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ORIGINAL ARTICLE

Identifying performance-based outcome measures of physical function in people with haemophilia (IPOP)

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Abstract

Introduction: Recent recommendations of core outcome sets for haemophilia highlight the need for including measures of performance-based physical health and physical function sustainability. To date, there is no consensus on what outcomes might be of value to clinicians and patients.

Aim: To identify instruments of performance-based physical function to monitor musculoskeletal health in people with haemophilia that are practical in the clinical setting.

Methods: Utilising components from the Activities and Participation Category of the WHO International Classification of Functioning (WHO-ICF), a consensus-based, decision analysis approach was used to: identify activities people with haemophilia have most difficulty performing; identify quantitative performance-based measures of identified activities via a scoping review; and obtain views on acceptability of the tests utilising a DELPHI approach.

Results: Eleven activities were identified: maintaining a standing position, walking long distances, walking up and down stairs, walking on different surfaces, running, hopping, jumping, squatting, kneeling, undertaking a complex lower limb task, undertaking a complex upper limb task. Following a 2-round DELPHI survey of international physiotherapists, the 6-min walk test, timed up and down stairs, 30-s sit to stand, single leg stance, tandem stance, single hop for distance (children only) and timed up and go (adults only) reached consensus.

Conclusion: This study is the first step in defining a core set of performance-based instruments to monitor physical health and sustainability of physical function outcomes in people with haemophilia. Establishing the psychometric properties of the instruments and whether they are meaningful to people with haemophilia is essential.

KEYWORDS
haemophilia, musculoskeletal, outcomes, physical function, physical health, physical performance

1 | INTRODUCTION

Haemophilia care is witnessing a significant shift towards a new era of potentially life changing treatments which offer a future aimed at zero bleeds and no joint damage. Children and young people that are treated with early prophylaxis to prevent or minimise arthropathy, may have a bleed-free life, whilst adults with existing joint arthropathy may see their physical health stabilise or decline at a slower rate.[1] Haemophilia care will range from monitoring people with zero bleeds and no arthropathy who expect to have no limitations on their physical activity, those with mild to moderate arthropathy in a single joint who participate in most physical activities, to those who have the majority of joints affected with some degree of arthropathy whose participation in physical activities is limited.[2]

Current assessment of musculoskeletal and physical health focuses on bleed-related events and after-effects, such as frequency of bleeds, pain, body structure and function and self-reported measures of activity and participation.[3] With the advent of new and improved medical management, established instruments assessing body structure and function, for example, the Haemophilia Joint Health Score,[4] may no longer be sufficiently discriminatory of musculoskeletal health status.[5–11] Consequently, it may not offer sufficient quantitative information to monitor musculoskeletal health in the future. Alternative instruments are sought which reflect one's comprehensive musculoskeletal health and physical ability, capacity and endurance. Recent recommendations of core outcome sets for haemophilia highlight the need for including measures of performance-based physical function and physical health sustainability.[12–13] However, to date, recommended instruments for these constructs are lacking. Haemophilia is a life-long condition, and therefore instruments that are compatible for use in young children, adolescents, young and older people are preferable.

The World Health Organisation International Classification of Functioning, Disability and Health (WHO-ICF) provides a framework for describing the profile of an individual's function, not a 'yes' or 'no' answer about whether he or she is disabled.[14] The Activities and Participation categories as opposed to the Body Structure and Function categories enable an individual's health to be described in terms of performance or execution of a task or action and their capacity to participate or be involved in life situations.

There are several self-reported functional tools for haemophilia such as the Haemophilia Activities List (HAL) and pediatric Haemophilia Activities List (pedHAL). The HAL/pedHAL includes seven domains: 'sitting/kneeling/standing', 'functions of the legs', 'functions of the arms', 'use of transportation', 'self-care', 'household tasks' and 'leisure activities and sports'.[15] In children, the pedHAL has been reported to be of limited clinical value in patients without joint and/or muscle bleeds[16] with ceiling effects in the arm and self-care domains.[17] When actual and perceived motor skills competence is evaluated, it is reported in children without health conditions that they unrealistically under/overestimated their competence in motor skills.[18] In older people, self-report tools appear to distinguish differences at the lower end of physical capacity but not at mid-to-high levels and that performance-based measures discriminate across a fuller spectrum[19] suggesting that self-report tools and performance-based tools are measuring different constructs. The Functional Independence Score in Hemophilia (FISH) is a haemophilia-specific performance-based tool measuring an individual's independence in performing activities of daily living, transfers and mobility. The FISH, designed for use in adults, includes eight activities in three categories: self-care, transfers and locomotion with each activity scored according to the amount of assistance required to perform the task.[20] Due the ceiling effect of the FISH in people with little arthropathy, it was recommended for populations with more advanced joint disease.[21]

Therefore, there is a need to identify performance-based instruments that can describe the performance or execution of a task or action and capacity to participate or be involved in life situations of individuals with haemophilia that can complement existing self-report instruments. The Osteoarthritis Research Society International (OARSI) recommends a set of performance-based instruments of physical function for people diagnosed with hip or knee osteoarthritis (OA).[22] A consensus-based approach involved a review of potential instruments, consensus ranking of the difficulty of instruments for people with hip or knee OA by an expert group, followed by wider consensus by clinicians of the feasibility of the instruments and review of measurement properties of the instruments. The ankle joint is the most commonly affected joint in haemophilia with elbow and knee joint arthropathy also impacting on function.[23] Our aim in the present initiative is to follow a similar methodology to OARSI to identify and recommend performance-based instruments of performance-based physical function to monitor musculoskeletal health in people with haemophilia that are practical in the clinical setting.

2 | METHODS

An Advisory Group (AG) (M.B., H.H., W.D., G.D., R.M., J.vdN, S.P.A., F.S., K.S., M.T., D.S.) was established in 2017 to identify performance-based instruments of physical ability and function for monitoring musculoskeletal health in people with haemophilia. Members were invited based on their international standing in paediatric and or adult haemophilia clinical practice and/or research and/or expertise in outcome measurement and included representatives from Canada, France, Netherlands, Spain and UK.

2.1 | Phases of project

Following consultation with the AG, the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guideline was adopted as the consensus approach for this initiative.[24] The COSMIN guideline recommends several steps: conceptual considerations; identifying existing outcome measurement instruments; and, quality assessment of outcome measurement instruments. Adhering to these steps, the consensus process consisted of five sequential phases (see Figure 1):

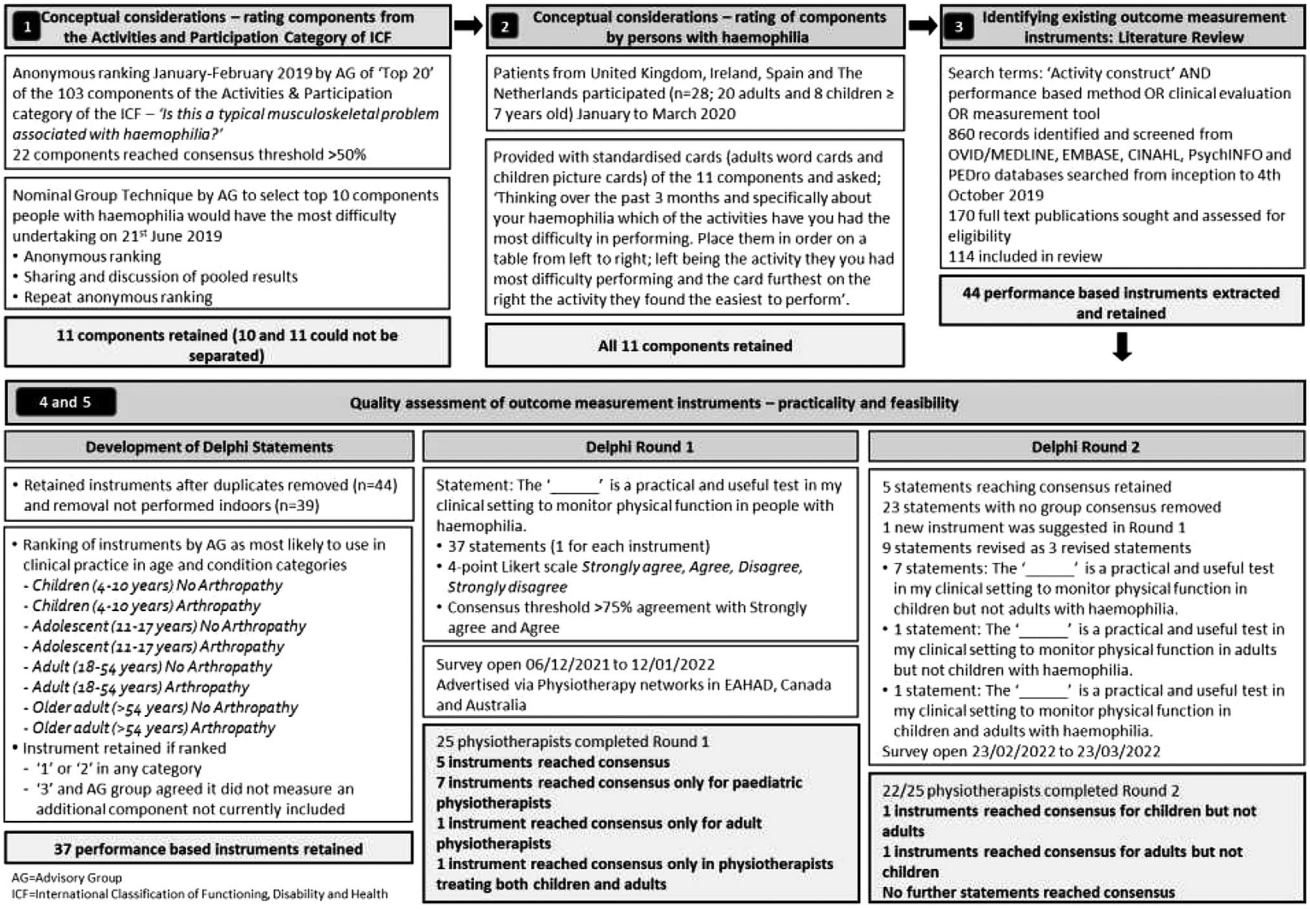

FIGURE 1 Overview of the project stages and results.

Conceptual considerations

1. The AG rated their individual perspectives of components from the Activities and Participation Category of the International Classification of Functioning, Disability and Health (WH0-ICF)[14] that they perceived people with haemophilia have most difficulty performing (January–June 2019).
2. Using the AG ranked components of Activities and Participation Category of the International Classification of Functioning, Disability and Health (WHO-ICF), people with haemophilia ranked the same components that they perceived they have most difficulty performing, but were not influenced or biased by the AG (2020).

Identifying existing outcome measurement instruments

3. Systematic review to identify quantitative performance-based instruments measuring the components identified in Phase 1 (October 2019).

Quality assessment of outcome measurement instruments—practicality and feasibility

4. The AG selected performance-based instruments that are suitable for the clinical setting, for example, performance outcomes not requiring access to complex/specific equipment/environment or complex training (2021).
5. Consensus ranking of acceptability of performance-based instruments by physiotherapists experienced in the field of haemophilia (2022).

2.2 | Phase 1. Perspectives and rating of components from the Activities and Participation Category of the WHO-ICF that people with haemophilia have most difficulty performing—completed by the AG

Utilising an online survey, distributed as a Microsoft Excel spreadsheet during January and February 2019, the AG (n = 11; M.B., H.H., W.D., G.D., R.M., J.vdN, S.P.A., F.S., K.S., M.T., D.S.) were asked to anonymously select components most relevant to people with haemophilia from the 103 individual components of the Activities & Participation category of the WHO-ICF, by answering the question, "Is this a typical musculoskeletal problem associated with haemophilia?". Components with more than 50% agreement across the AG were retained and those with less than 50% were eliminated. Utilising nominal group technique at a face-to-face meeting on 21/06/2019, the AG were asked to consider the retained components and select the top 10

components people with haemophilia would have the most difficulty undertaking. The process involved an initial anonymous ranking by individuals of the AG, followed by sharing and discussion of the pooled results (descriptions of central tendency, distribution and spread) and a subsequent anonymous ranking of components by individuals of the AG.

2.3 | Phase 2. Perspectives and rating of components from the Activities and Participation Category of the WHO-ICF that people with haemophilia have most difficulty performing—completed by people with haemophilia

Perspectives of people with haemophilia of the components identified in Phase 1 were obtained during January–March 2020 by inviting the patient-facing clinical members of the AG ($n = 7$; M.B., S.P.A., F.S., M.T., D.S., G.D., K.S.) to ask eligible patients (those with severe disease) to rank the component activities they had most difficulty in performing. The patient perspectives component of the study was undertaken during COVID and as such was a convenience-based sample of patients with severe haemophilia. Adults, children over 7 years of age and parents and parents of children under 7 years of age completed the patient perspectives.

Participants were provided with standardised cards (word cards for adults and picture cards for children) and asked "Thinking over the past 3 months and specifically about your haemophilia which of the activities have you had the most difficulty in performing? Place them in order on a table from left to right; left being the activity you had most difficulty performing and the card furthest on the right the activity they found the easiest to perform." Adults ranked based on their own perspectives, children over the age of 7 years ranked together with their parents/guardians, and parents of children with haemophilia younger than 7 years ranked based on their preferences.

Results were collated by MB using Microsoft Excel and the most frequently reported activities were collected for adults and children.

2.4 | Phase 3. Literature review to identify objective performance-based instruments

Utilising the search strategy contained in Supplementary File 1, the OVID/MEDLINE, EMBASE, CINAHL, PsychINFO and PEDro databases were searched on 4th October 2019, from inception to 2019 to retrieve studies using a performance-based method, clinical evaluation or measurement instrument to evaluate any of the component activities identified in Phase 1 (search completed by KS). The search was not restricted to haemophilia or age, but only English abstracts were included. All retrieved abstracts were screened for inclusion independently by two reviewers (MB and DS) and full text papers reviewed. Disagreement on inclusion was resolved by consensus discussion. Combined component and self-perceived tests were excluded and only those tests identified that included a performance measure matching one of the component activities identified were retained.

2.5 | Phase 4. Selection of performance-based instruments by AG suitable for the clinical setting

The clinical members of the AG ($n = 7$; M.B., J.vdN, S.P.A., F.S., K.S., M.T., D.S.) were sent an electronic spread sheet of the retained performance-based instruments and asked to anonymously rank each of the instruments on its usefulness in a clinical setting whereby 1 = "most likely to use in a clinical setting". They were asked to consider use of the instrument in a clinical setting for four categories of patients: young child (4–10 years); adolescent (11–17 years); young adult (18–54 years) and older adult (>54 years), and two condition sub-categories within each age category—presence of joint arthropathy or no joint arthropathy. Performance-based instruments were retained 'as useful in the clinical setting' based on the following criteria:

- instrument ranked '1' or '2' in any age or condition category by a member of the clinical AG;
- instrument did not require use of outdoor facilities (e.g., athletics track);
- instrument ranked '3' or below and the AG agreed by consensus the instrument measured an additional component not currently included.

Performance-based instruments 'not known' and not ranked by any member of the AG were not retained. Results were collated using Microsoft Excel.

2.6 | Phase 5. Consensus ranking of performance-based instruments by physiotherapists

Perspectives on the practicality and usefulness of the retained performance-based instruments in the clinical setting to monitor physical function in people with haemophilia were obtained from international physiotherapists experienced with haemophilia care. A two-round electronic Delphi approach was used.

2.6.1 | Participants

An invitation to participate in the 'Delphi survey' was distributed to the email contacts of the European (EAHAD), Canadian and Australian haemophilia physiotherapy networks. These groups were chosen as each had an established physiotherapist email network. The email included the purpose of the survey and outline of the 'Delphi' process. Those who wished to participate in the survey were invited to respond to the study co-ordinator (H.H.) who on receipt of a reply email, forwarded the respondent a link to the 'Delphi survey'. Inclusion criteria

for participation included a minimum of 1 year's haemophilia clinical experience. Each round of the survey was created in Smart Survey.

2.6.2 | Delphi Round 1

Each performance-based instrument was developed into a statement with a description of the instrument provided. Each participant was asked to consider each performance-based instrument in regards of time to complete the instrument, space, cost and feasibility of using the instrument by answering the following statement: 'The _____ is a practical and useful test in my clinical setting to monitor physical function in people with haemophilia'. Participants were asked to consider the instrument as described, rather than previous experience with the instrument which may have differed from the standardised version. Participants were asked to select whether they strongly agreed; agreed; disagreed; or, strongly disagreed with each statement. Participants were invited to suggest additional performance-based instruments not included in the Delphi survey. Data was collected on respondents' country practiced in; whether they treated children only; adults and children or adults only with haemophilia and the proportion of time spent in clinical practice treating patients; this data was self-reported.

The invitation e-mail was sent on 6th December 2021, and Round 1 of the Delphi was open for 6 weeks. Responses for each statement were grouped, analysed and reported as four groups: all respondents; participants who treated children only; participants who treated adults only; participants who treated both children and adults. Criteria for acceptance of statements that a performance-based instrument 'is practical and useful in the clinical setting' was consensus of >75% agreement/disagreement in all four groups. The 75% threshold was chosen as it has previously been reported as the median threshold, for determination of consensus.[24] Statements that reached agreement within one of groups 2, 3 or 4 but not all groups were revised for consideration in round 2 of the Delphi, as were additional performance-based instruments suggested by respondents. Results were collated by DS using Microsoft Excel.

2.6.3 | Delphi Round 2

Respondents who completed Round 1 were emailed on 23rd February 2022 and invited to participate in Round 2. For revised statements, each participant was asked to consider each performance-based instrument in regards of time to complete the instrument, space, cost and feasibility of using the instrument by answering the following statements:

a) The _____ is a practical and useful test in my clinical setting to monitor physical function in children but not adults with haemophilia, and;
b) The _____ is a practical and useful test in my clinical setting to monitor physical function in adults but not children with haemophilia.

Participants were asked to select whether they rank the test according to: strongly agreed; agreed; disagreed; or, strongly disagreed with each statement.

For example:

> *'The Timed up and go is a practical and useful test in my clinical setting to monitor physical function in children but not in adults with haemophilia. How strongly do you agree with this: strongly agreed; agreed; disagreed; or, strongly disagreed?'*

For additional performance-based instruments suggested in Round 1, each participant was asked to select level of agreement as per the process outlined in Round 1. Round 2 of the Delphi was open for 4 weeks. Participants were sent reminders at 2 weeks. Responses for each statement were grouped, analysed and reported as four groups: (1) all respondents; (2) participants who treated children only; (3) participants who treated adults only; (4) participants who treated both children and adults. Criteria for acceptance of statements 'in children but not adults' was consensus of >75% agreement/disagreement in group 2 and 4. Criteria for acceptance of statements 'in adults but not children' was consensus of >75% agreement/disagreement in group 3 and 4. Criteria for acceptance of statements for additional performance measures was consensus of >75% agreement/disagreement in all four groups. Results were collated using Microsoft Excel.

3 | RESULTS

3.1 | Phase 1. Perspectives and rating of components from the Activities and Participation Category of the ICF that people with haemophilia have most difficulty performing—AG completed

Twenty-two components from the Activities and Participation domain of the ICF achieved more than 50% consensus by the AG. Following discussion and further anonymous ranking by the AG, 11 components achieved more than 50% consensus agreement. The group could not come to a consensus on which to eliminate from the top 11, so all were included. The 11 components identified as problematic for patients with haemophilia were: maintaining a standing position; walking long distances; walking up and downstairs; walking on different surfaces; running; hopping; jumping; squatting; kneeling; undertaking a complex upper-limb task and undertaking a complex lower limb task.

3.2 | Phase 2. Perspectives and rating of components by people with haemophilia

AG clinical members from five countries (Canada, France, Netherlands, Spain, United Kingdom) were invited to participate in the patient perspectives study and provided with patient information sheets and data collection sheets. Due to the COVID pandemic in 2020 and reduced clinical patient interaction, limited patient data were col-

TABLE 1 Performance-based instruments identified from literature review.

Component	Performance-based Instruments
Maintaining a standing position	Timed up and go; Berg balance test; one leg balance; step test; star excursion; functional reach; tandem stance; semi-tandem stance
Walking long distances	Six-minute walk test; 50-foot walk; 10-metre incremental shuttle walk test; 1.5-mile walk/run
Walking up and downstairs;	Six-minute step-test; step-down test, timed up and down stairs; Chester step test
Walking on different surfaces	
Running	Twenty-metre Incremental Shuttle Run Test; 4 x 10-metre shuttle run test; 10-metre incremental shuttle walk/run test; 1.6 km run; 50-metre sprint; half-mile run/walk; 3-min run
Hopping	Single leg hop; triple hop; square hop test; single hop for height; side hop 30 s; figure of 8 hop; 6-metre timed hop; cross over hop; Fatigue single hop
Jumping	Vertical jump; broad jump
Squatting	30-s sit to stand; 5 and 10 chair raises; single leg squat
Kneeling	
Undertaking a complex upper-limb task	Basketball throw; grip strength; back scratch test
Undertaking a complex lower limb task	

lected. Patients ($n = 28$) from three of the five countries (UK, $n = 18$; Netherlands, $n = 4$; and Spain, $n = 6$ agreed to participate; 20 adults and eight children with a mean age of 33 years; range 7–71 years. All 11 components received a ranking. The most frequently reported components of difficulty for adults were walking long distances, hopping and running. Children reported most difficulty with walking long distances, hopping and complex lower limb tasks.

3.3 | Phase 3. Literature review of performance measures

Eight hundred and sixty potential studies were identified from the initial search. After screening of title and abstract, 170 publications were selected for full inspection; 27 studies included children only (<18 years), 79 adult participants (18–65 years), 33 older adult (>65 years) participants, eight were a mix of child and adult participants and 23 did not specify in the abstract. 114 performance-based instruments matching at least one of the 11 components were identified across studies with some using >1 method. Timed walking distance/speed and balance tests were most common (95 and 57 studies respectively). No performance measures were identified for kneeling or walking on different surfaces; complex tasks for upper limb and lower limb were ill-defined. Therefore, measures for upper limb and lower limb complex tasks were unable to be evaluated further. Following removal of duplicates, 44 performance-based instruments were retained for review (see Table 1).

3.4 | Phase 4 and 5. Quality assessment of outcome measurement instruments—practicality and feasibility

Following initial discussion of the 44 instruments by the AG, five instruments were removed by consensus due to inability to perform indoors; 1.5-mile walk/run, 1.6 km run, 50-metre sprint, half-mile run/walk, 3-min run. Following ranking of the remaining 39 instruments, two tests did not meet the criteria to retain; Berg Balance Test due to multiple components and Chester step test due to requirement for heart rate monitoring.

3.4.1 | Delphi Round 1

31 physiotherapists requested a link to the Delphi survey and 25 respondents completed Round 1 (See Table 2). Twenty-two of the 25 physiotherapists had >3 years clinical experience with patients with haemophilia, the remaining three had between 1- and 3-years' experience. Five of the instruments reached the consensus threshold for all patients; one-leg balance, tandem stance, 6-min walk test, timed up and down stairs and 30-s sit to stand. Seven additional instruments reached consensus threshold only for child physiotherapists; single leg hop, single hop for height, triple hop, side hop for 30 s, 6-metre timed hop, cross-over hop and broad jump. One additional instrument reached the consensus threshold only in adult physiotherapists; timed up and go. One further instrument reached the threshold consensus only in physiotherapists treating both children and adults; grip strength with a handheld dynamometer. The four-square step test and Hi-MAT were the only additional instruments suggested in Round 1 by respondents.

3.4.2 | Delphi Round 2

Of the 25 physiotherapists who responded in Delphi Round 1, 24 indicated they wished to participate in Delphi Round 2 and of those, 22 completed Round 2, a response rate of 88%. Nineteen of the 22 physiotherapists had >3 years clinical experience with patients with haemophilia, the remaining three had between 1- and 3-years' experience. One of the seven instruments reached the consensus threshold

TABLE 2 Summary of respondent characteristics for Delphi Survey Round 1 and 2.

	Physiotherapists treating children only		Physiotherapists treating adults only		Physiotherapists treating both children and adults		All physiotherapists	
Number of respondents	Round 1 9	Round 2 6	Round 1 7	Round 2 7	Round 1 9	Round 2 9	Round 1 25	Round 2 22
Country	Australia Canada Finland Ireland Netherlands United Kingdom	Australia Canada Ireland United Kingdom	Australia Spain United Kingdom	Australia Spain United Kingdom	Belgium Brazil Netherland New Zealand Norway Sweden Turkey United Kingdom	Belgium Brazil Netherland New Zealand Norway Sweden Turkey United Kingdom	Australia Belgium Brazil Canada Finland Ireland Netherland New Zealand Norway Spain Sweden Turkey United Kingdom	Australia Belgium Brazil Canada Ireland Netherland New Zealand Norway Spain Sweden Turkey United Kingdom
Clinical hours (per week) Median (IQR)	7.5 (4–15)	15 (6.75–15.75)	17 (7–19.5)	17 (7–19.5)	10 (5–18)	10 (5–18)	10 (5–18)	15 (5.25–18.75)

TABLE 3 Instruments identified as practical and useful performance-based outcomes in a clinical setting to monitor physical function in children and adults.

	Performance-based Instruments
Children and adults	One leg balance[a], Tandem stance[a], 6-min walk test[a], timed up and down stairs[a], 30-s sit to stand[a]
Children only	Single leg hop[b]
Adults only	Timed up and go[b]

[a]Instruments that reached consensus after Delphi round 1.
[b]Instruments that reached consensus after Delphi round 2.

for children; single leg hop (Table 3). One of the instruments reached the consensus threshold for adults; timed up and go (Table 3).

4 | DISCUSSION

In this study 11 components from the Activities & Participation category of the ICF were identified that might form the foundation for monitoring physical function in people with haemophilia. Instruments were identified for five of the eleven components: maintaining a standing position, walking long distances, walking up and downstairs, hopping and squatting. Two of these components, walking long distances and hopping were identified by children and adults with haemophilia as two activities they had the most difficulty performing. International physiotherapists were only able to identify performance-based tests that were practical and useful in a clinical setting for 5 of the 11 original Activities and Participation ICF components. They identified five performance-based instruments for use in children and adults, one for children only and one for adults only. One leg balance, tandem stance, 6-min walk test, timed up and down stairs and 30-s sit to stand were selected for children and adults with haemophilia. Single leg hop was chosen to monitor physical function in children only and timed up and go for adults only. To our knowledge, this is the first time that a set of performance-based outcomes have been identified to monitor physical function in people with haemophilia.

Recent studies in persons with haemophilia suggest some of these tests; one leg balance,[25–32] 6-min walk test,[26,30,33–37] timed up and down stairs[30,34] and timed up and go[38–46] may be responsive for monitoring physical function in people with haemophilia. However, confirmation of psychometric properties in people with haemophilia, such as test-retest repeatability, validity and minimal clinical important differences are required before recommendations can be made about longitudinal clinical use for all ages.

Standardised, validated assessment of observed and self-reported outcomes of activities has been recommended as essential for the clinical management of people with haemophilia by an international multidisciplinary group of clinicians.[21] The FISH and Hemophilia Activities List (HAL and pedHAL) were suggested as the recommended outcomes. The FISH is an objective assessment scored on an ordinal scale and the HAL/pedHAL are self-reported questionnaires. However, these instruments have limitations in terms of ceiling

and floor effects as well as inability to discriminate differences in actual execution of a task or action and capacity to participate or be involved in life situations.[16–17,21] Our approach to systematically review performance-based instruments in all musculoskeletal conditions identified objective instruments that may be suitable for all ages and stages of arthropathy once safety and acceptability are confirmed. As the instruments identified are assessed on a continuous scale, they are unlikely to be limited by ceiling effects.

Iorio and colleagues[47] recently published a core outcome set for gene therapy in haemophilia. The coreHEM aimed to identify outcomes to evaluate efficacy, safety, comparative effectiveness and value of gene therapy for haemophilia with the explicit objective of supporting all steps in the life cycle of drug development from clinical development through to market access. Frequency of bleeds, factor activity level, duration of expression, chronic pain, utilisation of healthcare system and mental health were the key clinical outcomes identified. Subsequently, Dover and colleagues[12] reported the outcome of a consensus process defining a core set of outcome measures based on the WHO-ICF framework. Using a modified nominal groups process involving clinicians and people with haemophilia they reported treatment satisfaction, joint health, access to treatment, treatment adherence and generic performance based physical function as core outcomes in children with haemophilia. In adults, Dover et al,[12] reported total bleeding events, the EuroQol five dimensions, treatment adherence, joint health and number and location of bleeds per unit time as core outcomes in adults. Van Balen[13] recently reported ten health outcomes relevant to people with haemophilia: cure, impact of disease on life expectancy, ability to engage in normal daily activities, severe bleeding episodes, number of days lost from school or work, chronic pain, disease and treatment complications, sustainability of physical functioning, social functioning and mental health. Our set of outcomes compliments the coreHEM outcomes[47] by providing a set of outcomes to support evaluation of the effectiveness of new treatments on relevant physical health outcomes, and builds on the generalised recommendations of Dover et al[12] and van Balen et al[13] by identifying a specific set of core instruments that measure objective performance-based function as well as the maintenance of physical function.

The structured consensus-based, decision analysis approach and use of the WHO-ICF framework, together with instrument selection based on empirical evidence, the Delphi process, patient involvement and clinicians who were active in haemophilia clinical care from multiple nations are strengths of our study. Inclusion of 26 physiotherapists with more than 1 year of clinical experience who treated patients across all age groups suggests the findings reflect the whole disease range. Furthermore, the process benefited from inclusion of research methods specialists in the advisory group.

Nonetheless, our study has a number of limitations. Participants in the advisory group and the Delphi process did not include other healthcare professionals from the multidisciplinary team. They were predominantly physiotherapists from high resource countries and English literate and as a result the findings may be more relevant to people with less impairment. We did not translate the Delphi survey into other languages. There is a lack of representation for under-resourced areas in this study. This requires further collaboration and research. To date, the views of people with haemophilia have been constrained to the perceptions of the Activities and Participation component of the WHO-ICF selected by the AG. Future work should focus on collaboration as to which core instruments offer meaningful information for patients with haemophilia.

No measures for upper limb and lower limb complex tasks were identified in the literature. This is an area that requires further research, given the presence of elbow arthropathy in patients with haemophilia and the functional impairments it imposes. Currently, the sensitivity and specificity of the instruments in terms of sustainability of physical function and health is currently not known and is required before these instruments can be recommended. Finally, we acknowledge that instruments were not identified for six of the components identified from the WHO-ICF: walking on different surfaces; running; jumping; kneeling; undertaking a complex upperlimb task and undertaking a complex lower limb task.

Further work is needed to identify valid and meaningful instruments for these components of activity.

5 | CONCLUSION

Rapid medical advances in haemophilia care demand performance measures that are sensitive and meaningful to both clinician and patient. This study is the first step in defining a core set of performance-based instruments to monitor physical health and sustainability of physical function outcomes in people with haemophilia. Establishing the psychometric properties of the identified instruments and whether they are meaningful to people with haemophilia is essential and is currently being investigated.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the project, the data interpretation, writing and approving the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [DS], upon reasonable request.

ETHICS STATEMENT

The project was reviewed and approved by the Research and Innovation Board, East Kent Hospitals University NHS Foundation Trust as not requiring further review by a research ethics committee (Reference: 2022/GAP/34).

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REFERENCES

1. Stephensen D, Bladen M, McLaughlin P. Recent advances in musculoskeletal physiotherapy for haemophilia. *TAH*. 2018;9(8):227-237.
2. Lobet S, Timmer M, Königs C, et al. The role of physiotherapy in the new treatment landscape for haemophilia. *J Clin Med*. 2021;10(13):2822. doi:10.3390/jcm10132822
3. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia panelists and co-authors. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26(Suppl 6):1-158. doi:10.1111/hae.14046
4. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12:518-525.
5. Bladen M, Main E, Hubert N, Koutoumanou E, Liesner R, Khair K. Factors affecting the Haemophilia Joint Health Score in children with severe haemophilia. *Haemophilia, Symp*. 2013;19:626-631.
6. Nijdam A, Bladen M, Hubert N, et al. Using routine Haemophilia Joint Health Score for international comparisons of haemophilia outcome: standardization is needed. *Haemophilia*. 2016;22:142-147.
7. Fischer K, Nijdam A, Holmström M, et al. Evaluating outcome of prophylaxis in haemophilia: objective and self-reported instruments should be combined. *Haemophilia*. 2016;22:e80-e86. https://doi.org/10.1111/hae.12901
8. Altisent C, Martorell M, Crespo A, Casas L, Torrents C, Parra R. Early prophylaxis in children with severe haemophilia A: clinical and ultrasound imaging outcomes. *Haemophilia*. 2016;22:218-224.
9. Foppen W, van der Schaaf IC, Fischer K. Value of routine ultrasound in detecting early joint changes in children with haemophilia using the 'Haemophilia Early Arthropathy Detection with Ultra-Sound' protocol. *Haemophilia*. 2015;22:121-125.
10. Stephensen D, Classey S, Harbidge H, Patel V, Taylor S, Wells A. Physiotherapist inter-rater reliability of the Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) protocol. *Haemophilia*. 2018. doi:10.1111/hae.13440. [Epub ahead of print].
11. Timmer MA, Foppen W, Schutgens RE, Pisters MF, Fischer K. Comparing findings of routine Haemophilia Joint Health Score and Haemophilia Early Arthropathy Detection with Ultrasound assessments in adults with haemophilia. *Haemophilia, Symp*. 2017;23:141-143.
12. Dover S, Blanchette VS, Srivastava A, Fischer K, Abad A, Feldman BM. Clinical outcomes in hemophilia: towards development of a core set of standardized outcome measures for research. *Res Pract Thromb Haemost*. 2020;4:652-658. doi:10.1002/rth2.12331
13. van Balen EC, O'Mahony B, Cnossen MH, et al. Patient-relevant health outcomes for hemophilia care: development of an international standard outcomes set. *Res Pract Thromb Haemost*. 2021;5:e12488. doi:10.1002/rth2.12488
14. World Health Organization. *International Classification of Functioning, Disability and Health (ICF)*. World Health Organization; 2001
15. van Genderen FR, van Meeteren NL, van der Bom JG, et al. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia*. 2004;10(5):565-571.
16. Kuijlaars IAR, van der Net J, Buckner TW, Kempton CL, Schutgens REG, Fischer K. Shortening the Haemophilia Activities List (HAL) from 42 items to 18 items. *Haemophilia*. 2021;27(6):1062-1070. doi:10.1111/hae.14408
17. Kuijlaars IAR, van der Net J, Schutgens REG, Fischer K. The Paediatric Haemophilia Activities List (pedHAL) in routine assessment: changes over time, child-parent agreement and informative domains. *Haemophilia*. 2019;25(6):953-959. doi:10.1111/hae.13835
18. Lawson C, Eyre ELJ, Tallis J, Watts M, Duncan MJ. Identifying actual and perceived motor competence based profiles among children. *J Sports Sci*. 2021;40(6):621-629.
19. Kasper JD, Chan KS, Freedman VA. Measuring physical capacity. *J Aging Health*. 2017;29(2):289-309.
20. Poonnoose PM, Thomas R, Bhattacharjee S, Shyamkumar NK, Manigandan C, Srivastava A. Functional Independence Score in Haemophilia (FISH): a new performance based instrument to measure disability. *Haemophilia*. 2005;11:598-602.
21. Fischer K, Poonnoose P, Dunn AL, et al. Choosing outcome assessment tools in haemophilia care and research: a multidisciplinary perspective. *Haemophilia*. 2017;23:11-24. doi:https://doi.org/10.1111/hae.13088
22. Dobson F, Bennell KL, Hinman RS, Abbott JH, Roos EW. Recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *OARSI*. 2023. Accessed 20th 2023. https://oarsi.org/research-oarsi-success/physical-performance-measures
23. Jiménez-Yuste V, de la Corte-Rodríguez H, Álvarez-Román MT, et al. Ultrasound evaluation of joint damage and disease activity in adult patients with severe haemophilia A using the HEAD-US system. *Haemophilia*. 2021;27(3):479-487.
24. Prinsen CA, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a 'Core Outcome Set'—a practical guideline. *Trials*. 2016;17:449.
25. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of delphi studies. *J Clin Epidemiol*. 2014;67:401-409.
26. Kennedy M, Roche S, McGowan M, et al. Physical activity, physical fitness and cardiometabolic risk amongst adults with moderate and severe haemophilia. *Haemophilia*. 2023;29(1):72-83.
27. Cruz-Montecinos C, Carrasco JJ, Guzmán-González B, et al. Effects of performing dual tasks on postural sway and postural control complexity in people with haemophilic arthropathy. *Haemophilia*. 2020;26(3):e81-e87.
28. Pérez-Alenda S, Carrasco JJ, Aguilar-Rodríguez M, et al. Balance evaluation in haemophilic preadolescent patients using Nintendo Wii Balance Board®. *Haemophilia*. 2017;23(1):e18-e24.
29. Runkel B, Czepa D, Hilberg T. RCT of a 6-month programmed sports therapy (PST) in patients with haemophilia—Improvement of physical fitness. *Haemophilia*. 2016;22(5):765-771.
30. Stephensen D, Taylor S, Bladen M, Drechsler WI. Relationship between physical function and biomechanical gait patterns in boys with haemophilia. *Haemophilia*. 2016;22(6):e512-e518.
31. Seuser A, Boehm P, Ochs S, Trunz-Carlisi E, Halimeh S, Klamroth R. How fit are children and adolescents with haemophilia in Germany? Results of a prospective study assessing the sport-specific motor performance by means of modern test procedures of sports science. *Haemophilia*. 2015;21(4):523-529.
32. Czepa D, von Mackensen S, Hilberg T. Haemophilia & Exercise Project (HEP): the impact of 1-year sports therapy programme on physical performance in adult haemophilia patients. *Haemophilia*. 2013;19(2):194-199.
33. Atay C, Tarakcı E, Yeldan İ, Zülfikar B. The effects of exercise training on physical activity level, daily living activities, and participation in children with hemophilia. *Turk Arch Pediatr*. 2023;58(3):274-281.
34. Bladen M, Carroll L, Dodd C, et al. Results of feasibility and safety of randomised controlled trial of a musculoskeletal exercise intervention versus usual care for children with haemophilia. *Haemophilia*. 2020;26(5):e223-e225.
35. Donoso-Úbeda E, Pérez-Llanes R, Meroño-Gallut J, Ucero-Lozano R, Cuesta-Barriuso R. Self-induced myofascial release in patients with

hemophilic ankle arthropathy: a pilot observational study. *Life(Basel)*. 2022;12(12):2008.
36. El-Shamy SM, Abdelaal AAM. Efficacy of pulsed high-intensity laser therapy on pain, functional capacity, and gait in children with haemophilic arthropathy. *Disabil Rehabil*. 2018;40(4):462-468.
37. Eid MA, Aly SM. LASER versus electromagnetic field in treatment of hemarthrosis in children with hemophilia. *Lasers Med Sci*. 2015;30(8):2179-2187.
38. Chantrain VA, Guillaume S, Foubert A, et al. Discordance between joint pain and imagery severity in the ankle joint and contributors of lower limb activity limitations in adults with haemophilia: a cross-sectional study. *Haemophilia*. 2023;29(2):648-657.
39. Gönen T, Yakut Y, Akbayram S. The effects of close kinetic chain exercises on proprioception and physical activity level in pediatric patients with hemophilia. *Haemophilia*. 2022;28(6):e189-e198.
40. Roussel NA, Chantrain VA, Foubert A, et al. Gaining more insight into ankle pain in haemophilia: a study exploring pain, structural and functional evaluation of the ankle joint. *Haemophilia*. 2022;28(3):480-490.
41. Taylor S, Pemberton S, Barker K. Validity of the four-square step test in persons with haemophilia. *Haemophilia*. 2022;28(2):334-342.
42. Tat NM, Can F, Sasmaz HI, Tat AM, Antmen AB. The effects of manual therapy on musculoskeletal system, functional level, joint health and kinesiophobia in young adults with severe haemophilia: a randomized pilot study. *Haemophilia*. 2021;27(2):e230-e238.
43. Calatayud J, Pérez-Alenda S, Carrasco JJ, et al. Safety and effectiveness of progressive moderate-to-vigorous intensity elastic resistance training on physical function and pain in people with hemophilia. *Phys Ther*. 2020;100(9):1632-1644.
44. Lobet S, Meité N, Koninckx MI, et al. Implementation and assessment of a self- and community-based rehabilitation programme in patients with haemophilia from Côte d'Ivoire. *Haemophilia*. 2019;25(5):859-866.
45. Digby-Bowl CJ, Brown MB, Stephensen D. Exploring postural stability in haemophilia: comparison between older males with and without haemophilia—a pilot study. *J Funct Morphol Kinesiol*. 2018;3(10). doi:10.3390/jfmk3010010
46. Baumgardner J, Elon L, Antun A, et al. Physical activity and functional abilities in adult males with haemophilia: a cross-sectional survey from a single US haemophilia treatment centre. *Haemophilia*. 2013;19(4):551-557.
47. Iorio A, Skinner MW, Clearfield E, et al. for the coreHEM panel. Core outcome set for gene therapy in haemophilia: results of the coreHEM multistakeholder project. *Haemophilia*. 2018;24:e167-e172. doi:10.1111/hae.13504

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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