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ORIGINAL ARTICLE

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Expert United Kingdom consensus on the preservation of joint health in people with moderate and severe haemophilia A: A modified Delphi panel

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Abstract

Aim: For people with haemophilia A (PwHA), bleeding in the joints leads to joint damage and haemophilia-related arthropathy, impacting range of motion and life expectancy. Existing guidelines for managing haemophilia A support healthcare professionals (HCPs) and PwHA in their efforts to preserve joint health. However, such guidance should be reviewed, considering emerging evidence and consensus as presented in this manuscript.

Methods: Fifteen HCPs experienced in the management of PwHA in the UK participated in a three-round Delphi panel. Consensus was defined at ≥70% of panellists agreeing or disagreeing for Likert-scale questions, and ≥70% selecting the same option for multiple- or single-choice questions. Questions not reaching consensus were revised for the next round.

Results: 26.8% (11/41), 44.8% (13/29) and 93.3% (14/15) of statements reached consensus in Rounds 1, 2 and 3, respectively. HCPs agreed that prophylaxis should be offered to patients with a baseline factor VIII (FVIII) level of ≤5 IU/dL and that, where there is no treatment burden, the aim of prophylaxis should be to achieve a trough FVIII level ≥15 IU/dL and maintain a longer period with FVIII levels of ≥20–30 IU/dL to provide better bleed protection. The aspirational goal for PwHA is to prevent all joint bleeds, which may be achieved by maintaining normalised (50–150 IU/dL) FVIII levels.

Conclusion: The panel of experts were largely aligned on approaches to preserving joint health in PwHA, and this consensus may help guide HCPs.

KEYWORDS
Delphi method, haemophilia A, joint pain, joints, United Kingdom

1 | INTRODUCTION

Haemophilia A (HA) is a rare, inherited bleeding disorder characterised by a reduced level of endogenous factor VIII (FVIII) compared with the general population.[1,2] The World Federation of Hemophilia (WFH) classifies moderate HA as a baseline FVIII level of 1—5 international units per decilitre (IU/dL), and severe HA as a baseline FVIII level of <1 IU/dL.[2]

In people with severe HA (PwSHA), more than 90% of bleeding episodes occur in joints (haemarthrosis), commonly the ankles, knees and elbows.[3] Haemarthrosis results in acute pain and swelling, triggering inflammation and synovial hypertrophy, leading to joint damage.[4] Damage to cartilage and bone culminates in haemophilia-related arthropathy, limiting movement in affected joints and impacting quality of life in people with HA (PwHA).[5-8] Individuals may develop joint arthropathy despite maintaining excellent bleeding outcomes, suggesting possible asymptomatic bleeds, termed 'micro' or 'subclinical' bleeds.[9,10]

The THUNDER study reported data from the UK HaemTrack application, illustrating that in 2015, 94.9% of Haemtrack-compliant children less than 12 years old with severe HA were receiving regular prophylaxis, compared with 68.8% of Haemtrack-compliant children with moderate HA.[11] Regardless of prophylactic treatment, the Haemophilia Joint Health Score (HJHS) of children with moderate HA was similar to those with severe HA, suggesting higher baseline FVIII levels in people with moderate HA (PwMHA) may provide false reassurances of bleed protection, leading to prophylaxis not being started pre-emptively.[11–13] This study also concluded that HJHS worsened progressively with age in PwSHA and PwMHA, highlighting the progressive nature of HA and that historical approaches to treatment have been insufficient in preserving joint health.[11]

The current standard of care in the UK for PwSHA, and PwMHA with a bleeding phenotype, is prophylactic replacement therapy with FVIII or non-factor-based therapies.[13,14] Prophylaxis with FVIII therapies aims to elevate the individual's trough FVIII level to prevent joint bleeding and associated synovitis; British Society for Haematology (BSH) guidance has suggested a trough FVIII level of >3 IU/dL with prophylaxis may be required to achieve this.[5,13,14] Considering the history of HA management, treatment goals have evolved from achieving normal life expectancy to preserving joint health, with an aim of decreasing spontaneous joint bleeds and reducing joint impairment.[8] Although the introduction of prophylaxis has improved outcomes for PwHA, standard of care treatment in the UK often only achieves decreased, rather than zero, joint bleeds, leading to impaired joint health for many individuals.[8,15] Furthermore, adherence to prophylaxis may be influenced by the perception that delivering more intensive and effective prophylaxis is limited by the burden of treatment.[2] Novel, less burdensome treatment approaches are needed to further raise the standard of care for PwHA, bringing them closer to the ultimate goal of normal haemostasis (Figure 1).[8]

While existing guidelines for clinicians in the UK identify approaches for preserving joint health in PwMHA and PwSHA,[2,12,13] the expert consensus presented here may provide further guidance for clinical practice. In this modified Delphi panel, conducted between September–November 2022, we sought to establish expert consensus on the best approaches to preserving joint health in PwMHA and PwSHA, through two objectives:

1. To understand how health care professionals (HCPs) identify and treat PwMHA who require prophylaxis, and PwSHA who may require enhanced or elevated protection to preserve their joint health;

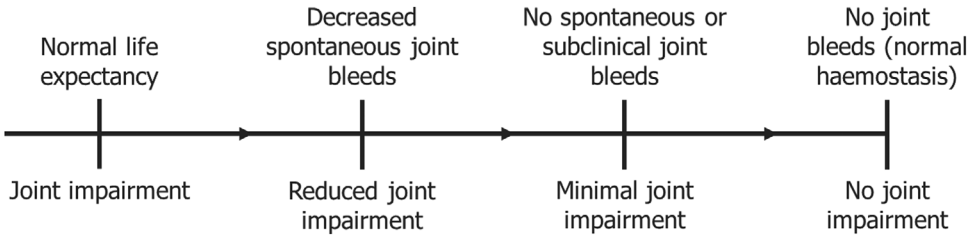

FIGURE 1 Evolution of treatment goals for people with haemophilia A. Adapted from Skinner MW et al. Haemophilia 2020;26:17–24.[8]

2. To understand the burden of disease and unmet needs, as perceived by HCPs, in individuals with moderate and severe HA.

Although HA may also be managed through non-factor treatments, with different considerations and approaches to preserving joint health, the scope of this study was FVIII therapy only.

2 | MATERIALS AND METHODS

2.1 | Delphi panellists

Three HCPs (ML, JM, and PM) were invited by the Sponsor (Swedish Orphan Biovitrum Ltd, Great Abington, UK, SS and AD) to form a steering committee (SC), guiding statement development alongside the Sponsor, who reviewed the questionnaires to ensure technical accuracy and regulatory compliance. To avoid bias, the SC and the Sponsor did not actively participate in the consensus gathering process.

Eligible panellists were UK-based HCPs with ≥3 years of clinical experience treating people with haemophilia. Panellists were active members of one or more relevant United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) working party (including the Advisory Committee, Musculoskeletal Working Party, Paediatric Working Party or Prophylaxis Task Force), a centre director of a UK Haemophilia Comprehensive Care Centre, a physiotherapist working at a specialist haemophilia clinic, or a nurse specialist caring for people with haemophilia. Panellists were invited via email and asked to confirm whether they wished to participate. In total, 23 HCPs were invited to participate, of whom 15 accepted.

2.2 | Study design

This study used a modified Delphi method, an iterative, anonymised approach to robustly elicit and synthesise responses over sequential survey rounds.[16,17] The decision to include a third round was decided by the SC and Sponsor, based on the previous rounds' results.

An in-person consensus meeting was held following Round 2, allowing panellists and the SC to discuss and provide additional context for statements that had not reached consensus. These statements were adapted for Round 3, held in-person during the meeting. The Sponsor attended this meeting, and reviewed the statements for technical accuracy and regulatory compliance but did not participate in discussions. One panellist was unable to attend and completed Round 3 virtually.

Each round was delivered through a web application for conducting Delphi panels, enforcing key methodological requirements such as preventing retrospective amendments to a questionnaire round. Statement types included Likert scale, single-choice (e.g., yes-no), multiple-choice, ranking, numerical and free-text. Likert scale statements were answered with a six-point scale: strongly agree, agree, slightly agree, slightly disagree, disagree or strongly disagree. An optional free-text box was included alongside all statements.

2.3 | Round 1 statement development

Round 1 statements were developed based on key literature, published guidelines on HA, and guidance from the SC and Sponsor, who also reviewed the statements.[2,12,13] Statements were grouped into seven categories: unmet need and burden of disease, current treatment goals, implementing existing guidance, target FVIII levels, personalised treatment, assessing joint health and future directions. The target population was PwMHA and PwSHA in the UK, and panellists were instructed to interpret 'moderate' HA as baseline FVIII levels between 1 and 5 IU/dL or a history of joint bleeds, and 'severe' HA as baseline FVIII levels <1 IU/dL.

2.4 | Rounds 2 and 3 statement development

Statements reaching consensus in Rounds 1 or 2 were removed from subsequent rounds. Statements close to consensus were restated or rephrased in the next round, and statements not close to achieving consensus (<60% consensus), or where subtopics were covered by rephrasing other statements, were removed from subsequent rounds. The decision to deprioritise, restate or rephrase a statement was also influenced by free-text responses. Statements that were rephrased or restated were presented in the application alongside anonymised, aggregated responses and the individual's response, to the relevant statements from the previous round.

2.5 | Statistical approach

The results from each round completed through the web-based Delphi application were analysed in Microsoft Excel. Consensus was defined

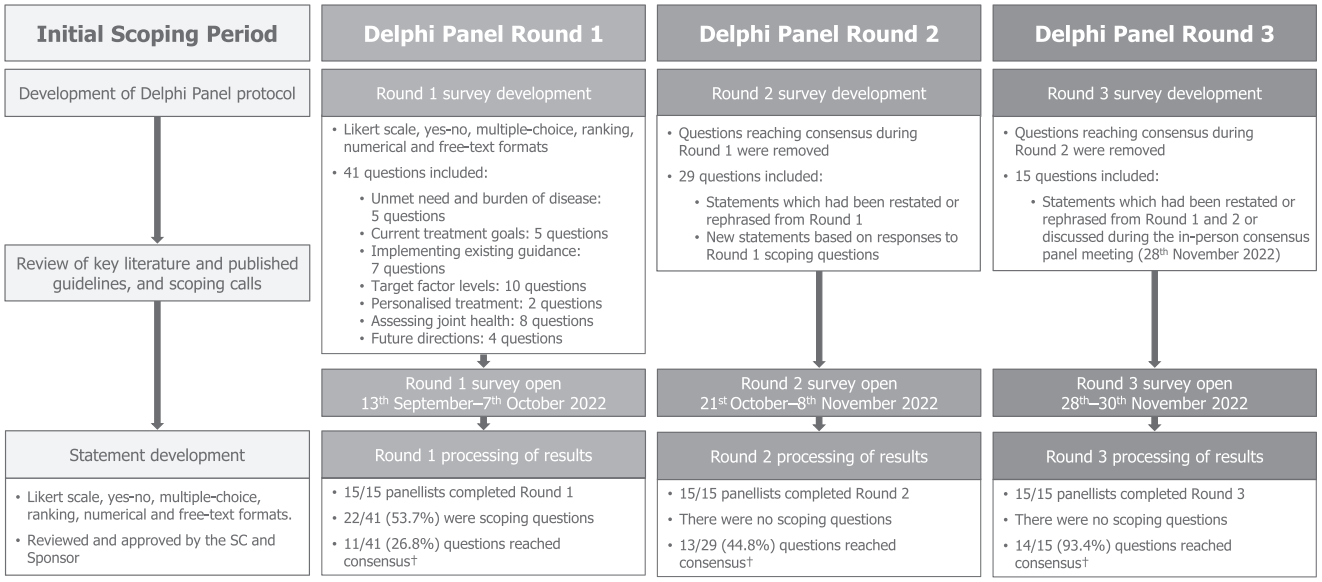

FIGURE 2 Delphi panel study design. †Consensus threshold: ≥70% agreement or ≥70% disagreement with a given statement. SC: steering committee.

at ≥70% of respondents selecting 'Strongly Agree/Agree' or 'Strongly Disagree/Disagree' for Likert scale statements, or ≥70% of panellists selecting the same option for yes-no or multiple-choice statements.[16] Ranking statements were able to reach consensus if Kendall's W ≥ 0.7. Consensus was not measured for numerical or free-text responses. Any 'Slightly Agree' or 'Slightly Disagree' responses to Likert scale statements were considered neutral and not included in the overall calculation of percentage 'agreement' or 'disagreement'.

3 | RESULTS

3.1 | Delphi rounds

Round 1 was open from 13 September to 7 October 2022, Round 2 was open between 21 October and 8 November 2022, the in-person consensus meeting took place on the 28 November 2022, and Round 3 was open from 28 to 30 November 2022 (Figure 2). Each round was completed by all 15 panellists.

Of the 41 Round 1 statements, 11 reached consensus (26.8%), 8 (19.5%) did not reach consensus and 22 (53.7%) were posed as scoping questions. From this, 20 statements were adapted or restated for Round 2, and 9 questions were added based on responses to scoping questions. In Round 2, of the 29 statements included, 13 (44.8%) reached consensus and 16 (55.2%) did not reach consensus. From this, 14 statements were adapted or restated for Round 3, and 1 question was added based on discussion at the in-person consensus meeting. Finally, in Round 3, of the 15 statements included in the questionnaire, 14 (93.3%) reached consensus and 1 (6.7%) did not reach consensus. The development process of statements between Delphi panel rounds is shown in Table S1.

3.2 | Unmet need and burden of disease

Panellists agreed a single bleed in a joint can result in long-term joint damage, and the level of joint damage following a spontaneous joint bleed is not impacted by whether the person has moderate or severe HA (Table 1). Panellists reported approximately 33% of their patients who had been on prophylaxis since childhood had developed joint arthropathy, compared with approximately 57% of patients who had only received on-demand treatment since childhood.

3.3 | Current treatment goals

Panellists agreed that a treatment goal for children and adults with HA should be preventing further spontaneous joint bleeds following diagnosis, with this goal equally important for people with moderate or severe HA (Table 2). Panellists also agreed a change in treatment regimen should be considered after a single spontaneous joint bleed.

3.4 | Implementing existing guidance

Panellists felt the guidance from the BSH on initiation of prophylaxis should be updated to include all PwMHA and should therefore include children with baseline FVIII levels of ≤5 IU/dL (Table 3).[13] Panellists agreed that clinical evidence of joint damage, without the need for imaging, is sufficient to warrant commencing tertiary prophylaxis in adults, and starting with a less intensive frequency of tertiary prophylaxis and gradually escalating the dose and/or injection frequency can be an effective way to ensure adherence. It was agreed that extended

TABLE 1 Statements and outcomes for unmet needs and burden of disease.

Statement	Question Type	Outcome
Round 1		
A single bleed in a joint can result in long-term joint damage.	Likert	**Agreement 87%**
A spontaneous joint bleed in a person with severe haemophilia A causes more damage than a spontaneous joint bleed in a person with moderate haemophilia A.	Likert	**Disagreement 73%**
What proportion of your patients with haemophilia A treated with prophylaxis experience ≥1 spontaneous joint bleed(s) per year?	Numerical	Mean 17% Median 15% Range 0–40%
What proportion of your patients who have been on prophylaxis since childhood have developed joint arthropathy?	Numerical	Mean 33% Median 30% Range 0–90%
What proportion of your patients who have only received on-demand treatment since childhood have developed joint arthropathy?	Numerical	Mean 57% Median 65% Range 0–100%

The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Numerical questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.

TABLE 2 Statements and outcomes for current treatment goals.

Statement	Question type	Outcome
Round 1		
A treatment goal for a child diagnosed with haemophilia A should be that they experience no spontaneous joint bleeds following their diagnosis and before reaching adulthood.	Likert	**Agreement 100%**
A treatment goal for adults with haemophilia A should be that they experience no further spontaneous joint bleeds.	Likert	**Agreement 100%**
Preventing spontaneous joint bleeds is as important for people with moderate haemophilia A as it is for people with severe haemophilia A.	Likert	**Agreement 100%**
What is the maximum acceptable number of spontaneous joint bleeds per year for children with haemophilia A before you would consider a change in class of treatment to be necessary?	Numerical	Mean 1.2 Median 1 Range 0–3
What is the maximum acceptable number of spontaneous joint bleeds per year for adults with haemophilia A before you would consider a change in class of treatment to be necessary?	Numerical	Mean 1.4 Median 1 Range 0–3
Round 2		
A change in treatment regimen should be considered after one spontaneous joint bleed in adults and children with haemophilia A. *Note: There may be other reasons for changing treatment class, however they are beyond the scope of this question.*	Likert	**Agreement 73%**

The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Numerical questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.

half-life (EHL) products may provide a clinical benefit over standard half-life (SHL) products. There was also consensus that, in cases of persistent non-compliance to prophylaxis by parents or carers of children with HA, safeguarding teams should be involved.

3.5 | Target factor levels

Consensus was achieved that all PwMHA should be offered prophylaxis (Table 4). Panellists agreed that, where possible, prophylaxis regimens for PwSHA should aim to prevent all bleeds from the outset, rather than aiming to initiate with a less intensive regimen and escalating prophylaxis following a bleeding episode. Consensus was obtained that the presence and extent of existing joint damage may influence the target peak and trough factor levels of prophylaxis more than the individual's baseline factor level. Furthermore, panellists agreed if there was no associated treatment burden, they would aim for a trough FVIII level of ≥15 IU/dl in all individuals, although this is unlikely to be achievable for all patients in clinical practice with currently available FVIII replacement therapy.

TABLE 3 Statements and outcomes for implementing existing guidance.

Statement	Question Type	Outcome
Round 1		
Current guidance from the British Society for Haematology (BSH) recommends primary prophylaxis should be started before or immediately after the first joint bleed, usually around 12 months of age and certainly before 24 months for paediatric patients with a baseline level 1–3 IU/dL.[13] I agree with this guidance and believe that it can be implemented in practice.	Likert	**Agreement 73%**
The guidance from the BSH on initiation of prophylaxis should be updated to include all patients with moderate haemophilia A and should therefore include children with baseline factor VIII levels of ≤5 IU/dL.[13]	Likert	**Agreement 80%**
Current guidance from the World Federation of Hemophilia (WFH) recommends that adults with haemophilia who show evidence of joint damage and have not as yet been on prophylaxis, should commence tertiary prophylaxis.[2] What would you consider to be sufficient "evidence of joint damage" to justify commencing tertiary prophylaxis?	Free text	
How do you approach commencing tertiary prophylaxis in your patients?	Free text	
Current guidance from the BSH suggests that extended half-life (EHL) products should be used only when they provide clear clinical benefit over standard half-life (SHL) products.[13] For which patients do EHL products provide a clear benefit over SHL products and how would you define "clear clinical benefit"?	Free text	
Is there any other guidance from WFH or BSH which you do not agree with or are unable to follow in practice? If you are unable to implement the guidance, what are the most significant barriers to this?	Free text	
How do you approach non-compliance or reluctance in patients who require prophylaxis to preserve their joint health? Please specify whether you are referring to paediatric patients, adult patients or both in your answer.	Free text	
Round 2		
Current guidance from the WFH recommends that adults with haemophilia who show evidence of joint damage and have not as yet been on prophylaxis, should commence tertiary prophylaxis.[2] Clinical evidence of joint damage (without imaging) is sufficient to warrant commencing tertiary prophylaxis in adults with haemophilia.	Likert	**Agreement 93%**
Starting with less intensive prophylaxis and gradually escalating the dose and/or injection frequency is an effective way to ensure adherence to treatment when commencing tertiary prophylaxis.	Likert	Consensus not reached Agree 33% Disagree 27% Neutral 40%
Current guidance from the BSH suggests that EHL products should be used only when they provide clear clinical benefit over standard half-life SHL products.[13] EHL products provide a clear clinical benefit over SHL products for all patients.	Likert	Consensus not reached Agree 33% Disagree 27% Neutral 40%
Persistent non-compliance to prophylaxis by parents/carers of children with haemophilia should be treated as a safeguarding issue.	Likert	Consensus not reached Agree 67% Disagree 0% Neutral 33%
Round 3		
When initiating tertiary prophylaxis, starting at a lower injection frequency and gradually escalating frequency can be an effective way to promote adherence to treatment.	Likert	**Agreement 93%**
EHL products may provide a 'clinical benefit' over SHL products for many patients.	Likert	**Agreement 100%**
To safeguard children, management of persistent noncompliance to prophylaxis by parents/carers of children with haemophilia A should involve support from the safeguarding team.	Likert	**Agreement 100%**

The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Free text questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.
Abbreviations: BSH, British Society for Haematology; EHL, extended half-life; SHL, standard half-life; WFH, World Federation of Hemophilia.

TABLE 4 Statements and outcomes for target factor levels.

Statement	Question type	Outcome
Round 1		
Individual pharmacokinetic studies give important information beyond achievement of target trough factor levels.	Likert	**Agreement 87%**
Current guidance from the British Society for Haematology suggests that prophylaxis should aim to prevent all bleeds, especially in young children. The prophylaxis regimen should not be based on target peak and trough factor levels but should be tailored to prevent bleeding for an individual within their usual daily activity schedule. A trough of >1 IU/dL or even >3 IU/dL may be required in many cases to achieve this. This guidance is sufficient for preventing all bleeds (not just joint bleeds).	Likert	Consensus not reached Agree 47% Disagree 40% Neutral 13%
In people with haemophilia A with pre-existing joint damage, target peak and trough factor levels are more heavily influenced by the extent of joint damage than by baseline factor level of the individual.	Likert	Consensus not reached Agree 67% Disagree 7% Neutral 26%
When personalising a prophylactic regimen for any people with haemophilia A, an assessment of the AUC, peak and trough factor levels are essential for preventing joint damage.	Likert	Consensus not reached Agree 67% Disagree 0% Neutral 33%
What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?	Numerical	Mean 17.7 IU/dL Median 15 IU/dL Range 3–50 IU/dL
What trough factor level would you consider high enough to prevent all bleeds (not just joint bleeds) in patients with haemophilia A?	Numerical	Mean 21.0 IU/dL Median 20 IU/dL Range 3–50 IU/dL
Should the factor level you indicated previously (The numerical question '*What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?'*) be the target trough factor level for all people with severe haemophilia A?	Single choice	Consensus not reached Yes 33% No 67%
Should the factor level you indicated previously (The numerical question '*What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?'*) be the target trough factor level for all people with moderate haemophilia A? ($n = 5$)[a]	Single choice	**Yes 100%**
Does the extent of pre-existing joint damage influence target trough factor levels for people with haemophilia A who are starting prophylaxis?	Single choice	**Yes 93%**
Which patients would benefit most from trough factor levels equal to your previous response? (The numerical question '*What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?'*)? ($n = 10$)[b]	Free text	
Round 2		
Den Uijl et al. (2011) observed that patients with a baseline factor level of >12 IU/dL experienced approximately zero joint bleeds. Klamroth et al. (2021) observed that of patients adhering to the elevated prophylaxis arm of the PROPEL study (target trough factor level 8–12 IU/dL), 91% experienced zero total spontaneous joint bleeds and 67% experienced zero total bleeds. In Delphi Round 1, the mean suggested trough factor level which would prevent all joint bleeds was 15.5 IU/dL.[c] [18,19] A trough factor level of ≥15 IU/dL would be an appropriate goal for all patients with haemophilia A.	Likert	Consensus not reached Agree 40% Disagree 0% Neutral 60%
A trough factor level of ≥15 IU/dL would be an appropriate goal for children and young adults with haemophilia A.	Likert	Consensus not reached Agree 50% Disagree 0% Neutral 50%
A trough factor level of ≥15 IU/dL would be an appropriate goal for all patients with haemophilia A who undergo frequent or unscheduled physical activity.	Likert	Consensus not reached Agree 67% Disagree 7% Neutral 26%
Considering treatment burden and other practical limitations, a trough factor level of ≥15 IU/dL is currently achievable for all patients in clinical practice.	Likert	Consensus not reached Agree 13% Disagree 53% Neutral 34%

(Continues)

TABLE 4 (Continued)

Statement	Question type	Outcome
In people with haemophilia A with pre-existing joint damage, target peak and trough factor levels are more heavily influenced by the extent of joint damage than by the baseline factor level of the individual.	Likert	Consensus not reached Agree 60% Disagree 0% Neutral 40%
All patients with moderate haemophilia A should be on prophylaxis in order to preserve their joint health.	Likert	Consensus not reached Agree 67% Disagree 7% Neutral 26%
Patients with severe haemophilia A who require elevated prophylaxis should be identified from diagnosis, rather than starting with a 'standardised' treatment plan and escalating if needed.	Likert	Consensus not reached Agree 40% Disagree 13% Neutral 47%
If there was no increased treatment burden, would you aim for a trough factor level of ≥15 IU/dL in all patients with haemophilia A?	Single choice	**Yes 80%**
Round 3		
Considering treatment burden and other practical limitations, a trough factor level of ≥15 IU/dL is currently achievable for all patients in clinical practice.	Likert	**Disagreement 73%**
In people with haemophilia A with pre-existing joint damage, target peak and trough factor levels are more heavily influenced by the presence and type of joint damage than by the baseline factor level of the individual.	Likert	**Agreement 87%**
All patients with moderate haemophilia A should be offered prophylaxis in order to preserve their joint health.	Likert	**Agreement 100%**
Prophylaxis regimens for patients with severe haemophilia A should be designed to prevent all bleeds from the outset, rather than aiming to initiate with a less intensive regimen with the plan to increase following a bleeding episode.	Likert	**Agreement 87%**

[a]Subset of panellists who answered 'yes' to the previous question: 'Should the factor level you indicated previously (The numerical question *"What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?"*) be the target trough factor level for all people with severe haemophilia A?'.

[b]Subset of panellists who answered 'no' to the question: 'Should the factor level you indicated previously (The numerical question *"What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?"*) be the target trough factor level for all people with severe haemophilia A?'.

[c]The mean in this statement is based on the Round 1 question: 'What trough factor level would you regard as sufficient to prevent all joint bleeds during prophylaxis for a person with haemophilia A?' This mean was updated following the closure of Round 2 in light of clarification from two panellists that their inputted answers had assumed different (international unit per millilitre (IU/mL) rather than IU/dL) units of measurement. The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Numerical and free text questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.

Abbreviations: AUC, area under the curve; BSH, British Society for Haematology.

3.6 | Personalised treatment

Panellists agreed that prophylaxis should be individualised, and assessing peak and trough factor levels is important when tailoring a prophylactic regimen (Table 5). It was also agreed that maintaining a higher area under the curve (AUC) and a greater period of time with factor levels of ≥20–30 IU/dL translates to better bleed protection.

3.7 | Assessing joint health

It was agreed that a 'problem joint' was of equal clinical relevance to a 'target joint', and any joint that has experienced one or more bleeds should be considered an 'at-risk' joint (Table 6). It was agreed that effective prophylaxis may lead to improvements in symptoms and joint function, however, consensus was not reached on whether prophylaxis could reverse damage to cartilage. Consensus was achieved on the use of MRI, HJHS and ultrasound for the assessment of joint health, though several other instruments were also used by panellists. Panellists also agreed subclinical bleeds present a challenge in preserving joint health. Consensus was achieved that the trough factor level is the most important pharmacokinetic effect when considering what injection frequency to prescribe patients, and that the maximum injection frequency for prophylaxis panellists would consider prescribing is seven per week.

3.8 | Future directions

By 2027, panellists agreed that a clinical treatment goal should be that patients experience zero spontaneous bleeds

TABLE 5 Statements and outcomes for personalised treatment.

Statement	Question type	Outcome
Round 1		
How do you identify patients with moderate haemophilia A who require prophylaxis to preserve joint health?	Free text	
How can we better identify patients with severe haemophilia A requiring elevated protection to preserve joint health from the outset, rather than gradually escalating prophylaxis?	Free text	
Round 2		
Assessing trough factor levels is important when tailoring a prophylactic regiment for people with haemophilia A.	Likert	**Agreement 100%**
Maintaining a higher area under the curve (AUC) translates to better bleed protection when treating people with haemophilia A.	Likert	**Agreement 93%**
Maintaining a greater period of time with factor levels ≥20–30 IU/dL provides better bleed protection when treating people with haemophilia A.	Likert	**Agreement 87%**
Current guidance from the British Society for Haematology (BSH) suggests that prophylaxis should aim to prevent all bleeds, especially in young children. The prophylaxis regimen should not be based on target peak and trough factor levels but should be tailored to prevent bleeding for an individual within their usual daily activity schedule.[13] This guidance gives sufficient detail to enable prevention of all bleeds (not just joint bleeds).	Likert	Consensus not reached Agree 64% Disagree 14% Neutral 22%
The AUC is a pharmacokinetic parameter, which indicates the exposure of FVIII over time. The higher the AUC value, the greater the exposure to FVIII. Valentino et al. (2016) discusses the impact this might have on joint bleeding.[20] Assessing the area under the curve is important when tailoring a prophylactic regimen for people with haemophilia A.	Likert	Consensus not reached Agree 67% Disagree 0% Neutral 33%
Assessing peak factor levels is important when tailoring a prophylactic regimen for people with haemophilia A.	Likert	Consensus not reached Agree 60% Disagree 7% Neutral 33%
Round 3		
Prophylaxis regimens should be individualised, determined jointly with the patient and based on pharmacokinetic data, patient activity and patient preferences.	Likert	**Agreement 100%**
Maximising the AUC can be beneficial when tailoring a prophylactic regimen for people with haemophilia A.	Likert	**Agreement 93%**
Assessing peak factor levels is important when tailoring a prophylactic regimen for people with haemophilia A.	Likert	**Agreement 93%**

The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Free text questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.
Abbreviations: AUC, area under the curve; BSH, British Society for Haematology; FVIII, factor VIII; PK, pharmacokinetic.

and develop no haemophilia-related arthropathy (Table 7). In addition, it was agreed that, by 2027, treatment should aim to maintain normalised factor levels, specified as 50–150 IU/dL.

4 | DISCUSSION

This modified Delphi panel gathered expert consensus on aspects of best practice for preserving joint health in PwMHA and PwSHA. These statements map to actions supporting HCPs in achieving evolving treatment goals for PwHA (Figure 3) and supplement existing guidelines.

4.1 | Moderate HA

It was agreed all PwHA with a baseline FVIII level of ≤5 IU/dL should be offered prophylaxis, regardless of previous joint bleeds. Minimising treatment burden, for example by reducing injection frequency, while maintaining efficacy, is important. However, it should be expected some PwMHA would not want to initiate prophylaxis; treatment intensity and goals should be tailored for the individual.[22] BSH guidance currently recommends commencing secondary prophylaxis in any PwHA who have a spontaneous joint bleed,[13] and additional longitudinal evidence may be needed prior to guidance being updated. In the meantime, further education for PwHA and their carers on recognising the signs and symptoms following a joint bleed may be helpful.

TABLE 6 Statements and outcomes for assessing joint health.

Statement	Question Type	Outcome
Round 1		
Subclinical bleeds present a major challenge in preserving joint health.	Likert	Consensus not reached Agree 60% Disagree 0% Neutral 40%
The definition of target joint should be updated to refer to any joint, which has experienced ≥1 spontaneous joint bleed(s) within a 6-month period.	Likert	Consensus not reached Agree 53% Disagree 7% Neutral 40%
Joint damage resulting from haemophilia can only be repaired through surgery.	Likert	Consensus not reached Agree 0% Disagree 53% Neutral 47%
When assessing joint health, which assessment instruments should be used?	Multiple choice	**MRI 100%** **HJHS 93%** **Ultrasound 93%** X-ray 67% HAL or PaedHAL 53% FISH 20% PROBE 20% SF-36 13% COPM 7% Other (specify)[a] 27%
What is the maximum injection frequency you would consider prescribing a patient in order to achieve zero joint bleeds?	Numerical	Mean 6.7 per week Median 7 per week Range 4–7 per week
How does your approach to a patient's prophylactic regimen change following a spontaneous joint bleed?	Free text	
How does your approach to a patient's prophylactic regimen change when they show signs of joint damage, but have no recorded joint bleeds?	Free text	
How do you assess the presence of subclinical bleeds and how do you approach treating them?	Free text	
Round 2		
McLaughlin et al. (2020) define a 'Problem Joint' as 'having chronic joint pain and/or limited range of movement due to compromised joint integrity (i.e., chronic synovitis and/or haemophilic arthropathy)'. 'Problem joints' are of equal clinical relevance to 'target joints'.[21]	Likert	**Agreement 87%**
The maximum injection frequency I would consider prescribing a patient in order to achieve zero joint bleeds is 7 per week.	Likert	**Agreement 73%**
Subclinical bleeds present a challenge in preserving joint health in patients with haemophilia A.	Likert	**Agreement 73%**
The definition of target joint should be updated to refer to any joint, which has experienced ≥1 spontaneous joint bleed(s) within a 6-month period.	Likert	Consensus not reached Agree 67% Disagree 0% Neutral 33%
Effective prophylaxis may cause some haemophilia-related joint damage to regress.	Likert	Consensus not reached Agree 53% Disagree 13% Neutral 34%
When considering what injection frequency to prescribe your patient, which of the following pharmacokinetic effects most impacts your decision? ($n = 11$)[b]	Multiple choice	**Trough factor level 91%** Area under the curve 45% Peak factor level 45% Time spent above ≥20–30 IU/dL 36%

(Continues)

TABLE 6 (Continued)

Statement	Question Type	Outcome
Round 3		
Any joint that has experienced one or more joint bleeds should be considered an at-risk joint.	Likert	**Agreement 100%**
Effective prophylaxis may lead to improvements in symptoms and function in relation to joint disease.	Likert	**Agreement 100%**
Effective prophylaxis can reverse joint damage (such as loss of cartilage).	Likert	Consensus not reached Agree 7% Disagree 60% Neutral 33%
When considering what injection frequency to prescribe your patient, which of the following pharmacokinetic effects most impacts your decision?	Single choice	**Trough factor level 93%**

[a]Other responses: Choklat, Measure of observed functional performance (as well as patient reported).
[b]Subset of patients who answered 'agree' or strongly agree' to the statement 'The maximum injection frequency I would consider prescribing a patient in order to achieve zero joint bleeds is 7 per week'. The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Numerical and free text questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.

TABLE 7 Statements and outcomes for future directions.

Statement	Question Type	Outcome
Round 1		
By 2027, what should be the clinical treatment goal for people with haemophilia A?	Ranking	Consensus not reached Kendall's W 0.48
How could your first-choice future treatment goal be achieved in existing clinical practice?	Free text	
Are there any clinical treatment goals not mentioned in the previous question, which you think should be a priority?	Free text	
How can the current unmet needs of people with haemophilia A be resolved through future guidelines?	Free text	
Round 2		
By 2027, a clinical treatment goal should be that patients experience zero spontaneous joint bleeds during prophylaxis.	Likert	**Agreement 100%**
By 2027, a clinical treatment goal should be that patients experience zero spontaneous bleeds (not just joint bleeds) during prophylaxis.	Likert	**Agreement 87%**
By 2027, a clinical treatment goal should be that patients develop no haemophilia-related arthropathy.	Likert	**Agreement 87%**
By 2027, a clinical treatment goal should be that patients maintain normalised factor levels for longer post-injection.	Likert	Consensus not reached Agree 53% Disagree 20% Neutral 27%
Round 3		
By 2027, a clinical treatment goal should be that patients maintain normalised (50 to 150 IU/dL) factor levels.	Likert	**Agreement 73%**

The consensus threshold was set at ≥70% agreement or ≥70% disagreement with a given statement. Free text questions were regarded as scoping questions and were not used to measure consensus but were used in Round 1 to help inform more specific questions for subsequent rounds.

4.2 | Preventing joint bleeds

Panellists agreed the first goal of treatment is that PwHA experience no further spontaneous joint bleeds, and a change in treatment regimen should be considered following a breakthrough bleed. However, for PwHA trying to achieve higher activity levels, preventing all joint bleeds may be a more pertinent goal. The median trough FVIII level suggested by panellists as sufficient to prevent all joint bleeds was 15 IU/dL (range 3–50 IU/dL) in Round 1, in keeping with literature on PK studies and PwMHA.[18,20] Panellists would aim for a trough FVIII level of ≥15 IU/dL if there was no increased treatment burden; however, this may not be feasible with current FVIII replacement therapy. The specific target trough FVIII level depends on the activity level of the individual, with larger real-world studies needed on the efficacy of a trough

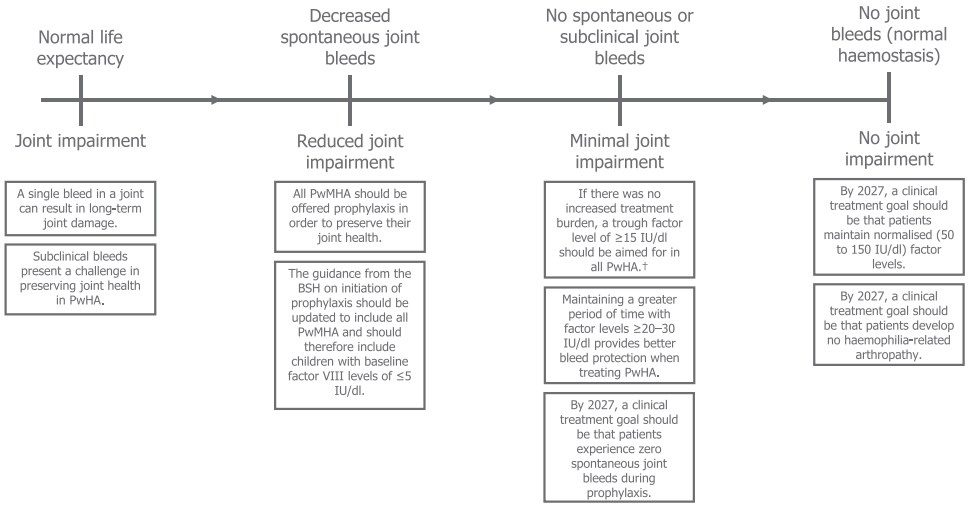

FIGURE 3 Mapping consensus statements to the evolution of treatment goals for people with haemophilia A. Adapted from Skinner MW et al. Haemophilia 2020;26:17–24.[8] Statements presented used the Likert scale and achieved 'agree' consensus. †Rephrased based on the original question: 'If there was no increased treatment burden, would you aim for a trough factor level of ≥15 IU/dl in all patients with haemophilia A?', which achieved consensus for the answer 'yes'. BSH: British Society for Haematology.

FVIII level of ≥15 IU/dL in practice. It was also agreed that effective prophylaxis may lead to improvements in joint function and symptoms, as supported by literature.[23]

Panellists discussed the potential problem of subclinical bleeds and agreed these present a challenge in preserving joint health as important causes of synovitis and arthropathy. While subclinical joint bleeds are referenced in the BSH and WFH guidelines, no formal recommendations are made for preventing them.[2,13] Studies have highlighted the importance of prophylaxis in preventing subclinical bleeds, ensuring freedom from spontaneous bleeds and associated synovitis for PwHA.[5,8]

4.3 | Tailoring prophylaxis

Trough FVIII levels were regarded as the most important pharmacokinetic effect impacting injection frequency. It was agreed that maintaining a higher AUC and a greater period of time with FVIII levels above ≥20–30 IU/dL results in better bleed protection, as supported by literature,[20] and may be particularly beneficial at times of peak activity. However, panellists noted they do not usually measure AUC in their clinics. Maintaining a higher trough FVIII level of ≥15 IU/dL together with peaks up to normal FVIII levels may be a more relevant goal for clinicians, increasing the likelihood of achieving a higher AUC and therefore greater exposure to FVIII.

The burden of prophylaxis was flagged as a barrier for some PwHA initiating tertiary prophylaxis. In this scenario, starting at a lower injection frequency and gradually escalating can be effective in promoting adherence to treatment. As protection of bleeding in childhood is so important, poor adherence to prophylaxis by the parents or carers of children should necessitate a detailed exploration of all potential prophylactic regimes to secure adherence, with persistent non-compliance eventually progressing to involve safeguarding teams.

4.4 | Future aspirations

While all panellists agreed that EHL products may provide clinical benefits over SHL products, in particular delivering equivalent or higher levels of prophylaxis with fewer injections, data from UK prescribing patterns show a significant number of PwSHA remain on SHL therapeutic agents.[24] Regular, in-depth reviews of bleed rates and adherence to prophylaxis may help ensure that all PwHA receive the therapy most likely to preserve joint function.[2] As aspirations for HA care evolve, it may be feasible to aim for zero joint bleeds for all PwHA. For those with pre-existing haemophilia-related arthropathy, the term 'target joint' may be more appropriately replaced by 'problem' or 'at-risk' joint and should be prevented by prophylaxis.[21] The clinical treatment goal over the next 5 years should be to ensure that people on prophylaxis experience no haemophilia-related arthropathy if commencing prophylaxis from a position of no existing arthropathy. An aspirational clinical treatment goal should be PwHA maintaining normal (50–150 IU/dL) FVIII levels to achieve normal haemostasis.[8] Until haemophilia therapy evolves to the point that this is feasible, a trough FVIII level of ≥15 IU/dL in all PwHA and maintenance of a greater period of time with FVIII levels above ≥20–30 IU/dL should be aimed for, if treatment burden decreases with future innovation.

4.5 | Strengths and limitations

The modified Delphi panel is a systematic method to gather expert consensus. Although the panellist number was limited, they had substantial

experience in UK-based haemophilia centres with wide geographical representation. There was no panellist attrition across rounds, ensuring a robust process. The SC reviewed statements to ensure clinical relevance. Use of the bespoke Delphi application ensured panellist anonymity. While the consensus meeting was in-person, panellists voted through the Delphi application and results were presented anonymously. Most statements were applicable to both adult and paediatric HA treatment, and where statements were unable to be worded for both groups, this was clearly stated.

5 | CONCLUSION

The panel of experts were largely aligned on approaches to preserving joint health in PwMHA and PwSHA. Consensus was obtained that PwMHA and PwSHA should be offered prophylaxis to prevent joint bleeds. Within prophylaxis, a trough FVIII level of ≥15 IU/dL should be aimed for, although this is unlikely to be achievable in practice due to the burden of current treatments. Where feasible, prophylaxis should maximise the AUC to ensure a greater period of time with FVIII levels above ≥20–30 IU/dL, which may provide better bleed protection. Future clinical treatment goals should be to prevent all joint bleeds in PwMHA and PwSHA, which may be achieved by ensuring FVIII levels of 50–150 IU/dL are maintained through treatment. The information from this consensus study may guide HCPs in the preservation of joint health in PwMHA and PwSHA.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception and design: Andrew Danquah, Mike Laffan, Paul McLaughlin, Jayashree Motwani, Shaneil Sonecha. *Substantial contributions to analysis and interpretation of the data, drafting the article or revising it critically for important intellectual content and final approval of the version of the article to be published*: Jayanthi Alamelu, Steve Austin, Stephen Classey, Andrew Danquah, Gerard Dolan, Marie Eales, Richard Gooding, John Grainger, Catherine Harrison, April Jones, Anne M. Kelly, Mike Laffan, Paul McLaughlin, Jayashree Motwani, Lara Oyesiku, Ryan Rodgers, Shaneil Sonecha, David Stephensen, Kate Talks.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

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

ETHICS APPROVAL

As no patients were involved in the study, ethical approval was not required.

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REFERENCES

1. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus*. 2018;16(6):535-544.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26:1-158.
3. Simpson ML, Valentino LA. Management of joint bleeding in hemophilia. *Expert Rev Hematol*. 2012;5(4):459-468.
4. World Federation of Hemophilia. Chronic hemophilic synovitis: the role of radiosynovectomy 2004. https://www1.wfh.org/publication/files/pdf-1176.pdf
5. Mancuso ME, Holstein K, O'Donnell JS, et al. Synovitis and joint health in patients with haemophilia: statements from a European e-Delphi consensus study. *Haemophilia*. 2023;29(2):619-628.
6. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1(1):51-59.
7. McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study. *Disabil Rehabil*. 2022;44(26):8412-8419.
8. Skinner MW, Nugent D, Wilton P, et al. Achieving the unimaginable: health equity in haemophilia. *Haemophilia*. 2020;26(1):17-24.
9. Gooding R, Thachil J, Alamelu J, Motwani J, Chowdary P. Asymptomatic joint bleeding and joint health in hemophilia: a review of variables, methods, and biomarkers. *J Blood Med*. 2021;12:209-220.
10. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.
11. Scott MJ, Xiang H, Hart DP, et al. Treatment regimens and outcomes in severe and moderate haemophilia A in the UK: the THUNDER study. *Haemophilia*. 2019;25(2):205-212.
12. Collins PW, Obaji SG, Roberts H, Gorsani D, Rayment R. Clinical phenotype of severe and moderate haemophilia: who should receive prophylaxis and what is the target trough level? *Haemophilia*. 2021;27(2):192-198.
13. Rayment R, Chalmers E, Forsyth K, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. *Br J Haematol*. 2020;190(5):684-695.
14. Tagliaferri A, Feola G, Molinari AC, et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost*. 2015;114(07):35-45.
15. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125(13):2038-2044.
16. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12(1):1-8.
17. Jünger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: recommendations based on a methodological systematic review. *Palliative Med*. 2017;31(8):684-706.
18. Den Uijl I, Mauser Bunschoten E, Roosendaal G, et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? *Haemophilia*. 2011;17(6):849-853.
19. Klamroth R, Windyga J, Radulescu V, et al. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study. *Blood*. 2021;137(13):1818-1827.
20. Valentino LA, Pipe SW, Collins PW, et al. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. *Haemophilia*. 2016;22(4):514-520.
21. McLaughlin P, Hermans C, Asghar S, et al. Problem joints and their clinical and humanistic burden in children and adults with moderate and severe hemophilia A: cHESS paediatrics and CHESS II. *Blood*. 2020;136:33-34.
22. Konkle BA, Skinner M, Iorio A. Hemophilia trials in the twenty-first century: defining patient important outcomes. *Res Pract Thromb Haemost*. 2019;3(2):e12195.
23. Valentino L. Secondary prophylaxis therapy: what are the benefits, limitations and unknowns? *Haemophilia*. 2004;10(2):147-157.
24. United Kingdom Haemophilia Centre Doctors' Organisation. UKHCDO Annual Report 2022. http://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf

SUPPORTING INFORMATION

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

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