Clinical outcomes in hemophilia: Towards development of a core set of standardized outcome measures for research

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Abstract

Introduction: A lack of uniformity in the choice of outcome measurement in hemophilia care and research has led to studies with incomparable results. We identified a need to define core outcome measures for use in research and clinical care of persons with hemophilia.

Objective: To move toward a core set of outcome measures for the assessment of persons with hemophilia in research and practice.

Methods: A modified nominal groups process was conducted with an international group of hemophilia experts, including persons with hemophilia as follows. Step 1: item generation for all potential outcome measures. Step 2: survey where respondents voted on the relative importance and usefulness of each item. Steps 3/4: 2-day meeting where attendees voted for items they valued, followed by open discussion and a second round of voting. Step 5: survey where respondents selected their top five items from those with >50% agreement at the meeting.

Results: The highest ranked items for the pediatric core set (% agreement) are treatment satisfaction (92.7%), joint health (83.3%), a measure of access to treatment (82.5%), a measure of treatment adherence (72.5%), and generic performance based physical function (72.1%). The highest ranked items for the adult core set (% agreement) are total bleeding events (88.1%), EuroQol five dimensions (85.4%), treatment adherence (82.1%), joint health (79.1%), and number/location of bleeds per unit time (78.6%).

Conclusion: This process generated a list of preferred outcome measures to consider for assessment in persons with hemophilia. This information now requires refinement to define optimal core sets for use in different clinical/research contexts.

Keywords: core set, hemophilia, nominal groups process, outcome assessment (health care), outcome measure
Many well-validated outcome measures have been developed for use in hemophilia clinical trials and observational studies. A lack of uniformity in the choice of which outcome measures to use has led to prospective/retrospective observational studies and clinical trials with results that are not comparable.

In hemophilia, the International Classification of Functioning, Disability and Health, a framework developed by the World Health Organization, (WHO-ICF) has been embraced as a potential conceptual model to guide the selection of outcome measures. Over the last decades, the community of health care professionals working in the area of assessment and care of persons with hemophilia have developed outcome measurement tools that cover most of the WHO-ICF domains: disease factors, structure and function, activities, participation, health-related quality of life, and personal and environmental barriers and enablers.

A problem for hemophilia researchers and healthcare professionals is redundancy among existing outcome measures. For example, within the body structures and function domain for joint examinations, there are at least 4 different tools that have been developed and extensively studied to measure the same construct, all with varying quality. These include the World Federation of Hemophilia Score: Physical Joint Examination (the Gilbert Score), the Colorado Physical Examination scales, the Paediatric Orthopedic Joint Score, and the Hemophilia Joint Health Score, v2.1.

In recent years, the advent of new therapies, and an emphasis on outcome measurement in clinical research and care mandated by regulatory bodies (eg the FDA, EAMA) and funding agencies, has resulted in unprecedented activity in outcome measures research specific to hemophilia. Following a meeting of interested stakeholders, held in 2014, which focused on the identification of outcome measures research specific to hemophilia, a series of systematic reviews were completed. These reviews provided a critical overview of the outcome measures that have been developed for use in persons with hemophilia and point to gaps in information regarding the various outcome measures. A common theme emerging from these systematic reviews is the urgent need for consolidation of relevant outcome measures; the field requires, in most cases, fewer well-developed and studied outcome measures rather than more measures that are often inadequately studied with regard to their measurement properties.

In other chronic conditions, there has been great value in the implementation of a common, practical, ‘core set’ of standardized outcome measures for use both clinically and in research. For example, in the field of rheumatology, ‘core sets’ have been developed and successfully adopted for use in rheumatoid arthritis, childhood arthritis, and vasculitis. A core set – known as the IMMPACT Guidelines – have also been implemented successfully in chronic pain research.

In hemophilia, a core set of outcome measures was recently defined for use in trials specifically relating to gene therapy (CoreHem). This set of measures, which includes only one “legacy” measure in hemophilia (annualized bleeding rate, ABR) was developed to enable easier evaluation of the safety, efficacy, comparative effectiveness and value of gene therapy in the context of clinical trials. However, ABR has been criticized as a subjective measure of limited value, especially in patients receiving intensive treatment with already very low bleeding rates. Parameters and outcomes beyond ABR should be considered, as bleeding rates lack the sensitivity to show potential benefits of newer therapies.

Assessment of patient outcomes beyond ABR and functional status is a high priority area for clinicians, researchers, and persons with hemophilia alike. There is emerging interest in including PROs as key endpoints in clinical trials as well as to assess the effectiveness of clinical care. For example, the Patient Reported Outcomes, Burdens and Experiences (PROBE) Project developed a questionnaire centred on patient-important outcomes that enables efficient collection of information for advocacy purposes.

Given this background, we identified a need to define core outcome measures that should be considered for use in research studies and clinical care of persons with hemophilia, using a consensus driven process. The ‘core set’ should be both comprehensive across the WHO-ICF construct and practical, and should include outcomes that are important to multiple stakeholders including persons with hemophilia, health care providers, regulatory bodies and funding agencies.

This communication aims to report the outcome of a consensus process aimed to define a core set of outcome measures, defined within the WHO-ICF framework, that should be considered for the assessment of persons with hemophilia in research and practice.

## 2 | METHODS

As a follow-up to the 2014 Outcome Measures meeting, a 5 step, modified nominal groups process was followed to promote the definition of a core set, guided by the findings of the results of that meeting, and especially the systematic reviews of tools for joint health
scores, activity/participation, health related quality of life, and radiology.

Step 1 was to develop a list of potential outcome measures by conducting a survey of a multidisciplinary group of international experts in hemophilia care and persons with hemophilia. The health care professionals were hemophilia treatment centre (HTC) based and included a number of the attendees from the 2014 Outcome Measures meeting. These HTCs included members of the International Prophylaxis Study Group (IPSG) and others identified as experts/leaders in the musculoskeletal (MSK) assessment of persons with hemophilia. The individuals and HTCs were selected by consensus of the organizing committee (BF, VB, SD, KF, AS, and AA) with input from international world leaders in the care of persons with hemophilia. The steering committee did not influence or change the data or results in any way. The outcomes are reported exactly as chosen by the attendees and survey respondents.

The survey required respondents to list all of the items that they/members of their HTC felt should be considered as part of a core set for clinical hemophilia studies in children (defined as patients ≤ 18 years of age) and in adults (defined as patients > 18 years of age). Once the items were generated, they were classified into the WHO-ICF domains.

In Step 2, a preliminary vote was conducted on the items generated in Step 1. To achieve this, a second survey was distributed to a targeted list of individuals representing a wide range of experience and expertise in hemophilia care and research. Each individual was asked to rate each item generated in the first survey on three scales: how likely the item is to detect abnormalities, how important the item is if abnormalities are detected, and if the item should be measured in every clinical trial of a new treatment in hemophilia.

Steps 3 and 4 involved a 2-day consensus meeting in Toronto, Canada in 2016. Invites to this meeting were selected to include not only invitees from the 2014 Outcome Measures meeting, but expanded to include a patient perspective, as well as some selected respondents from the surveys. The consensus meeting consisted of three components. First, the results of the two pre-meeting surveys (Steps 1 and 2) were presented as background. Second, key findings from the systematic reviews were presented, along with other summary presentations from experts split into each major WHO-ICF domain. In Step 3, the participants voted during the 2 day consensus meeting for those items they felt should be included as part of a core set for each ICF domain separately. The responses to the first vote were analyzed in real time to allow open discussion of the provoked responses. The inclusion of new items or re-wording of existing items felt by attendees to be important was allowed. Finally, in Step 4, a second round of voting was held on all the identified items.

In the final step, Step 5, the meeting attendees, plus persons invited to attend the 2 day consensus meeting but who were unable to attend in person, were surveyed and requested to vote for their top 5 items from a list of those with >50% agreement identified during the consensus meeting in steps 3 and 4.

### 3 | RESULTS

Responses were received from 55/76 (72.4%) of HTCs surveyed in Step 1. A total of 117 pediatric specific and 129 adult specific outcomes parameters and measurement tools were identified in this initial step that included items respondents felt should be considered as part of a core set for clinical studies in persons with hemophilia. Items were grouped for consistency and to remove duplicates, and were then classified into the WHO-ICF domains (Table 1).

Responses were received from 74/106 (69.8%) of individuals surveyed in Step 2. These responses were tabulated to identify those items felt likely by respondents to detect abnormalities, the median importance of the item should abnormalities be detected, and the proportion of respondents who thought that the item should be included as part of a core set (Supplementary Tables S1-S12). These detailed, itemized results were distributed as part of the pre-meeting briefing packages for attendees at the 2-day consensus conference.

Forty-six of 52 invited individuals (88.5%) attended the consensus conference. Invites included pediatric and adult hematologists, radiologists, orthopedic surgeons, physical therapists, health economists and quality of life specialists, patient representatives and other select individuals with expertise in hemophilia (Figure 1). All items that reached at least 50% consensus were kept in the list of items to be considered for the core set. Table 2 shows a breakdown of those items for both children (pediatric) (A) and adults (B) following 2 rounds of voting at the meeting (Steps 3 and 4).

Following the consensus meeting in the final voting round (Step 5), responses were received from 92.3% (48/52) of individuals surveyed. The 5 highest ranked items to be considered for a pediatric core set that emerged from this process were: a (validated) measure of treatment satisfaction, joint health using the HJHS, a measure of access to treatment, a measure of treatment adherence, and generic performance based physical function (Table 3). The 5 highest ranked items to be considered for an adult core set that emerged from this process were: total bleeding events, the EuroQol five dimensions, a (validated) measure of treatment adherence, joint health using

| ICF Domain                     | Pediatric outcome measures | Adult outcome measures |
|--------------------------------|-----------------------------|------------------------|
| Disease factors                | 30                          | 35                     |
| Structure & Function           | 23                          | 34                     |
| Activities                     | 21                          | 14                     |
| Participation                  | 8                           | 6                      |
| Health related quality of life | 10                          | 7                      |
| Barriers & Enablers            | 25                          | 33                     |
| Total                          | 117                         | 129                    |

**Table 1** Breakdown of the number of suggested outcome measures according to each of the six ICF domains: disease factors, structure and function, activities, participation, health related quality of life (HRQoL), and barriers and enablers.
the HJHS, and then number and location of bleeds per unit time (Table 3).

4 | DISCUSSION

Using a modified nominal groups process, the top 5 outcome measures that should be considered for use in research and practice for persons with hemophilia were identified. These proposed measures provide an excellent starting point for future refinements and eventual adoption by funding agencies, regulators, and HTCs.

The respondents were all experienced and invested in measuring outcomes in persons with hemophilia and suggested a broad and varied list of tools to assess outcomes, which were probably related to their context of clinical/research settings and may have lacked objectivity. As such, this is not a representative sample of all stakeholders that might have been surveyed. Given the group’s experience in the area, we believe that it was an acceptable group to begin this work; future iterations and refinements of the core sets may survey a more representative group of stakeholders.

Our respondents/experts chose, in many cases, to describe broad areas of measurement (for example, “a measure of treatment adherence”) rather than specific tools for two reasons. First, for some outcomes, hemophilia specific and well-validated tools do not yet exist; these outcome areas should form a research priority. Second, where specific or well-validated tools do exist, it is not yet clear which should be preferred; again, this should be a research priority. In those cases where a specific tool was considered to be mature and well-validated, it was chosen or suggested (eg, EQ-5D and HJHS). However, in some cases, this did not occur, despite the evidence presented from the systematic reviews.

The modified nominal groups methodology used in this process was selected in order to allow for a portion of the consensus discussions to occur in person. While a Delphi process is often employed to arrive at a consensus, it is traditionally completed in a distributed fashion using an anonymous survey or surveys and does not generally include a face-to-face meeting. The in person meeting was considered vital to this initiative as it allowed for in-depth discussion among the participants to facilitate identification of important outcome measures across the ICF domains.

Despite the rigorous methodology employed in this process, some items are notably missing from the highly ranked items. In the pediatric core set, there is no proposed measure of bleeding. Some measure of bleeding, typically ABR or annualized joint bleeding rate (AJBR) has historically been included as an outcome in most clinical trials for hemophilia. It is unlikely that any core set could be developed without this legacy measure included, since bleeding episodes have been included by all current groups developing hemophilia specific core sets. Missing from the proposed adult core set is any measure of performance based physical function. As patients transition from pediatric to adult care and begin to take responsibility for their own management, their physical function becomes an important indicator of health status.

The outcomes that emerged in both the pediatric and adult sets have very little overlap, except for the measure of joint function (HJHS) and a measure of treatment adherence. This lack of harmonization may make it difficult to follow young children and adolescents through to adulthood. While there is a difference between what is considered important for pediatrics (young children and adolescents) compared to adulthood, a future focus should be on the items that overlap and how those can best be tailored to suit the needs of each patient group.

Other groups are carrying out similar work in outcome measures and core sets in hemophilia, demonstrating the timeliness of this approach. The International Haemophilia Access Strategy Council (IHASC) has developed a patient-centred value-based framework using a small interdisciplinary panel of health economists, hematologists, health payers and a patient representative. Gouw et al have convened an international group of experts to work on a health value-based set of outcomes (the HemoValue initiative). The resulting framework of outcomes is broad, and informs but does not direct which
TABLE 2  A. Summary of the items to be considered for the pediatrics core set, defined as reaching at least 50% consensus following 2 rounds of voting (Steps 3 and 4) at the consensus meeting. B. Summary of the items to be considered for the adults core set, defined as reaching at least 50% consensus following 2 rounds of voting (Steps 3 and 4) at the consensus meeting

(A)

| ICF Domain                | Items/Concepts                                                                 | % Yes to core set |
|---------------------------|-------------------------------------------------------------------------------|-------------------|
| **Activities**            |                                                                               |                   |
|                           | Generic performance based physical function                                  | 72.1              |
|                           | Pediatric Hemophilia Activities List (PedHAL)                                 | 67.4              |
|                           | Enhanced Functional Independence Scores in Hemophilia (eFISH)                  | 65.1              |
|                           | Activity modification due to hemophilia                                       | 58.1              |
|                           | Functional Independence Scores in Hemophilia (FISH)/Enhanced Functional       | 51.2              |
|                           | Independence Scores in Hemophilia (eFISH)                                     |                   |
| **Barriers & Enablers**   |                                                                               |                   |
|                           | Access to treatment                                                           | 82.5              |
|                           | Treatment adherence                                                           | 72.5              |
|                           | PROBE (when validated)                                                        | 70                |
|                           | Satisfaction with treatment                                                   | 62.5              |
|                           | Enrollment in Hemophilia Treatment Centre (HTC)                               | 52.5              |
| **Disease factors**       |                                                                               |                   |
|                           | Annualized Joint Bleeding Rate                                                | 59.5              |
|                           | Treatment schedule/dosage                                                     | 59.5              |
|                           | Trough clotting factor level                                                   | 57.1              |
|                           | Number of joint bleeds                                                        | 54.8              |
|                           | Age at start of prophylaxis                                                   | 52.4              |
|                           | Number and location of bleeds per unit time                                   | 52.4              |
|                           | Annual bleed frequency                                                        | 50                |
| **Health related quality of life** |                                                                               |                   |
|                           | Treatment satisfaction questionnaire                                          | 92.7              |
|                           | Canadian Hemophilia Outcomes – Kid’s Life Assessment Tool (CHO-KLAT)          | 61                |
|                           | EuroQol-5 Dimensions (EQ-5D) child version                                   | 51.2              |
| **Participation**         |                                                                               |                   |
|                           | Generic, age appropriate participation questionnaire                            | 69.8              |
|                           | School attendance                                                             | 65.1              |
|                           | Participation in school activities                                            | 53.5              |
| **Structure & Function**  |                                                                               |                   |
|                           | Hemophilia Joint Health Score (HJHS)                                          | 83.3              |
|                           | Pain visual analog scale                                                       | 66.7              |
|                           | Active/passive joint range of motion                                          | 64.3              |

(B)

| ICF Domain                | Items/Concepts                                                                 | % Yes to core set |
|---------------------------|-------------------------------------------------------------------------------|-------------------|
| **Activities**            |                                                                               |                   |
|                           | Hemophilia Activities List (HAL)                                              | 69.8              |
|                           | Functional Independence Scores in Hemophilia (FISH)/ Electronic Functional     | 62.8              |
|                           | Independence Scores in Hemophilia (eFISH)                                     |                   |
|                           | Functional Independence Scores in Hemophilia (FISH)                          | 58.1              |
|                           | Canadian Occupational Performance Measure (COPM)                             | 55.8              |
|                           | Electronic Functional Independence Scores in Hemophilia (eFISH)               | 53.5              |
| **Barriers & Enablers**   |                                                                               |                   |
|                           | Treatment adherence – no particular tool                                       | 82.1              |
|                           | Enrollment in hemophilia treatment centre                                     | 71.8              |
|                           | Access to treatment                                                           | 71.8              |
|                           | Work absenteeism                                                              | 66.7              |
|                           | Burden of treatment                                                           | 59                |
|                           | Cost of treatment                                                             | 53.9              |
|                           | PROBE                                                                         | 53.9              |
|                           | Clotting factor usage                                                         | 51.3              |

(Continues)
specific measures should be considered for each identified health outcomes. Both of these approaches defined their framework in terms
of health value, that is to say in terms of the value created for patients, rather than on quality per se. There are also initiatives that take a
patient-reported outcome centred approach; The PROBE questionnaire was developed with patient-important outcomes at its focus.

While, undoubtedly, different sets of measures reflect different perspectives, a future goal should be to harmonize these approaches. The context of the application of the tools may require some tailoring of measures used, such as clinical trials vs. clinical practice, prophylaxis vs. episodic treatment, factor vs. non-factor therapies, or short term vs. long term studies. However, the global hemophilia community should aspire to soon develop a core set of outcome measures that can be universally applied no matter the clinical or research situation.

5 | CONCLUSION

This initiative was a first step in moving towards a core set of measures, which should be considered for assessment of outcomes in persons with hemophilia. This information now requires refinement to define optimal core sets for use in different clinical/research contexts using consensus-driven, value-based approaches. Advancements in the adoption of core sets of value-based outcome measures, the development of which expand on the foundations established in this process, are currently in progress.

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AUTHOR CONTRIBUTIONS

Saunya Dover was a member of the 2016 MSK Meeting Steering Committee, coordinated the data collection, conducted data analysis, contributed to data interpretation and wrote the first draft of the manuscript. Victor S. Blanchette developed the research question, was the chair of the 2016 MSK Meeting Steering Committee, contributed to data analysis and interpretation and critically revised the manuscript. Alok Srivastava was a member of the 2016 MSK Meeting Steering Committee and critically revised the manuscript. Kathelijn Fischer was a member of the 2016 MSK Meeting Steering Committee and critically revised the manuscript. Audrey Abad was a member of the 2016 MSK Meeting Steering Committee, facilitated the consensus meeting, contributed to data analysis and interpretation, assisted with the first draft of the manuscript, and critically revised the manuscript. Brian M. Feldman was a member of the 2016 MSK Meeting Steering Committee and critically revised the manuscript. Audrey Abad was a member of the 2016 MSK Meeting Steering Committee, coordinated the data collection, conducted data analysis, and critically revised the manuscript. Alok Srivastava was a member of the 2016 MSK Meeting Steering Committee and critically revised the manuscript. Kathelijn Fischer was a member of the 2016 MSK Meeting Steering Committee and critically revised the manuscript. Brian M. Feldman was a member of the 2016 MSK Meeting Steering Committee, facilitated the consensus meeting, contributed to data analysis and interpretation, assisted with the first draft of the manuscript, and critically revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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