given in Table 4.

It is important to note that haemophilia-specific QoL questionnaires should be adapted for each country or culture.

Mortality

For several years, mortality and bleeding frequency were the main criteria for outcome measurements. The natural history of haemophilia revealed that almost 3/4 of PWH died before 15 yr of age and only a few survived beyond the age of 40 yr. The introduction of treatment with factor concentrates had a huge influence on mortality rate, but the development of inhibitors was still a major cause of death in the 1980s (47). During the 1980s and 1990s, mortality was also highly affected by HIV infection (48). According to recent surveys performed in developed countries, life expectancy of PWH approaches that of the non-affected male population (49) (Table 5).

Bleeding frequency

The pattern of bleeding is different in PWH depending on the severity of the disease, physical activity and age, but also other parameters. The evaluation of bleeding frequency is often the main clinical outcome in clinical studies. Several studies have been performed to evaluate the efficacy of prophylaxis and have shown a significant decrease of mean number of joint bleeds with prophylaxis (50, 51) (Table 6).

Economic data/cost and outcome

For many years, pharmacoeconomic analyses primarily focused on clinical outcomes and the costs of factor concentrates. Introduction of prophylaxis and use of bypassing agents in PWH with inhibitors led to a major increase in the cost of haemophilia treatment.

Joint damage usually leads to disability, often at a very young age in severe haemophilia in the absence of prophylactic treatment. It can lead to joint replacement (arthroplasty). The aim of prophylaxis is to convert severe haemophilia to moderate haemophilia (by maintaining the

Table 5 Mortality

References, country	Study design	Population characteristics number	Intervention	Outcome measures	Results
Ludlam *et al.*, Scotland (47)	Multicentre retrospective observational study	413 patients with haemophilia A and B, 1980–1994	Investigation of demographic features	Mortality, causes of deaths, hospital admissions	Totally 61 deaths, 12 deaths from haemorrhages, lower hospital admission rate for haemophilia B than haemophilia A, double rate of hospital admissions for patients with a factor VIII inhibitor
Plug *et al.*, The Netherlands (48)	Prospective cohort study	967 patients with haemophilia A and B	Investigation of overall and cause-specific death rates and comparison with national mortality figures for males between 1992 and 2001	Standardised mortality ratio (SMR), life expectancy LE	94 (9.7%) patients had died; SMR 2.3 95% confidence interval 1.9–2.8); LE 1972–1985: 63 yr; LE 1992–2001 59 yr; Exclusion of virus-related deaths 72 yr
Tagliaferri *et al.*, Italy (49)	Multicentre retrospective observational study	443 persons with haemophilia (PWH) who died between 1980 and 2007, 30 Italian haemophilia centres	Investigation of mortality, causes of deaths, life expectancy and co-morbidities in Italian PWH	Standardised mortality rate (SMR), life expectancy (LE)	SMR 1990–1999: 1.98 95% CI 1.54–2.51; SMR 2000–2007: 1.08 95% CI 0.83–1.40; LE 1990–1999: 64.0 yr; LE 2000–2007: 71.2 yr

Table 6 Bleeding frequency

References	Study design	Population characteristics number	Intervention	Outcome measures	Results
Fischer *et al.* (50)	Retrospective cohort study	49 Dutch patients with severe haemophilia and prophylaxis; 106 French patients with severe haemophilia treated on demand	Combination of two retrospective studies that measured clotting factor use and outcome	Joint bleeds, clinical scores, arthropathy	Prophylaxis: fewer joint bleeds per year (2.8 vs. 11.5), more patients without joint bleeds (29% vs. 9%), lower clinical scores, less arthropathy
Manco-Johnson *et al.* (51)	Prospective randomised single-centre study	65 boys younger than 30 months with severe haemophilia A	Randomisation on prophylaxis (32 boys) or enhanced episodic therapy (33 boys); follow-up until boys were 6 yr old	Primary outcome: incidence of bone or cartilage damage; further outcomes: haemorrhages, hospitalisations, infections	After 6 yr joints structure more often normal with prophylaxis (93% vs. 55%, $P = 0.006$), more haemorrhages with episodic therapy ($P < 0.001$), no differences for infections and hospitalisations

factor trough level above 1%) and thus to decrease haemophilic arthropathy. A literature-based modelling was performed in 2008 with two hypothetical cohorts of high-titre inhibitor patients with frequent bleeding episodes, one virtual cohort underwent knee surgery, and the other did not. Direct medical costs and QoL were analysed showing that the cost of quality-adjusted life year with knee arthrodesis and total knee replacement was below USD 50 000 (52).

In one study, the clotting factor consumption was compared between patients with single and those with multiple surgical procedures during the same hospitalisation with demonstration of an important estimated cost reduction per joint in multijoint procedures (53). More details of the two cited studies are given in Table 7.

Table 7 Economic data

References, country	Study design	Population number	Intervention	Outcome measures	Results
Ballal *et al.*, United States (52)	Literature-based modelling	Two hypothetical cohorts of high-titre inhibitor patients with frequent bleeding episodes	One virtual cohort underwent knee surgery; the other did not. An exploratory literature-based life-table model was developed	Direct medical costs, quality of life	Cost of quality-adjusted life year with knee arthrodesis and total knee replacement was below 50 000 USD
Schild *et al.*, The Netherlands (53)	Single-centre observational retrospective study	55 consecutive procedures in patients with haemophilic arthropathy, including 32 multijoint procedures	Clotting factor consumption was compared between patients with single and those with multiple surgical procedures during the same hospitalisation	Clotting factor consumption, duration of hospital stay after surgery, estimation of cost reduction	Factor consumption 708 U/kg in single-joint procedures vs. 326 U/kg in multijoint procedures ($P < 0.0005$); estimated cost reduction of €22 350 per joint in multijoint procedure

Bone mineral density

PWH may be at risk of developing osteopenia or even osteoporosis for many reasons such as immobilisation, decreased activity and recurrent haemarthrosis. BMD can be used as an indicator of osteoporosis and fracture risk to identify PWH who might benefit from measures to improve bone strength.

Some studies have compared BMD in PWH and controls either in children or in adults. Significant differences were found between BMD in PWH and controls (54, 55), and a correlation was found between BMD and the age of starting prophylaxis (56). No significant difference in BMD was shown between PWH of mild and severe type (57).

Other studies have compared different methods to identify the risk of osteoporosis. Christoforidis *et al.* found no agreement between dual-energy X-ray absorptiometry and quantitative ultrasonography in identifying patients at risk of osteoporosis. However, significantly higher levels of nuclear κB ligand and osteocalcin and significantly lower levels of osteoprotegerin were found in PWH compared with controls (58). Significantly higher excretion of urinary calcium and higher serum calcium were found in PWH (55).

Trials have been performed to determine risk factors associated with decreased BMD and have found an association between blood loss and low serum 25-hydroxyvitamin D, lower BMI, low activity scores, decreased joint range of motion, increased number of affected joints, HIV, HCV and history of inhibitor and age (59). See Table 8 for further details.

Discussion

Various outcome measures have been evaluated in PWH, and in some items, various scoring systems are proposed. Some points need to be discussed:

Why do we need outcome measures?

Clearly defined outcomes in haemophilia care are important for many reasons, to evaluate new treatments, to justify

Table 8 Bone mineral density

References	Study design	Population characteristics number	Intervention	Outcome measures	Results
Tlacuilo-Parra *et al.* (54)	Single-centre case–control study	62 children with haemophilia, 62 sex-, race- and age-matched healthy boys.	DXA scan [lumbar spine bone mineral density. (BMD)]; assessment of physical activity (questionnaire) and calcium intake.	Low BMD, calcium intake, physical activity	38% of persons with haemophilia (PWH) low BMD (controls 16%, $P = 0.014$); lumbar BMD lower in PWH than controls ($P = 0.0004$). More sedentary and low-grade exercise in PWH than controls ($P = 0.003$). No difference in calcium intake.
Ranta *et al.* (55)	Single-centre case–control study	29 children with haemophilia (two mild, six moderate, 21 severe), 58 aged matched controls	Assessment of fracture history, blood and urine biochemistry, BMD, spinal imaging	Bone health	BMD lower in PWH than controls but no significantly increased fracture rate. PWH significantly higher excretion of urinary calcium, an higher serum calcium
Khawaji *et al.* (56)	Cross-sectional single-centre study	Two groups of patients: group A (started prophylaxis at age <3 yr; $n = 22$) and group B (started prophylaxis at age >3 yr; $n = 15$)	DXA scan of different sites, assessment of quality of life by SF-36 questionnaire	Health-related quality of life, compared with general population and with bone density	Group A: normal BMD *T*-scores at all sites. Group B: low mean BMD *T*-score 8< to 1.0 at hip region, normal *T*-scores at other sites; lower SF-36 scores than reference population. Significant correlation between BMD (femoral neck and total body) and physical domains
Khawaji *et al.* (57)	Cross-sectional single-centre study	26 patients with severe (aged 33.6 ± 2.1) and 16 patients with moderate (aged 40.2 ± 3.3) haemophilia	DXA scan, assessment of physical activity (questionnaire), physical examination score	BMD in PWH of different severity types and treatment	No significant difference in BMD at lumbar spine L1-L4 (mild, 1.214 vs. severe, 1.175; $P = 0.329$), total hip (1.085 vs. 1.001, $P = 0.114$), femoral neck (1.036 vs. 0.977, $P = 0.265$), trochanter (0.896 vs. 0.820, $P = 0.131$) and whole body (1.215 vs. 1.183, $P = 0.325$) between PWH of mild and severe type. No significant correlation between joint evaluation score and BMD at total hip ($P < 0.0001$), femoral neck ($P = 0.0003$) and trochanter ($P = 0.003$) in patients with severe haemophilia. No correlation between physical activity an disease severity and between BMD and severity of haemophilia
Christoforidis *et al.* (58)	Cross-sectional single-centre study	26 boys with haemophilia (age 12.08 ± 4.44 yr)	Dual-energy X-ray absorptiometry (DXA scan) at lumbar spine and radial, tibial quantitative ultrasonography (QUS). Measure of nuclear κB ligand (sRANK-L), osteoprotegrin (OPG) and osteocalcin (OC)	Bone status	2/26 patients had *Z*-scores < -2, 4/26 had *Z*-scores between -1 and -2. No agreement between QUS and DXA in identifying patients at risk for osteoporosis ($k = 0.275$, $P = 0.063$). Significantly higher levels of sRANK-L ($P = 0.038$) and OC ($P = 0.002$) and significantly decreased levels of OPG ($P < 0.001$) compared with controls
Gerstner *et al.* (59)	Cross-sectional single-centre study	30 PWH, moderate and severe, median age 41.5 yr (range 18–61)	DXA scan, laboratory (25-hydroxyvitamin D), measurement of joint mobility, physical activity questionnaire	Risk factors associated with decreased BMD	low serum 25-hydroxyvitamin D ($P = 0.03$), lower BMI ($P = 0.047$), low activity scores ($P = 0.02$), decreased joint range of motion ($P = 0.046$), HIV ($P = 0.03$), HCV ($P = 0.02$), history of inhibitor ($P = 0.01$) and age ($P = 0.03$) were associated with increased bone loss

treatment strategies, to allow a good follow-up, to perform studies and to allocate resources. It is also important from an educational point of view and for research purposes. This need is emphasised by the high cost of haemophilia care. Several outcomes have been described: clinical, radiological and economical. Scoring systems have been proposed. However, studies performed on these outcomes have limitations and validation is not always available.

Why do centres not use outcome measures?

The use of such scoring systems is clearly recommended by experts in haemophilia care. However, most centres do not perform such scores outside clinical trials. The main reasons are lack of time, lack of specialised resources and lack of money. In developing countries, it is also difficult to propose scoring systems without being able to offer a specific treatment. It is therefore important to propose minimal required outcome measures that can be done on a routine basis for regular follow-up. First of all, it is necessary to define what is really needed to perform an appropriate follow-up of PWH. Are some outcome measures only used in highly specialised centres that can propose such a follow-up? Working groups are responsible for developing recommendations for the most appropriate outcome measures that can be used in routine clinical practice.

What is the goal of haemophilia care?

Before developing such minimal outcome measures, it is necessary to clearly identify the goal of haemophilia care. In fact, experts do not agree about the aim of treatment in PWH. Of course, the first goal, especially in developing countries, is to be able to treat bleeds. In developed countries, the aim is to prevent bleeds by the use of prophylaxis. But, is the aim to have PWH with totally morphological intact joints? If yes, what is the cost of keeping the joints completely intact? Imaging techniques such as MRI now show very minor changes, but we are far from understanding what such small MRI changes mean.

What about economic aspects?

Finally, the economic issue has to be analysed. Cost analysis of outcome measurements is not always available but is very important due to the high cost of treatments and limited resources in all countries. In the next few years, some restrictions in haemophilia care will be asked for by payers in terms of choice of product as well as treatment regimen. There is a consensus on the need to have outcome data to demonstrate the value of treatment and to justify costs. Indeed, reimbursement agencies will focus on resource allocation and ask for cost-effectiveness, cost–utility or cost–benefit analyses.

Conclusion

Despite the fact that many outcome measures are now available, the optimal way to evaluate haemophilia care is not well defined. A clarification of an aim for haemophilia treatment is necessary. Due to economic restrictions, simplified outcome measures have to be determined and the place of potential future markers has to be developed such as bone markers, cytokines or other inflammatory markers. There is a real need for determining recommendations for the future standard of care of PWH, taking into account economical considerations.

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Author's contributions

F. Boehlen and L. Graf searched for the data and wrote the paper. E. Berntorp proposed the subject of the review and the conception of the manuscript and critically revised the text and the tables.

Conflicts of interests

Françoise Boehlen, Lukas Graf and Erik Berntorp have no conflicts of interest to declare.

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