



REVIEW ARTICLE

Choosing outcome assessment tools in haemophilia care
and research: a multidisciplinary perspective

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Introduction: The implementation of early long-term, regular clotting factor concentrate (CFC) replacement therapy ('prophylaxis') has made it possible to offer boys with haemophilia a near normal life. Many different regimens have reported favourable results, but the optimum treatment regimens have not been established and the cost of prophylaxis is very high. Both for optimizing treatment and reimbursement issues, there is a need to provide objective evidence of both short- and long-term results and benefits of prophylactic regimens. **Aims:** This report presents a critical review of outcome measures for use in the assessment of musculoskeletal health in persons with haemophilia according to the International Classification of Functioning, Disability and Health (ICF). This framework considers structural and functional changes, activities and participation in a context of both personal and environmental factors. **Methods:** Results were generated by a combination of a critical review of available literature plus expert opinion derived from a two day consensus conference between 48 health care experts from different disciplines involved in haemophilia assessment and care. Outcome tools used in haemophilia were reviewed for reliability and validity in different patient groups and for resources required. **Results and conclusion:** Recommendations for choice of outcome tools were made according to the ICF domains, economic setting, and reason for use (clinical or research). The next step will be to identify a 'core' set of outcome measures for use in clinical care or studies evaluating treatment.

Keywords: activity, arthropathy, evaluation instruments, haemophilia, outcomes research, participation

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Introduction

The natural history of persons with haemophilia is characterized by repeated intramuscular and intra-articular bleeding, especially into ankles, knees and elbows. Eventually, repeated bleeding results in chronic synovitis and haemophilic arthropathy. Both arthropathy and pain lead to serious disability. Since the introduction of safe clotting factor concentrates (CFCs), regular replacement therapy ('prophylaxis'), and the establishment of comprehensive care haemophilia treatment centres, the outcome of severe haemophilia has improved dramatically. However, optimal programmes of prophylaxis are not yet established and treatment-related complications such as inhibitor development are a major problem. Furthermore, many patients still have limited access to treatment and even in resource unconstrained countries some patients continue to experience joint damage despite prophylaxis. Consequently, clinicians still are striving to optimize treatment, which can only be achieved through prospective evaluation of different CFC replacement protocols, longitudinal cohort studies, and the use of reliable, valid and sensitive outcome assessments. Standardization of outcome assessment will permit meaningful comparison across studies and reduce heterogeneity in knowledge acquisition in this rare but expensive to treat condition.

Outcome assessment is a complex undertaking involving many factors. To include the full spectrum of consequences of a disease, outcome assessment should follow the WHO proposed International Classification of Functioning, Disability and Health (ICF) [1]. 'This model provides a framework to qualify the different interactive components of the main disease-disability pathway: *Body Functions and Structures, Activities, Participation, and Environmental and Personal factors*. Each of these components is further categorized and coded. Several factors need to be considered while assessing functioning and disability in this manner. First, in a chronic condition such as haemophilia it is important to consider the time window of observation. In haemophilia, the time of observation ranges mostly from a minimum of 6–12 months (e.g. for assessment of bleeding), to decades or even lifelong (e.g. for assessment of musculoskeletal results of prophylaxis). Second, it is important to consider the specific aim (i.e. perspective) of the outcome assessment. While patients and health care providers are both interested in achieving optimum treatment outcomes, it is the patient that faces the burden of treatment and this may lead to different perspectives. At the same time, health outcomes research is used to inform decisions regarding reimbursement of treatment. These economic studies evaluate patient relevant outcomes of the health care process in the real-life world; this includes the patient's functional status,

well-being and satisfaction with care, as well as direct medical costs and days lost from work/school. These data are used for cost-effectiveness or cost-utility analyses to compare the value of different treatment strategies.

The aim of this initiative was to provide an evidence-supported expert review on tools to use for outcome assessment in haemophilia care and research, including different settings and perspectives.

Methods

The present review is based on face-to-face group discussions among 48 multidisciplinary experts from North America ($n = 25$), Europe ($n = 11$) and other countries ($n = 12$). Disciplines represented included haematology, orthopaedic surgery, physical therapy, physiatry, radiology, ultrasonography and health economics. A list of meeting attendees is provided in the Acknowledgements section.

Separate discussions were held on four topics in outcome assessment of health: (i) physical examination, (ii) imaging, (iii) activity and participation, and (iv) health economics and quality of life.

During the discussions, available literature on measurement properties and tools was identified. In addition, full text original articles in English (PubMed) pertaining to development, validation, and ability to discriminate between haemophilia patient groups were considered for each tool. Summary reports for each topic identified the following characteristics: classification (generic/disease specific), target population for the tool (age, and/or extent of joint damage), setting (clinical care and/or research), assessment time, validation and discriminative abilities of the tool, optimum interval between assessments, remarks regarding additional research, and final recommendation (mandatory, recommended, optional, limited value, unknown).

Results

Bleeding

As the main symptom of haemophilia, bleeding frequency is the primary parameter for treatment decisions. Standard assessment of bleeding frequency considers the number of bleeds optimally collected over a period of twelve consecutive months (annualized bleeding rate or ABR). This parameter suffers from many caveats, limiting its usefulness for both clinical practice and research. First, the diagnosis of a bleeding episode is generally subjective and based on patient (or proxy) reported symptoms. Most bleeds are not confirmed by health care providers as patients with severe haemophilia usually treat bleeding episodes at home. Thus, lack of a gold standard and/or objective assessment may result in over- or under-

reporting of bleeds. Under-reporting will be worse in patients who fail to keep adequate diaries. Especially soft tissue and minor bleeds are likely to be underreported. In patients with haemophilic arthropathy, pain related to pre-existing arthritis may be misinterpreted as bleeds. Major and life-threatening bleeds requiring immediate medical attention are easier to capture.

Documentation of bleeds by either patients or health care providers should be performed according to pre-specified definitions. Published definitions [2,3] of bleeds focus on location and symptoms of bleeding without distinguishing between major and minor bleeding. The PedNet group have added severity to the previous definitions: (i) a major bleed is defined as ‘a bleed characterized by pain, swelling, restriction of motion and failure to respond within 24 hours of treatment’; and (ii) a minor bleed is ‘characterized by mild pain, minimal swelling, minimal restriction of motion, and resolving within 24 hours of treatment’ [4]. In both cases, treatment response is defined as a complete resolution of symptoms.

As bleeding rates on prophylaxis or in persons with mild/moderate haemophilia are generally low, it is recommended to collect bleeding data prospectively, for a minimum of 12 months to produce reliable annual bleeding rates. In addition to ABR, annual joint bleed rates (AJBR) should be reported. Furthermore, it is recommended to distinguish between major and minor bleeding, between provoked (i.e. traumatic) and unprovoked bleeding, as well as between target joint- or non-target joint bleeding. The distinction between provoked and unprovoked bleeding may be difficult in young children who are often unable to verbalize that trauma has occurred. Target joints have been defined as joints suffering three or more spontaneous bleeds within six months [3] and their presence often drives high AJBR.

Musculoskeletal outcome: structure and function

Joint health based on physical examination. Joint function assessed by physical joint examination performed by an experienced health care professional is often used as the primary outcome for haemophilic arthropathy. Tools and scores for objective physical assessment of joint health are shown in Table 1. Joint health of the ankles, knees and elbows, was first assessed by collecting Active Range of Motion (AROM) [5], which was followed by the World Federation of Haemophilia (WFH) Orthopaedic Joint Score (or Clinical Score) described by Gilbert [6]. Although widely used in clinical and research studies, the Gilbert score was never designed for use in (young) patients with minimal arthropathy, and was never formally validated. Investigators in the USA (Colorado) and Sweden (Stockholm) independently developed modified versions of the Gilbert score [7].

Table 1. Joint health assessment based on physical examination.

Outcome tool	Disease-specific (SPEC) or generic (GEN)	Patient population (most suitable for:)	Time (minimum)	Setting (most useful in:)	Validated	Discrimination	Optimum interval	Additional research needed	Final recommendation	
									Clinic	Research
HJHS [8,20]	SPEC	Age ≥ 4 No or limited joint changes	30 min	Unrestricted Clinic and Research	Y	Y	1–2 years	Training beneficial Validation in adults ongoing	R/M*	M
Gilbert [6]	SPEC	Advanced joint changes	20–30 min	Unrestricted Clinic and Research	±	Y	≥2–3 years	Not standardized, not validated	L	L
AROM [5]	GEN	Age > 1 All joints	5 min	Unrestricted Clinic and Research	±	Y	1 year	Included in all physical examination scores	M	M

Final recommendation: M, mandatory; O, optional; R, recommended; L, limited value; U, unknown; NR, not recommended.

*Depending on the clinical setting and patient joint status; clinical follow-up should always include regular physical examination with one/more standardized tools.

These instruments were combined by the International Prophylaxis Study Group (IPSG) into a single joint score focused on the detection of early joint changes in young boys with haemophilia. This new joint scoring instrument, the Haemophilia Joint Health Score (HJHS), was the first to undergo formal reliability and validation studies in boys with haemophilia ages 4–18 years [8,9]. Following initial development several changes were made, resulting in the current version (HJHS 2.1) consisting of 8 items and a global gait score.

As expected, the HJHS is more sensitive to early joint changes than the Gilbert score [9]. It can distinguish between different prophylactic strategies in young adults with severe haemophilia [10], between severe and non-severe haemophilia in children [9,11] and is responsive to changes following physiotherapy treatment [12]. However, it is so sensitive that it showed positive scores in 40% of unaffected young adults (total score ≤ 3 points) [13].

Administering the HJHS requires training and experience in joint assessment. A teaching video and instruction manual in multiple languages are available on-line (www.ipsg.ca) [14–16]. For comparative studies including multiple raters, it is recommended that physiotherapists initially score patients together and harmonize scoring as there is evidence for considerable inter-rater variability of routinely collected scores [17]. For the HJHS version 2.1 (maximum total score 124 points), the first data on the limits of agreement between raters show values of 9.6 points for children [18,19] and 6.4 points for young adults [20].

Imaging studies. While bleeding, function and pain drive most clinical decisions in haemophilia care, imaging offers an objective assessment of joint structural outcome that can be compared directly within or between patients. Imaging tools for assessment of haemophilic joint changes are shown in Table 2.

Historically, plain radiographs of the ankles, knees and elbows were used to quantify the severity of haemophilic arthropathy. Using almost identical items, two scoring systems were developed; one progressive (Arnold and Hilgartner [21]), the other additive (Pettersson [22]). Although both can be used in clinical practice to assess changes in individual patients, the Pettersson score has been more widely used in research as it allows evaluation of detailed changes. The Pettersson scoring system has excellent reliability when used by radiologists experienced in reading musculoskeletal images [23]; a recently developed scoring atlas is likely to further improve scoring reliability [24]. In young adults, correlations between Pettersson scores and HJHS are strong [25].

Over the past few decades the ability to assess soft-tissue changes has improved dramatically.

Magnetic Resonance Imaging (MRI) is more sensitive than plain radiography for detection of early soft-tissue changes including synovial hypertrophy, hemosiderin deposition and early osteochondral changes in persons with musculoskeletal disease [26]. In parallel with the X-ray scoring systems, MRI scoring started with a progressive [27] and an additive scoring system [28]. These were subsequently combined into a single MRI scoring system with good measurement properties by the Imaging Expert Working Group of the International Prophylaxis Study Group (IPSG) [29,30]. Studies on MRI in healthy young males playing sports [31,32], healthy children [33], and children with haemophilia [30,34] have recently been published. In addition, following reports of MRI changes in joints without any reported bleeds [35,36] there is a growing interest in the association of bleeding history with MRI changes [37–40]. However, MRI has practical disadvantages such as difficulties in standardizing MRI-scanner settings according to different MRI manufacturers, long scanning time required, high cost, limited availability, and the need for sedation in young children. These aspects limit the widespread use of MRI for research and assessment of specific clinical situations such as unexplained complaints or pre-operative assessment [41].

Ultrasound is a useful modality for assessing musculoskeletal disease in persons with haemophilia (PWH), especially for the evaluation of soft-tissue changes such as synovial hypertrophy and peripheral cartilage changes; its ability to detect acute bleeding (i.e. distinguish between bloody and serous effusion) and hemosiderin deposits has been debated [42–45]. Compared to MRI, it offers advantages such as lower cost, better availability, no need for sedation, and a shorter examination time. In addition, ultrasound can be incorporated into haemophilia clinic visits allowing real time feed-back to patients. Disadvantages include a high degree of operator dependency and inability to assess the deeper central part of joints, as well as the time needed for assessment using full diagnostic protocols. Standardized protocols for ultrasound assessment of ankles, knees and elbows have been published [46–48] and tested against MRI [34,49,50]. Recently, Martinoli and colleagues have reported details of a simplified ultrasound scanning protocol and scoring system – the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) [51]. This scoring system is specifically developed for point of care use by non-radiologists and can be practiced after a short training period. It evaluates synovium, cartilage and bone, resulting in a total score ranging from 0 (no changes) to 8 points (severe changes). The inter-operator reliability among 5 haematologists was high with an intraclass-correlation of 0.72 (95% CI 0.62–0.82) [52]. Although promising, the HEAD-US method requires validation against physical examination,

Table 2. Joint health assessment based on imaging.

Outcome tool	Disease-specific (SPEC) or generic (GEN)	Patient population (most suitable for:)	Time	Setting (most useful in: Economically restricted/unrestricted Clinic and/or research)			Validated	Discrimination	Optimum interval	Additional research needed	Final recommendation	
				Unrestricted	More useful in Research than Clinic	Unrestricted Research					Clinic	Research
X-ray Petterson [22]	SPEC	Age > 6 Moderate-advanced joint changes	30 min/6 joints	Unrestricted	More useful in Research than Clinic	Unrestricted Research	Y	Y	3-5 years	Correlation with clinical function limited/unknown	O/R	R/M
X-ray Arnold Hilgartner [21]	SPEC	Age > 6 Moderate-advanced joint changes	30 min/6 joints	Unrestricted	Unrestricted Research	Research	N	Y	3-5 years		NR	NR
MRI IPSG scale [29]	SPEC	All ages Minimum-moderate joint changes -Sedation needed in young children	30 min/joint	Restricted	-Specific clinical questions -Selected research	Research	Y	Y	1-5 years	- Association of findings with clinical changes - Reversibility of changes	O (for specific information)	O/R
US radiologist operated [46-48]	SPEC	Age > 5-6 Minimum-moderate joint changes	20 min/joint	Unrestricted	Unrestricted Clinic and Research	Research	Y	Y	1-2 weeks (clinic) 1 year (research)	- Assessment of haemarthrosis - Atlas of images - Assessment of haemosiderin, joint effusion, haemarthrosis - Correlation with clinical presentation	O/R	O
HEAD-US point of care [42,51]	SPEC	Age > 5-6 Minimum-moderate changes	3-5 min/joint	Unrestricted	Unrestricted Clinic and Research	Research	±Y	±Y	1-2 weeks (clinic) 1 year (research)	- Atlas of images - Performance in non-radiologists - Correlation with clinical presentation	O/R	O

Final recommendation: M, mandatory; O, optional; R, recommended; L, limited value; U, unknown; NR, not recommended.

radiography, full diagnostic ultrasound and MRI in a large series of individuals with haemophilia and varying degrees of arthropathy. Overall, the value of ultrasound in clinical practice and research remains to be determined [42,53]. While not representing joint function, imaging of soft tissue and cartilage may offer an opportunity for earlier intervention to limit osteochondral damage.

Musculoskeletal outcome: activities and participation

Activities and participation are very closely related: according to the ICF model an activity is defined as 'the execution of a task or action by an individual' while participation encompasses 'involvement in a life situation'. Measurements of activities and participation used in haemophilia are shown in Table 3, these include both objective and self-reported assessments.

Objective assessment of activities. The patient perspective of outcome is concerned with functional physical ability and social participation. A few tools (haemophilia specific and generic) have been used to objectively assess the ability of PWH to perform certain tasks (Table 3).

The only disease-specific tool currently available is the Functional Independence Score for Haemophilia (FISH), which was developed in India to assess the functional ability of individuals with haemophilia to perform activities of daily living [54,55]. The assessment can be performed after a short training session and does not require advanced skills of physical examination. The FISH includes eight activities in three categories: self-care (eating and grooming, bathing and dressing), transfers (chair and squatting) and locomotion (walking, climbing stairs and running). Each activity is scored according to the amount of assistance required to perform the task [54]. The FISH has been validated (in 63 patients aged 7–40 years) and was able to discriminate between patients and healthy controls and between different levels of severity of haemophilia [56,57]. However, the FISH shows a ceiling effect in subjects with only limited arthropathy [12]. Development of an updated version (eFISH) including more demanding activities is currently underway (P Poonnoose, personal communication).

The other generic instruments for objective assessment of activities listed include gait analysis and functional tests [58–60]. Three-dimensional gait analysis (3DGA) provides information on the functional performance of arthopathic joints. However specialized equipment is required for measuring kinematic, kinetic and the temporal spatial gait parameters [58,59].

Generic instruments for assessment of activities are primarily focused on mobility and physical movement. Generic instruments used in haemophilia include the

Figure 8 test, originally part of the Timed Movement Battery, developed to evaluate mobility in the elderly. For the adapted Figure 8 test, a patient is asked to walk a Figure 8 around two pylons placed at a 5-metre distance, at a preferred speed and at a maximum speed. However, this test showed no correlation with self-reported limitations in activities [61] and was too insensitive to distinguish between adults who discontinued and those who continued prophylaxis [62].

The Six Minute Walk Test (6MWT) reflects aerobic capacity in patients without musculoskeletal disease, and is expected to reflect both aerobic capacity and joint function in patients with haemophilia. The 50-metre walking test (50WT) generally takes less than 1 minute, and is expected to be mostly sensitive to musculoskeletal changes. There is some experience with both the 6MWT and 50WT tests in haemophilia [12,61,63,64], including limited evidence that especially the 6MWT is able to discriminate between paediatric patient groups. Accelerometry has been used for objective assessment of the intensity and duration of physical activity in haemophilia in a limited number of studies to date [65,66]. Although most current accelerometers provide no information on the specific physical activities or the risk of associated injury, new devices that can distinguish between lying, sitting, standing, walking, cycling and running are being developed.

Indirect 'objective' assessment of activities and participation is provided by registration of work participation and days lost from work or school due to haemophilia. These parameters can also be used for economic evaluations [67].

Self-reported assessment of activity and participation-disease-specific instruments. The Haemophilia Activities List (HAL) is a questionnaire developed from interviews with Dutch patients. It assesses self-reported limitations in activities in adults [68]. A paediatric version for children aged 8–18 years (ped-HAL), including a proxy version to be completed by parents/caregivers of children aged 4–12 years, is also available [69]. The questionnaire has seven domains: lying/sitting/transferring/standing (i), leg functions (ii), arm functions (iii), use of transportation (iv), self-care (v), household tasks(vi), and leisure activities/sports (vii). In addition to domain-scores, it generates four summary scores: (i) upper extremities, (ii) lower extremities, (iii) complex lower extremities, and (iv) sum score. The internal consistency and convergent validity of the HAL were tested in 211 adults [61,70] and 133 children from various European countries and Brazil; this showed good measurement properties with the exception of some variability in test-retest agreement in children [12,71]. The HAL is easy to use and available in many languages. In patients treated

Table 3. Outcome tools for assessment of activities and/or participation.

Outcome tool	Disease-specific (SPEC) or generic (GEN)	Patient population (most suitable for:)	Time	Setting (most useful in: Economically restricted/unrestricted Clinic and/or research)	Validated	Discrimination	Optimum interval	Additional research needed	Final recommendation	
									Clinic	Research
Objective tools FISH [54]	SPEC	Age > 7 years Advanced joint changes	10 min observation	Unrestricted Clinic and Research	Y	Y	1 years	Validation in age group 5 to 7 years	R/M	R
Gait analysis [58,59]	GEN	3 years All joint statuses	20–30 min	Unrestricted Research	Y	Y	U	– May be very sensitive – Specialized tools and experience needed	L	L
Figure 8 test [61]	GEN	Age > 8 years Advanced joint changes	5 min observation	Unrestricted Research and Clinic	Y	N	U	No discrimination between groups	NR	L
6MWT [61,63]	GEN	All ages All joint status	8–10 min observation	Unrestricted Research	Y	Y	U		L	L/O
50-meter walk test [61]	GEN	All ages All joint status	8–10 min observation	Unrestricted Clinic and Research	Y	Y	1–2 years	Little experience in haemophilia	O	L/O
Self-reported tools HAL [68]	SPEC	Age ≥ 18 years All joint statuses	Questionnaire 10–15 min	Culturally restricted Clinic and Research	Y	Y	≥1 years	Validation in different socio-cultural contexts	R	R
pedHAL [69]	SPEC	Children 4–18 All joint statuses	Questionnaire 10–15 min	Restricted Clinic and Research	Y	Y	≥1 years	Validation in different socio-cultural contexts	O	R
COPM [72]	GEN	All ages All joint statuses	Interview 10–15 min	Unrestricted Clinic	NA	NA	1 year	– Test responsiveness	O	L
MACTAR [73]	GEN	All ages All joint statuses	Interview 10–15 min	Unrestricted Clinic	NA	NA	1 year		O	L
IPA [75]	GEN	Age ≥ 18 years	Questionnaire 10–15 min	Culturally restricted Clinic and Research	Y	Y	U		O	O
Paid employment	GEN	Age ≥ 18 years	Interview 1 min	Unrestricted Research and Clinic	NA	Y	1 year		M	M

Final recommendation: M, mandatory; O, optional; R, recommended; L, limited value; U, unknown; NR, not recommended.

with early prophylaxis, the HAL was able to discriminate between different prophylactic regimens [10], but the high proportion of both children and adults with maximum scores (ceiling effect) can be a limitation to the instrument [12,25,69]. As a tool developed in Western Europe, there are certain nuances in the items that are culturally dependent and may not adapt well to other countries/regions without cultural adaptation [12,54]. Finally, items on participation are underrepresented in both the HAL and pedHAL and may be best captured in a separate questionnaire.

Self-reported assessment of activity and participation-generic instruments. For day-to-day patient management, the Canadian Occupational Measure (COPM) [72] and the McMaster Toronto Patient Disability Questionnaire (MACTAR) [73] can be very useful. Both instruments are administered as a semi-structured interview to assess the patient's perception in their actual performance in various activities and their satisfaction with this performance over time. Both include identification of key activities in daily life that a patient wishes to improve upon. The targeted activities can be used to both guide and evaluate interventions. The COPM has been validated for haemophilia care [74] and the MACTAR was used in the development of the HAL questionnaire [68].

Although several age-specific generic participation questionnaires are available, only the Impact on Participation and Autonomy (IPA [75]) questionnaire has been used in haemophilia research [76,77]. This tool scores five domains: (i) autonomy indoors, (ii) autonomy outdoors, (iii) family role, (iv) social role and (v) work and education. It is focussed on independence in performing certain activities (autonomy), rather than on the ability to perform a certain activity. The IPA has no summary scores.

Parameters for economic evaluation

Due to the high cost of treatment, economic evaluation is important in both haemophilia research and care. Economic evaluations of health care measure both outcome and costs of therapy. Key parameters for economic evaluation are shown in Table 4.

A cost-utility analysis estimates cost per quality-adjusted life year (QALY); it is the decision makers' preferred tool to assess the value of interventions. Costs are expressed in monetary terms, while QALYs represent the value of outcome. QALYs are a composite measure, which take into consideration both an individual's lifespan (in years) and preferences for different health states reflected in quality of life (QOL). Preferences are expressed as a value between 0 (equivalent to death) and 1 (a value signifying perfect health) [78]. A disease-specific tool for utility measurement in haemophilia has been developed but has not been applied in

research [79]. All published research to date have used the generic EuroQol questionnaire (EQ5D) [80]. From its five questions, the utility value is calculated according to a local tariff. The UK tariff is used most frequently [81]; however, any tariff is a valuation of health states and therefore is culturally dependent. Potential differences must be taken into account for the interpretation of international comparisons. In adults with haemophilia, utility values were able to distinguish between patients treated on demand and those treated on prophylaxis [82–84], but not between patients treated with different prophylactic regimens [10]. Recently, a paediatric version of the EQ5D was developed (EQ5D-Y), but this has not yet been used in boys with haemophilia [85,86]. For adults, utility values can also be derived from the generic Short Form 36 (SF36) questionnaire [87]; this derivation is named the SF6D [88,89]. The SF36 has been widely used in haemophilia, and the first studies using the SF6D were recently published [90,91]. Although these instruments provide a way for comparing overall impact of the disease and the care provided in a socio-economic context, their use for the evaluation of management in individual patients is limited [92]. When comparing results of different cohorts managed with different treatment protocols, the added value of Utilities is limited compared to significant differences in clinical outcome. These data are therefore more useful when comparing outcomes between different diseases; in such a context the data can be very useful for advocacy and lobbying efforts.

With respect to costs, clotting factor consumption accounts for >90% of direct medical costs; therefore, it is generally considered to be the most important parameter for economic evaluations [10,67,93]. Additional direct medical costs to be considered include the cost of clinic visits, hospital admissions, orthopaedic surgery and days in hospital. For economic evaluations from a societal perspective, indirect costs including days lost from work/school for both patients and caregivers should be considered, as should the costs of disabilities and missed enjoyment of leisure/sports activities.

Recommended and/or mandatory outcome parameters

Based on the group discussions and the literature, a list of recommended and/or mandatory outcome parameters in haemophilia according to field of use and ICF domain was generated by the authors and is shown in Table 5. When choosing instruments, it is very important to consider the aim of the assessment, patient characteristics and setting. The setting includes aspects such as access to replacement therapy and the use of prophylaxis. The age of the population and the duration of follow-up should also be considered. Age should always be included in the analyses as joint changes are highly dependent on the bleeding history

Table 4. Outcome tools for economic evaluations.

Outcome tool	Disease-specific (SPEC) or generic (GEN)	Patient population (most suitable for:)	Time	Setting (most useful in:)			Discrimination	Optimum interval	Additional research needed	Final recommendation	
				Economically restricted/unrestricted Clinic and/or research	Validated	Discrimination				Clinic	Research
Objective tools											
Clotting factor consumption	SPEC	All	NA	Unrestricted	N	Y	6–12 mo	Depends on local availability and regimen	M	M	
Orthopaedic surgery	SPEC	Advanced joint disease	NA	Restricted	N	U	Lifetime >5 years	Depends on local treatment regimens	M	L	
Days lost from work	GEN	<18 years parents ≥18 years patients	NA	Unrestricted	N	Y	1 year	Compare with population	R	R/M	
Hospital visits outpatient	GEN	All	NA	Unrestricted	N	Y	1 year		O	R/O	
Emergency visits	GEN	All	NA	Unrestricted	N	U	1 year		O	R/O	
Physiotherapist visits	GEN	All	NA	Unrestricted	N	U	1 year		O	R/O	
Days in hospital (in patient)	GEN	All	NA	Unrestricted	N	Y	1 year	Compare with population	M/R	M/R	
Self-reported tools (questionnaires)											
Euroqol EQ-5D [80]	GEN	≥16 years	5 min	Restricted	Y	Y	2–4 years	Utilities are culturally dependent	O	R/M	
EQ-5D-Y [85]	GEN	4–7 proxy 8–15 patient	5 min	Restricted	Y	U	Unknown	No experience in haemophilia	O	U	
Disease-specific utility [79]	SPEC	≥18 years	15 min	Restricted	U	U	Unknown	Very limited experience	NR	NR	
SF 6D from SF36 [88]	GEN	≥16 years	15–20 min	Restricted	Y	Y	1–2 years	Utilities are culturally dependent	O	R	

Final recommendation: M, mandatory; O, optional; R, recommended; L, limited value; U, unknown; NR, not recommended.

Table 5. Recommended and/or mandatory outcome parameters in haemophilia according to field of use and ICF domain.

ICF domain	Tool	Clinical	Research	Comments
Joint function and structure	Bleeding	M	M	– At least an annual review of bleeding – Reporting on periods of no less than 12 months – Use recommended definitions
	Physical examination	M	M	– HJHS v2.1 when including patients with early joint changes (all paediatric studies)
	Imaging	O	R	– If using HJHS is impossible, collect AROM – US or MRI for evaluation of early changes – Pettersson score (X-ray) for advanced osteochondral changes (interval no shorter than 3 years)
Activities	Observed activities	R	O/R	– FISH in populations with more advanced joint disease
	Self-reported activities	R	R (adults) R (children)	– HAL, from age 18 upwards – pedHAL, from age 4 onwards
Participation	Days lost from school/work	M	M	
Economic	Paid employment	M	M	Include information on full-time yes/no
	Clotting factor consumption	M	M	Combine with body weight and treatment regimen
	Haemophilia-related surgeries	M	L	Not for short term studies
	Hospital visits	M	O/R	
	Days in hospital.	M	O/R	
	Utility assessment	O	R/M	Not for short term studies Choice of tariff (calculation method) affects results

M, mandatory; O, optional; R, recommended; L, limited value; U, unknown; NR, not recommended.

and the cumulative number of bleeds, even in patients on intensive, high-dose prophylaxis [48,49]. Likewise treatment history, that is, age at diagnosis, age at first treatment, details of prophylaxis and a history orthopaedic surgery should always be included in the evaluation and interpretation of results.

Discussion

It is recognized that standardized, validated outcome assessments of haemophilia are essential for clinical management of the individual patient, as well as for research to develop and optimize new therapies. Outcome assessment tools range from measures of joint structure and function to activity capacity, social participation and economic cost/benefit; some are constructed from the perspective of the haemophilia health care provider while others are based in the perspective of the patient. Most are suitable to describe representative groups of patients, while a few are rooted in individual goals and values. From the myriad of outcome tools and parameters discussed, it is clear that the eventual choice should depend on the aim of outcome assessment, the setting, the age of the patient, joint status and the duration of follow-up.

Data collection from different perspectives

For clinical management and research, information on treatment, bleeding (ABR and AJBR) and clotting factor consumption should be collected at least annually, and preferably prospectively. Clinical follow-up should always include a regular physical examination with a standardized instrument (e.g. the HJHS). Imaging studies remain optional for clinical management, as it is not clear how much these contribute to

treatment modification in day-to-day practice. However, utilization of imaging is expected to increase as more information becomes available.

For research, however, aspects of cultural (in)dependence and inter-rater reliability become more important in the choice of outcome parameters. In addition, it is important to consider the duration of follow-up – for example, studies with one year follow-up are unlikely to show differences in physical examination scores or imaging scores, or activity scores, but may show clear differences in bleeding rates, clotting factor consumption and/or activity.

When using a combination of different outcome tools, it is important to combine objective and patient-reported outcomes (PRO). Objective parameters may be considered less relevant for patients; a patient may not notice a clinical difference in functioning if he has minimal changes on the HJHS score or Pettersson score [94]. However, patients may also under-report limitations due to the phenomenon of ‘response-shift’ [95]: patients get used to certain limitations and therefore report less burden despite similar or increased objective limitations [62,96]. In this regard, objective reporting of activities and exercises performed, work participation and the like can provide an objective basis for comparison over time and with other patients. An issue to be considered with PROs, is that questionnaires are dependent on literacy and cultural issues, and that in addition to simple translation, cultural adaptation may be required.

Comparison with the literature

The present review performed a broad assessment of available tools and their optimal use in specific situations, and many of its recommendations are in agreement with previous reports. The recent WFH

treatment guidelines make no stringent recommendations, but list tools for physical and radiological examination, for assessment of activities, and for assessment of disease-specific QOL [97]. Based on a series of consensus meetings, de Moerloose *et al.* published recommendations for assessment, monitoring and follow-up in haemophilia [98]. The recommendations included collection of detailed information on bleeding, clotting factor consumption and activities including the HAL. The HJHS and AROM were recommended for joint assessment while imaging studies were considered optional. The EQ-5D was recommended for economic evaluation. Based on a Delphi process, Nicholson *et al.* provided recommendations regarding reporting of economic evaluations of prophylaxis [67]. For cost data, this group recommended collecting clotting factor consumption, number of hospitalization days, surgical procedures and productivity. For outcome assessment, their minimum recommendation was to assess generic utility (EQ-5D), while collection of disease-specific QOL, joint bleeding, and joint status (HJHS) was considered optional. A recent commentary on the role of QOL assessment recommended that the choice of outcome tools should be dependent on access to treatment (particularly clotting factor concentrates), use of prophylaxis and joint status. It was suggested that outcome assessment should focus on joint health, activities, and participation, rather than on QOL only [94].

The added value of this review lies in the provision of separate recommendations for a clinical and a research perspective, as well as providing priorities for certain outcome parameters.

Unresolved issues and future developments

In a disease as rare as haemophilia, international collaboration is mandatory to advance the field and enable research on optimal treatment strategies. Both treatment and outcome should be captured. Standardization of outcome assessment is key; it is clear that inter-observer variation of assessment is an issue in the HJHS and in imaging. For the HJHS, this may be resolved by training and for imaging studies by the use of atlases. This was corroborated by observations that at least one joint training session among physiotherapists harmonized performance and scoring of the HJHS [14,15,17,20]. For questionnaires, the issues of literacy and cultural validation should be considered – for example, performing household chores may be relevant to men in some cultures [12,55]. Questionnaires should be translated according to the procedures described by the World Health Organisation (http://www.who.int/substance_abuse/research_tools/translation/en/). Cross-cultural validation is also recommended, but this is more important in assessment of QOL than in assessment of physical activities.

In general, the time and burden for the patient associated with outcome assessment should be considered. Ideally, one would have a set of very short and concise assessments and/or questions that are able to detect changes within patients over time and discriminate between different groups. One strategy to achieve this goal for PRO is the use of Computer Adaptive Testing (CAT): relevant questions are selected from patient based responses to previous questions [99]. As a result, all relevant information is collected and the number of questions is minimized. However, this technique requires on-line platforms, collection of extensive item pools and calibration studies. At this time, there is no experience using CAT in comparative studies of PWH.

Recent developments in treatment such as longer acting CFC, gene therapy or bypassing agents are unlikely to affect our choice of outcome tools as bleeding and its consequences will remain the main symptoms of haemophilia.

Use in other bleeding disorders

For conditions other than haemophilia, the applicability of the suggested outcome parameters and tools will depend on the clinical phenotype of the bleeding disorder. In conditions resulting in joint bleeding, many of the recommended tools can be used in clinical practice, but their validity should be established before using them for research. For conditions resulting in bleeding in other locations, limitations in activities, participation, pain and eventually Health Related Quality of Life can be collected. Again, age and treatment history should be included in the analyses.

Conclusion

Outcome assessment in haemophilia should be performed for clinical care purposes and/or for research. Minimum data to be collected for both clinical use and research are bleeding, self-reported and objective joint function and activities, information on work and school participation, clotting factor consumption, health care services utilization and patient preferences. Identification of the optimum ‘tool box’ for outcome assessment may promote objective and PRO assessment and may speed up the generation of information on treatment outcomes in persons with haemophilia.

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Authors' contributions

Background for this review was provided by the summary Reports from four targeted workshops, prepared by the workshop co-chairs: JN and MMJ for group 1, PB and KF for group 2, JD and MD for group 3, and KB and MC for group 4. The first draft of this manuscript was written by KF, the literature search was performed by SG and reviewed by all authors. All Co-Chairs of the Workshops were asked to review the manuscript drafts. Comments received from the Open Sessions and Workshop Chairs/Co-Chairs were discussed as an internal writing committee until consensus was reached and a final manuscript was approved.

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