CLINICAL RESEARCH

Exploring patient and clinician perspectives on the benefits and risks of emerging therapies for the treatment of haemophilia: a qualitative study

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A qualitative study exploring clinician and patient perspectives on the benefits and risks of emerging haemophilia treatments found a broad range of influences on patient choice, with clinicians playing a key role in framing discussions

Background: Enhanced horizon scanning for emerging treatments has identified that both haemophilia A and haemophilia B pathways will be enriched with a range of new medicines with varying benefit-risk profiles. Patient and clinician views on the balance of the benefits and risks associated with emerging therapies will affect their use for the treatment of haemophilia, while also introducing the need for effective communication strategies to enable informed patient-clinician decision-making. **Aim:** This study aimed to explore patient and clinician views on the perceived benefits and risks of emerging therapies for the treatment of haemophilia. The study also aimed to gain insight into clinician-patient communication on benefit and risk and how this shapes decision-making on new therapeutic options. **Methods:** Qualitative methods, using online focus groups and one-to-one interviews, were guided by a defined set of questions. Data were collected in 2022 and 2023 from a sample of adult patients identified through

the national patient group (The Haemophilia Society) and clinicians identified through the NHS England Clinical Reference Group (CRG) and HAEM-NET. Data were analysed thematically. **Findings:** Seven patients and ten clinicians (seven consultant haematologists; three advanced nurse practitioners) participated. Five summary themes were identified, three of which related to clinician-patient communication: (i) active vs. passive patients; (ii) health literacy; (iii) external factors. One theme related to gene therapy perspectives on benefit-risk, and one theme concerned the legacy of the infected blood scandal. **Conclusion:** There remains scepticism about gene therapy across all research participant groups, which suggests that uptake is likely to be relatively slow, with divergence anticipated between haemophilia A and B. Treatment decision-making and benefit-risk discussions are complex and multifaceted issues which in haemophilia are heavily influenced by the infected blood scandal. Clinicians frame treatment decision-making which necessitates the requirement for benefit-risk training and high-quality tailored patient gene therapy information materials.

Enhanced late-stage medicine horizon scanning has highlighted that both haemophilia A and haemophilia B pathways will be enriched with a range of new technologies with varying benefit-risk profiles [1]. Eleven forthcoming products or products with new indications were identified for haemophilia A and seven for haemophilia B. Four advanced therapy medicinal products (ATMPs), which are gene, cell or tissue engineered products [2], are being developed for haemophilia A and two for haemophilia B [1].

Whilst these technological and clinical developments have potential to improve patient outcomes, the integration of products, or multiple products, into complex and dynamic care pathways, such as those involved in the treatment of haemophilia, presents patients, clinicians and healthcare systems with a dilemma [3,4]. Studies to date in haemophilia suggest the clinical decision to proceed with technologies such as gene therapy in haemophilia is likely to be complicated, and the true impact on patients, caregivers and families is not fully understood [5-8]. The ongoing infected blood inquiry [9] adds an additional layer of emotional complexity to patient-clinician decision-making.

Patient demand is complex and subject to a range of external and temporal factors [3]. Understanding patient demand for a technology is vital, not only to assist with budget impact discussions [7,10], but to ensure the necessary infrastructure, diagnostic and staffing requirements are in place to optimise the integration of the future technology, and to maximise potential for improving patient outcomes [1].

Patient choice and shared decision-making is widely regarded as a positive attribute for health systems, and much work has been conducted in relation to beliefs about medicines and the importance of active patient participation in treatment decisions [11-14]. However, it is unclear whether patients have the ability (and information available) to accurately convey their preferences and what influence clinicians have on patient choice [15]. The evidential uncertainty regarding duration/variability of effect and side effect profile associated with gene therapy has the potential to exacerbate the issue [3]. There is extensive literature on the challenges when communicating the benefits and risks of healthcare interventions [16] and how health literacy [17-19], affect and emotion [20-22], and clinician influence [23-26] impact treatment decision-making.

This study aimed to explore the perspectives of patients and clinicians on the perceived benefits and risks of emerging gene therapies for the treatment of haemophilia. The study also aimed to gain insight into clinician-patient communication on benefit and risk and how this shapes decisions on new therapeutic options.

METHODS

The study received ethical approval from the NHS Health Research Authority (HRA) (IRAS ID 318248) and the London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee (LEO Ref 28099).

The study sought to explore the perspectives of clinicians who would be involved in future discussions on the initiation and delivery of gene therapies and patients with severe haemophilia A and B who would potentially receive them.

A combination of focus groups and one-to-one qualitative interviews were utilised. Semi-structured focus groups were the preferred methodology due to participant interaction and group dynamics, but one-to-one qualitative interviews were also necessary to accommodate participant availability.

Recruitment and participation were undertaken in line with the study protocol through collaboration with national patient organisations (The Haemophilia

Society) and clinician networks (NHS England Clinical Reference Group (CRG) and HAEM-NET).

The focus groups and interviews were held virtually via Microsoft Teams due to the geographic spread of participants and were audio-recorded using the transcription function. Transcripts were manually corrected in Microsoft Word and NVivo 12 [27] software was utilised to facilitate thematic analysis.

In line with the protocol, prior consent to take part in the study was obtained and participants were sent the topic guides in advance (see Appendix). The topic guide was developed within the research team, building on literature, horizon scanning and preliminary discussions with clinicians.

Qualitative data from the focus groups and discussions were analysed thematically following the guidelines suggested by Braun and Clarke [28]. The analysis involved familiarisation with the data, transcription, generating codes, searching for and reviewing themes, defining and naming themes, and reporting [28]. An independent member of the research team assessed the qualitative data to confirm consensus on the included themes.

FINDINGS

The study participants comprised seven UK-based consultant haematologists, three advanced nurse practitioners, and seven adult severe haemophilia patients. Six patients in the sample had severe haemophilia A and one had severe haemophilia B.

All patients were on prophylaxis therapy and none had received gene therapy. Four of the seven patients were affiliated with The Haemophilia Society. Affiliation was defined as being a current active member of The Haemophilia Society and holding a specific role within the organisation either currently or in the past. Recruitment success to the study was high, with only one patient being excluded due to having mild haemophilia.

A total of four focus groups (involving a total of ten participants) and seven one-to-one qualitative interviews were conducted between November 2022 and October 2023 (Table 1). The focus groups lasted 90 minutes and the interviews lasted between 30-60 minutes.

Thematic analysis identified five summary themes (Table 2). Three themes related to clinician-patient communication: (i) active vs. passive patients; (ii) health literacy; (iii) external factors. One theme related to gene therapy perspectives on benefit-risk, and one theme concerned the scar of the infected blood scandal.

Active vs. passive patients

The responses across participant groups brought the concept of patients playing an active role in their healthcare and treatment decisions into focus, particularly the ability of clinicians to influence decisions and if patients can choose to proactively delegate treatment decisions. This was important to understand, given the study objectives to assess clinician-patient communication on new therapeutic options in haemophilia.

Table 1. Study methodology and participation

PARTICIPANT ID	METHODOLOGY
Consultant Haematologist 1 Consultant Haematologist 2	Focus groups
Advanced Nurse Practitioner 1 Advanced Nurse Practitioner 2 Advanced Nurse Practitioner 3	
Patient 1 Patient 2 Patient 3	
Patient 5 Patient 6	
Consultant Haematologist 3 Consultant Haematologist 4 Consultant Haematologist 5 Consultant Haematologist 6 Consultant Haematologist 7	1:1 qualitative interviews
Patient 4 Patient 7	

Table 2. Summary of thematic codes

PARTICIPANT GROUP	CONSULTANT HAEMATOLOGISTS (N=7)	ADVANCED NURSE PRACTITIONERS (N=3)	PATIENTS (N=7)
Minor themes (n)	50	18	30
Major themes (n)	13	8	11
Major themes (list)	• Bias • Clinician influence • Clinician risk-training • Clinician gateway for the NHS • Cost containment • Gene therapy • Importance of MDT • Media influence • Nature of haemophilia as a disease • Patient communication • Risk • Structure of consultations • Uncertainty	• Benefit-risk • Bias • Gene therapy • Inequity of focus • Importance of MDT • Timing of consultation • Training • Treatment choices	• Active vs. passive patients • Consultation structure • Evidence sources for new treatments • Experience with current treatment and care • Gateway for the NHS • Gene therapy • Geographical differences in care • Health literacy • Impact of blood inquiry • Importance of MDT • Treatment choices
SUMMARY THEMES (N=5)			

• Active vs. passive patients
• Health literacy
• Gene therapy perspectives
• External factors
• Scar of blood infection scandal

MDT: Multidisciplinary team
NHS: National Health Service

Clinicians were reflective on the topic of bias and acknowledged that they brought unconscious bias into the clinic when discussing benefit-risk associated with treatments. It was stressed that this was often personality driven and that the clinical scenarios observed in the clinic could be complex. It was seen as challenging for clinicians not to let their external influences or past experiences impact decisions, and this was exacerbated with chronic conditions such as haemophilia where clinicians got to know patients over time.

"I think that clinicians need to accept they influence patients, but it is then as soon as you accept that you influence patients, then comes an additional responsibility of actually moving to how do you then make sure you are able to get your patient around to thinking from a different perspective? How to control the disease?" – Consultant Haematologist 2

Clinicians were aware they had the potential to, and actively did influence patient therapeutic choice. A range of opinions were expressed on the topic: some clinicians were bold about their ability to influence patients and utilise their clinical expertise to drive health outcomes. These clinicians felt that by diluting this approach they would be taking away part of what defined them as clinicians. It was highlighted that if a clinician took a less directive stance, this might actually increase the anxiety of a patient if they are unable or unwilling to make a decision. Other clinicians adopted a more balanced approach and felt that as long as the patient had capacity to make the decision they were happy to support this, even if they recommended an alternative approach.

Clinicians also acknowledged that with experience, knowledge and influence came a deep responsibility to inform patients and advise them to achieve the best possible medical outcome. It was considered perfectly legitimate for a patient to choose to be passive and allow the doctor to make recommendations.

"It's OK for patients to have different attitudes and different levels of involvement. It's OK for patients to not engage as much as you think they should engage, or listen as much as you think they should listen." – Consultant Haematologist 2

Clinicians highlighted that patients often bring in lists of questions, but that these tended to be unstructured and focused on short-term issues. It was reported that very few patients email clinicians in advance to highlight what they would like to discuss at a consultation.

"I've not had many people emailing in advance... A few come with lists of questions, but they tend to be more kind of abstract questions." – Consultant Haematologist 4

Clinicians unanimously agreed that requests for second opinions were rare, and some estimated this occurred with less than 1% of their patients. The clinicians interviewed were more regularly involved as providing a second opinion. Overall, there was a view that requesting second opinions was perfectly acceptable and this became more comfortable over time as clinicians gained clinical experience.

Conversely, the patients interviewed had all requested a second opinion and felt comfortable doing so if they disagreed with a decision. There was an acknowledgement that this could potentially be difficult for clinicians, as experts, to accept. Clinicians were considered to be open to embracing challenge, however it was acknowledged that this might not be universal.

"Yeah, I've done a second opinion, because in previous hospitals I sought a second opinion because I just felt like my doctor was actually trying to force me down routes and I just wasn't happy at being forced down the route at all." – Patient 3

The patients affiliated with The Haemophilia Society highlighted the importance of taking an active role in consultations with doctors. It was stressed that patients had a responsibility to communicate issues clearly to doctors to enhance treatment and care decisions. Participants all gave examples of where they had actively engaged or tried to manage interactions with consultant haematologists. It was highlighted that doctors could not know everything related to care and therefore actively challenging them was beneficial to ensure the patient perspective was fully taken into account.

"Last year, and it sort of was a bit of an eye opener, I kind of learnt what I have access to if I speak loud enough, which wrongly or rightly, it is what it is." – Patient 2

Patient respondents who were not affiliated with The Haemophilia Society were generally less active than their Haemophilia Society-affiliated counterparts. However, these patients did give examples of being active in their consultations, either via being an advocate for gene therapy, proceeding with surgery or resisting attempts from clinicians to switch them to particular therapies. At the centre of decision-making was trust and experience of care, which shaped their desire to be active or passive in treatment decisions.

"I think you have to put trust in your doctors. You have to, because they're the ones that know and they know their jobs. And if you're gonna turn up there because you've read an article somewhere in Google about gene therapy and now you think you know everything, it's not right." – Patient 6

Patients associated with The Haemophilia Society said they often 'pre-loaded' consultations by emailing or speaking to clinicians in advance regarding issues they would like to discuss. It was felt that this approach was helpful as time with consultants was often limited and this could facilitate optimal engagement. This was in contrast to patients who were not affiliated with The Haemophilia Society, who were generally less active in the pre-consultation phase.

"I have a pretty similar technique to him, pre-load the appointment and say here are my problems.....Also yeah, keep pretty good notes of when things go wrong." – Patient 3

Advanced nurse practitioners (ANPs) highlighted the difficultly for patients to challenge clinicians on treatment decisions, a situation exacerbated when centres adopt blanket policies towards treatment. ANPs felt empowered to challenge treatment decisions they felt were wrong or were influenced by bias, however it was hinted that this environment might not be universally applied across NHS treatment centres.

"I don't know of a centre where one consultant will do one thing and then another would do another, so it's not like you can even swap consultants. That is the centre's policy because the centre director's policy is what they think." – Advanced Nurse Practitioner 2

ANPs highlighted that patients often have very high opinions of consultant haematologists and that they might therefore find it disconcerting when healthcare professionals admit to being unsure about the long-term outcomes of a treatment such as gene therapy.

Health literacy

Health literacy was a key theme identified during the research and a central pillar for understanding how benefits and risks were communicated and understood for existing and new therapeutic options in haemophilia.

Clinicians universally acknowledged the challenge of comprehension and that what was articulated in consultation may not have been fully understood by patients. They were reflective on this and often used subsequent consultations to check back on a patient's understanding.

"I mean it's well known that what you tell people and what they perceive and what they take in, it can be very different." – Consultant Haematologist 7

Clinicians observed that patients often suffer from poor concentration, struggle to remember key details or have challenges dealing with complex topics such as ATMPs. They highlighted that health literacy and education varied widely in the patient population, ranging from the highest level of academic achievement to some patients not being able to read or write. Understanding health literacy was considered not only crucial to establish the level of information delivered to the patient, but also for the patient to be able to articulate to the doctor about their clinical and life scenario, and any challenges with current therapy.

Clinicians stated that they tailored their language to the individual, with the main driver for this being education and health literacy. Other key factors included age, family history and specific acute concerns.

"So the way I speak to someone and kind of what I say, yes, I do individualise it – but within that, I don't think it's based on age, I think it's based on their level of education and a level of medical understanding." – Consultant Haematologist 6

There was clear evidence of using analogies, drawings or simple examples to try and communicate trial data results, benefit-risk and highlight uncertainty. It was stressed that the majority of patients did not want detailed statistical information.

"I do end up drawing quite a lot in clinic – I think that everyone responds really differently. But certainly for something like factor levels and different products, I find like a graph just where I can scribble." – Consultant Haematologist 6

It was acknowledged that patients also research treatment elements by themselves, and clinicians therefore provided leaflets or directed patients to websites to help facilitate this. The challenge of educating patients and their parents over a long time period was stressed; lifelong learning was considered essential and, ideally, knowledge given to parents would then be passed on to children as they grew up.

ANPs were cognisant of the need to account for health literacy and how messages were communicated to patients, and they adapted their approach accordingly. Individual patient comprehension of the message communicated could be quite different and therefore repetition was important to reinforce key advice. Ensuring that comprehension of key messages happened early in patient engagement was considered important to avoid any misunderstandings which could take patients on a trajectory that becomes harder to influence over time.

"You know they can often go away and have conversations in their own head and come back with a completely different idea of what has been said. They take a bit of information and then they build their own story, their own narrative around that. And sometimes it's quite hard to rein that back in if they've got it wrong." – Advanced Nurse Practitioner 3

ANPs linked confidence to talk about benefit-risk of therapies to patients with knowledge and experience. The rapidly evolving treatment pipeline and novel mechanism of actions were considered to be challenging to explain to patients, parents and families without a medical background.

Patients associated with The Haemophilia Society highlighted the advantages of being involved with the national patient organisation in terms of access to information and networks. They felt better informed and more empowered regarding treatment decisions. Interestingly, as a result of this position, they felt a greater responsibility to share knowledge with the haemophilia community.

"I think I have a responsibility now, taking on a role to actually get better informed and speak to those who are actually impacted." – Patient 1

External factors

Clinicians highlighted how they were aware that patients are influenced by external factors in their lives, which in turn will impact consultations. This could include family issues, employment or other elements which impact mood and affect. Understanding the influence of this was vital for the study objectives on both the perception of and communication of benefit-risk.

It was stressed that body language was important and both consultant haematologists and ANPs reacted accordingly to this when undertaking consultations and tailored sessions.

Clinicians highlighted the influence of family, friends and peer networks. All of the respondents were able to cite examples of where this had directly occurred when switching therapy.

"You know, it's a small community, often more than one person in the same family, often friends, and I think that has quite a big influence." – Consultant Haematologist 7

Clinicians facilitated close contacts of patients attending clinics to provide patients with support, assist with questioning and add an additional layer of comprehension to the consultation outcome. They also mentioned bringing in additional staff members for potentially challenging clinics and to ensure robustness of follow-up.

Clinicians acknowledged the influence of a patient's family and wider social network on treatment decisions. There were a number of elements linked to this including the family history with haemophilia, the number of haemophilia patients in the household, and broader social networks. It was flagged that a patient's life and family scenario changes over time and that their attitudes were therefore likely to evolve accordingly.

"And then you've all of those other things that you know, cultural influences, whether you're talking to the mum, the dad, the granddad who's also got haemophilia? All those things come into play." – Advanced Nurse Practitioner 2

It was stressed that mental health played a large role in patients' treatment decision-making. ANPs highlighted that patients have general anxieties linked to the world around them, with work, economic, political and social issues all impacting their ability to make treatment decisions.

"I think mental health plays a huge factor in decision-making around treatment... they're anxious about climate change, they're anxious about the government, they're anxious about working life, they're anxious about COVID. They're just generally anxious about the state of the world, and that completely detracts from any other decision they have to make." – Advanced Nurse Practitioner 1

Patients were reflective on a number of external factors which influenced their treatment choice. The type of haemophilia was considered important, as the rarity of haemophilia B limited the number of other patients available to engage with.

"As someone with haemophilia B, to kind of get a message of what's out there... because there's just so few of us, trying to find another haemophilia B patient is like actually pretty difficult." – Patient 3

Family, friends and social networks were considered vital; not only in managing treatment choice but also in tackling issues with ongoing care. Patient respondents associated with The Haemophilia Society stressed that being part of a patient organisation was considered influential in terms of hearing from world-leading doctors, engaging with other patients, and hearing active discussions on the latest treatment developments.

Clinicians and patients stressed the importance of the multidisciplinary team (MDT) in decision-making. It was felt that sometimes there is a barrier between the patient and the consultant, which other members of the MDT can overcome, allowing life and treatment issues that patients did not feel able to or want to talk to the consultant about to be raised. Members of the MDT might be in role longer than some of the clinical

team, which facilitates a growing bond between staff members and patients.

> *"The patient might go off separately with a nurse to have bloods and then kind of do a more detailed thing with our physio and the conversation can kind of keep on going." – Consultant Haematologist 6*

Clinicians thought that the media had a relatively limited impact on therapeutic choice. However, they did acknowledge that the number of queries about new therapies increased when articles were published online. Clinicians saw social media as more of a networking source which had a marginal impact on treatment decisions.

Clinicians cautioned against the extremes of social media and how this polarised communication of outcomes and experience which was likely to be unhelpful in assisting decision-making. It was stressed that false information made social media a potentially dangerous place, and this has been previously observed with treatments such as emicizumab.

> *"Having social media is obviously quite influential in people, but the problem with social media is that it is uncontrolled, so you can talk to anybody and they just give you any opinion whatsoever really." – Consultant Haematologist 7*

Patients gave a wide range of evidential sources that they accessed for new treatments. This included undertaking pharmaceutical company surveys, engagement with clinicians, websites, and engagement through patient organisations. Participants were aware of the pitfalls of using social media and were clear that they did not exclusively use it to help them with treatment decisions. However, they did follow particular accounts for information and utilise internet sources to access information. It is likely that these resources indirectly influence decisions, even if patients are vigilant to the potential risks.

> *"The straight answer is no [I don't use social media for information on therapeutic choice] ... I think there's a lot of nonsense out there I believe." – Patient 2*

Gene therapy perspectives on benefit-risk
Understanding perspectives on gene therapy benefit-risk was a core study objective. Clinicians were cautious about using gene therapy and stressed the burden of delivering gene therapy and concerns about the requirements for long-term steroids or other immunosuppressants. It was felt that the logistical burden of monitoring patients would be high and that this would temper demand. The extensive monitoring and follow-up requirements may make gene therapy challenging with employment and lifestyle commitments.

Clinicians highlighted that precise adoption rates were difficult to predict for gene therapy, but they anticipated uptake to be relatively modest and slow. It was highlighted that negative patient experiences could significantly impact early adoption, particularly the clinical burden of care.

> *"I think it will be really interesting to see how many people take it up because I think we're in a really different situation with longer acting therapies and novel therapies now compared to ten years ago." – Consultant Haematologist 6*

Clinicians were concerned about the durability of gene therapy and variability of patient response. The efficacy of gene therapy for haemophilia B was expected to be more durable than the efficacy of gene therapy for haemophilia A. The significant impact of emicizumab in haemophilia A, which had framed the decision to potentially proceed with gene therapy, was also highlighted.

> *"I don't think it's a straightforward decision at all and that's particularly true for haemophilia A, where there are big question marks about the durability of the effect." – Consultant Haematologist 5*

Clinicians were also unsure about future therapeutic options (including gene therapy) for patients if gene therapy efficacy waned or failed and aired concerns about the irreversibility of the treatment in comparison to existing therapeutic options.

There was a concern from clinicians about long-term unknown adverse effects with gene therapy, and that in some areas of research there is evidence that gene therapies may increase the risk of tumorigenesis via integration. There was a general feeling that using the word 'cancer' in a consultation would be a powerful motivation for patients not to progress with therapy.

> *"If you mention cancer, that's the end of the conversation." – Consultant Haematologist 7*

The patients who were not affiliated with The Haemophilia Society were much more positive towards gene therapy than their Haemophilia Society-affiliated counterparts. They had all heard of gene therapy from various sources (internet resources, social media, face-to-face consultations) and, fuelled by reporting in the media, had very high expectations for it. The main advantage that patients associated with gene therapy was convenience; it would allow them to be free from regular treatment and give them confidence to go on holidays without the worry of transporting treatment.

"I mean it's the Holy Grail, isn't it? It's just as good as we're gonna get." – Patient 6

The Haemophilia Society-affiliated patients interviewed were negative towards gene therapy; there was a concern the technology was immature and potentially unsafe. There was also apparent mistrust, reflecting the ongoing scars left by the infected blood scandal.

"Two weeks ago at a conference, someone presented on stage saying we're all a bunch of guinea pigs and he wouldn't trust it with a barge pole and especially haemophilia A …. And yeah, I don't wanna be the guinea pig." – Patient 4

They highlighted their concern about the lack of data with gene therapy, which made them nervous about the long-term effects (efficacy and safety). This ranged from an increased risk of cancer to having negative outcomes from overexpression of clotting factor. They were aware of the expected financial impact of gene therapy and the high cost associated with the technology. It was suggested that funds could be better spent on optimising and expanding existing services, rather than on gene therapy. There was an anxiety that gene therapy might not provide the confidence and flexibility to fit into lifestyles.

Both patient groups articulated the physical and mental burden the process of gene therapy would put on them, their families and friends, which was considered to be underrepresented in current conversations about gene therapy. It was stressed that the burden was likely to be unacceptable to many patients, who would be unable or unwilling to put their life on hold for it. There was a concern about the lack of widespread expertise in UK centres when it came to delivering these technologies.

"Yeah, it would take six months and it might not even work. See, you've gone through all of that stress. You've put your family and friends, loved ones through that stress as well. And it might not even work." – Patient 2

"The kind of heartache of not getting on the previous gene therapy was kind of like, I don't want anything for a good couple of years. I was like, I don't want anything to do with haemophilia anymore. It was my life – it broke me." – Patient 7

Scar of the infected blood scandal

During the 1970s and 1980s, people with haemophilia (and other blood disorders) were infected with viruses including hepatitis and HIV via contaminated blood products. A statutory inquiry in the UK was set up in 2017 to investigate the infected blood scandal and is anticipated to conclude in May 2024. It was therefore vital to understand the impact of the infected blood scandal on participant's risk appetite, and how this impacted treatment decision-making and patient-clinician relationships.

Clinicians were clearly influenced by the current infected blood inquiry, expressing caution around risk communication and being more diligent with recording conversations, particularly about unknown risks. There was acknowledgement that uncertainty should have been communicated better in the past and more consideration given to patient comprehension. Clinicians flagged that generational attitudes, practice and technology all played a role in the contaminated blood scandal.

"I am scarred, the patients certainly are scarred and I'm having a lot more conversations with my patients about it because they've been retraumatised by the inquiry." – Consultant Haematologist 5

It was felt that the trauma caused by the infected blood scandal could be deep-rooted within individual patients and families and could impact therapeutic choices. Adverse effects of therapies to deal with the consequences of infected blood (e.g. Hepatitis C) were acutely remembered and clearly impacted therapeutic choice. ANPs referenced the negative impact of subcutaneous injections, which was mentioned frequently as a barrier for starting emicizumab.

"So lots of talk about emicizumab when it came in about actually the ease of sub- cut[aneous] injections versus IV injections, but for many of our adult patients, they'd had hepatitis C treatment and the side effects of sub-cut[aneous] hepatitis C treatment were horrific."
– Advanced Nurse Practitioner 1

Three of the patient participants were directly impacted by the infected blood scandal via receiving contaminated blood. It has had a lasting impact on their lives, and they still live with the effects day-to-day. Key issues such as survivor's guilt, the shame and stigma of having haemophilia and the impact of the medications required to clear hepatitis C were all stressed.

"I had quite a bit of survivor guilt frankly, so that when in 1993-94, they said you've got hepatitis, and here's what you've got to do. And I was just thinking, I've got something you know, I didn't get off scot-free, that makes me feel a little bit better if anything." – Patient 4

Participants highlighted that due to the infected blood scandal, there was a mistrust with the healthcare system and government. However, patients flagged that trust with clinicians was built up over time and highlighted the importance of personal relationships in their ongoing care.

"I mean, my cousin, he had his windows smashed at his house and things like that... some people might say, oh, you know, just try and put it out your mind. You can't put it out your mind.....You can't have a day off, you have it everyday. It's as simple as that."
– Patient 5

DISCUSSION

Benefit-risk communication in the clinic remains challenging, reflecting the vast and diverse literature which crosses multiple contributing disciplines [16]. The evolution of the care pathway to include highly uncertain ATMPs only further exacerbates this. Clinicians in this study reported that previous or ongoing benefit-risk training is not routinely available to the clinical community. This is concerning, given that how treatment effects are communicated to a patient, and the influence on therapeutic choice, is well documented [29-31]. Clinicians were trained on elements of patient communication, but not specifically

benefit-risk, and it was therefore considered that formal benefit-risk training would be useful to clinicians.

Clinicians highlighted that they do have a consistent structure to their consultation, but this tended to be based on a mental checklist rather than a physical or electronic one. This reflects the current evidence on patient decision aids, which acknowledges their potential to enhance shared decision-making but also the challenges in development, application and cost-effectiveness [32-34].

It was stressed that, as consultations are tailored and treatment decisions are often taken over multiple consultations, clinicians were keen to give patients time and space to make decisions. When it came to gene therapy, clinicians were more forward about the requirement to have checklists, consent forms and structured consultations. It was universally agreed that a one consultation model for gene therapy was unrealistic, which is consistent with views expressed on this topic [35,36].

This study has suggested that although there is a broad range of influences on patient choice, clinicians clearly play a key role in framing the discussion, which is consistent with prospect theory [37,38]. Social media remains a double-edged sword [39-41], and whilst it remains impossible to fully influence this, informed members of the community should actively encourage stakeholders to utilise trusted and reliable sources of information.

There is a wide range of health literacy within the haemophilia patient population, which is consistent with other study findings [36,42]. Due to the heterogeneity observed in the population, and evolving treatment and life scenarios, it is unfeasible to mandate that all patients are active and challenge their clinician with data-based scientific arguments, request second opinions and email in advance of consultations. More relevant is ensuring that patients have time and space to make decisions, based on tailored information, and have a safe decision-making environment which can include family, friends, social networks and the broader haemophilia community [35].

All parties should recognise that external factors such as climate change and the economy are likely to influence risk appetite, and therefore treatment decisions are subject to temporal factors and do not exist in a vacuum [3]. The clinicians in this study showed a high-level of emotional sensitivity, and body-language, mood and affect should continue to be observed when engaging with patients on treatment decisions. Mental health remains underrepresented within treatment decision-making [43-45].
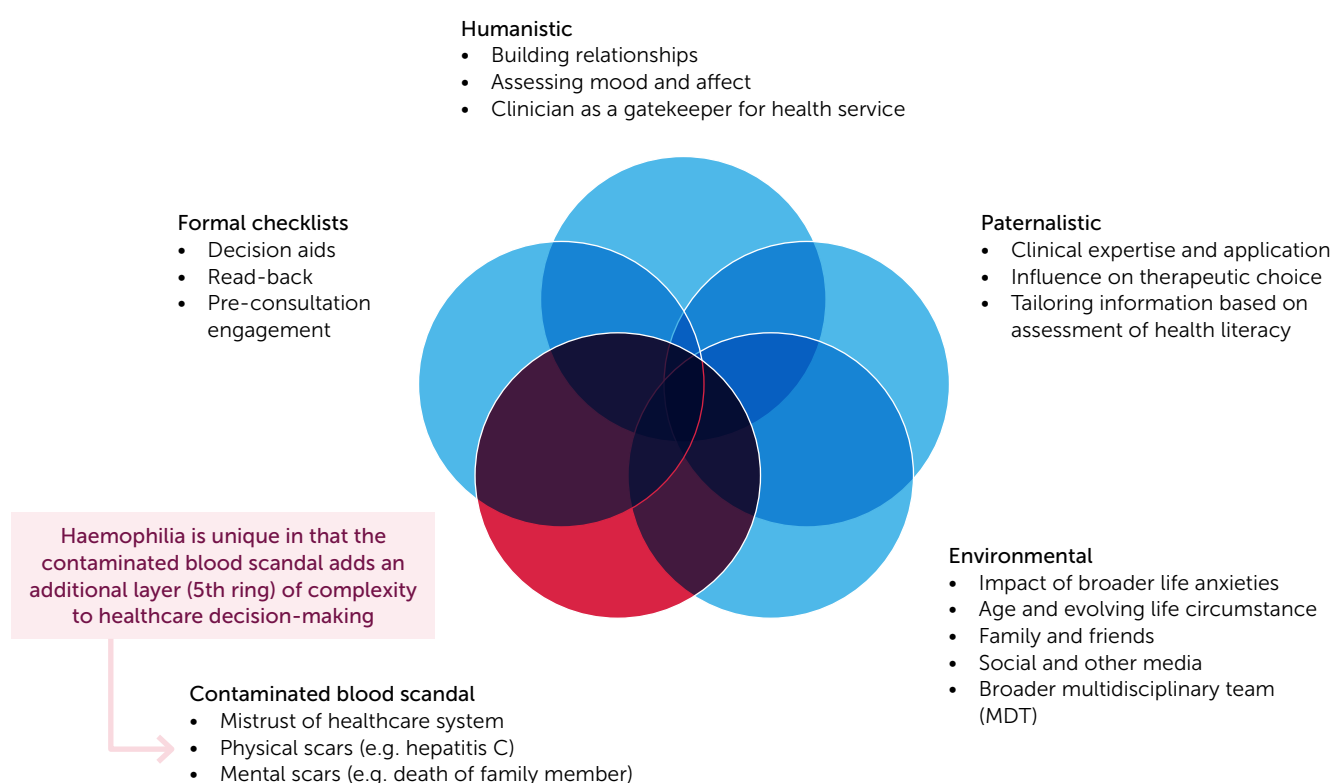
Overall, ANPs and consultant haematologists were broadly aligned on the topics discussed and placed response emphasis on areas linked to their experience and responsibility. ANPs commented more in depth on practical, operational issues, whilst clinicians were more expressive on gene therapy and patient communication.

This research has demonstrated that shared decision-making in the clinic is a complex phenomenon which transcends the concept of active vs. passive patients and reflects the changing patient-clinician relationship observed over time [46]. There are a number of consultation elements, including mechanistic, humanistic, paternalistic and environmental factors, which impact treatment decision-making. Haemophilia is unique in that the infected blood scandal has left a scar in the community which adds an additional layer, or 'fifth ring' of complexity to healthcare decision-making (Figure 1) which makes stakeholders more risk averse. Uptake of gene therapy is therefore likely to be slow, with an even more challenging scenario for haemophilia A driven by existing treatment options and observed performance in the clinical trials to date.

Study limitations

The study has a number of limitations. The majority of patients (six out of seven) in the study had severe haemophilia A. Although this split is reflective of the disease epidemiology [47], there is the potential for bias in the results, given the difference in anticipated clinical outcomes for gene therapy between the two diseases. The sample focused on severe adult male patients with haemophilia. Whilst ATMPs are currently being developed for severe adult male patients, the broader haemophilia community will have extensive views on the topic of benefit-risk communication. The clinicians interviewed pointed out that a minority of patients requested a second opinion, yet all patients in the study had done so. This could highlight that the patient sample is not representative of persons with haemophilia more generally. The sample comprised UK-based participants and views from the international community with different healthcare structures, treatments and patient scenarios would add further granularity and depth to the research results. Finally, there was a need to utilise both qualitative one-to-one interviews and focus groups to accommodate participant availability. Whilst using two qualitative

Figure 1. The unique nature of haemophilia in benefit-risk discussions

Humanistic
- Building relationships
- Assessing mood and affect
- Clinician as a gatekeeper for health service

Formal checklists
- Decision aids
- Read-back
- Pre-consultation engagement

Paternalistic
- Clinical expertise and application
- Influence on therapeutic choice
- Tailoring information based on assessment of health literacy

Haemophilia is unique in that the contaminated blood scandal adds an additional layer (5th ring) of complexity to healthcare decision-making

Environmental
- Impact of broader life anxieties
- Age and evolving life circumstance
- Family and friends
- Social and other media
- Broader multidisciplinary team (MDT)

Contaminated blood scandal
- Mistrust of healthcare system
- Physical scars (e.g. hepatitis C)
- Mental scars (e.g. death of family member)

methodologies enriched the dataset by expanding participation, it made analysing the data more methodologically challenging [48]. The focus groups and qualitative interviews ran concurrently and the authors aimed to counteract confirmation bias by following topic guides to ensure that information arose independently and that similar topics were covered, regardless of the methodology employed.

Areas for future research

This study and associated dataset have identified a number of areas which warrant further research.

The exploration of the balance in patient-clinician decision-making for complex technologies such as gene therapy is required. Whilst there is a clear direction of travel for patients to be engaged in consultations to positively shape health outcomes [46], the research reported here uncovered examples where patients were content to delegate treatment decisions to expert clinical decision-makers, particularly for complex and irreversible treatment decisions as with gene therapy. Given the range of opinions expressed, and the uncertainty associated with gene therapy, this topic would merit further exploration.

The impact of the infected blood scandal is unique to haemophilia and the research concludes that this adds an additional layer of complexity to treatment decision making. With gene therapies being developed in oncology, other blood disorders and rare conditions [49], research on unique, therapy area specific drivers of treatment decision-making, and a subsequent cross-therapeutic area comparison, would help in understanding decision-making in more depth.

There was a clear difference in patient attitudes between those who were associated with The Haemophilia Society and those who were not. A deeper assessment of the motivations and membership of national patient organisations would support further understanding of the vital role they can play in being a trusted source of information, and also if potential attitudes of patients to new treatments are linked to membership.

Social media was identified as a polarising phenomenon, and despite scepticism about its value in treatment decision-making, there is no doubt that these platforms have the ability to reach large numbers of patients. Understanding the potential of social media to enhance access to high-quality, balanced information for gene therapy and novel treatments, whilst tackling the pitfalls of misinformation and abuse, would be a fertile area of research.

Finally, the role mental health and broader life influences play in treatment decision-making needs to be explored further. The decision to proceed with an irreversible treatment such as gene therapy is a pivotal one; and therefore understanding how mental health and wellbeing influences treatment decision-making, and the psychological impact before and after gene therapy, particularly if the outcome is sub-optimal, will be important to explore.

CONCLUSION

This study aimed to explore the views of patients and clinicians about the perceived benefits and risks of emerging therapies for the treatment of haemophilia. There remains scepticism about gene therapy across all research participant groups, which suggests that uptake is likely to be relatively slow with divergence anticipated between haemophilia A and B. The study also aimed to gain insight into clinician-patient communication on benefit and risk and how this shapes decisions on new therapeutic options. The research suggests that treatment decision-making and benefit-risk discussions are complex and multi-faceted issues which in haemophilia are heavily influenced by the infected blood scandal. Clinicians frame treatment decision-making which necessitates the requirement for benefit-risk training and high-quality tailored patient gene therapy information materials.

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CORRECTION NOTE
This article was amended at the request of the authors on 22 April 2024.
Changes to the version originally published on 8 April 2024 are as follows:
- p. 24: removal of the word 'delete' in the sentence beginning 'It was stressed that...'
- p. 27: insertion of hyphen in 'decision-making' (Advanced Nurse Practitioner 1 quote)
- p. 28: 'Twitter accounts' changed to 'accounts'
- 13 instances of 'risk-benefit' changed to 'benefit-risk' (pp. 22, 24, 26, 31, 35-37)

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

APPENDIX
TOPIC GUIDE FOR QUALITATIVE FOCUS GROUPS AND INTERVIEWS

PATIENTS

Section 1: Current Treatment
Q1: How do members of the group feel that haemophilia care has evolved since their treatment initiation?
- Probe: Positive and negative perspectives
- Probe: Impact of the contaminated blood scandal and inquiry

Q2: How would members of the group describe themselves regarding being informed about current treatment options? Why?
- Probe: Evidence sources and motivation for health literacy

Q3: Have members of the group experienced any challenges with your treatment to date?
- Probe: Side effects
- Probe: Development of an inhibitor
- Probe: Convenience of administration

Q4: Have members of the group ever switched therapy? If so, why was this? When did this occur?
- Probe: Factors behind the switch:
    - Higher efficacy
    - Preferred administration
    - Adverse event
    - Clinician influence
    - Family/friends influence
    - Patients/patient group influence
    - Employment
    - Other

Section 2A: Future Treatment (General)
Q5: How would members of the group describe themselves regarding being informed about future treatment options? Why?
- Probe: Evidence sources and motivation for health literacy

Q6: What do group members feel are the most important factors which guide and influence decisions around new treatments?
- Probe key elements
    - Clinician influence
    - Progression of condition

- New treatments becoming available
- Adverse event
- Change in life circumstance
- Influence of social network
- Media (including social media)
    - Probe: Expectation setting
    - Probe: Language and influence
- Other

Q7: Could group members comment on how experience from the haemophilia community impacts their assessment of new or existing treatments?
- Probe: Impact of early adoption within clinical and patient community
- Probe: Information sharing and social networks

Section 2B: Future Treatment (Gene Therapy)
Q8: Have members of the group heard about gene therapy?
- Probe: Evidence sources for new therapies

Q9: How do members of the group feel about gene therapy in haemophilia?
- Probe: Positive (e.g. high levels of efficacy) and negative (e.g. treatment failure) perspectives
- Probe: What influences this?
    - Friends and family
    - Media/social media
    - Clinician
    - Patients/Patient groups
    - Other

Section 3: Consultation
Q10: When you speak with your clinicians and multi-disciplinary teams about the benefits and risks with current and future therapies – do you use tools such as decision-aids?
- Probe: assess the extent of usage of the following:
    - Decision-aids
    - Published materials (e.g. evidence-based patient leaflets)
    - Written or electronic summaries of the consultation
    - Patient read-back to ensure comprehension
    - Other

Q11: When you leave the consultation room – do you feel that you have a clear understanding of the risks and benefits associated with current and future treatments?
- Probe: Key barriers to benefit-risk communication
- Limited consultation time

- Language
- Understanding
- Social, cultural, and educational factors
- Motivation and other emotions
- Other

Q12: Do members of the group feel that clinicians tailor information to their individual scenario?
- Probe: How do they do this (e.g. trial evidence, anecdotes)?
- Probe: Has this changed over time?
- Probe: How has your treatment history impacted this?
- Probe: Do you have family members with haemophilia and does this have an impact?

Q13: Do you feel empowered to challenge opinions or counter suspected bias? How do you do this?
- Probe: Have you ever sought a second opinion? Why/Why not?

Q14: How do group members deal with emotions and affect (feelings and mood) during consultations?
- Probe: Do you think that you would act differently or would make different choices depending on how you are feeling?
- Probe: Do you employ any strategies to actively tackle this issue?

CLINICIANS

Section 1: Communicating Risk
Q1: How comfortable do members feel communicating benefit-risk to patients?

Q2: How do members of the group communicate benefit-risk information to patients for (a) existing and (b) forthcoming treatments?
- Probe: What format do group members present risk in? (e.g. percentage, frequency, Number Needed to Treat (NNT))
- Probe: Do group members present both relative and absolute risk?
- Probe: Do group members utilise descriptive terms (e.g. high, low, medium) in addition to numerical figures?

Q3: How do members of the group tailor benefit-risk information to the individual patient's scenario?
- Probe: Does this vary with age?
- Probe: Does this vary between new patients/existing patients?

- Probe: Does this vary according to treatment history?
- Probe: Does this vary according to inheritance and treating families?
- Probe: Does this vary according to health literacy?
- Probe: Does this vary according to social and/or cultural factors?
- Probe: Other

Q4: Do members feel there are any key barriers to risk-benefit communication for current and new therapies?
- Probe: Limited consultation time
- Probe: Social, cultural, and educational factors
- Probe: Motivation and other emotions
- Probe: Other

Section 2: Evidence, Materials and Training
Q5: Can members of the group please comment on whether they have received any formal training regarding benefit-risk communication?
- Probe: If yes, when was the last time this was refreshed?
- Probe: If no, why not? Do you feel it is required?

Q6: What evidential sources do group members use to communicate benefit-risk information to patients?
- Probe: Trial evidence vs. Real world/anecdotal evidence
- Probe: Format – written, visual, verbal

Q7: Could members of the group comment on any materials, tools or practices that they use to assist with benefit-risk communication?
- Probe: Assess the extent of usage of the following:
  - Decision aids
  - Published materials (e.g. evidence-based patient leaflets)
  - Providing written or electronic summaries of the consultation
  - Patient read-back to ensure comprehension

Section 3: External Influence and Bias
Q8: Apart from clinicians and patients, what do group members feel are the most important factors which guide and influence decisions around new treatments?

Q9: How do group members feel that biases (both patient and clinician) influence clinical conversations on current and new therapies?
- Probe: Strategies to counteract this
- Probe: Dominance – which (if any) bias prevails

Q10: Could group members comment on how early experience with a new therapy impacts the communication of benefit-risk information?
- Probe: Impact of early adoption within clinical and patient community

Q11: How do group members deal with emotions and affect (feelings and mood) during consultations with patients?
- Probe: Compensation for risk adjustment linked to specific emotions (e.g. anger/fear)
- Probe: Clinician emotions and affect vs. Patient emotions and affect

Q12: What role do group members feel the media play in terms of influencing people's perception of risk?
- Probe: Expectation setting
- Probe: Language and influence

Section 4: Gene Therapy

Q13: Do members believe that benefit-risk communication for a gene therapy poses any different challenges compared with 'standard' medicines?
- Probe: Evidential uncertainty
- Probe: Trial design and patient numbers
- Probe: Size of the effect ('Cure')
- Probe: Potential side effects
- Probe: Other?

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