BMJ Open Sport & Exercise Medicine

Improving functional capacity in haemophilia through adapted physical activity: a pilot study protocol

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To cite: Pinelli E, Valdrè L, Piscitelli L, *et al*. Improving functional capacity in haemophilia through adapted physical activity: a pilot study protocol. *BMJ Open Sport & Exercise Medicine* 2025;**11**:e002494. doi:10.1136/bmjsem-2025-002494

Accepted 16 February 2025

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ABSTRACT

Haemophilia, a genetic disorder characterised by deficient clotting factors, often leads to musculoskeletal complications such as haemophilic arthropathy. These complications result in reduced functional capacity, muscle weakness and kinesiophobia, which further exacerbate physical inactivity and psychological distress. The World Federation of Haemophilia recommends including regular physical activity in the management plans for individuals with haemophilia, emphasising its benefits for bone and muscle strengthening, improved coordination, maintenance of healthy body weight and enhanced self-esteem.

This study aims to evaluate the effectiveness of an adapted physical activity (APA) programme in individuals with haemophilia. The primary objective is to analyse changes in functional capacity following participants' completion of the exercise programme. Additionally, the study evaluates the programme's impact on joint mobility, kinesiophobia, limitations in daily activities and static and dynamic balance. It is hypothesised that the APA programme may improve or maintain joint mobility, increase muscle strength, enhance proprioception and reduce fear of movement (kinesiophobia), thus contributing to an overall improvement in physical function in participants.

The intervention is carefully designed to prioritise safety and proper execution. It incorporates low-impact, low- to moderate-intensity exercises tailored to individual joint functionality. Supervised by qualified professionals, the programme aims to minimise excessive joint loading and prevent haemarthrosis while promoting muscle strength, joint mobility and proprioception. The programme is structured into 1-hour sessions held twice weekly for 6 months. Each session has three sections: warm-up, the main part (strength, mobility, proprioception and balance exercises) and cool-down.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Repeated joint bleeding often leads to haemophilic arthropathy, a degenerative condition that severely impacts joint function, mobility and quality of life.
⇒ Physical inactivity leads to further deterioration in musculoskeletal health, with consequences not only physically but also psychologically and socially, such as increased isolation and reduced self-esteem.
⇒ Fear of movement and inactivity exacerbate the cycle of disability and psychological distress in individuals with haemophilia.

WHAT THIS STUDY ADDS

⇒ This study evaluates the effectiveness of a structured adapted physical activity (APA) programme in improving functional capacity and joint mobility and reducing kinesiophobia.
⇒ It provides insights into the impact of tailored exercise programmes on both physical and fear of movement outcomes in individuals with haemophilia.
⇒ The use of accessible, low-cost tools ensures the programme's scalability and applicability in diverse healthcare settings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings could inform the development of evidence-based guidelines for incorporating APA into standard haemophilia care.
⇒ Demonstrating the programme's feasibility and safety could encourage policymakers to support and fund structured APA interventions in clinical practice.

INTRODUCTION

Haemophilia is a rare genetic disorder characterised by a deficiency in blood clotting factors (factor VIII and IX in haemophilia A and B, respectively), predisposing affected individuals to spontaneous bleeding or bleeding from even minor trauma.[1] Although the standard of care for all patients with severe haemophilia today is prophylaxis (regular replacement therapy with clotting factor concentrates or non-replacement therapy) to prevent bleeding and musculoskeletal complications, the development of arthropathy is still a problem. In addition, many adult patients have not had access to regular prophylaxis, especially during childhood and young age.

Repeated bleeding, especially in joints, leads over time to the development of haemophilic

arthropathy, a chronic and degenerative condition that severely impacts the quality of life for these patients. The joints most commonly affected include knees, ankles and elbows—structures that, once damaged, make it difficult to maintain adequate functional mobility.[2] Consequently, the quality of life for haemophilia patients is greatly affected by physical limitations and the need to manage painful and debilitating symptoms related to the condition.[3]

From a functional perspective, individuals with haemophilia often exhibit reduced muscle strength and low aerobic and anaerobic endurance. Proprioception, the ability to perceive and control the position and movement of one's body in space, is also compromised. The combination of these issues leads to a significant reduction in movement capacity and alterations in postural balance.[4–11] Impaired balance and muscle weakness increase the risk of falls—a particularly concerning scenario for haemophilia patients, as a fall can lead to bleeding with potentially severe outcomes. Additionally, the fear of falling and incurring new bleeds can create a condition known as 'kinesiophobia', or fear of movement, which further aggravates the sedentary lifestyle observed in haemophilia patients.[2 12–14]

Physical inactivity leads to further deterioration in musculoskeletal health, with consequences not only physically but also psychologically and socially, such as increased isolation and reduced self-esteem. This vicious cycle of immobility, loss of function and fear of movement contributes to increased disability associated with the condition and leads to an escalation in healthcare costs related to secondary complications.[6 12–14] In this context, physical activity emerges as a key element in breaking this negative cycle. Targeted physical exercise can improve the physical, psychological and social conditions of individuals with haemophilia by increasing muscle strength, aerobic capacity and joint stability.[4 12 15 16]

The importance of adapted physical activity (APA) has recently been widely recognised for haemophilia patients. Several studies have shown that exercise, when supervised by specialised professionals, is safe and can be highly beneficial, significantly improving the quality of life for these patients.[17] For those with significant musculoskeletal issues, a resistance exercise programme is essential to help maintain and improve bone density, thereby limiting the progression of osteopenia—a common condition in haemophilia patients who do not engage in sufficient physical activity. Moreover, APA contributes to maintaining muscle strength, joint function and range of motion, promoting joint circulation, which nourishes cartilage and may prevent further joint deterioration.[8–12]

Promoting regular and structured physical activity for haemophilia patients is not solely aimed at improving physical conditions. An adapted, supervised exercise programme has also been shown to have a positive impact on psychological well-being and social interaction, contributing to an overall improvement in quality of life[10 18 19]

The World Federation of Haemophilia supports this evidence, recommending regular physical activity in the management plans for individuals with haemophilia. It emphasises its benefits on bone and muscle strengthening, improved coordination, maintenance of healthy body weight and enhanced self-esteem.

This study aims to evaluate the effectiveness of an APA programme in individuals with haemophilia. The primary objective is to analyse changes in functional capacity over time. Additionally, the study examines the programme's impact on joint mobility, kinesiophobia, limitations in daily activities and static and dynamic balance. It is hypothesised that the APA programme may improve or maintain joint mobility, increase muscle strength, improve proprioception and reduce fear of movement (kinesiophobia), thus contributing to an overall improvement in physical function in participants.

MATERIALS AND METHODS

Study design

This is an interventional prospective study. The study was approved by the Local Ethics Committee (Comitato Etico Indipendente di Area Vasta Emilia Centro, CE-AVEC) of the Emilia-Romagna Region (reference number AVEC: 37/2024/Sper/IOR).

Participant recruitment

Patients with haemophilia A or B will be recruited from the 'MEC Physio' outpatient clinic for the Physical Medicine and Rehabilitation Department haemophilic patients at the Rizzoli Orthopaedic Institute. This clinic provides specialised physiatric consultations for haemophilia patients managed by the Inherited Bleeding Disorders Unit of the IRCCS University Hospital of Bologna, which will continue to oversee their haematological monitoring as per clinical practice.

All patients will be advised during the study to maintain their pharmacological therapy as their physician prescribes. The research staff will evaluate all recruited subjects at baseline, 3 months and 6 months.

The research staff will propose participation in the study to all people with haemophilia after verifying the presence of inclusion/exclusion criteria. Subjects will subsequently receive information about the study and will be asked to sign the informed consent form. Subjects will be enrolled after signing the informed consent form.

Inclusion and exclusion procedures

A medical doctor will verify the inclusion/exclusion criteria (table 1) associated with age, diagnosis and comorbid conditions during the baseline assessment. In contrast, criteria linked to motor function and physical activity will be verified by a researcher in

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Diagnosis of haemophilia A or B; ► Signed informed consent; ► Availability of a medical certificate for non-competitive activity; ► Both sexes, aged between 18 and 80 years.	► Active bleeding ► Severe joint deformities that prevent exercise ► Any other condition that the physicians of the Physical Medicine and Rehabilitation Department and the Congenital Haemorrhagic Diseases Unit deem contraindicated for participation in a low/moderate-intensity exercise programme. Severe impairment of communicative and/or sensory functions to the extent that understanding or executing trainer instructions is impossible (dementia, aphasia, blindness and deafness). ► Heart failure (NYHA class >2) ► Unstable angina ► Lung disease requiring oxygen therapy ► Symptomatic peripheral artery disease ► Myocardial infarction or hospitalisation within the previous 6 months ► Hypertension is poorly controlled with medication (diastolic >95 mm Hg, systolic >160 mm Hg) ► Relevant neurological conditions compromising motor or cognitive function ► Any other condition deemed contraindicated for participation in a mild/moderate-intensity exercise programme by the attending physician (MD) ► Engagement in structured physical activity ► Inability to understand the Italian language.

NYHA, New York Heart Association.

sports science. Personal information (first and last name, address, telephone number(s)) will only be recorded on the informed consent form, together with a study code, if the subject is eligible for the study. Subjects will be identified by their assigned study code on all other forms used in the study.

Sample size

The sample size was calculated through a priori power analysis based on the study's primary outcome, namely the distance covered in the 6-minute walking test (6MWT), evaluated before the intervention with the physical activity protocol and at a 6-month follow-up. A recent interventional pilot study with a similar rationale found in the literature was used as a reference.[18] In that study, which used the 6MWT with assessments immediately postintervention and at a 6-month follow-up, an SD of 21.1 m at follow-up and 18.8 m at baseline was reported, along with a mean difference between baseline and 6-month follow-up of 23.9 m. From this, an effect size of 1.19 (considered 'high') was derived. To maintain a more conservative sample estimate, a smaller effect size of 0.8 was assumed for this study, lower than that derived from the literature. The power analysis was thus conducted using a one-tailed paired t-test with an alpha error of 0.05 and a sample power (1-β) of 0.8, resulting in a minimum sample size of 12 patients, in line with current literature. A 25% dropout rate was then considered, leading to a minimum estimated sample size of 16 patients.

Data collection and measures

The instruments used to collect the primary and secondary outcome measures and the timing of their use are summarised in table 2.

Primary outcome

The primary endpoint is the change in functional capacity, calculated as the difference between baseline and the 3- and 6-month assessments by the 6-minute walking test (6MWT)[20] measured with the G-Walk (BTS Bioengineering S.p.A).

Secondary outcome

The secondary endpoints of this study include a series of validated assessments administered at baseline, 3 and 6 months. These evaluations aim to capture a comprehensive view of each patient's functional capacity, joint mobility, kinesiophobia, limitations in daily living activities and static and dynamic balance.

To assess the degree of independence patients have in performing daily living activities, a standardised questionnaire is used to evaluate essential tasks such as personal hygiene, eating, dressing, moving from a chair, squatting, walking, climbing stairs and running. This is measured

Table 2 Outcome assessment

	Baseline (T0)	3 months (T1)	6 months (T2)
Sociodemographic parameters			
Date of birth	X		
Gender	X		
Anthropometric parameters			
Weight (kg)	X		
Height (m)	X		
Assessment scales			
6MWT	X	X	X
FISH	X	X	X
HJHS	X	X	X
TSK	X	X	X
HAL	X	X	X
30CST	X	X	X
30ACT	X	X	X
MIS	X	X	X
SLST	X	X	X
TUG	X	X	X
VAS	X	X	X
Exercise programme satisfaction		X	X

30ACT, 30" arm curl test; 30CST, 30" chair stand test; FISH, Functional Independence Score in Haemophilia; HAL, Haemophilia Activity List; HJHS, Haemophilia Joint Health Score; MIS, maximum isometric strength; 6MWT, 6-minute walking test; SLST, single leg stand test; TSK, Tampa Scale of Kinesiophobia; TUG, timed up and go; VAS, Visual Analogue Scale.

with the Functional Independence Score in Haemophilia,[21] which rates each activity according to the level of assistance required.

Joint health is another critical focus of the study, specifically in joints frequently affected by bleeding episodes in haemophilia patients, such as the knees, ankles and elbows. For this purpose, the Haemophilia Joint Health Score[22] is used, an operator-administered scale that assesses the structural and functional aspects of these key joints, providing insights into any biomechanical limitations.

Understanding the psychological impact of haemophilia on movement is also crucial. Many patients experience an intense fear of movement due to concerns about pain or injury, a condition known as kinesiophobia. To measure this fear, participants complete the Tampa Scale of Kinesiophobia,[23] an internationally recognised tool that reveals how much fear of movement influences their daily lives and potentially hinders their ability to engage in physical and social activities.

To examine the limitations in specific activities and the overall impact of haemophilia on functional capacity, the study employs a patient-completed questionnaire that covers a range of daily and recreational activities. Known as the Haemophilia Activity List,[24] this tool comprises 42 questions across seven domains: lying/sitting/kneeling/standing, leg functions, arm functions, transportation, self-care, domestic activities and leisure and sports activities. This assessment helps highlight areas where patients may struggle with independence or physical capability due to their condition.

The research team will assess muscle strength using various tools to capture a comprehensive picture of the participants' physical capacity. The 30-second chair stand test[25] will evaluate lower body strength by counting the number of times a participant can stand from a seated position within 30 s. Additionally, the 30-second arm curl test[26] will measure upper body strength by having the participant lift a specified weight a maximum number of times. The maximum isometric strength[27] of both hip and knee flexors and extensors will be measured to gain more detailed insights into muscle strength. This will be done using a handheld dynamometer, which accurately assesses the force generated by these muscle groups.

Balance will also be evaluated through standardised tests administered by the research team. The single leg stand test[28] will measure the participant's ability to maintain balance while standing on one leg, providing information about stability and postural control. The timed up and go test[29] will assess functional mobility, requiring the participant to stand up from a seated position, walk a short distance, turn and return to the seat as quickly and safely as possible.

The visual analogue scale[30] will assess pain levels in target joints. This tool, completed by the participant, provides a simple and direct way to quantify pain by marking a point along a scale that best represents their current level of discomfort in the joints most affected by haemophilia.

Each patient's adherence to the exercise programme will be monitored. Adherence will be measured as the percentage of training sessions completed relative to the total number of scheduled sessions.

Moreover, participant satisfaction with the physical activity programme will be assessed at 3 and 6 months using a specific questionnaire based on the Likert scale to evaluate adherence to the programme. Reasons for discontinuing the exercise programme will also be documented, with structured response questions completed by the patient.

Safety

Adverse clinical events (ACEs) that will occur to participants during the study will be carefully recorded. The trainer will record the ACEs that occurred during the exercise sessions at the end of each session. In the case of three consecutive absences, the coordinating centre will contact the participant by telephone to investigate whether the cause of non-attendance at the sessions was an ACE. Based on the records, ACEs will be classified

for severity (severe: if the ACE involved hospitalisation/access to the emergency room; moderate: if the ACE required the intervention of a doctor and/or modification of the usual pharmacological therapy; mild: if the ACE did not require medical intervention and/or modification of the usual pharmacological therapy), place (home: ACE occurred at home; outside: ACE exercise occurred outside the home) and apparatus (apparatus/system involved).

Exercise programme

The exercise programme aims to maintain/improve joint mobility, muscle strength and balance. The programme is structured into 1-hour sessions, held twice a week for 6 months, conducted under the supervision of highly specialised personnel and in small groups. Each session is structured into the following sections: warm-up, main part (strength, mobility, proprioception and balance exercises) and cool-down. Only common-use low-cost tools, such as elastic bands, dumbbells, mats and soft dumbbells, are used during exercise sessions. The trainer will tailor the exercise programme to the needs and preferences of the participants.

The protocol includes specific strategies to instruct participants on the correct and safe execution of the exercise, ensuring they are adequately guided throughout the entire programme. Additionally, clear criteria are defined to adjust workload and the number of repetitions, adapting them to the individual functional capacities of each participant. This approach aims to ensure proper progression in the exercise programme, maintaining an appropriate and safe level of challenge for each involved individual.

Statistical analysis

Qualitative variables will be summarised in frequency, while quantitative variables will be summarised in terms of mean and standard deviation (or median and IQR) for the three assessment times. The Friedman non-parametric analysis of variance for repeated measures will be used to evaluate the progression of scale scores over time (baseline, 6 weeks and 3 months) at a probability level of 0.05. Additionally, the Wilcoxon non-parametric posthoc test will be used for multiple comparisons: from baseline to 6 weeks and from 6 weeks to 3 months, with a probability level of $p<0.025$. Spearman's correlation (ρ) will evaluate potential relationships between demographic factors and outcomes. The strength of the association will be defined as weak for $\rho<0.30$, moderate for $\rho=0.30–0.50$ and strong for $\rho>0.50$.

Since the data will be collected by research staff, who are adequately trained in administering the tests, we anticipate a low probability of missing data. However, should the missing data occur, we have planned to use clustering-based imputation. This method will allow us to estimate missing questionnaire scores for participants with incomplete data. With clustering-based imputation, participants will be grouped into clusters based on their responses to the questionnaire. If a participant is missing only some responses within the questionnaire, we can estimate the missing responses using the cluster, applying it to the available complete responses. However, if a participant is missing data for the entire questionnaire, we cannot estimate the missing responses using clustering-based imputation. In this case, the participant will be excluded from the analysis, as it is impossible to estimate missing data without complete information on the questionnaire. This approach will allow us to effectively manage missing data, ensuring the integrity of our results.

DISCUSSION

This protocol explores whether a structured exercise programme can enhance functional capacity in patients with haemophilia. The intervention is carefully designed to prioritise safety and proper execution, incorporating low-impact, low- to moderate-intensity exercises tailored to individual joint functionality. Supervised by qualified professionals, the programme aims to minimise excessive joint loading and prevent haemarthrosis while promoting muscle strength, joint mobility and proprioception.

A significant challenge this study addresses is participant adherence to the exercise programme. People with haemophilia often face barriers to physical activity, including pain, fear of injury and logistical obstacles. This study aims to gather insights that could inform future strategies for sustained engagement in similar interventions by closely monitoring adherence rates and investigating reasons for non-compliance or dropout. Understanding these adherence challenges is crucial, as long-term commitment to APA is necessary for substantial health improvements and sustained functional gains.

This study has some limitations, including the absence of a control group. This decision was driven by the high heterogeneity of the sample of individuals with haemophilia, which made it challenging to divide participants into comparable groups. While this limitation is acceptable in the context of a pilot study, future research would benefit from adopting a randomised controlled trial design to enhance methodological rigour. Further studies with larger and more homogeneous samples would be essential to confirm these preliminary findings and explore APA interventions' long-term effects in this population.

This study also highlights the value of a multidisciplinary approach in managing haemophilia, integrating the expertise of physiatrists, physical therapists, haematologists, internal medicine specialists, doctors and exercise scientists. Such collaboration ensures that the exercise programme is safe and tailored to the specific functional limitations and health risks faced by patients with haemophilia. By fostering a supportive environment for physical activity, this approach may help break the cycle of inactivity and functional decline often observed in this population, paving the way for improved physical and psychological well-being.

CONCLUSION

This protocol represents a step towards integrating structured APA into standard haemophilia care. Focusing on both physical functionality and quality of life, it underscores the potential of exercise to complement pharmacological treatments and address broader aspects of health in haemophilia management. The insights gained from this study could guide the development of future exercise guidelines for haemophilia patients, ultimately supporting a more active and independent lifestyle for individuals affected by this condition.

Contributors Study conception and design: LB, EP, LV, GMF, LP and MGB. Writing—original draft preparation: EP. Supervision: LB. All authors read and agreed to the published version of the manuscript. The guarantor is GMF.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study protocol was approved by Comitato Etico Indipendente di Area Vasta Emilia Centro, CE-AVEC of the Emilia-Romagna Region (reference number AVEC: 37/2024/Sper/IOR). Participants gave informed consent to participate in the study before taking part. The study processes will follow the study protocol, and any protocol amendments will be submitted to the Bioethics Committee of the University of Bologna. All documents will be kept confidential.The study protocol will be published in an academic journal. The study results will be disseminated via conference presentations, reports to the grant funder, websites or social media and publications in peer-reviewed journals. The presentation of the study will keep the anonymity of participants.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. No data are available. NA.

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