Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), 1–8 DOI: 10.1111/hae.13066

REVIEW ARTICLE

Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era

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The safety and efficacy of treatment options for patients with haemophilia have significantly improved over the last two decades, particularly with greater utilization of prophylactic approaches. Consequently, it is becoming increasingly difficult to differentiate the treatment benefits of available choices based on standard endpoints such as annualized bleeding rates and joint health scores. Patient-reported outcomes (PROs) have shown limited ability to discriminate between treatment outcomes, in part because of their comprehensive nature; i.e. differences in specific outcomes meaningful to individual patients are masked by a global scoring system based on a fixed set of items, many of which may be unimportant for any given patient. There is a clear need for new outcome measures. Initiatives to develop patient-centric outcomes that capture clinically meaningful change are ongoing. One such approach, goal attainment scaling (GAS), allows patients, in collaboration with a trained clinician, to select goals from a medical condition-specific menu of options and subsequently facilitates quantitative assessment of goal realization. Thus, it is fully personalized and sensitive to small, often idiosyncratic, treatment benefits, such as improvements in functional capacity. In this paper, we present the underlying rationale for GAS and one other novel approach to PRO personalization, and discuss their potential to augment current outcome measures by reliably detecting and quantifying treatment effects in individuals with haemophilia on prophylaxis.

Keywords: function, haemophilia, outcomes, patient-reported outcomes, personalized medicine, quality of life

Introduction

Controlled clinical studies in persons with haemophilia (PwH) have confirmed the superior efficacy of prophylactic factor replacement regimens compared to episodic treatment [1,2]. As a result, prophylaxis regimens have been adopted as standard of care in patients with severe disease, significantly reducing bleeding rates and improving joint health in this population [1]. PwH residing in industrialized countries now aim to live a life with little to no bleeding. Thus, the positive changes effected by prophylaxis regimens have established an elevated state of health and have fundamentally changed the goals of therapy. In addition, these goals are individualized, based on life circumstances and personal aspirations that differ considerably among individuals over a lifespan.

Outcome measures currently used in haemophilia clinical studies are variably applied in clinical practice, having not been designed to identify or measure the most important treatment goals for individuals. Current treatment outcome measures, including the annualized bleeding rate (ABR), joint health scores and validated quality-of-life (QoL) instruments, were designed to measure common or global endpoints that are not personalized. Therefore, these instruments, while relevant in clinical research, may be of limited value in the current and future practice of clinical care for haemophilia, where individual perspectives on improved health outcomes vary widely. New tools are needed that can detect the benefits of treatment that

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Accepted after revision 2 July 2016

matter to individual patients and be readily integrated with routine patient care. In addition, as ABR approaches zero, the clinical meaningfulness of small differences among prophylaxis regimens is unclear. Thus, we also envision the use of such tools as adjunctive measures in clinical research, particularly with respect to comparative effectiveness studies.

Furthermore, patient perspectives on treatment goals and success may differ from those of their physicians and caregivers [3]. For example, with the advent of prophylaxis, treatment adherence is an important consideration in the management of haemophilia from the health care provider's perspective. From the patient's perspective, however, adherence to treatment recommendations depends on whether, and to what extent, such adherence serves as a means to realize personal goals [4–6]. While clinicians intuitively recognize and incorporate patients' goals in treatment planning, the field lacks a formal patient-reported outcome (PRO) measure to document this aspect of treatment and serve as a means to evaluate treatment effectiveness. Therefore, a new outcome measure that can enhance the ability to compare effectiveness among available treatment options is needed. Indeed, using patient-centric approaches to define outcomes is becoming increasingly common in the medical management of chronic conditions, including diabetes [7], multiple sclerosis [8] and allergic disease [9].

Individualized goal-setting represents a form of personalized medicine distinct from molecular-based approaches to treatment selection for individual patients, commonly known as precision medicine [10]. Although precision medicine offers personalization from the perspective of genes and proteins, it cannot take into account the patient's goals or preferences and the impact of treatment on daily living. Ideally, such patient-centric metrics would encompass the patient's clinical course, lifestyle preferences and personal aspirations, and provide an objective/semi-quantitative output to gauge treatment success. This would require that the tool be comprehensive in scope, comprising an array of clinical/functional parameters, while allowing each patient to select only those endpoints that are personally meaningful. It is also of critical importance that this should be achievable in a time- and resource-efficient manner, particularly when administered in a real-world setting.

In this article, we review the strengths and limitations of outcome measures used currently in haemophilia clinical practice and research. Ongoing efforts to develop novel outcome measures that address these common limitations are then introduced.

Clinically assessed outcome measures

Key endpoints traditionally evaluated in PwH are based on clinical manifestations of the disease, such as bleeding events and joint dysfunction. The latter is critical because the majority of bleeding events occur in joints [11,12]. To further evaluate joint status, anatomical evaluations using various imaging modalities are commonly employed.

Annualized bleeding rate

The ABR is a measure of bleeding frequency and treatment effectiveness in the clinic, and is often the primary outcome in clinical studies involving PwH [13,14]. With respect to the latter, it has been especially valuable as a means of documenting the superior efficacy of prophylaxis in comparison with on-demand therapy [2,12]. However, because ABR is strictly a measure of frequency, it does not account for the highly variable functional limitations that may result from bleeding. For example, a haemorrhage in the knee may limit overall mobility, whereas bleeding in an elbow may only limit the function of that single limb. Further, even qualitatively similar joint bleeding episodes vary in the degree to which they impact function. Moreover, an ABR of 0 in a patient with a sedentary lifestyle is very different from the same ABR in a patient with an active lifestyle. Thus, ABR cannot account for inter-individual variability in bleeding patterns and their functional sequelae, which are dependent on factors such as disease severity, physical activity and age [14,15]. Finally, evaluating ABR in patients with pre-existing severe arthropathy is difficult, as the distinction between a new bleeding event and a flare of arthritis pain cannot be readily assessed [16].

With respect to clinical studies, the primary limitation of the ABR is its lesser discriminatory capacity in the era of prophylaxis. This limitation stems from the fact that improvements in ABR are comparable across clinical studies evaluating prophylaxis, with all studies showing low mean/median frequencies of bleeding [2,14,17–19]. Thus, using ABR as the sole endpoint to discriminate among prophylactic approaches would require an impractically large patient enrolment to provide statistically meaningful power to discriminate efficacy.

Joint status

Physical examination. Two current standards used for research studies include the World Federation of Hemophilia (WFH) Physical Examination Score (aka Gilbert score) and the Haemophilia Joint Health Score (HJHS) [11,14]. These tools assess joint status, incorporating range of motion, pain, deformity and swelling, in the joints most commonly affected by bleeding in haemophilia: the knees, ankles and elbows. The HJHS is more commonly used, but requires extensive training; it is best administered by physiotherapists

experienced in haemophilia care. The HJHS provides a total score, a joint-specific score and a global gait score. It is available in four languages, can be used for monitoring joint change over time in patients on prophylaxis, and has been widely tested in children [20,21]. It has also demonstrated good correlation with the WFH score, haemarthroses and radiographic damage [11]. However, neither the HJHS nor the WFH score correlate well with bleeding rates, and neither instrument is sensitive enough to discriminate change in patients at the extremes of the arthropathy spectrum (i.e. with late-stage or early-stage joint damage) [19]. More importantly, neither instrument measures functional status in daily life (e.g. the ability to play a sport or to do a particular job).

Imaging. Various radiographic modalities have been explored as a means to monitor haemophilia and the effects of treatment, including X-rays, magnetic resonance imaging (MRI) and ultrasonography [14]. X-ray imaging has been used for many decades, with results typically classified using the Arnold–Hilgartner system [22] (progressive scale) or the Pettersson score [23] (additive scale). Because X-ray detects changes in bone structure, it is a widely accessible modality for measuring change in advanced stages of arthropathy, but it is insensitive to early changes in cartilage and soft tissue [14].

In contrast, MRI is much more sensitive to changes in cartilage and soft tissue compared with X-ray. There are several MRI scales in current use, including the Denver MRI score and the European MRI score. This makes it difficult to compare data across treatment centres, although a compatible scoring system has been developed by the International Prophylaxis Study Group [24]. Other drawbacks of MRI are its high cost and the need for sedation when evaluating children. Finally, MRI will not necessarily detect clinically meaningful differences in joint outcomes in adults [14], as in the SPINART study, where after 3 years, the prophylaxis group did not differ significantly from the on-demand group on MRI despite a significant reduction in ABR [25].

Ultrasonography is also sensitive to changes in cartilage and soft tissues and has the advantages of being inexpensive, well accepted by patients and capable of identifying and monitoring bleeding events in real time [14,26]. In the recently reported Haemophilia Early Arthropathy Detection with UltraSound (HEAD-US) study, high-resolution ultrasonography detected a higher percentage of abnormalities than the physical evaluation and was concordant with the HJHS score in 73% of joints [26]. Differences among operators and instrument resolutions, however, can hinder comparability across treatment centres and/or across studies. While clearly promising as an outcome measure, the use of ultrasound imaging techniques requires further assessment to standardize operator training, scoring systems and data interpretation [11,14].

Patient-reported outcome measures

Given the proven efficacy of prophylactic therapy for reducing haemophilia-related morbidity, treatment goals have shifted towards improving daily functioning and QoL, which are primarily assessed using PROs [27,28].

Quality of life

Health-related QoL (HRQoL) tools evaluate the various dimensions in the International Classification of Functioning, Disability and Health (ICF) model of health [29]. The overall health state in patients with chronic medical conditions may be conceived of as a complex interaction between specific impairments in body structure and function, treatment effects on disease and symptoms, and occupation and lifestyle (Fig. 1). Clinical studies in haemophilia have used both generic and disease-specific instruments.

Generic HRQoL instruments such as the Medical Outcomes Study Short-form 36 (SF36) and, more recently, the EuroQoL (EQ-5D) have been used in studies enrolling adult patients. These instruments are designed to provide a comprehensive measure of various aspects of daily life in functional, emotional and social subscales, and have quantitative scoring systems [6]. However, it should be noted that there is potential for such measures to be influenced by social or economic factors unrelated to the specifics of disease management or by patient acceptance of compromised function. In addition, for the sake of improved accuracy of recall, many such questionnaires restrict the period of inquiry to the past 4 weeks; this creates short-term perspectives that do not capture fluctuation over longer time intervals, limiting applicability to longitudinal assessments.

A number of haemophilia-specific HRQoL questionnaires have also been developed and used successfully in clinical studies, including the HaemoQoL-A [30,31] and HaemoQoL [32,33], Canadian Haemophilia Outcomes-Kids Life Assessment (CHO-KLAT) and Hemofilia-QoL. These instruments are used to evaluate a patient's current life experience across physical, psychological and social domains. The HaemoQoL-A (a self-report questionnaire for adults) and the HaemoQoL (a self-report questionnaire for children) have both demonstrated good internal consistency, but only the adult version meets the US Food and Drug Administration (FDA) criterion of using direct input from patients to generate item content [3,34]. The CHO-KLAT [35] is validated for use in five different languages and cultures [36], but also does not meet the FDA criterion for direct patient input during item

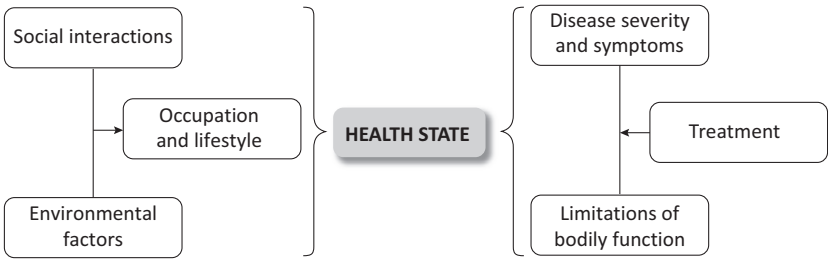

Fig. 1. Interactions between disease parameters, treatment effects and patient lifestyle determine overall health state.

development [37]. Inconsistencies have been observed in the use of some response options [3,32] and, as commonly observed in a paediatric population, parent-proxy results were more reproducible than the children's results [36]. In addition, there is also the Hemofilia-QoL, a 36-item questionnaire that has demonstrated acceptable reliability and adequate convergent validity with the SF-36 Health Survey [31]. However, similar to CHO-KLAT and HaemQoL, it does not meet the FDA criterion of using direct input from patients to generate item content [3] and its use is limited to Spanish-speaking populations [31,38].

Of greater relevance to our concerns here, the common limitations of all haemophilia-specific QoL outcome measures are that they were designed for use in clinical research and may be time-consuming; consequently, they have not been adopted in clinical practice. In addition, these instruments tend to be comprehensive in their scope; consequently, not every query may be of value to an individual patient [39]. Given that scoring systems are based on whole domains or instruments, with raw scores normalized to a predefined scale, the resultant integrated score may mask the effect of treatment on a specific endpoint for an individual or subset of patients. For example, knee and/or ankle arthropathy can limit mobility but may not affect performance of a desk job; in contrast, elbow arthropathy may not limit mobility but would be more likely to have a deleterious impact on many job-related and domestic tasks. Further, although either form of arthropathy may result in low scores on a physical health domain, a patient who is coping well might still score highly on mental health. It is also possible for a similar masking effect to occur in the same patient evaluated at different timepoints because the parameters of change, even within specific domains, vary across time. However, the authors are not aware of any empirical evidence of masking effects using haemophilia-specific QoL instruments.

A recent review of the limitations of outcome measures in haemophilia observed that, to satisfy the requirements for autonomy, a QoL measure should allow patients to pick those domains and items of life that have the most meaning to them; moreover, to be truly individualized, a QoL tool should allow patients to define their own values, expectations, hopes and realizations for each of these items [12]. No current haemophilia QoL measure satisfies these criteria.

Functional assessment

Currently, two haemophilia-specific tools evaluate performance in everyday activities. These are the Haemophilia Activities List (HAL) and its paediatric version (PedHAL), and the Functional Independence Score in Haemophilia (FISH) [12–14]. The HAL covers a wider range of activities, including work, hobbies, social and sporting activities, takes approximately 10 minutes to complete and is available in numerous languages [40]. However, it is not applicable to certain cultures and has demonstrated limited ability to detect clinical changes over time. Further, the test–retest reliability of the HAL has not been assessed, nor has the PedHAL been validated in children [13,14].

The FISH allows for an in-clinic evaluation of activities of daily living [13,41] and is particularly useful for physically impaired patients. It can evaluate changes in functional independence and takes into account daily-life activities that could be affected by haemophilia. It is relatively easy to administer, does not require special training and has demonstrated high internal consistency and excellent reliability [11–14]. In addition, FISH has demonstrated good correlation with general functional ability tests (Health Assessment Questionnaire [HAQ], Western Ontario McMaster [WOMAC], Canadian Occupational Performance Measure [COPM]) [42–44], and is currently being modified for use in children. Despite these strengths, the instrument has several limitations. It is least useful in patients with mild arthropathy (i.e. it is not sensitive to minor functional impairment), and it does not consider impact on vocational aspects such as education or employment [13,14].

Overall, the comprehensive nature of PROs discussed thus far render them prone to the loss of sensitivity to change in specific domains relevant to each patient, which occurs because patients must respond to every item of a fixed instrument, including those that are of little or no importance to them. Thus, clinicians are unable to assess functional or other

treatment outcomes of particular relevance to the individual patient. Taken together, it is clear that the fixed nature of most PRO instruments inherently limits their discriminative capacity, suggesting that a less comprehensive but more individually defined instrument may be warranted to better measure treatment effects. The challenge would be to execute this process in a systematic and valid manner to allow for the consistent evaluation of diverse treatment effects [39].

Development of new outcome measures

The key limitation of the outcome measures discussed thus far, whether clinical or patient-reported, is *lack of personalization*, resulting in the inability to measure what matters most to an individual patient. In addition, many of these measures have limited applicability to routine clinical care, primarily because of the large investment of time required, and are therefore used almost exclusively in research studies. Here, we present a brief introduction to outcome measures in development that are designed to accommodate customization/personalization of outcomes, thereby providing adequate discriminatory capacity to detect longitudinal changes in the short and long term, in clinical care and in research.

Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS program was launched in 2004 by the US National Institutes of Health to provide clinicians and researchers access to 'efficient, precise, valid and responsive adult- and child-reported measures' in the physical, mental and social domains that could be applied across a broad range of chronic medical conditions [45]. The PROMIS program uses modern measurement theory to develop and improve PRO measures in part through utilizing item response theory, a psychometric method used to produce probabilistic scores (calibrations) associated with answers to questions (items) [39].These calibrations can be used by computerized adaptive testing (CAT) to select the most informative follow-up question to an initial question from a predetermined bank of questions. Alternatively, customized short-form questionnaires could be developed from these banks.

In essence, PROMIS instruments represent an incremental improvement in psychometric assessment of QoL, achieved through more sophisticated item development and selection. The domains and their respective comprehensive bank of items are available for both adult and paediatric populations and in many cases have been translated into several international languages. Questionnaires may be customized by user-based selection of items. From a structural perspective, there is a well-described trade-off between comprehensiveness and the ability to discriminate change. The more items included, the more comprehensive the measure, but the less likely it is to discriminate change [39]. Conversely, although including fewer items reduces this potential masking effect, it also increases the likelihood that items of importance to some patients will be excluded. To some degree, the CAT approach may ameliorate this inherent problem because the algorithm can select the most appropriate item from a predefined bank based on the individual's response to a prior question [45]. Disease states in which PROMIS measures have been used include: sickle cell disease [46] asthma [47] and rheumatoid arthritis [48].

The PROMIS website also provides a secure platform and automated scoring system that can be deployed in the clinical trial or everyday practice settings. While further development would need to incorporate some items specific to haemophilia populations, the overall concept and design is a step in the direction of providing a more robust, and to some extent, customized approach to measuring PROs. Nonetheless, there are inherent limitations on how personalized PROMIS instruments can be used because they are not based on the preferences or values of individual patients.

Goal attainment scaling

An established approach for identifying and quantitating change in individuals and groups affected by chronic conditions is the strategy of goal attainment scaling (GAS). The concept was first developed in the 1960s by Kiresuk and Sherman for patients with mental illness [49]. This alternative approach does not use a questionnaire-type instrument and does not measure patient experience or functioning across various domains. Instead, GAS assesses the extent to which treatment, after a specified period of time, results in the attainment of a set of personally important goals, selected by the patient at the outset, that are related to clinical or functional impacts of a particular condition. GAS can be thought of as a standardized approach to patient-centred, solution-oriented care, which is often practised informally, without clear measurement or quantification [50–52]. GAS has been applied successfully in both clinical practice and research in patients with a broad range of other chronic conditions, including dementia [51], diabetes [7], acquired brain injury [53] and various types of physical disability [50]. The critical feature of GAS that allows for the detection of small but clinically meaningful change is the fact that it is personalized for every patient, comprising only outcomes of importance to the individual patient.

Table 1. Goal attainment scaling (GAS) scale.

Score value	Goal outcome
+2	Much better than expected
+1	Somewhat better than expected
0	Expected outcome (goal)
−1	Somewhat worse than expected (baseline)
−2	Much worse than expected

Table 2. Selected goal areas in haemophilia.

General category	Goal area
Managing haemophilia	Being able to administer factor
	Weight, exercise and nutrition
Haemophilia complications	Joint problems
	Pain
Impact of haemophilia on life	Work attendance
	Self-esteem
	Attending school
	Relationships with friends
	Relationships with family
	Narcotic use
	Career planning
	Leisure activities

A comprehensive discussion of GAS methodology is beyond the scope of this paper. In brief, GAS requires patients and health care providers to work together to identify treatment goals that have the greatest relevance. Predefined outcomes are used to define a scale that provides a quantitative measure of the extent of achievement of the individual's goal(s). Goal attainment is scored on a five-point scale (Table 1). The baseline state is set at −1 and the specified goal at 0, with progressively better outcomes scored as +1 and +2 and an outcome worse than baseline as −2. For example, a relevant goal for a juvenile or adult patient with severe haemophilia A may be 'not missing more than 20 days of school or work in a year,' and 5-day increments or decrements thereof may represent better or worse outcome levels. Using a standard formula, goal attainment scores may be generated for individuals or groups, and these scores compared with one another [54].

We are currently working to adapt GAS for use in haemophilia [55]. In some settings, such as geriatric rehabilitation [56] and dementia [51], menus of likely goal areas and descriptions of a range of attainment levels for each goal area have been developed to aid patients in goal setting. The authors and an interdisciplinary group of colleagues are involved in a systematic approach to accomplish a similar objective in haemophilia (i.e. to provide multiple examples of goal areas and descriptions of attainment levels) (Table 2). First, cross-disciplinary workshops were held to construct a menu of goal areas (Fig. 2) and associated levels of goal attainment. This initial work was followed by systematic gathering of patient and family input to refine the language, validate the goals and identify any gaps. Input from patients and families confirmed that this approach may be particularly relevant in haemophilia, where patients represent a wide spectrum of variation in age, disease severity, disability and psychosocial characteristics [54]. The instrument developed by this process, called Goal Attainment Scaling for Hemophilia (GOAL-Hēm), is currently being evaluated in a multi-centre, North America-based feasibility study, using an online platform to facilitate training, implementation and data management (Fig. 2). The feasibility study will help address the issues of what constitutes clinically meaningful change and whether it can be reliably measured. The study will also evaluate the versatility of

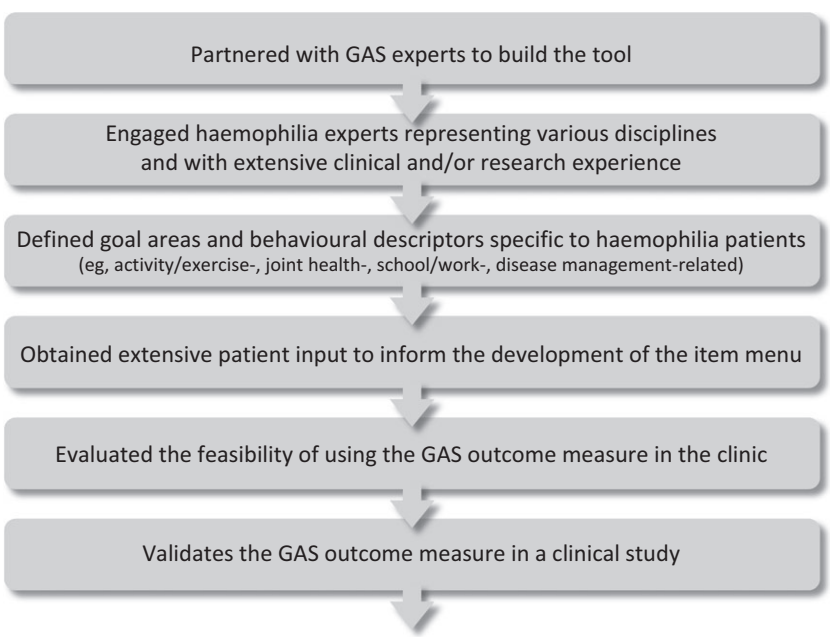

Fig. 2. [Concept Illustration] Flow Chart of development of the Goal Attainment Scaling for Haemophilia instruments.

GOAL-Hēm [52,55]; i.e. use across all age groups with all levels of disease severity, and in different socioeconomic circumstances. Finally, by facilitating collaboration between patients and their healthcare providers, GOAL-Hēm may encourage patients to engage more actively in their treatment.

The fundamental advantage of GOAL-Hēm is that it allows for individualization of the outcome measure itself. For example, a common goal for paediatric patients (approximate ages 10–15) is to become competent and responsible for self-infusion of factor concentrate. This goal area can be selected, current baseline functioning assessed and quantifiable degrees of improvement described to define potential outcomes. In this way, the GAS-based PRO tool provides a truly personalized outcome measure.

The main limitation of GAS as an outcome measure is the degree to which it is operator dependent. In addition, there are operational challenges, including the need for initial staff training and the time and other resources required for implementation and ongoing use of the instrument. These issues will be a major focus of the feasibility study.

Conclusions

In the era of prophylaxis, outcome measures that can discriminate treatment effects important to individual patients are needed in both clinical care and research. While recognizing the strengths of the various outcome measures currently used in haemophilia research, none of these measures are personalized or have sufficient discriminatory capacity to detect change in clinically meaningful parameters that are important to patients with haemophilia in the developed world today. In addition, the existing PRO measures have all been designed for use in clinical research and have limited applicability to real-world treatment.

Efforts to develop more powerful tools to measure PROs in haemophilia are underway. We have presented two of these here. The first, PROMIS, optimizes the value of the questionnaire-based approach common to most PROs. The other, GAS, represents a fundamentally different approach that is based on patient-selected goals and measures the extent to which these goals are attained. We believe that this approach most directly addresses the need for personalization of outcome measurement in haemophilia. Adoption of this or a similarly qualified patient-centric outcome measure will provide clinicians and researchers with an important innovation that addresses the contemporary challenge of measuring incremental but clinically meaningful improvement in haemophilia patients.

Author contributions

KR originated and supervised development of the GOAL-Hēm tool. EJN, MR, BAK, SP and SJ participated in development of the GOAL-Hēm tool. All authors contributed to the writing, review and revision of the manuscript and approved the final version.

Disclosures

Medical editorial assistance was provided by Jerome F. Sah, PhD, and William Kadish, MD, and funded by Baxalta US Inc, now part of Shire. MR's institution receives research support from Baxalta US Inc, now part of Shire, Novo Nordisk, and Genentech. He has served on advisory boards for Novo Nordisk, CLS-Behring, Genentech, and Kedrion. BAK has acted as a paid consultant to Baxalta US Inc, now part of Shire, Biogen, CSL Behring, Kedrion, Novo Nordisk and Pfizer and her institution has received research funding from Baxalta US Inc, now part of Shire, Biogen and Octapharma. SJ has no interests to declare. EJN has acted as a paid consultant to Baxalta US Inc, now part of Shire, Novo Nordisk, CSL-Behring, Biogen-Idec, Pfizer, and Bayer and his institution receives research funding on his behalf from Baxalta US Inc, now part of Shire, Octapharma, and Novo Nordisk. KR is the founder and principal shareholder in DGI Clinical, which has a contract with Baxalta US Inc, now part of Shire, to study individualized outcome measures in haemophilia. SWP has served as a consultant to Baxalta US Inc, now part of Shire.

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