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ORIGINAL ARTICLE

Synovitis and joint health in patients with haemophilia: Statements from a European e-Delphi consensus study

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Abstract

Introduction: Synovitis, a common feature in haemophilia, is triggered by the presence of blood in joints, and represents the first step towards the development of chronic arthropathy. Synovitis may be detected early by means of ultrasound or magnetic resonance imaging scan; clinical joint scores are less sensitive in this setting. Regular long-term prophylaxis with clotting factor concentrates, as primary prophylaxis and tailored to individual needs, has high efficacy in preventing synovitis. In general, higher factor levels lower bleeding risk, but no direct correlation between factor levels and synovitis incidence has been demonstrated.

Aim: This study aimed to develop an expert consensus relating to the definition, pathophysiology, diagnosis, prevention, follow-up and treatment of synovitis, recognising its relevance for joint health and taking into account existing knowledge gaps.

Methods: A Delphi consensus study was designed and performed. An expert group prepared 22 statements based on existing literature; a wider expert panel subsequently voted on these.

Results: Retention of panellists was high. Four statements required amending and consensus on all statements was achieved after three rounds of voting.

Conclusion: This e-Delphi consensus study addressed the importance of synovitis in joint health of people with haemophilia and highlighted knowledge gaps in this field. Studies on the natural course of synovitis are lacking and the biological mechanisms underlying this process are not yet fully elucidated. While basic and clinical research proceeds in this field, expert consensus can help guide clinicians in their routine clinical practice, and Delphi methodology is often used to produce best-practice guidelines.

KEYWORDS
Delphi consensus, haemophilia, joint health, point-of-care ultrasound, synovitis

1 | INTRODUCTION

Synovitis, which is defined by inflammation of the synovial tissue, is a common feature in patients with haemophilia as a reaction to the presence of blood into joints and represents the first step of the path towards the development of chronic arthropathy.[1] There is evidence that a single episode of bleeding may be sufficient to initiate synovial inflammation that may persist and become chronic synovitis when bleeds recur frequently and are not prevented adequately.[2]

Synovitis may be detected in joints apparently free from clinically relevant bleeds and in these cases its detection is more challenging, especially in early childhood. The Haemophilia Joint Health Score (HJHS) has been originally developed to assess joint status in children with haemophilia to reveal early signs of joint involvement,[3] however it has been shown to have poor correlation with early detection of synovitis.[4]

Synovitis can be detected through imaging tools among which magnetic resonance imaging (MRI) represents the most sensitive one and for which dedicated scores have been developed.[5–8] MRI is considered to be the gold standard for joint imaging,[9] however, it is not universally available, is costly, time consuming, and sedation is often required in children.[10] A valuable alternative is musculoskeletal ultrasound (MSKUS), which allows affordable bedside monitoring of joint health and good visualisation of joint structures. Such technique, used as a point-of-care (POC) assessment, may allow detection of synovitis by healthcare professionals (HCPs) who are not specialised radiologists through the use of simple scoring systems.[11,12] The evaluation of joint status using MSKUS also facilitates patient involvement in informed treatment decision making which is of utmost relevance to improve compliance and adherence to treatment (i.e. prophylaxis).[13]

Regular long-term prophylaxis with clotting factor concentrates, initiated as primary prophylaxis before the onset of joint damage and tailored to the individual needs of each case, is the best treatment strategy to prevent the vicious cycle of joint bleeds and synovitis.[14] Clotting factor levels should be persistently protective over time as it has been shown that the time spent at non-protective levels is linearly correlated with joint bleeding risk.[15] In general, the higher the factor level, the lower the frequency of bleeding. To date, no direct correlation between clotting factor levels and incidence and/or prevalence of synovitis has been demonstrated.

Haemostatic treatment is not always enough to solve synovitis, because in some cases it is highly likely that there is a mechanical conflict between the hypertrophic synovium and the joint surface that causes bleeding. Therefore, for those cases where synovitis and recurrent bleeding episodes persist despite adequate and individual tailored prophylaxis, additional interventions are required as synovectomy that can solve the mechanical conflict, although it is not able to halt disease progression.[1]

Owing to the knowledge gap on synovitis in haemophilia but considering its great relevance for joint health in patients with haemophilia, the aim of this study was to develop an expert consensus regarding the definition, pathophysiology, diagnosis, prevention, follow-up and treatment of synovitis through the Delphi methodology, which is often used to produce best-practice guidelines where evidence is missing.

2 | MATERIALS AND METHODS

A Delphi consensus study[16,17] was designed and performed between March 2021 and March 2022. This was initiated by the establishment of a steering committee in January 2021 of five experts (MEM, KH, JSO'D, SL and RK) in the field of haemophilia based on their clinical expertise, scientific interest, publications and participation in scientific meetings, expert panels and clinical trials. The steering committee included four haematologists (MEM, KH, JSO'D and RK) and one physiotherapist (SL). The steering committee identified five domains pertaining to synovitis and joint health in patients with haemophilia that should have covered the main relevant aspects on this topic. These were: (1) definition and pathophysiology of synovitis; (2) diagnosis of synovitis; (3) impact of synovitis on joint health; (4) follow-up of synovitis; and (5) prevention and treatment of synovitis.

Due to the COVID-19 pandemic, all meetings needed to formulate and discuss the statements that would have been evaluated through Delphi methodology were organised virtually and the Delphi rounds were accomplished through an electronic platform, resulting in an electronic online (e-Delphi) process. Steering committee agreement on the five domains to be covered by the Delphi consensus approach was achieved through discussion during three virtual meetings in which various aspects of synovitis were considered in detail based on existing published data as well as relevant gaps in the field. Documentation capturing the consolidated outcomes was subsequently circulated to ensure full agreement. Similar methodology was adopted after each e-Delphi round, whereby an online meeting was convened to discuss statements that had not reached consensus and how to amend them for the following round.

The literature used to draft the statements was based on the list of 102 references quoted in the 'German Guideline on Diagnosis and Treatment of Synovitis' published in 2018[18] to which additional 34 references were added after a literature search was performed on PubMed in March 2021, using the terms [synovitis] and [haemophilia] and according to the following search criteria: date range from 2017 to 2021 and English language. Of these 136 references, 16 were off topic and were excluded. Of the remaining 120 references, 37 were reviews, 61 were clinical studies, 17 were preclinical studies and five were expert guidelines/recommendations.

The steering committee evaluated the available literature, discussed the content in the light of the aforementioned domains of interest and proposed a list of statements that were collated into a questionnaire. This questionnaire was sent through an electronic platform to an external expert panel invited to vote on each statement to gather consensus according to the e-Delphi methodology.

The level of agreement/disagreement on each statement was expressed anonymously according to a five-point Likert-type scale (1 = strongly agree, 2 = somewhat agree, 3 = neither agree or disagree, 4 = somewhat disagree and 5 = strongly disagree). Free-text space

was available for each expert to add comments on each statement if deemed necessary. Agreement/consensus was considered achieved when ≥75% of respondents answered either 'strongly agree' or 'somewhat agree'.[19] Statements for which such consensus had not been reached were discussed based on the comments received (if any), amended and submitted for subsequent additional rounds of voting to the same external expert panel. This process was repeated until consensus was reached for all statements.

3 | RESULTS AND DISCUSSION

After the literature review, the steering committee agreed on 22 statements (four for Domain 1; four for Domain 2; three for Domain 3; five for Domain 4 and six for Domain 5; see Table 1) to be submitted for the first e-Delphi round.

The external expert panel was formed by 38 European experts in haemophilia including seven paediatricians, 23 haematologists and eight musculoskeletal experts (i.e. orthopaedic surgeons, physiotherapists, and physiatrists) (see the complete list of names in the Appendix) who were invited by e-mail to answer the online questionnaire. They all accepted the invitation to complete the first round that was sent out on 21st September 2021 and finalised on 10th November 2021. The response rate to the first round was 100%, with 18 of the 22 statements (82%) already reaching consensus (see Figure 1 for agreement percentage of single statements).

Except for the domain of 'Impact of synovitis' for which consensus was reached on all statements already after the first round, one statement per each other domain did not reach consensus at this stage and those four statements were amended for the second e-Delphi round (Table 1 and Figure 1).

3.1 | Definition and pathophysiology of synovitis (Statements 1–4)

The World Federation of Haemophilia (WFH) and the German Society for Thrombosis and Haemostasis (GTH) define chronic synovitis as synovial inflammation persisting over and beyond 3 months.[14,18] Elsewhere in the literature, the presence of chronic synovitis has been related to multiple bleeds over 6 months and thus to the presence of target joints.[20,21] Likewise, although there are multiple publications discussing chronic synovitis, its definition is unclear and, when defined, it is not based on clinical data. In fact, no data are available on the time point/clinical stage at which synovitis becomes persistent and irreversible.

Although not all the underlying pathophysiological mechanisms have been elucidated, the role of intra-articular iron and haemosiderin as the main triggers of the pro-inflammatory response, together with hydroxy radicals and cytokines is clear as they lead to synovitis and ultimately to the apoptosis of chondrocytes and bone rearrangement.[2,22–33] In this light, basic research on cell and animal models, as well as translational research on human tissues, is highly valuable and deemed necessary to increase knowledge in this field. The panel largely agreed on these concepts and related statements, except for Statement 4 which introduced a tentative definition of chronic synovitis: *"Chronic synovitis is synovial hypertrophy which is not reversible over a 3-month period"* due to the lack of literature-based support for such definition.

3.2 | Diagnosis of synovitis (Statements 5–8)

Overt synovitis can be clinically detected by assessing signs of inflammation in the joint, such as swelling, warmth, limited range of motion and pain, which also are symptoms of acute haemarthrosis.[14,34,35] Tingling or tightness around the joint can precede such symptoms.

Imaging confirmation is useful to better define the severity of synovial hyperplasia and follow its progression over time. In fact, clinical assessment by means of HJHS has proven to not be sensitive enough for the detection of early signs of synovitis[36] and imaging assessment is highly recommended.

MRI is the gold standard imaging technique to assess joint structure because it enables direct analysis of the joint, including the soft-tissue, joint effusions, cartilage and haemosiderin.[9] However, differentiation between bloody and non-bloody effusions is not that clear by MRI, and joint fluid can only be distinguished from synovitis using contrast.

Despite its high sensitivity, the routine use of MRI is limited by several drawbacks including availability, cost and the difficulty of being performed on a frequent basis.[9] Moreover, sedation in very young paediatric patients is often necessary due to the extended time needed to assess multiple joints. These challenges have resulted in the extensive development of POC-MSKUS, which currently represents a good tool to detect and monitor synovitis in clinical practice, that is both practical and readily available.

Different scanning protocols have been proposed with the goal of making joint evaluation comparable across haemophilia treatment centres in different countries: the most used protocols are the Haemophilia Early Arthropathy Detection with Ultrasound Score (HEAD-US) and the Joint Tissue Activity and Damage Examination protocol (JADE).[11,12] Whilst they both include the evaluation of presence/absence of synovial hypertrophy, cartilage integrity and bony changes, HEAD-US assesses synovial hypertrophy without measuring synovial thickness, whereas JADE includes such measurement as well as the use of Power Doppler as a marker of disease activity.[11,12] It has been recently suggested that the quantitative and more detailed protocols that utilise Power Doppler are better suited to research and clinical trials rather than for POC-MSKUS.[37]

The panel largely agreed on these concepts, although consensus was not achieved on Statement 8, which focused on the importance of using a score based on MRI to assess synovitis: '*The MRI scale of the International Prophylaxis Study Group (IPSG) is recommended to quantify, detect and monitor synovitis*', thus reflecting the aforementioned difficulties in the routine adoption of MRI despite its recognised sensitivity.

TABLE 1 Statements on synovitis submitted for the first e-Delphi round

Statements
Domain: Definition and pathophysiology of synovitis
1 Synovitis is the synovial hypertrophy generated in response to the inflammatory trigger represented by the presence of haemoglobin and iron deposition in the joint
2 Haemoglobin, iron deposition, cytokines, hydroxyl radicals and neoangiogenesis contribute to synovitis
3 The pathophysiology of synovitis in patients with haemophilia is still poorly understood and needs more basic research
4 Chronic synovitis is synovial hypertrophy which is not reversible over a 3 month-period
Domain: Diagnosis of synovitis
5 HJHS 2.1 as a clinical assessment tool is not sensitive enough to detect synovitis
6 Point-of-care MSKUS assessment using standardized protocols is a sensitive tool to detect and monitor synovitis and early joint changes
7 The added value of Power Doppler imaging during MSKUS assessment to detect markers of disease activity needs to be confirmed
8 The MRI scale of the IPSG is recommended to quantify, detect and monitor synovitis
Domain: Impact of synovitis on joint health
9 Synovitis is the major cause for haemophiliac arthropathy
10 A single joint bleed can lead to synovitis and subsequent joint damage irrespective of haemophilia severity
11 In asymptomatic joints, presence of synovitis is indicative of silent bleeds or microbleeds
Domain: Follow-up of synovitis
12 Patients with synovitis need more frequent musculoskeletal assessment than patients without synovitis
13 The frequency of POC-MSKUS assessment of index joints to detect synovitis varies taking into account age, pre-existing synovitis/joint damage and physical activity
14 In the presence of chronic synovitis and no/limited joint damage POC-MSKUS assessment must be repeated every 4–6 months
15 At first detection of synovitis by POC-MSKUS, MRI is recommended
16 At first detection of synovitis in asymptomatic joints, re-assessment by POC-MSKUS is needed within 6 months
Domain: Prevention and treatment of synovitis
17 Synovitis can be prevented by early primary prophylaxis started before or at least soon after the first joint bleed
18 Patients with moderate haemophilia A, with a baseline FVIII of 1–3 IU/dL, are at risk of synovitis and deserve prophylaxis
19 To prevent synovitis time spent within the normal range of FVIII levels and FVIII trough levels above 3–5 IU/dL are needed
20 Treatment tailoring and prophylaxis intensification with factor replacement is needed in the presence of synovitis
21 Management of synovitis always requires conservative treatments (i.e., anti-inflammatory drugs, physiotherapy) beyond prophylaxis with factor replacement
22 For chronic synovitis resistant to intensified factor replacement and appropriate conservative treatment, radio- or chemical synoviorthesis, arthroscopic/surgical synovectomy or selective arterial embolization are recommended

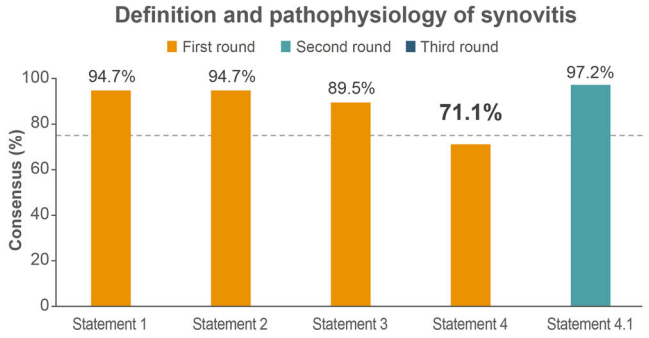
In italic bold those statements for which agreement had not been achieved.
FVIII, factor VIII; HJHS, Haemophilia Joint Health Score; IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging; MSKUS, musculoskeletal ultrasound; POC-MSKUS, point-of-care musculoskeletal ultrasound.
*Respondents for the first e-Delphi round were 38.

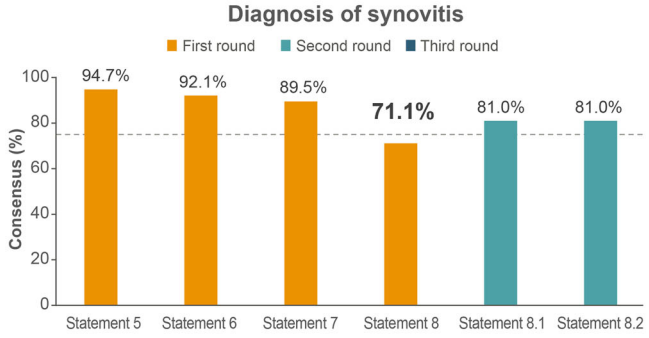
3.3 | Impact of synovitis on joint health (Statements 9–11)

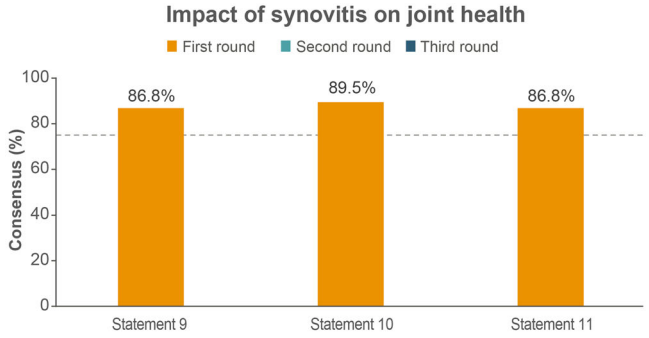
The major role synovitis plays in the development of joint damage is clear from both basic and clinical research, with the presence of intraarticular blood as the main trigger.[38–43] Therefore, to explain the accidental finding during routine MSKUS check of synovial hypertrophy in asymptomatic joints, the occurrence of silent bleeds or microbleeds has been advocated despite the lack of direct evidence of such phenomena.[44–49]

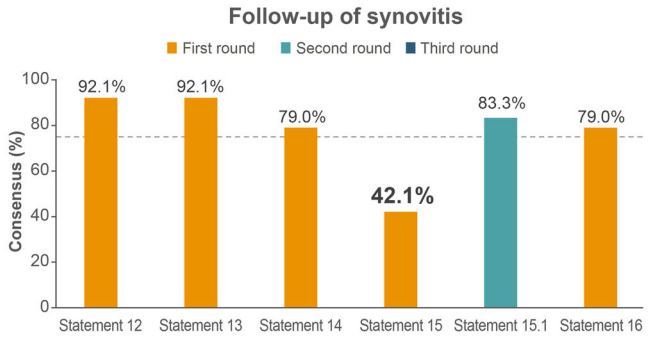
3.4 | Follow-up of synovitis (Statements 12–16)

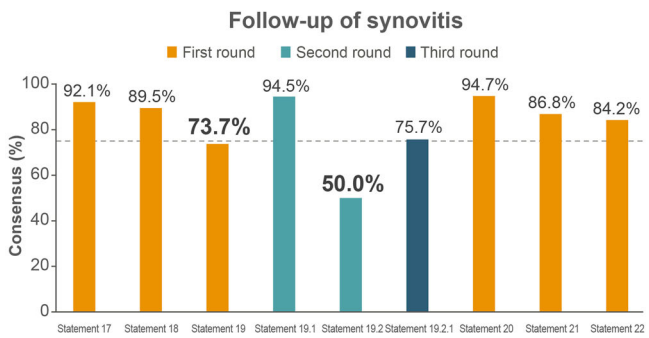
As previously stated, by means of simple scanning protocols, POC-MSKUS represents a non-invasive tool to monitor the course of synovitis over time.[50–53] In general, POC-MSKUS assessment can be an imaging tool that complements regular clinical assessment, however, there is no unique schedule suitable for all patients. The frequency of US assessment changes according to several variables that impact the relative risk of synovitis, including age, pre-existing synovitis and type and intensity of physical activity. On the whole, agreement exists on











the need to assess patients with synovitis more frequently than those without. In particular, the panel agreed on the importance of MSKUS re-assessment within 6 months for individuals in whom asymptomatic synovitis is detected for the first time, to determine the potential for reversibility. Additionally, for cases with chronic synovitis and no cartilage/bone damage, a regular MSKUS assessment every 4–6 months might be of help in defining the best follow-up protocol for these patients.

The panel did not reach consensus on Statement 15: '*At first detection of synovitis by POC-MSKUS, MRI is recommended*' with 29% of respondents being neutral ('neither agree or disagree') and around 25% against the recommendation of MRI as soon as synovitis is detected by POC-MSKUS. Indeed, from published data, the sensitivity of MSKUS in detecting synovitis is relatively high[54,48] eliminating the need for confirmation by means of MRI, which is more useful to provide a deeper analysis of joint structures beyond the presence of synovitis.[9]

3.5 | Prevention and treatment of synovitis (Statements 17–22)

Synovitis prevention is key to protect joints from long-term irreversible structural damage.[1] With this in mind, early initiation of prophylaxis has been shown to preserve normal joint structure and reduce bleeds in individuals with severe haemophilia.[46] Recently, it has been shown that joint damage may also occur in patients with moderate haemophilia, where progression is only marginally delayed compared with patients with severe haemophilia.[55,56] Indeed, this resonates with the recommendation of increasing trough levels from 1—3% to at least 3—5% during prophylaxis[14] in order to achieve better protection and underlines the need for extending the indication for prophylaxis to patients with moderate haemophilia as well as to those with a severe bleeding phenotype, irrespective of baseline levels.[14] Furthermore, treatment tailoring and individualisation of prophylaxis regimens have been increasingly implemented in order to meet the clinical needs of each individual patient, and this can also be beneficial in the prevention of synovitis.

Careful joint assessment has demonstrated that joint damage (starting with synovitis as early stage) can be detected in a significant proportion of patients treated with standard prophylaxis,[57] underlining the need for treatment optimisation. Such optimisation could be achieved through the use of prophylactic regimens that maintain higher factor levels as it is possible with clotting factors with an

FIGURE 1 Percentage of agreement achieved during the subsequent e-Delphi rounds for each statement. Statements are grouped based on the five domains (panels A to E). Orange bars depict results for first round, blue bars those for second round and green bars those for third round. Agreement/consensus was considered achieved when ≥75% of respondents answered either 'strongly agree' or 'somewhat agree'

TABLE 2 Amended statements voted during the second e-Delphi round

Original statement		Amended statements
	Domain: Definition and pathophysiology of synovitis	
4	4.1	Chronic synovitis is synovial hypertrophy, which is persistent for at least 3 months
	Domain: Diagnosis of synovitis	
8	8.1	The use of MRI is more accurate than POC-MSKUS to detect, quantify and monitor synovitis
8	8.2	The use of POC-MSKUS is enough to detect, quantify and monitor synovitis
	Domain: Follow-up of synovitis	
15	15.1	Following detection of synovitis by POC-MSKUS, MRI provides additional diagnostic information
	Domain: Prevention and treatment of synovitis	
19	19.1	To prevent synovitis, joint bleeds and microbleeds need to be avoided through effective prophylaxis
19	***19.2***	***FVIII levels above 3 IU/dL are needed to prevent synovitis in patients without a history of synovitis***

In italic bold the statement for which agreement had not been achieved.
FVIII, factor VIII; MRI, magnetic resonance imaging; MSKUS, musculoskeletal ultrasound; POC-MSKUS, point-of-care musculoskeletal ultrasound.

improved pharmacokinetic profile (referred to as extended half-life [EHL] products), or by means of non-replacement therapies.[58]

Despite agreeing on the usefulness of prophylaxis for individuals with moderate haemophilia, hence underlying the need for higher factor levels to achieve better protection, the panel did not reach consensus on Statement 19: '*To prevent synovitis time spent within the normal range of FVIII levels and FVIII trough levels above 3–5 IU/dL are needed*', due to the paucity of data available to set a universal cut-off value which suits all.

On the other hand, with respect to treatment of synovitis, it is important to consider that factor replacement might not be enough to completely solve the problem and that other conservative treatments, such as anti-inflammatory drugs and physiotherapy, should also be considered to rapidly achieve a positive outcome.[59,60]

Finally, for synovitis not controlled/reverted by factor replacement in association with other conservative approaches, the panel agreed on the utility of surgical solutions that may range from selective arterial embolisation to open surgical synovectomy including chemical, radioisotopic and arthroscopic synovectomy[61–67] as these approaches aim at solving the mechanical impingement caused by hypertrophic synovium in the joint space which cannot be controlled by medical therapies.

3.6 | Amended statements for subsequent e-Delphi rounds

According to the e-Delphi methodology, the four statements that did not reach consensus were amended and redrafted for a second round (see Table 2). Two statements were split into two new statements each to better focus on single concepts that were indeed combined in the first version. Two experts withdrew after the first round due to personal circumstances and the remaining 36 (95%) answered the second round, which included a total of six statements. The second round was sent out on 22nd December 2021 and finalised on 04th February 2022. After the second round, consensus was reached for five of the six amended statements (83%) (see Figure 1 for agreement percentage of each amended statement).

With Statement 4.1 the panel agreed on identifying 3 months as a reasonable time frame beyond which persistent synovitis can be considered as a chronic clinical feature, although there is lack of scientific evidence based on follow-up clinical studies designed to address this.

By splitting Statement 8 into two statements, the specific roles of MRI and POC-MSKUS to detect, quantify and monitor synovitis were highlighted and MSKUS assessment was specified as being adequate for routine use in clinical practice whereas it was indicated that MRI could serve to better define individual cases owing to greater accuracy. These amendments were well received by the panel and consensus was reached for both statements. Indeed, the use of specific scales as the IPSG score are not routine and they are most useful in the frame of clinical studies.

Statement 15.1 identified the importance of using MRI to provide a more complete description of joint status in patients with synovitis. The amendment was needed because the panel reached the understanding that recommending MRI in all patients with synovitis was not universally applicable and also not supported by current clinical data. The choice to perform MRI should be based on individual evaluation, considering several variables such as age, response to prophylaxis personalisation/intensification, intensity of physical activity, and lifestyle.

Statement 19 was also split into two new statements that better highlighted two aspects related to the importance of adequate haemostatic protection against bleeds to prevent synovitis. In the original statement, time spent with factor levels within the normal range and trough levels above 3—5% were considered useful to prevent synovitis. However, the panel concluded that direct translation of minimum factor levels needed to prevent the development of joint damage was not straightforwardly applicable to synovitis. In Statement 19.1, the preventative role of prophylaxis against any joint bleed (including microbleeds), to avoid synovitis was underlined and consensus was achieved on this concept. On the contrary, Statement 19.2 did not achieve consensus, despite having been amended, with 30% of

TABLE 3 Amended statement voted during the third e-Delphi round

Original statement	Statement	
	Domain: Prevention and treatment of synovitis	
19.2	19.2.1	Levels of 3% FVIII are not adequate to fully prevent synovitis in all patients

FVIII, factor VIII.

respondents being neutral. This reveals the difficulties and uncertainties in defining a specific trough level suitable for all. Indeed 17% of respondents gave feedback that synovitis could also be detected with levels above 3% because many other variables play a role in the pathogenesis.

Therefore, the statement was amended for the third round (see Table 3) that was sent out on 22nd February 2022 and finalised on 24th March 2022. Thirty-seven experts answered the third round (including one who did not participate in the second round) and consensus was achieved on statement 19.2.1 '*Levels of 3% FVIII are not adequate to fully prevent synovitis in all patients*' with a 76% agreement (Figure 1). Indeed, after this third and last round, four respondents remained neutral and four somewhat disagreed commenting that despite being convinced that letting a patient never drop below 3% will improve joint status, full prevention in all cannot be warranted. Only one expert strongly disagreed because he/she believes that levels below 5% are not enough to prevent synovitis.

4 | CONCLUSION

This e-Delphi consensus study addressed the importance of synovitis in joint health of people with haemophilia and highlighted the knowledge gap in this field. In fact, studies on the natural course of synovitis are lacking and the biological mechanisms underlying this process are not yet fully elucidated. Hence, whilst basic and clinical research proceeds in this field, expert consensus can be useful to help clinicians in their routine clinical practice and the Delphi methodology is often used to produce best-practice guidelines.

Recently the Musculoskeletal Working Group of the Italian Association of Hemophilia Centers published the results of a modified Delphi consensus study on unmet needs in the evaluation and management of synovitis in haemophilia that included 37 statements pertaining diagnosis and treatment of synovitis.[6] After two rounds, agreement was reached only for 11 statements and no subsequent rounds were run to amend those statements for which the panel failed to achieve agreement. At variance with our study, this was a single country study and statements pertained the imaging techniques useful for diagnosis, different medical approaches in case of chronic synovitis, and the role of physiotherapy and orthopaedic surgery.[6] Of note, no definition of chronic synovitis was given in this study, the no indications on the exact timing of the suggested periodical follow-up in case of detection of chronic synovitis. With respect to haemostatic treatment, despite recommendations on treatment regimen modifications, there was no mention of haemostatic levels that should be maintained in case of detection of synovitis. On the other hand, as in our study, the use of MSKUS as an imaging tool to investigate synovitis was considered preferable over MRI.

One possible limitation of our study is that the size and composition of the expert panel might not be representative of all HCPs also considering that only European experts were included, and final statements might not reflect the opinion of haemophilia treaters from countries outside Europe. However, retention of panellists was very good and nearly 100% completed each new round providing useful comments and suggestions that favoured a successful amendment of the statements.

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AUTHOR CONTRIBUTIONS

Maria Elisa Mancuso, Katharina Holstein, James S O'Donnell, Sébastien Lobet and Robert Klamroth reviewed the literature and drafted the statements for the Delphi rounds; Maria Elisa Mancuso wrote the first draft of the manuscript; Katharina Holstein, James S O'Donnell, Sébastien Lobet and Robert Klamroth reviewed the manuscript and all authors finalised it. All authors approved the final version of the manuscript.

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The FVIII Think Tank Study Group is listed in the Appendix.

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CONFLICT OF INTEREST

MEM received research funding, honoraria and speaker fees from Bayer, BioMarin, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark Therapeutics, Takeda and UniQure. KH received honoraria and/or speaker fees from Bayer, Biotest, Chugai, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi, Takeda and research grants from Bayer, CSL Behring, Sobi and Pfizer. JSO'D has served on the speaker's bureau for Baxter, Bayer, Novo Nordisk, Sobi, Boehringer Ingelheim, Leo Pharma, Takeda and Octapharma. He has also served on the advisory boards of Baxter, Sobi, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, Takeda and Pfizer. JSO'D has also received research grant funding awards from 3 M, Baxter, Bayer, Pfizer, Shire, Takeda, 3M and Novo Nordisk. SL has no conflicts of interest to disclose. RK received research funding, honoraria and speaker fees from Bayer, Biotest,

BioMarin, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Sobi, Takeda/Shire.

DATA AVAILABILITY STATEMENT

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

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APPENDIX

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