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CLINICAL RESEARCH

Development of a patient-reported outcomes tool to monitor changes in joint health and wellbeing for young people with haemophilia B

Melanie Bladen, Janet McDonagh, Paul McLaughlin, Richard Gooding, Kerry-Ann Holder, Sharon Thind, Brittany Klooster, Alan Shields, Diane M. Turner-Bowker, Kaitlin Chatterton, Allison Leso, Connor Volpi, Sujan Sivasubramaniyam, Jiawula Abulizi, Nisa Khan

MELANIE BLADEN
Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.
Email: melanie.bladen@gosh.nhs.uk

JANET MCDONAGH
Manchester Academic Health Science Centre, University of Manchester, Manchester, UK; National Institute for Health Research Biomedical Research Centre, Manchester University Hospital NHS Trust, Manchester, UK

PAUL MCLAUGHLIN
Katharine Dornandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK

RICHARD GOODING
Haemophilia Comprehensive Care Centre, Belfast Health and Social Care Trust, Belfast City Hospital, Belfast, UK

KERRY-ANN HOLDER
Child Health Psychology, Inherited Bleeding Disorders and Hereditary Anaemias, Noah's Ark Children's Hospital for Wales, Cardiff, UK

SHARON THIND
Haemophilia Comprehensive Care Centre, Alder Hey Children's Hospital, Liverpool, UK

BRITTANY KLOOSTER
Adelphi Values Patient-Centered Outcomes, Boston, MA, US

ALAN SHIELDS
Adelphi Values Patient-Centered Outcomes, Boston, MA, US

DIANE M TURNER-BOWKER
Adelphi Values Patient-Centered Outcomes, Boston, MA, US

KAITLIN CHATTERTON
Ultragenyx Pharmaceutical, Novato, CA, US

ALLISON LESO
Adelphi Values Patient-Centered Outcomes, Boston, MA, US

CONNOR VOLPI
Adelphi Values Patient-Centered Outcomes, Boston, MA, US

SUJAN SIVASUBRAMANIYAM
CSL Behring, London, UK

JIAWULA ABULIZI
CSL Behring, London, UK

NISA KHAN
CSL Behring, London, UK

Introduction: Early detection of joint bleeds is challenging yet critical for preserving joint health among individuals with haemophilia. This work explored early indicators of joint bleeds and young people with haemophilia B (YPwHB) self-monitoring practices to develop a joint health patient-reported outcome (PRO) tool for YPwHB aged between 8-25 years. **Methods:** A targeted concept-focused literature review, an advisory panel of haemophilia care providers (n=8), followed by a focus group of YPwHB (n=5, 10–21 years), caregivers (n=5), and haemophilia specialists (n=1 physiotherapist; n=1 psychologist) were consulted to gain insights on joint bleed experience and monitoring of YPwHB. Qualitative data were analysed, and outputs were

used to develop a preliminary PRO tool. **Results:** The literature review identified joint bleed symptoms, including preferred position of the joint, skin discolouration, pain, and swelling. Impacts specific to joint bleeds include inability to load the joint, limited mobility, and restricted range of motion. Advisory board panellists expressed the value of a PRO tool that explores physical symptoms and well-being and facilitates a shared language between YPwHB, caregivers, and healthcare professionals while also improving body confidence and body awareness in YPwHB. Focus group participants reported symptoms of joint bleeds as 'different than normal', 'deep' pain, tingling, stiffness, and inability to bend the joint. Impacts on daily life included emotional aspects, sleep, and interference with daily activities. Participants reported a need to increase knowledge of joint bleed symptoms and how to distinguish from other symptoms. **Conclusion:** A PRO tool could support YPwHB and their caregivers, increase awareness of joint health, and support conversations among YPwHB, caregivers and healthcare providers. A feasibility study is planned for the PRO tool. Use of the PRO tool may be of clinical relevance to other inherited bleeding disorders.

Patient or Public Contribution: YPwHB and their caregivers participated in an independent focus group to share their experience of joint bleeds, and how they detect and track joint bleeds, and to provide their view on a self-monitoring tool to monitor joint health. This informed the language used in the PRO tool questions developed for the feasibility study but is not presented in this publication.

Keywords: *Haemophilia, Joint bleeds, Self-monitoring, Patient-reported outcomes, Quality of life*

Haemophilia is a rare, typically genetic disorder characterised by abnormal bleeding due to insufficient blood clotting factors. Haemophilia A is the most prevalent (17.1 cases per 100,000 males), followed by haemophilia B (3.8 cases per 100,000 males). As of 2019, the number of individuals living with haemophilia A and B across the world was estimated to be 1.1 million, approximately 35% of whom were expected to have severe haemophilia, defined as <1% of clotting factor VIII and IX (respectively) present [1,2].

Insufficient blood clotting factors produced in the body can cause bleeding into muscles and joints spontaneously during normal activities or prolonged periods of bleeding following injuries [3]. Bleeds are associated with swelling in the muscles and joints, manifesting as pain, numbness, or reduced range of motion. Long-term sequelae include arthritis, joint destruction, and negative impacts in the areas of physical health, emotional function, school, leisure, sports, and daily activities [3,4].

The landscape of treatment options has evolved significantly, offering a range of licensed therapies including both standard and extended half-life factor replacement products, non-factor replacement therapy, as well as gene therapy treatments that are either licensed or currently undergoing clinical trials. Primary prophylaxis has reduced the frequency of bleeds and has contributed to young people with haemophilia (YPwH) and caregivers having a reduced or limited awareness of how to recognise a bleed [5]. As a result, early subclinical symptoms of a joint bleed may go underreported. Likewise, clinicians face challenges in understanding and determining early symptoms of joint bleeds that present in YPwHB [6,7]. However, research is emerging on joint damage despite patients not reporting experiencing joint bleeds [8].

The occurrence of asymptomatic bleeding in joints among people with haemophilia can lead to early onset long-term joint damage and poorer joint health outcomes [8]. In the United Kingdom (UK), YPwH have six-monthly or yearly musculoskeletal reviews. With infrequent reviews and the absence of a joint bleed, any subtle changes or differences in the joint may go unreported. Developing a self-monitoring tool, accompanied by educational resources, could assist YPwH and their caregivers in recognising early alterations in joint health. This tool would be tailored to reflect the individual experiences associated with haemophilia. The purpose of developing a tool for YPwH and their caregivers is to intervene early enough to support potentially improved long-term joint health and well-being outcomes.

The All-Party Parliamentary Group (APPG) emphasises the importance of shared decision-making between people with haemophilia (PwH) and healthcare providers, focusing on PwH's access to information about their condition and treatment options. They stress that outcome measures for haemophilia should not only consider bleed occurrences but also include factors related to quality of life and PwH's experiences [9]. The aim of this project was to develop a patient-reported outcome (PRO) tool for young people with haemophilia B (YPwHB), aged 8-25 years, and/or

their caregivers to self-monitor changes in joint health and wellbeing, and to support YPwHB and parents to communicate better with healthcare professionals and improve understanding of ideal joint health. We present the process of developing a preliminary PRO tool intended to (1) support early and ongoing conversations around joint health between YPwHB, their families, and their healthcare providers; (2) raise overall awareness and understanding among YPwHB (and/or their caregivers) about the importance of preserving joint health and management; and (3) provide joint health education.

METHODS

Three key activities were conducted to develop the PRO tool: a targeted concept-focused review of the scientific literature; an advisory board meeting with haemophilia experts who treat and manage YPwHB; and a focus group with YPwHB, parents, and healthcare professionals. The National Institute for Health and Care Research (NIHR) Research Ethics Committee decision tree was used to determine that the activities did not meet the criteria for research requiring ethical approval [10]. Results from these activities informed concepts of measurement as well as questionnaire language, format, and structure within the tool.

Literature review

A targeted literature review was conducted to identify the signs, symptoms, and impacts experienced by people with haemophilia B of any age having joint bleeds.

The OvidSP platform was used to search MEDLINE®, Embase, and PsycINFO® databases, and included articles limited to English-language studies in humans that were published between December 2010 and December 2020. Search terms included were: haemophilia, joint bleed, microbleed, symptom, impact, health-related quality of life. Google and Google Scholar were searched to identify additional articles of interest using combinations of the search terms used in the database search.

Abstracts were included if they primarily focused on the symptoms (defined as self-reported from the patient perspective, which can best be reported by YPwHB themselves) and impacts (with a focus on joint bleeds and associated wellbeing) associated with haemophilia B (or related conditions, such as haemophilia A). Due to limited literature pertaining to haemophilia B only, literature concerning haemophilia A was included as the effects on joint health are similar.

Abstracts were excluded if they did not primarily focus on a condition closely related to haemophilia B; focussed on aspects of haemophilia B other than joint bleeds or joint pain and associated wellbeing; were derived from non-peer reviewed research; involved non-human research; were solely case studies on one patient. Case studies of more than one patient were included if relevant. All publications prior to 2010 and not in English were excluded.

Abstracts were screened by two researchers. A meeting was held with the full research team to review decisions regarding abstract relevance against the inclusion/exclusion criteria. Full text articles were reviewed, relevant data and results were extracted, and reference lists were used to identify relevant articles not captured in the database search. The full text review was a targeted, concept-focused literature review; it might also be referred to as a qualitative evidence synthesis. The results were used to create a literature-based haemophilia conceptual model highlighting concepts (i.e., symptoms and impacts) that suggest early indicators of a joint bleed. The symptoms of haemophilia were organised based on how they were reported in the literature. The concept of impact in haemophilia was characterised as the experiences that are indirectly related to the disease, highlighting how symptoms adversely affect the activities, functionality, wellbeing, and quality of life of individuals with the condition. Following the extraction of concepts, a draft version of the PRO tool was created, including descriptions of its intended value, purpose, and rationale for its structure and content.

Advisory board meeting

An advisory board meeting was held to obtain clinical insights from eight healthcare professionals on the purpose, value, and utility of a PRO tool for YPwHB and their caregivers for joint health management. The advisory board meeting, held virtually in March 2021 over two three-hour sessions, aimed to understand the PRO tool's usage, outcome measurement, assessment structure, usage barriers, and implementation options. The advisory board sessions, which were facilitated by a health outcomes and measurement scientist, were recorded and transcribed. Post-meeting, the research team synthesized panellists' contributions from transcripts and minutes using thematic analysis. The process involved an initial independent analysis by one researcher, followed by a review and resolution of differences with another researcher. Proposed changes to the self-monitoring tool were compiled into a table.

Focus group

A focus group was held with the aim of better understanding the YPwHB/caregiver experience of joints bleeds and perspectives about self-monitoring their joint health.

A screening questionnaire was distributed by The Haemophilia Society advertising for volunteers for a focus group through their social media account. A convenience sample was identified and The Haemophilia Society sent out the pre-advisory board survey, including: survey introduction, participant consent form, GDPR statement, privacy notice, adverse event statement, participant screening survey and the questionnaire. Eligible participants completed a survey and received £15 Amazon voucher for their time. The results of the survey are not presented in this manuscript.

Participants were considered eligible for the focus group if they had children aged 8-17 years who were diagnosed with mild, moderate, or severe haemophilia B; if they had one or more children affected by the condition and were available for a single three-hour virtual focus group meeting held via a web-based platform. The purpose of the focus group was to better understand the YPwHB/caregiver experience of joints bleeds and perspectives about self-monitoring their joint health.

The participants were grouped in to two groups by haemophilia severity and age, accompanied by healthcare professionals experienced in caring for YPwHB, and facilitated by two health outcomes scientists and medical affairs managers. Within each of the groups, the discussion was facilitated with a semi-structured guide, focused on the experience of joint bleeds (e.g., participants shared insights on their joint bleed experiences, focusing on its influence on their emotions, daily functionality, and activities); tracking joint bleeds (e.g., participants outlined their approaches for tracking joint health and managing the physical and emotional consequences of joint bleeds); how YPwHB talk with parents and caregivers about joint symptoms and health (e.g., helpful topics for conversations about joint health, focusing on key aspects to address); and preferences for self-monitoring joint bleeds (e.g., participants provided feedback on response types, practical recall periods, and usage frequency).

Focus group outcomes were anonymised and documented in tabular format (data were stored on a secure, password-protected server). Suggestions and considerations for the PRO tool were documented and presented in tabular format.

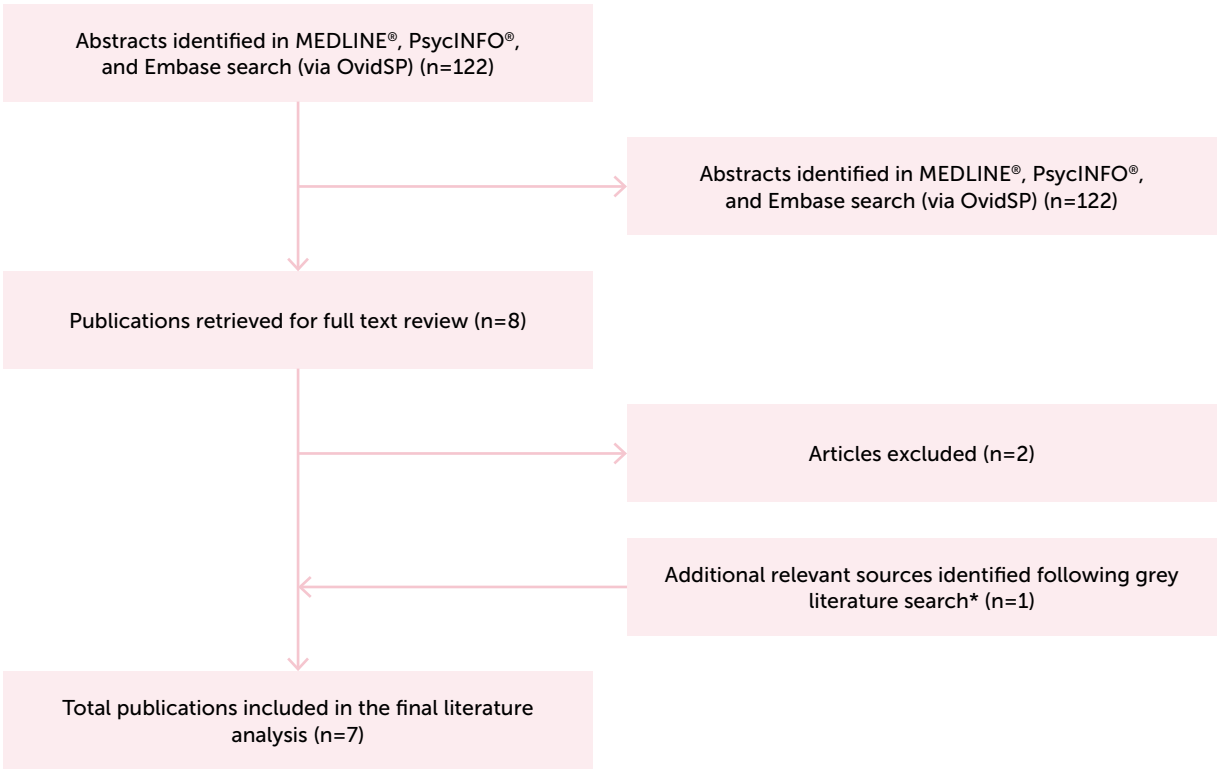
Table 1. Literature review search strategy

Databases searched included Embase 1996 to 2020 Week 50, MEDLINE® 1946 to 16 December 2020, and PsycINFO® 2002 to December Week 1 2020.

STEP	SEARCH TERMS	SEARCH TYPE	HITS
1.	H?emophilia* or Christmas disease or factor IX deficien* or FIX deficien*	All fields	76,045
2.	joint bleed* or microbleed* or asymptomatic bleed* or synovial bleed* or silent bleed* or subclinical bleed* or h?emophilic arthropathy or h?emarthtro* or joint pain	All fields	32,949
3.	symptom* or impact* or daily activit* or QOL or health related quality life or HRQOL or activit* daily living or ADL	All fields	6,918,773
4.	Qualitative or (focus ADJ group)* or interview* or patient report* or self report* or parent report* or caregiver report* or CareRO or observer report* or ObsRO or P?ediatri* or adolescen*	All fields	8,836,985
5.	(1) AND (2) AND (3) AND (4)	-	514
6.	Limited to English language	-	500
7.	Limit to full text	-	198
8.	Limited to Human	-	177
9.	Limit to last 10 years ("2010-Current")	-	147
10.	Duplicates removed	-	122

ADJ indicates search terms should appear adjacent to each other
? indicates multiple letters used in search term
* indicates truncation used for search term

Figure 1. Literature search flow diagram



*Including review of reference lists of full-text articles reviewed or online searches

RESULTS

Targeted literature review

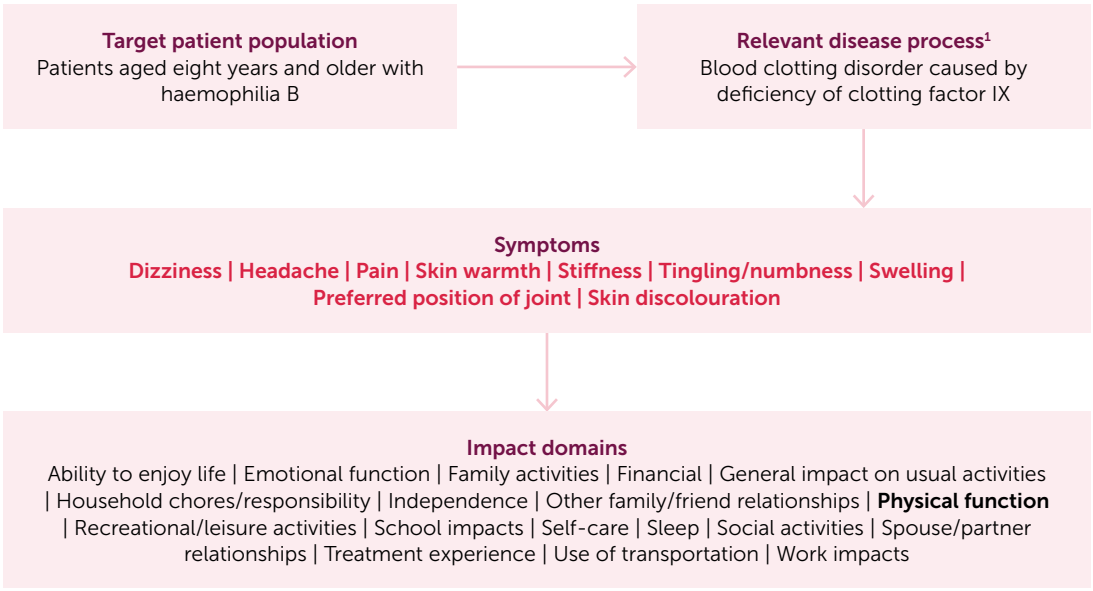
The literature search was performed on 18 December 2020 in OvidSP, using MEDLINE®, PsycINFO®, and Embase (Table 1). The search identified 122 abstracts.

From the initial screening of 122 abstracts, eight were selected for in-depth data extraction. Excluding two articles focused on PwH with inhibitors, and adding one from a supplementary search, the final analysis included seven publications [6,14-19] (Figure 1). These comprised seven journal articles and a conference poster, featuring a mix of qualitative interviews, focus groups, and reviews of medical records. The results of the literature review are a synthesis of both haemophilia A and B literature and not specifically haemophilia B.

Concepts identified from the literature review were organised into a conceptual model and used to inform questionnaire development in terms of which joint-bleed experiences might be most relevant and/or important to discuss. Nine symptoms were reported in the literature as specific to joint bleeds: dizziness, headache, joint pain, skin warmth, stiffness, tingling/numbness, swelling, preferred position of joint, and skin discolouration (Figure 2). Pain was the most frequently presented symptom (7/7 articles, 100.0%) and swelling (5/7 articles, 71.4%).

A total of 70 impact concepts emerged from the literature review and were organised across 18 domains. Impact concepts were organised in the conceptual framework (Figure 2). Symptoms included inability to load the joint, limited joint rotation, limited mobility, and restricted range of motion; impact domains with the most documented concepts included emotional function and physical function. The most frequently reported impact concepts were limited mobility (physical function domain; 5/7 articles, 71.4%) and anxiety and depression (emotional domain; 4/7 articles, 57.1%). Concepts identified in the literature described the experience of people with haemophilia generally (haemophilia A and haemophilia B) and are presented in the model as relevant to the haemophilia B experience. Where possible, joint bleed-specific concepts specific to younger individuals (ages 8-17 years) are noted.

Figure 2. Literature-based conceptual model of haemophilia B symptoms and impacts of a joint bleed



Bolded, red text indicates a concept specific to joint bleed in the literature

Advisory board meeting

A total of eight panellists participated in the advisory board (Table 2), all of whom work in the UK.

Feedback reported by the panellists relevant to the primary areas of discussion was summarised according to the following topics:

1. Value of a joint health self-monitoring tool
2. Purpose of a joint health self-monitoring tool
3. Assessment context of use
4. Target concepts of measurement
5. Assessment structure and approach.

Value of a joint health self-monitoring tool

A significant discussion topic during the advisory board was gaining input and alignment regarding the promise and purpose of developing a joint health self-monitoring tool for YPwHB and their caregivers. Panellists noted the tool could enable a common language among the YPwHB, parent, and clinical team to describe joint health experience based on the language used by the YPwHB. Panellists expressed frustration with existing questionnaires as outdated and/or not relevant to what they see in day-to-day practice, and indicated that there was an unmet need for a YPwHB-centred tool in haemophilia that would be of value for YPwHB and their caregivers. No specific tool was mentioned.

Another benefit of having a joint health self-monitoring tool for YPwHB and their caregivers noted by panellists was that the tool could enhance body confidence among respondents and increase self-awareness of joint health. It was suggested that if YPwHB were more attuned to what their bodies 'can do', they may be less hesitant to engage in physical activities because of what 'might happen'.

"I think that I'm helping someone to get more confident in understanding their own body and how that works, and I think that's a good thing. I think... the emphasis is on them and how they manage their haemophilia. And they may choose to... engage with healthcare professionals more frequently, or they may think... I'm okay... I can manage this myself and that's equally a very positive thing, so I think, helping them to understand their bodies and what's happening is... a good output." – Clinical Specialist Physiotherapist (#5)

"We're trying to encourage people to self-monitor so that they're aware of their symptoms, so that they can self-regulate and participate and be active in adulthood, rather than preoccupied on symptomology, but it's balancing that self-

education with over medicalisation…" –Clinical Specialist Physiotherapist (#6)

Purpose of a joint health self-monitoring tool

Panellists were in alignment with the intended purpose of the assessment, which is to help YPwHB (with their caregivers) detect and self-monitor early or subtle changes in joint health and changes in wellbeing. Additionally, panellists agreed that such a tool would raise awareness and education about the importance of joint health among YPwHB (and their caregivers) as well as support early and ongoing conversations around joint bleeding among young people, their families, and their healthcare providers.

"You could look at the quality of interaction that follows feedback from the tool, does it improve communication between… person with haemophilia and parents or… with the clinic or all three or… that sort of assessment may be helpful in a sense… it's an assessment tool, but there is a potential for it to have… almost like a therapeutic element from a psychological perspective… in terms of encouraging communication and an understanding so, that's always helpful in all situations…" – Haematology Consultant (#2)

Assessment context of use

The promise and value of an assessment tool can go unfulfilled if its context of use is not considered. In this regard, panellists noted differences in cognition, activity, and priorities among YPwHB in terms of their age. An effective self-report of joint health should take these differences into account and multiple tools may perhaps be required based on age groupings. Additionally, panellists noted that observer reports (e.g., caregiver) do not often agree with YPwHB reports, and it is important to ask YPwHB directly about their experience.

"Young children… may… grow up with mild discomfort I think they just get used to it and don't know how to express it so if this can enable that expression of symptoms, that would be really valuable…

To stop them at age 30 having some sort of chronic ankle problem and actually when you're 11 or 12 and you've not really seen anything massively wrong, we just find that balance of over medicalisation of a problem… also trying to… get some sort of internal reasoning process builder, and I think… that this can be used as… a certain pattern recognition, because actually that's an awful lot of what symptoms are, pattern recognition, certainly bleeding. And actually this may just be a prompt to help them develop their own pattern recognition for them that gets them into a habit of a lifetime of… 'this doesn't feel quite right'…" – Haematology Consultant (#2)

Target concepts of measurement

A target concept of measurement is the 'what' that questionnaire items measure and should reflect what is relevant to a given condition and important to people living with that condition. In the present context, panellists indicated that items should target for measurement early changes in joint health rather than an established joint bleed, as the tool should not replace clinical intervention. Panellists indicated that joint health impacts mood and wellbeing, and that these concepts would be of value to include in the joint-health self-monitoring tool. Because panellists also discussed a current lack of understanding of symptoms associated with sub-clinical bleeds, they suggested including an item asking respondents to simply note whether their joints feel 'different' (e.g., 'In the past 30 days, how often did any of your joints feel different from how they usually feel?') as one possible way of collecting information on these types of experience.

"I think the difference before and what you've got here is the behavioural stuff, the affective quality,… and I think that's never been looked at before that actually is perhaps something else… subtleties of movement, subtleties of just change in behaviour slightly that… maybe there's something else… is it hot, red, and swollen yes, no and then there's a whole other things around all these other bits that I've… never seen looked at. So you may have a predictive quality of some of this now." – Clinical Specialist Physiotherapist (#7)

Assessment structure and approach

During discussions of how the assessment should look and how respondents might interact with the tool, experts indicated that it would be important for the tool to provide an opportunity for YPwHB and/or caregivers to make notes, record questions, and answer items

Table 2. Advisory board participant information (N=8)

ROLE	WORK SETTING	EXPERIENCE
Consultant Haematologist (#1) (Adults)	CCC; haemophilia database; HaemTrack	Experience working with young people with haemophilia B that have transitioned into adult services
Consultant Haematologist and Centre Director (Adults and Children) (#2)	CCC	Experience working with adults and children with haemophilia
Haemophilia Nurse Specialist (Children) (#3)	CCC; haemophilia database review group	Significant experience working with children with haemophilia
Haemophilia Nurse Specialist (Children) (#4)	CCC	Significant experience working with people with haemophilia, both adults and children
Clinical Specialist Physiotherapist in Haemophilia (Adults) (#5)	CCC; HCPA	Significant clinical and research experience
Clinical Specialist Physiotherapist in Haemophilia (Children) (#6)	CCC	Significant clinical and research experience
Clinical Specialist Physiotherapist in Haemophilia (Adults) (#7)	CCC	Significant clinical and research experience
Paediatric and Adolescent Rheumatologist and Senior Clinical Lecturer (#8)	Rheumatology clinic for adolescents and university centre for musculoskeletal research	Significant experience researching PRO measures and patient-reported experience measures, working with adolescents with musculoskeletal complaints in their clinical practice

CCC: Comprehensive care centre
HCPA: Haemophilia Chartered Physiotherapists Association (UK)

Table 3. Focus group participant information (N=12)

HEALTHCARE PROFESSIONAL	YPWHB (AGE)	HAEMOPHILIA SEVERITY	PARENT (N)
Group 1			
Clinical psychologist	9 years*	Moderate	1
	10 years	Moderate	1
	10 years	Mild	1
	11 years	Mild	1
Group 2			
Physiotherapist	14 years	Severe	1
	21 years	Severe	

*YPwHB did not attend focus group

'in their own words' (i.e., include 'open text' items). Panellists were not in favour of including a body map to identify which joint is currently problematic; several panellists reported previous experience suggesting people have difficulty understanding the task.

Focus group

A single three-hour virtual meeting was held via a web-based platform, with 12 individuals participating in two subgroups. The participants included 5 YPwHB (aged 10-21 years, median 11 years), 5 parents (of YPwHB aged 9-14 years), and 2 healthcare professionals (Table 3).

Feedback from YPwHB and caregivers was summarised based on the broad discussion topics, including:

1. What it is like to have joint bleeds with haemophilia?
2. How do you keep track of changes in your joint health?
3. What do you think of a new questionnaire to help track changes related to joint health?

Key takeaways of YPwHB and caregiver discussion on these topics are described below.

What is it like to have joint bleeds with haemophilia?

Both YPwHB in Group 2 reported experiencing joint bleeds and described the following symptoms that they characterised broadly as feeling 'different than normal': pain, tingling, stiffness, numbness, skin near the joint feeling hot, and inability to bend the joint. In contrast, most parent and YPwHB participants in Group 1 were unsure if the child had a joint bleed.

> *"I'm not really sure if [child] has had a joint bleed... it's still relatively new to us and he does have mild haemophilia so and I know he's he can be quite accident prone... my only concern is not knowing what to look for." – Parent participant 1*

In addition to symptoms, participants also reported impacts of a joint bleed on mood, mental health, sleep, mobility, and ability to apply pressure on the foot (ankle joint).

> *"With his emotional well-being after an injury... we always get a downward spiral... and [he] can't sleep and always sleepwalks and then when I look... at it afterwards I realised there's always a pattern... after an injury after a hospital visit after with [his] mood at school and things like that so." – Parent participant 2*

When discussing indicators of a joint bleed, one young person with haemophilia who reported experiencing a joint bleed characterised the joint pain as "weird", "deep", "dull", and "stiff". Additional signals of a joint bleed were feeling "tingling", "stiff", "hot", "numb", and leading to an inability to bend the joint.

In answering what participants believed to be important to know about joint bleeds, they mentioned the importance of knowing when to seek treatment, key symptoms, prevention methods, and how to distinguish between joint bleeds and non-haemophilia symptoms. Additionally, one young person with haemophilia reported the importance of joint bleed avoidance, recovery, and rehabilitation, as well as the long-term effects of joint bleeds.

> *"For us, it would be to know at what point you should be seeking treatment and not in not injury ones, spontaneous ones, you know if they occur, when should we go to hospital and yeah that's, the main thing so obviously... if he bangs it and then it's... you know, within a few hours it's really stiff and everything you like oh yeah it's worse than just a bruise but if he was to wake up and his... knee's all sore you know how sore does it need to be to think right I've got a phone work take him to hospital, you know get treatment that sort of thing. So, it's the spontaneous ones at what point do you... need to phone in the haemophilia nurse and... having a discussion." – Parent participant 3*

How do you keep track of changes in your joint health?

YPwHB and caregivers were given an opportunity to discuss how they have tracked joint bleeds and joint health in the past. In this regard, two of the YPwHB described formally tracking changes in their joint health. Specifically, one reported keeping detailed notes, and the other reported keeping a mental record. The parent of the participant who kept a mental record also reported keeping a formal record of any joint health incidents on their household calendar. Although only some YPwHB participants reported tracking their joint health, all YPwHB and caregiver participants confirmed the value of a self-monitoring tool to track changes related to joint health. It is important to note that at least one YPwHB each from Group 1 and Group 2 expressed hesitancy to discuss changes in symptoms with their parents due to concern of causing them additional worry. All caregivers of YPwHB and healthcare professionals participating confirmed the importance of a tool to facilitate communication about joint health, although it is not always discussed at clinical appointments.

What do you think of a new questionnaire to help track changes related to joint health?

During the focus groups, participants were given the opportunity to share their thoughts on the development of a new assessment to help YPwHB and their caregivers track joint health. While open to different response options, Group 2 expressed preferences for a tool that included 'open text' response options so they could provide context surrounding the concept reported. Participants in Group 1 reported that the use of closed questions, instead of a Likert scale, would be easiest for younger respondents to understand and participants suggested a seven-day recall period, especially for younger respondents.

DISCUSSION

This study explored early indicators of joint bleeds and YPwHB's self-monitoring practices to develop a joint health PRO tool for YPwHB aged between 8-25 years. The activities conducted demonstrate that the joint-bleed experience among YPwHB is variable and

associated with a variety of symptoms and impacts that can only be known, or best observed, by the people with the condition themselves. Historically, while studies of this nature are common in similar musculoskeletal disorders, e.g. haemophilia A and juvenile idiopathic arthritis [20], they have not been conducted previously in the specific context of haemophilia B.

It is unknown if YPwHB need developmentally appropriate knowledge and skills training in self-management as part of their transitional care during adolescence and young adulthood that is different to haemophilia A. The effects on joint health are similar. Training and skills management are, however, relevant to both populations and as such the PRO tool may be relevant to both populations. This is shared by health professionals in the literature [21].

In addition, their caregivers need support and guidance to enable their children to gradually learn such skills and for their role to gradually evolve into a more consultative role [22,23]. Thus, it becomes increasingly important for YPwHB to self-monitor their joint health and share these experiences with their healthcare providers as they develop through adolescence and into adulthood. At present, no such tool exists.

Without a tool to support YPwHB in tracking their joint health and communicating changes in their joint health to healthcare providers, differences may arise among clinical expert observations and YPwHB's experiences in monitoring and responding to joint bleeds. Existing research also suggests differences that arise between clinician observations and YPwH self-reports [24,25], as well as between parents and children/YPwH [26]. Further, parents and caregivers of YPwH may feel that it is necessary to report the experience of their child to a healthcare professional rather than the child self-report; however, research has shown that young people (eight years and older) can self-report, especially when PRO development has been carefully tailored to age and developmental abilities [13]. Therefore, to centre YPwH's perspective of joint health and improve joint-health-related communications with healthcare providers, a self-monitoring tool is critical to provide evidence of changes in joint health. This approach is also consistent with research centring YPwH's experiences and preferences to improve quality of care [27-29].Furthermore, research also reports that self-monitoring tools help people with hereditary or chronic conditions to assess changes in their symptoms and overall health that lead to early intervention or changes in treatment [30].

The literature review identified many symptoms, and impact experiences related to haemophilia and joint bleeds. Collaboration from clinical experts, YPwHB, and caregivers have allowed developers to identify which aspects are most relevant. Specifically, the joint-bleed-related experiences which clinicians and YPwHB would find useful to self-monitor using the PRO tool could include pain, stiffness, joints feeling or looking different compared to the opposite joint, problems putting weight through a joint, avoiding using certain joints, how joints feel in the context of different activities, inability to do certain activities, and changes in generalised well-being concepts (i.e., mood, anxiety or worry, and problems with sleep).

In the present scenario, it is relevant to specify the target YPwH population and distinguish it by age. Tool developers aspired to create a PRO tool for use among young people of eight years of age and older with haemophilia B; however, the creation of a paediatric-focused PRO creates unique challenges compared to creating a tool for adolescents and adults [13,31,32]. Among the challenges is ensuring that the concepts assessed and the language used in the PRO are relevant and appropriate for the age group. A PRO questionnaire has been developed for the target population with adaptations made to reflect three age ranges within the 8-25 years age group (8-12 years, 13-17 years, 18-25 years) based on perceived natural development stages and the likely reduced need for carer support from the age of 13 years. The developers acknowledge that more research is needed to tailor the content for age subgroups within that wide range. A prototype tool will be administered in a pilot study with YPwHB (N=15; ages 8-25 years). Upon completion of the pilot study, further research activities may be considered to modify or support the use of the self-monitoring tool.

Limitations

YPwHB and caregivers' viewpoints are essential to effective interaction with the PRO tool, and they should be involved in all stages of the project. There are however limitations to this study.

There is limited literature pertaining to haemophilia B, and the results of the literature review are therefore a synthesis of both haemophilia A and B literature, and not specifically haemophilia B. The focus group in this study only interviewed patients with haemophilia B and as such no comparison to haemophilia A can be made. Further research needs to be convened to explore if there are, indeed, differences in the clinical presentation and needs of patients with haemophilia A and B.

The small sample size of this study is a limitation. Eligibility and patient selection for the focus groups was

based on convenience and as such may represent a bias sample. Focus groups require small enough group sizes to permit discussion but limit wider viewpoints.

Further studies could potentially offer an increased number of focus groups, widen the literature search and feedback to include those with haemophilia A and consider all aspect of musculoskeletal health.

CONCLUSIONS

This study has supported the development and modification of a PRO tool to self-monitor changes in joint health and well-being and has highlighted its importance to YPwHB, caregivers and healthcare providers. It has highlighted a need for a PRO tool to monitor joint health in people with haemophilia aged 8-25 from clinicians, YPwHB, and their caregivers. A future feasibility study will pilot how the tool can be implemented in practice. The tool may potentially help YPwHB and their caregivers detect and track early changes in joint health, raise awareness about the importance of managing joint health, and support joint health conversations with healthcare providers. This is of particular current relevance in the context of newer treatments and reduced bleeding frequency, and associated limited previous experience or recognition of a bleed.

Additional benefits highlighted by experts include empowering YPwH B, fostering body positivity and confidence by encouraging understanding and ownership of their joint health. Similarly, caregivers can gain confidence in the young person's ability to recognise, report and respond to their changes in joint status' through planning and modifying activities.

The use of the PRO tool may be of clinical relevance to other inherited bleeding disorders; this would require further research.

DATA AVAILABILITY

The data that support this study and supplementary information are available from the data collection company upon reasonable request.

ACKNOWLEDGEMENTS

Informed consent has been obtained from the participants in the study reported in this paper.

Funding for this project and manuscript development was provided by CSL Behring. Brainsell Ltd hosted the parent online survey and shared anonymised results with CSL Behring UK.

Medical writing support was provided by Adelphi Values and CSL Behring in accordance with Good Publication Practice guidelines. The sponsor was not involved in developing this manuscript but reviewed the content for scientific accuracy. This paper reports on the development of a PRO tool and did not require research board approval.

Conflict of Interest

All authors received consultancy fees from CSL Behring for participating in the focus groups; there were no payments to authors for development of this manuscript.

ORCID

Melanie Bladen https://orcid.org/0000-0002-7413-1906
Janet McDonagh https://orcid.org/0000-0002-4555-7270
Paul McLaughlin https://orcid.org/0000-0002-5962-7647
Brittany Klooster https://orcid.org/0000-0002-2018-8982
Alan Shields https://orcid.org/0000-0003-3362-3135
Diane M. Turner-Bowker https://orcid.org/0000-0002-8491-5704
Kaitlin Chatterton https://orcid.org/0000-0002-0781-8716
Connor Volpi https://orcid.org/0000-0002-6292-6306
Sujan Sivasubramaniyam https://orcid.org/0000-0002-0859-0370
Jiawula Abulizi https://orcid.org/0000-0002-7576-5150

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HOW TO CITE THIS ARTICLE:
Bladen M, McDonagh J, McLaughlin P, Gooding R, Holder K-A, Thind S, Klooster B, Shields A, Turner-Bowker DM, Chatterton K, Leso A, Volpi C, Sivasubramaniyam S, Abulizi J, Khan N. Development of a patient-reported outcomes tool to monitor changes in joint health and well-being for young people with haemophilia B. *J Haem Pract* 2024; 11(1): 108-122. *https://doi.org/10.2478/jhp-2024-0014*

CORRECTION NOTE
This article was amended at the request of the authors on 8 October 2024. Changes to the version originally published on 20 September 2024 are as follows:

- p. 108: correction to the affiliation for Sharon Thind from Oncology and Haematology, Alder Hey NHS Foundation Trust, to Haemophilia Comprehensive Care Centre, Alder Hey Children's Hospital

An archived version of the article as originally published is available on request.

APPENDIX

FOCUS GROUP CONSENT AND SCREENING

The following comprises questions from the focus group consent and screening questionnaire only. Introductory and remuneration information is not reproduced.

Participant Screening

Please select the statement that best describes you:

- I am a parent. One or more of my children have mild, moderate or severe haemophilia.
- I am a parent. None of my children have mild, moderate or severe haemophilia. Screenout
- I am not a parent. Screenout

Note: Only participants who tick the first box can proceed.

How many of your children with mild, moderate or severe haemophilia are in the following age groups?
For each age group, please indicate whether you have none, one, or two or more children.

AGE (YEARS)	NUMBER OF CHILDREN WITH MILD, MODERATE, OR SEVERE HAEMOPHILIA		
	NONE	ONE	TWO OR MORE
7 or younger	Screenout	Screenout	Screenout
8 to 17	Screenout	Proceed	Proceed
18 or older	Screenout	Screenout	Screenout

1. **What type of haemophilia does your child have?** If you have more than one child aged 8 to 17 with haemophilia, please select the response most appropriate for the child for whom you are most worried about their joint health.
   - Mild
   - Moderate
   - Severe

2. **How many years ago was your child diagnosed with haemophilia?** If you have more than one child aged 8 to 17 with haemophilia, please select the response most appropriate for the child for whom you are most worried about their joint health.
   - _____ Years ago

   If screener 2 = Aged 8 -17, 2 or more

For the following questions, if you have more than one child aged 8 to 17 with haemophilia, please select all the signs or symptoms you have noticed in any of your children.

1. **What symptoms do you see when your child has a joint bleed?** Please select all the symptoms your child/children have experienced. These are some examples but please state any other symptoms.
   - the joint is hot
   - the joint is painful,
   - the joint is swollen,
   - difficulty using the joint such as a change in movement

   Other symptoms:

2. **We are also interested to learn if your child has experienced muscle bleeds. Has your child had any of these symptoms during a joint bleed?**
   Please select all the symptoms your child/children have experienced. These are some examples but please state any other symptoms. If none of these symptoms have been experienced, please select the option "none of these".
   - The muscle is hot,
   - The muscle is painful,
   - The muscle is swollen,
   - The muscle function/ ability to use is reduced,
   - There is a sensation of pins and needles in the muscle
   - None of these

   Other symptoms:

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3. **In the week preceding a joint bleed, has your child experienced any of the following symptoms?**
   Please select all the symptoms your child/children have experienced. These are some examples but please state any other symptoms, however minor or unrelated it may seem. We are particularly interested in symptoms that may not be typically associated with a joint bleed but may give us an insight into changes you experience prior to a bleed. If none of these symptoms are experienced, please select the option "none of these".

- For some of these options it may be useful to think back to your experiences pre-COVID 19 lockdown.

a. **Mood and behaviour:**
   - Not wanting to play
   - Disinterested in activities
   - Less energetic / enthusiastic
   - Irritable, uncooperative, fussy
   - Shorter temper / angry
   - Feeling down / sad
   - Fighting with siblings
   - More irritable / sad in the morning
   - Withdrawn
   - Reduction in concentration / reports from teachers of reduced attention/engagement at school
   - None of these

   Other symptoms relating to mood and behaviour:

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b. **Biological functions**
   - Disturbed sleep: difficulty getting to / early waking
   - Overly fatigued / daytime sleeping
   - Changes in appetite [specify if increase or decrease]
   - Difficulty eating, using cutlery
   - Reluctance to go to the toilet / changes in frequency
   - None of these

   Other symptoms relating to biological functions:

---

c. Activities

- For some of these options it may be useful to think back to your experiences pre-COVID 19 lockdown.
  - Doesn't want to go to school / after school group activities with friends
  - Shorter time spent playing / being outside
  - Reluctance to visit family / take weekend trips / playing with pets
  - Difficulty going up stairs / reluctance to use stairs
  - Need more help / taking longer time to get dressed, shower
  - Discomfort kneeling, sitting / frequent adjustment to position
  - Discomfort / difficulty holding games console controller
  - Regression in movement e.g. no longer walking but crawling
  - None of these

Other symptoms relating to activities:

---

d. Physical symptoms

- Joint pain
- Tired
- Nausea
- Headache
- Change in colour e.g. looks pale
- Dizziness
- Muscle ache / heaviness
- Raised temperature
- Tingling or numbness in muscle or joint
- Give medication e.g. Paracetamol [pain killers], help with sleep, nausea
- None of these

Other symptoms relating to physical symptoms:

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4. Expectations of an ideal questionnaire on symptoms at home:

This is to explore your preferences for a tool for parents and children to use alongside doctors/ nurses/physiotherapists to identify symptoms which could indicate a joint bleed might occur soon. Our aim is to create a simple questionnaire that you can use independently with your child.

- Which format would you prefer?
  - Paper
  - Electronic – Mobile Phone
  - Electronic – Tablet / Laptop

- What would be the maximum time you would be willing to spend on answering a questionnaire about potential symptoms?
  - 5 – 10 minutes
  - 10 – 15 minutes
  - 15 - 30 minutes
  - 30 – 45 minutes

- Based on what would be most convenient for you, how often do you think it would be helpful to complete this questionnaire about symptoms in order to monitor changes in your child's joints?
  - Once a month
  - Once every 3 months
  - Once every 6 months
  - Following the occurrence of a joint bleed
  - Other, please specify....

- Where would be the most convenient place for you to complete this questionnaire?
  - at home
  - at your appointment just before you see the doctor/physio/nurse
  - A combination of both

- What else could be included to help you manage your child's symptoms / help raise your concerns with your doctor?

J Haem Pract 2024; 11(1). doi: 10.2478/jhp-2024-0014