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"I'd go on a hike with my kids… that would make me feel so happy." Recognising what people with haemophilia B identify as meaningful when considering personal goals and the potential for gene therapy

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Introduction: Historically people with haemophilia B (PwHB) have experienced adverse clinical outcomes including joint bleeds, pain and arthropathy. The current management of severe and moderate haemophilia B in the UK is largely through the use of factor replacement therapy often given as prophylaxis. Despite this, research reveals reduced quality of life (QoL) and psychological burden in PwHB of all severities, highlighting unmet need. Contemporary therapeutic developments including extended half-life factor IX products, novel non-factor agents, and gene therapy offer opportunities to address treatment-related issues and improve QoL. We investigated what PwHB identify as meaningful when considering their personal goals and the potential for gene therapy.

Methods: UK men (aged >16 years) with severe or moderate haemophilia B were invited to take part in a face-to-face workshop or one-to-one online audio recorded interview. The recordings were transcribed verbatim, the transcripts were reviewed and coded using a process of inductive thematic analysis. We then used an iterative process to explore, review, reflect, and refine emergent codes and final themes. Ethical approval was not required based on the UK Health Research Authority decision tool.

Results: Nine men, all with severe haemophilia B, aged 21 to 64 (median 34 years) participated. All were diagnosed as children; four had a previous family history and all described themselves as 'well treated' with self-managed home therapy and prophylaxis. None had received gene therapy.

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Parallels were observed in their goals. Thematic analysis classified them as achievable, unachievable and future goals.

Achievable goals: Achieved despite living with haemophilia B, included education and employment, strong personal relationships, having a family, travelling, having a good social life and being able to participate in sports.

Unachievable goals: Things that participants felt unable to achieve either now or in the future. These included changing attitudes of others, a recognition of lost opportunities including more physical, sporting and employment activities.

Future goals: Those which might be achieved as treatments evolve. This included being more physically active, improved QoL for affected individuals and their families, greater ability to travel, and optimism for future treatments and their potential impact for future generations.

The goals of PwHB often focused on personally meaningful everyday activities. Seemingly modest changes in individual circumstances could impact on QoL and wellbeing. QoL improvements were defined as equitable access to education and employment, increased confidence in undertaking physical activities, and greater ability to travel. Treatment innovations were identified as enhancing individualised patient preferences and reduced fear of bleeding along with its sequelae of pain and limited mobility.

Conclusion: With improved access to novel therapeutic options, including gene therapy, PwHB are potentially able to experience equity to people without haemophilia in day-to-day life and activities. This will enable them to reimagine individual goals, their sense of what is 'achievable' and live their lives in personally meaningful ways.

Haemophilia B (Factor IX (FIX) deficiency) is a rare congenital disorder caused by an inherited genetic defect of the X chromosome. Its prevalence at birth is 5 per 100,000 males, of which 1.5 have severe disease [1]; although extremely rare, severe or moderate haemophilia B is occasionally seen in women [2]. The level of FIX determines the severity of haemophilia B: severe (FIX activity <1%), moderate (FIX 1-5%) and mild (FIX 6-40%) [3].

Haemophilia is characterised by spontaneous and post-traumatic bleeding, most commonly in in the weight bearing joints, leading to haemophilic arthropathy with impaired joint function and chronic pain [4]. This limits individuals' ability to participate in activities of daily living or to live spontaneously, impacting quality of life (QoL) [5,6]. Psychological burden is reported in people with haemophilia (PwH); anxiety and depression are common due to bleeding, but also as a result of frustration with treatment and issues with venous access [7,8].

Prophylactic factor replacement therapy is the standard management of severe and moderate haemophilia [9]. Prophylaxis aims to prevent joint bleeding and reduce mortality and morbidity, but is burdensome due to frequent injections and is associated with poor adherence [10,11,12]. Restricted access to therapy also remains an issue for PwH worldwide. In recent years, novel subcutaneously delivered molecules have been developed that appear to provide effective prophylaxis [13,14]. In addition, bioengineered clotting factors with extended half-lives have improved treatment adherence [15] and reduced treatment burden [16].

While a range of treatment options exist for PwH, gene therapy, a one-off single infusion, with a longer lasting mechanism of bleed management, is available [17]. Gene therapies have shown sufficient safety and efficacy evidence to have gained market approval in some geographical areas [18,19,20]. Why PwH may consider gene therapy as a treatment option now or in the future, including the impact on goals and life attainments, needs to be better understood [21,22,23].

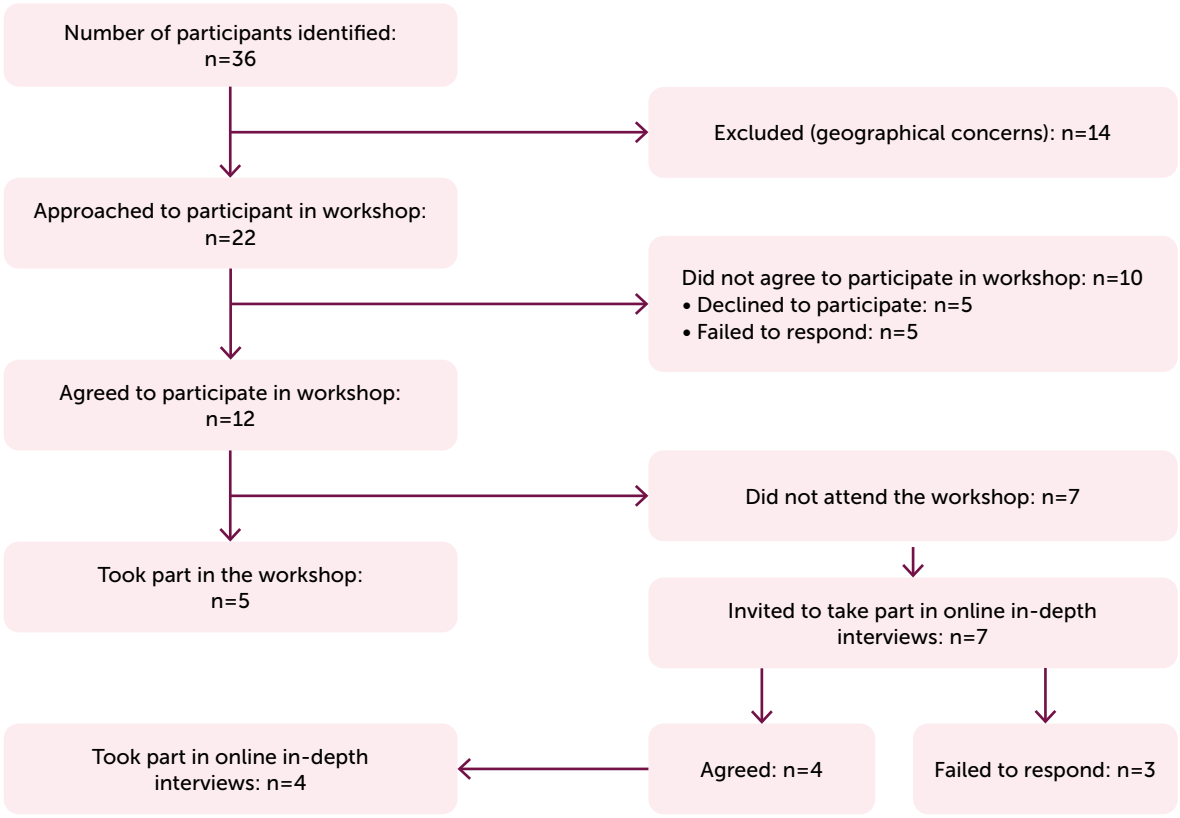
There is little published data on expectations or experiences of people with haemophilia B (PwHB) with regard to new treatments and potential outcomes. The aims of this study were to:

1. explore and understand the lived experience of PwHB,
2. investigate the real-world goals of PwHB, and
3. evaluate the hopes, knowledge and expectations of gene therapy as a future treatment.

METHODS

Haemnet is a research and communications agency embedded in the bleeding disorders community. Through Haemnet's research database, we identified males from the UK, aged over 16 years, with severe or moderate haemophilia B, currently treated with prophylaxis, and invited potential participants to take part in an audio recorded, four-hour face-to-face workshop. Those who were unable to attend the

Figure 1. Recruitment flow diagram



workshop participated in individual two-hour online qualitative research interviews, which were audio recorded.

An 'Open Space' methodology was used to stimulate discussion among the participants [24]. Recognising the subject matter as an area where discordance may exist between health care professionals' (HCPs') perceptions of patient understanding and preference and patients' actual lived experience, it was important to create a space for active listening [25]. The Open Space methodology invites participants to contribute, listens to their responses and perspectives, and notes their experiences and views, rather than holding an actively led discussion. In the context of the workshop, this allowed participants to raise topics they classified as important, rather than pursuing preconceived assumptions about PwHB's priorities. As such, it also enabled the identification of areas where there is tangible energy for deeper understanding of the issues that directly affect PwHB.

A broad outline guide was used to help prompt the discussion, focusing on:

- Experience of living with haemophilia B and its treatment
- Relationships with HCPs and treatment centres
- Personal goals, including the influence future treatment opportunities such as gene therapy may have.

Ethical approval was not required based on the UK Health Research Authority decision tool [26]. However, written consent to use direct quotes was given by all participants on the understanding that no personal details would be shared. Participants were free to withdraw at any stage. All data collected were anonymised and managed in line with the UK Data Protection Act 1998.

Each participant was assigned an individual study number. Audio recordings were transcribed verbatim. The transcripts were thematically analysed and coded in NVivo using an inductive approach to explore themes, review emergent codes, reflect, refine and identify final themes. To ensure that codes and/or themes emerged from the workshop and interviews, and not pre-existing researcher experience or literature, no pre-defined code trees were created [27,28]. Field notes and observations made during the workshop and interviews were used to provide further context for the analysis.

Participants were advised that the research was funded by an unnamed pharmaceutical company. They

Table 1: Code tree, themes and sub-themes identified through workshops and interviews

CODE TREE		
OVERARCHING THEMES	**THEMES**	**SUB-THEMES**
Living with haemophilia	Frustrations	Bleeds
		Mobility
		Joints
		Pain
		Treatment
		IV access
	Not being held back	
	Infected blood	
	The next generation	
Goals	Achievable goals	Family/relationships
		Education
		Employment
		Sport
		Travel
	Unachievable goals	Family/relationships
		Education
		Employment
		Sport
		Travel
	Future goals	Family/relationships
		Employment
		Sport
		Travel
Gene therapy	Uncertainty	Need for more information
	Equitable access	
	The next generation	
	Psychological support	
	What gene therapy might offer	

received an honorarium for their time and all travel costs were reimbursed.

Partnership with patients is increasingly recognised as enabling health research to address questions of impact [29], and has been noted specifically with regards to haemophilia as a way of ensuring research outcomes are meaningful and relevant to those who live with it [30]. The value of patient authorship is increasingly recognised in medical publishing [31]. To bring the value of such approaches into this study, we actively involved a person who lives with severe haemophilia in its development, analysis, and write-up.

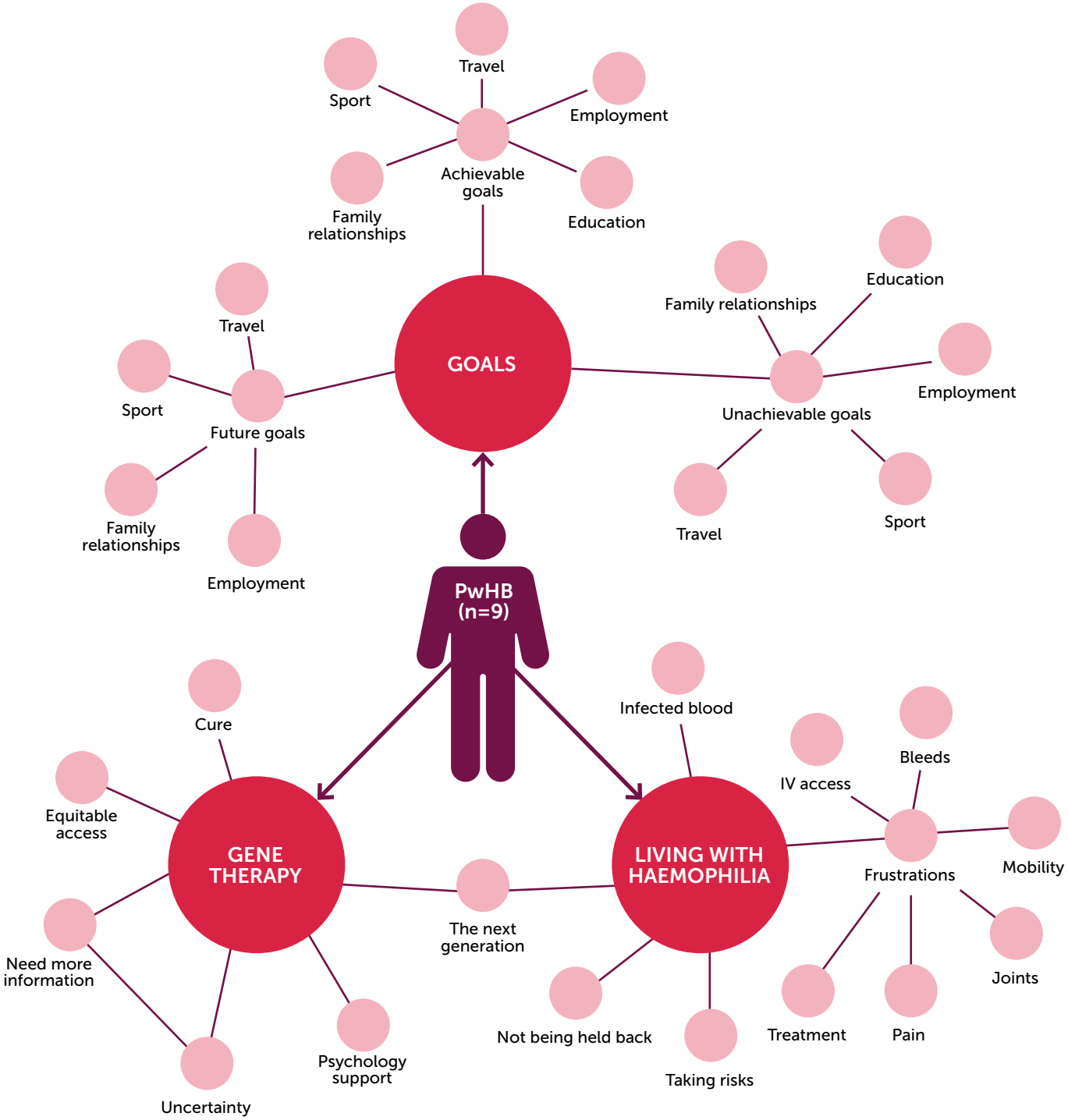
RESULTS

Of 61 PwHB in Haemnet's research database, 36 were identified as adults (over 16 years) with a confirmed diagnosis of severe or moderate haemophilia B treated with prophylaxis, and therefore eligible to participate in the study. The recruitment process is outlined in Figure 1.

The participants were aged 21 to 64 (median 34 years) and represented a wide geographical area within the UK. All had severe haemophilia B and were diagnosed in childhood. They reflected a broad mix of awareness, knowledge, and engagement with haemophilia: some were involved in scientific teaching and/or haemophilia advocacy with a high level of knowledge due to personal histories, however others were relatively unfamiliar with scientific, medical or advocacy influences, terminologies, and developments.

All participants considered themselves 'well treated', having received prophylaxis for many years; all those under 40 had been treated prophylactically from early childhood whilst older participants received prophylaxis

Figure 2. Core themes identified in workshops and interviews: living with haemophilia, goals, and gene therapy



later in childhood/adolescence. One participant was treated with standard half-life factor, five with extended half-life factor and three were participating in clinical trials of investigational medical products. All were able to self-infuse and treated themselves at home using tailored prophylaxis based on individual pharmacokinetics and physical activity.

During the analysis, emergent codes were refined into three overarching themes (Table 1; Figure 2):

- Living with haemophilia
- Goals
- Gene therapy.

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These are discussed in depth here with supporting quotes, anonymised to participant number [e.g. P01].

Living with haemophilia

The pervasive nature of haemophilia B and its impact on multiple aspects of life created a series of inter-related frustrations grouped around the sub-themes of mobility, joints, pain, and treatment. Duality was observed whereby participants demonstrated a mindset of 'not being held back' by haemophilia, while tacitly acknowledging that living with haemophilia caused them to adapt and/or redefine their individual expectations and decision-making processes.

Frustrations

Impaired **mobility** was a key cause of frustration impacting all aspects of life, from routine day-to-day activities to limiting spur-of-the-moment decisions.

> *"Speaking as somebody who has, you know, really painful long-term joint damage, it really affects my mobility and so I can't be as spontaneous as I would like to be." [P07]*

Participants exhibited a stoicism about the **pain** they experienced, highlighting its impact on their lives and the known inadequacies of how it can be managed.

> *"[Pain is] an occupational hazard ... you get pain whatever, don't you, really, so you just deal with it." [P07]*

A specific hope was for future haemophilia treatments that might reduce the likelihood of joint impairment. Participants agreed that **joint health** was key to maintaining mobility, being pain-free and goal achievement.

> *"The higher their clotting factor levels are going to be the more likely it will be that as they grow through their teenage years that they don't get any joint damage and so they're going to be protected from it in their older years and they're going to absolutely be able to have the kind of spontaneous normal life I can only wish for." [P01]*

Treatment experience varied based on health status at different points in participant's lives. Some described frustration around limitations in knowledge of and access to different or new treatments and 'gatekeeping' by physicians.

> *"At least if [my consultant] would have said, 'Yes, it's out but we don't think it's going to suit you,' that's fine. But he just wouldn't entertain me having any other treatment." [P07]*

When discussing treatment, it was evident that frequent intravenous **infusing** was a notable burden but considered a 'necessary evil'.

> *"It's a bit frustrating to treat every three days, and some days you think, 'Oh God, is it the third day already?'" [P08]*

Not being held back

All participants expressed a desire to achieve 'normality'. However, the definition of normality differed based on experience, expectations, the influence of haemophilia B on decision-making, and whether actions and goals were subconsciously shaped by mobility issues. One participant spoke of constant 'risk assessment', which could be seen to separate the thought processes of PwHB.

> *"I have lived years in crisis management mode ... I'm constantly risk assessing everything I do, I risk assess everywhere I go... getting out of that and changing that psychologically for me would be an absolutely massive thing to do." [P01]*

Goals

Living with haemophilia B had affected the lives of participants to different degrees in terms of physical impacts (e.g., joint health, mobility, pain), but their goals shared many parallels. Participants' aspirations were identified as 'achievable', 'unachievable' and 'future' goals, within which there were recurrent and cross-cutting sub-themes including 'family/relationships', 'education', 'employment', 'sport', and 'travel'.

Achievable goals

Participants identified current achievements and goals they considered achievable despite their haemophilia. Examples included getting married and starting a family, building friendships and 'fitting in', having social interactions, spending quality time with family (without bleed/treatment interruptions), and walking the dog.

> *"We've just come back from [holiday]... with the family and that. Took our granddaughter away for the first time, which was nice." [P07]*

"We've got a dog now... I walk him during the week... I'm glad to be able to do that." [P08]

Participants described some sports-related goals as being 'achievable', even where negative consequences could be anticipated. For some, sports were an integral part of life. Within this frame, sports-related achievable goals can be viewed as 'negotiated'.

"The trainer said, 'Are you going to have a go?' and I said, 'I'd love to but I can't, I've got haemophilia, I've got arthritis.' He adapted it for me and it got me hooked. He's designed a special syllabus around me and what I can do... it's probably the best exercise I've had in a long time." [P01]

However, as well as describing taking part in sports in a more limited way than they would prefer, participants also described hiding activities from HCPs and potentially exposing themselves to degrees of risk.

"I did karate when I was younger and enjoyed it... I didn't ask their permission." [P01]

Not all achievable goals were sports and activity related. One participant reported wanting to get a tattoo, which was discouraged due to need for additional treatment and/or bleeding risk.

"I was like, 'Can I have a tattoo?' and she's [the doctor] like, "I'll be honest with you, there's lots of people that have tattoos that have haemophilia, you will probably have a bit of excess bleeding," and she said, "I don't love the idea of prescribing extra treatment to have a tattoo" ... I did and you know, it was completely fine." [P03]

Participants discussed the limitations of travelling with medical products, particularly liquids and syringes. Despite carrying the necessary paperwork to take such items on aircraft, a number of examples were described where an achievable goal was met with an unexpected limitation or impact which can have a negative effect on wellbeing.

"I haven't been out of the country until this year for nine years. Going out of a UK airport I feel like a criminal every time [because of needles and syringes] even though I've got the hospital letters, etc." [P08]

Unachievable goals

Unachievable goals were defined as those that participants had been unable to achieve currently and considered unachievable in the future.

Employment was one of the most notable unachievable goals. A number of participants had harboured ambitions to join the armed forces or police, but were automatically disbarred due to their haemophilia and the necessity of being 'fit for frontline service'.

"I wanted to be in the Royal Navy. I even went to the recruitment and I passed the tests and I went for the medical and... he said I'd be a liability to everyone." [P01]

Despite having achieved a successful career in education, one participant stated that it had not been his first occupational choice; his health had imposed limitations that led him to consider occupations seen as less physically demanding.

"Teaching was definitely the second choice. If I had my way and didn't have haemophilia, I wanted to be a police officer... sometimes I think, 'Oh, I still wish I could do that, I'd love that.'" [P08]

Another participant, with a complex treatment history, had been severely limited with regard to employment opportunities, making almost any goal around employment unachievable.

"I've never been able to work because my haemophilia has been so severe." [P07]

Participants acknowledged that playing sport at elite levels was a common goal for many but achieved by few. They interpreted not being able to attain this goal as being indicative of the limitations that come with living with haemophilia B.

"I remember going to the centre and saying, 'What treatment have they [the treatment centre] got, because I want that.' If it's good enough for them to do professional sports, I want that for my daily life." [P04]

While some participants were prepared to travel with their treatment, others were less keen, leading them to self-police achievable travel.

"There's certainly countries I've always been told, you know, go to where they've got a haemophilia centre, etc." [P08]

Future goals

Future goals were identified as those participants hoped to achieve as treatments evolve. Due to the diversity of lived experiences within the group, there was crossover in themes where participants considered goals either 'unachievable' or 'future' based on their anticipation of how treatment advances may influence their individual situations.

"I'd go on a hike with my kids. And that would really make my day. That would make me feel so happy." [P01]

For family and relationships, future goals ranged from the 'everyday' to those that might be considered more existential. Regardless of how achievable goals were, they were frequently linked with potential benefits of future treatments. Existential hopes included the psychological impacts that haemophilia can have on family members – in particular, the guilt experienced by mothers, and hopes that future treatments may lessen this emotional burden.

"I'm just thinking, my poor mother... if I could take that [guilt complex] away from her..." [P03]

While acknowledging that future treatments were unlikely to influence the hereditary nature of haemophilia, recent and ongoing treatment developments had given participants hope for future generations. This included increased confidence around having children.

"When I think about it, I definitely think it's easier and... it would be something that I'd think about more seriously and have less reservations about saying no to because of my condition." [P09]

Future sporting goals were strongly related to advancing standards of treatment. Despite not wanting to be limited by haemophilia and a desire to do more physical and contact sports, a number of participants spoke about imposed physical limitations. One discussed his hope that treatment advancements might one day enable him to play rugby.

"I would be more comfortable in joining a rugby team... even playing tag or touch, I'm always a little bit nervous... of getting a problem." [P08]

With regard to travel, participants noted the potential for gene therapy to remove the need for regimented treatment and carrying quantities of medical supplies. This raised the concept of 'treatment freedom' and opportunities for longer trips or living overseas.

"Moving abroad is something I've thought about ... that is something that I seriously think about." [P09]

One participant expressed a desire to travel without limitation or anticipated frustrations related to his haemophilia. He noted that this goal was a realistic reflection of what people without haemophilia take for granted.

"Just enjoy life, really... take the granddaughter places without having to worry about 'oh, I'm going to get a bleed on the way back'... just normal life, really. Just things that normal people do." [P07]

Gene therapy

Discussions about gene therapy focused on participants' understanding of what it involves from medical and personal perspectives, their thoughts and hopes for what it may offer, and its potential to positively impact their lives and enable them to achieve their goals. Five themes were identified: 'uncertainty', 'equitable access', 'the next generation', 'psychological support', and the concept of whether gene therapy could be considered a 'cure'.

Uncertainty

Participants' knowledge and understanding of gene therapy was mixed. Most knew about it as a concept but their understanding of the processes involved was variable. Those with backgrounds in science, research and advocacy demonstrated greater knowledge, whereas some acknowledged they knew very little about it.

"I'll be honest I don't know what gene therapy is. I don't have a clue. I don't know how it impacts." [P03]

Lack of knowledge contributed to uncertainty for many participants around whether they would consider gene therapy as a treatment option in the future; however, there was a desire to learn more about it. It was apparent that participants considered

it important to have sufficient knowledge to make an informed decisions about treatment. The level of what was considered sufficient varied based on individual experiences and expectations.

> *"I like to do my research and give it plenty of thought, consult with other people, particularly people at the haemophilia unit." [P06]*

The opportunity to speak with people who had undergone gene therapy was identified as important:

> *"it would be super-helpful." [P09]*

Despite uncertainties around whether gene therapy would be a treatment option they would consider personally, there was agreement across the participant group that it is a positive development for the wider haemophilia community.

Equitable access

Participants agreed that gene therapy should be made available to PwHB as one of a range of options to be considered as part of a personalised care plan. They felt that PwHB should participate in a shared decision-making process with their clinicians, but should be able to determine for themselves whether they had 'enough understanding' of gene therapy to be able to engage in this.

Participants were aware of the complexities of access to and funding of novel therapies but felt strongly that older age should not be a barrier to gene therapy. It was suggested that initial costs should be balanced against long-term considerations.

> *"If you have to live in a [care] home or if you're single with mobility issues, if you have gene therapy you don't need to go out and collect your factor, or risk falling down the stairs for the delivery person, you don't need a [care] home that has one of the nurses trained specifically in haemophilia care." [P04]*

The next generation

There was a general belief that gene therapy would have a significant impact for the next and future generations of PwHB, and that they would be keen to have it.

> *"I think gene therapy is going to be slightly transformational for our generation, maybe a little bit more transformational for your generation, but it's going to be absolutely huge for the next generation." [P01]*

Participants with complex treatment histories saw the potential for gene therapy to prevent the health burdens they had experienced. However, it was strongly voiced that all existing approved treatments have an important role in helping to maintain joint health until PwHB who may consider gene therapy become eligible for it.

Psychological support

The possibility of living a life without prophylaxis after gene therapy treatment raised issues around identity. As the burdens and limitations of living with haemophilia B impacted all facets of life, participants had to plan and work around them. As haemophilia therefore provided a framework for their lives, however limiting it might be, there was concern that removing this could result in psychological impacts around loss of identity and sense of community.

> *"I know who I am being a haemophiliac, I know what I can do, I know what I can't do, I've pushed those limits and I know where they are." [P01]*

Perceptions of gene therapy

Gene therapy for haemophilia is not a cure but rather a practical term to describe 'normalisation of the body, obtaining a normal life or a change of identity' [32]. Although gene therapy is often seen as a 'cure' within the wider haemophilia community, participants were sceptical about this vocabulary and voiced the importance of appropriate educational resources to assist people's understanding.

> *"I would never call myself cured even if I've had it, because you can never take away the lasting [joint] damage of what you've had ... and actually you are still not at a level that an average person on the street down there would be at. So I wouldn't call it a cure." [P04]*

Participants highlighted bleed prevention as an essential part of treatment to avoid joint damage early in life and preserve joint function later on. The need for better treatments targeting arthritis and pain for those with existing joint damage was also considered important.

There was uncertainty around whether gene therapy would impact the hereditary nature of haemophilia B, with some participants questioning whether the haemophilia gene would still be passed to their children. This broadened to participants reflecting that while the defective gene could still be passed on, gene therapy had the potential to alleviate the impact of haemophilia B for future generations, reducing the psychological burden of familial guilt. Acknowledging that gene therapy should not be considered a cure, they agreed it had the potential to alleviate the burden and to redefine what living with haemophilia B entails.

DISCUSSION

On a superficial level, the goals of the PwHB who participated in this research can be viewed as little different from those of peers who are not affected by haemophilia. They reflect a desire to have strong secure relationships with family and friends, to enjoy success in education, to find a good job, to engage in sport and other physical activities, and to travel and see the world. Some of the goals expressed could be seen as modest in nature, but they should not be underestimated. In the context of living with haemophilia B, they should be considered for their potential impact on QoL rather than the material difficulty of achieving them. From many of the goals expressed – walking the dog or going on a hike with children – it is evident that seemingly small changes in personal circumstances could significantly amplify positive outcomes in an individual's sense of wellbeing.

The study participants' goals should be considered through the lens of their lived experience as PwHB, including the inherent limitations they have learned to live with and accommodate as a matter of course into daily life. This is a phenomenon that could be attributed to living with a 'haemophilia mind' [33,34]. All participants, irrespective of their circumstances, expressed a strong desire not to be held back by haemophilia B. However, despite 'normality' being a core motivation underpinning and influencing their goals, their actions and decisions are determined by their haemophilia, which presents a need for constant 'risk assessment' and a psychological burden. This common ambition to strive for 'normality', not be treated differently, and 'prove people wrong' presents a paradox, in that the 'normality' PwHB perceive represents a life far from normal [35,36]. This is supported by the work of O'Hara et al who identified the 'disability paradox', which showed that PwH report good or excellent QoL while the general population characterise the daily struggles of living with haemophilia much less favourably [37]. Our research in this study further enhances the understanding of the burdens that affect PwHB whilst recognising that the perception of those burdens differs between people with and without haemophilia.

Despite some goals being identified as 'achievable', they reflect significant levels of drive and determination. The participant group included a number of highly motivated, goal-orientated individuals, and some of the goals they considered 'achievable' would perhaps not be so for all PwHB. The group as a whole shared a view that they had not been held back by their haemophilia, expressing a desire to 'just get on with things' or an attitude that 'it is what it is'. However, they also had aspirations that were not recognised as goals due to their belief that the likelihood of them being achievable was low. In this sense, participants normalised the limitations they live with [38] rather than normalising their goals.

The 'social model' of disability [39] encourages us to question the ways in which PwH's goals are rendered intrinsically unachievable through their haemophilia, rather than the broader social lack of reasonable adjustments that might allow PwH to participate; i.e., that social and environmental factors also impact the limitations imposed by haemophilia. This is clearly seen in the experience of participant P08, for example, who felt unable to achieve travel goals due to incidents of feeling stigmatised for carrying needles. This limitation has little to do with the clinical characteristics of haemophilia itself; it is the result of a social response to disability and difference. Similarly, participants' sense that they are unable to participate in sports speaks to lack of opportunities and funding for parasports, rather than a straightforward limitation of haemophilia. The social model of disability has been used to understand lived experience in various chronic conditions [40,41], but has had little application in haemophilia. There are opportunities for future research to better understand how PwH's goals are circumscribed not only by bleeding or joint damage, but by socio-environmental factors.

The psychological impact of being told to avoid or moderate activities to minimise risk meant participants often adapted their goals to what they believed to be achievable, rather than allowing themselves to consider activities they had been repeatedly told they could not do. These limitations are often rooted deeply in the haemophilia mind [30,31]. The research team noted that even well-treated participants with relatively good joint health precluded themselves from certain activities or engaged in them at a lower level (e.g., non-contact sport alternatives, watching activities they would like

to take part in). As such, they can be understood to present acceptance, as 'normal', of a lower QoL than they would hope to achieve without haemophilia B [12,34].

Similarly, we noted a reluctance to celebrate what were perceived as more mundane forms of activity. For example, one participant felt his career in education, albeit successful, was imposed by the limitations of his haemophilia. He had harboured ambitions to join the police; while teaching is not as physically demanding, hours spent standing at the front of a classroom is an achievement that previous generations of PwHB may have only dreamed of.

Although not set out as an objective or explicitly sought by this research, this sense of loss within the haemophilia mind can be interpreted as one of the most significant impacts of current standards of treatment. This was not directly acknowledged by participants but evidenced in comments such as:

> *"My greatest regret in life is when my kids were young I couldn't kick a football with them and I still can't." [P01]*

> *"Haemophilia has made me more cautious as a person, it's made me more cautious, more anxious, and I don't know whether it's potentially the reason I stopped playing football and cricket." [P05]*

'Unachievable goals' were defined as those that participants had been unable to achieve as a result of their current situation, and that they considered unachievable in the future. Underlying the desire to live a 'normal' life was the recognition that living with haemophilia B has limitations, in particular the nature of the jobs they felt able to aspire to do (and in some cases were allowed to do), their ability to engage in sport and other physical activities, and, to some extent, their ability to travel.

Participants saw some goals as unachievable due to the effectiveness and limitations of treatment, including associated physical impacts, and the self-limiting behaviour described above. Those with complex treatment histories experienced mobility limitations due to joint disease and living with pain, though comments about joint damage, pain and mobility were not entirely absent among those who had benefitted from access to prophylactic treatment from a young age. All participants expressed common frustrations with treatment, including the need for frequent infusions [12], impacts on joint health and mobility [42], the stigma associated with infusing factor products [43], and limited access to physiotherapy and dental care. These represent known frustrations and unmet needs.

While not a primary objective of this research, the themes identified as frustrations represent a broad range of treatment-related goals which influence how PwHB perceive their ability to achieve other goals in their lives. These are inter-related and include:

- Reducing bleeds and their disruption to health status and activities of daily living
- Maintaining mobility
- Preserving joint health, or retaining joint health status and slowing further deterioration
- Reducing pain
- Overall improvement of treatment options and related education, including access to allied health services
- Developing treatment options that reduce the stigma around infused treatments.

Future goals remain for all participants in this research, including improved QoL for forthcoming generations of PwHB. Their achievement may be facilitated as future treatments evolve, and the theme of travel in particular illustrated how treatment advances could influence the ambitions of PwHB. Alongside this, the research team noted participants' shared sense of what 'should be' achievable for PwHB. Novel treatments offering enhanced factor half-lives clearly provide greater protection against joint and muscle bleeds [10]. Treatments such as gene therapy for haemophilia B offer the potential for a 'once and done' approach with a prolonged durability of FIX expression equivalent to mild haemophilia or into the 'normal' range [16]. In offering a functional 'cure' for a period of time, it has the potential to offer relief from the less obvious burdens associated with treatment (such as the need for intravenous therapy and constant 'risk management') and a step towards the 'haemophilia free mind' that has been posited as a new aim of future therapies [30,31]. However, participants' concerns about their identity as PwH indicate a need to offer psychological support to PwHB both pre-gene therapy and when adjusting to life post-gene therapy [44]. Challenges remain in addressing the more intangible limitations imposed by pre-existing joint damage and chronic pain, and it is essential that efforts around patient education for gene therapy continue to keep pace as these treatments enter the market. Future research, following access to innovative therapies for PwHB, will reveal how, or if, these treatments reduce

previously imposed lifestyle limitations including career choices, sports participation and impact on overall QoL.

Limitations

There are limitations to our study findings, which are based on the views of a small number of adult men with severe haemophilia B who are resident in the UK. Their views may not be representative of the wider haemophilia community per se. Certain themes (e.g., sport, travel) spanned the themes of achievable, unachievable and future goals, suggesting variances in individual perceptions of how living with haemophilia B has held participants back. This was linked to participant age, early access to treatment, and the long-term sequelae of joint bleeds.

CONCLUSION

It is important to recognise that the goals of PwHB can be influenced by seemingly small changes to lifestyle factors that result in a significantly amplified positive influence on an individual's lived experience – for example, the ability to be more spontaneous in everyday decision-making.

In many respects, the goals of PwHB are aligned to those of people without haemophilia: desires to form strong personal relationships, have equitable access to education and employment, and to feel confident when engaging in sports, physical activity and travel. Innovations in treatment will, undoubtedly, impact these findings. Equity for PwHB can be achieved by enhancing access to appropriate treatments, including education and guidance to enable informed treatment decisions, and the removal of the inherent limitations that have traditionally influenced their ambitions and life choices.

While significant therapeutic advances have been made in recent years, gene therapy for haemophilia B is not yet widely available despite being authorised in the UK [45]. Future studies of the impact of gene therapy for PwHB should investigate the impact on psychological health and wellbeing, alongside long-term physical outcomes, to promote and enhance lived experience and goal achievement.

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Author contributions

The project was designed by KK, RN, SC and JT. The data was acquired and analysed by KK, KJ and SF. RG is a patient representative. All authors were involved in the interpretations of the results and the development of the manuscript.

Consent

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

Disclosures

This study was sponsored by Pfizer Ltd. SC, RN and JT are employees of Pfizer Ltd and may hold stock or stock options. KK, SF and KJ are employees of Haemnet Ltd, which was a paid consultant to Pfizer in connection with the development of this manuscript and conduct of the study.

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