ECONOMIST IMPACT

Harnessing innovation in bleeding disorders

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Contents

About this report

"Harnessing innovation in bleeding disorders" is an Economist Impact report that is supported by CSL Behring. Centred on the insights of experts based in Europe and North America (drawn together in workshops and one-to-one interviews), the report focuses on past, present and future innovations in the treatment and management of rare, inherited bleeding disorders, and where these innovations have been and can be utilised to address current unmet health needs in patients. It focuses on the three most common of these bleeding disorders—haemophilia A, haemophilia B and von Willebrand disease (vWD) as a starting point. While there is no explicit geographic focus to the report, we have concentrated on opportunities and challenges for innovation in higher-income countries.

The research programme incorporated a literature review, extensive desk research, two workshops and five interviews—attendees and interviewees are listed below. The first had a European focus, the second North American. They brought together patient groups, health professionals and policy experts to discuss the role of innovation in rare bleeding disorders and how the future of innovation may be able to address patients' unmet needs. The interviews complemented the discussions held at each workshop, and also offered us an opportunity to dive further into key areas of innovation.

We would like to thank the following individuals for sharing their insight and experience:

Workshop participants:

Victor Blanchette, medical director of the Paediatric Thrombosis and Haemostasis Programme in the Division of Haematology/ Oncology at the Hospital for Sick Children, Toronto

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Brendan Hayes, director of education—innovative therapies at the National Hemophilia Foundation

Glenn Mones, advocacy/non-profit consultant at the Coalition for Hemophilia B

Brian O'Mahony, chief executive officer of the Irish Haemophilia Society

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Michael Recht, chief science officer of the American Thrombosis and Hemostasis Network and professor of clinical paediatrics at Yale University School of Medicine

Dawn Rotellini, chief operating officer at the National Hemophilia Foundation and Board Member for the World Federation of Hemophilia

Naja Skouw-Rasmussen, think-tank officer at the European Haemophilia Consortium

Clive Smith, chair of the Haemophilia Society

Leonard Valentino, president and chief executive officer of the National Hemophilia Foundation

Christopher E Walsh, associate professor and director of Icahn School of Medicine at Mount Sinai, New York City

Sonji Wilkes, former vice-president of the Hemophilia Federation of America

Interviewees:

Manon Degenaar-Dujardin, steering committee member at the European Haemophilia Consortium

Barbara A Konkle, professor of medicine at the University of Washington School of Medicine and research director at the Washington Centre for Bleeding Disorders in Seattle, WA

Flora Peyvandi, director and former president of the European Association for Haemophilia and Allied Disorders and president of the International Society of Thrombosis and Haemostasis

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Economist Impact bears sole responsibility for the content of this report. The findings and views expressed in the report do not necessarily reflect the views of the sponsor, nor the workshop attendees or interviewees. The project team consisted of Michael Guterbock, Alan Lovell, Radha Raghupathy, Yogita Srivastava, Emily Tiemann and Paul Tucker.

Executive Summary

A history of innovation has improved outcomes

Bleeding disorders—the most common of which are haemophilia A, haemophilia B and von Willebrand disease (vWD)—affect the way that the body controls blood clotting. They are difficult conditions to live with, characterised by bleeding, pain and long-term complications. Treatment regimens can be arduous, severe cases can be fatal, and even if managed well they have a profound impact on quality of life.

But things are better than they were. Over the last 50 years waves of innovative treatments and models of care have revolutionised the lives of people with bleeding disorders. Innovation can be defined as a novel treatment, product, service or care pathway that has clear benefits when compared to what is currently being done or what has been done in the past. Therapeutic innovations include the development of concentrated and purified clotting factors for replacement therapy, desmopressin and recombinant factor-replacement treatments. More recently, extended half-life factor replacement treatments have not only reduced the frequency of infusions and improved bleed protection but can also be given in the comfort of a patient's home rather than in a hospital.

These waves of innovation are ongoing. We see them in the world of apps and technology, in the organisation and integration of specialist centres, and in new therapeutics such as gene therapy. This spirit of innovation in the pursuit of better outcomes and improved quality of life needs to be supported because, notwithstanding the improvements of the last 50 years, people with bleeding disorders still face many unmet needs.

Unmet needs remain

People with bleeding disorders often have impaired joint health, because of uncontrolled or breakthrough bleeds despite current treatments. Breakthrough bleeding can occur between prophylaxis treatments, when factor level drops. This uncontrolled or sporadic bleeding can also lead to longer-term issues such as impairments in mobility and functional status, as well as acute and chronic pain associated with damaged muscles and joints. Some treatment regimens remain onerous, with infusions and injections required several times a week. Inhibitors, antibodies that are developed due to an immune response to infused clotting factor and render exogenous factor replacement therapy ineffective, further increase the burden on some patients and lead to poorer health outcomes. Many patients must assess—every time—whether it is safe to engage in physical activity. Lives are interrupted in other ways, including hospitalisations and absenteeism from work and school. People living with a bleeding disorder also often require—but do not necessarily receive—comprehensive care that incorporates other health-related services such as psychiatric care and physiotherapy.

Wider challenges exist to the delivery of care. Accessibility to specialist care is sometimes limited, particularly outside of urban areas, and GPs may not always have experience of managing people with bleeding disorders. Women sometimes miss out on quality care, even though vWD is more common in women than

men. And although shared decision-making is a goal, in reality it is often limited, partly because of the rapid expansion of therapeutic options.

The innovations that will transform lives

While a range of unmet needs continues to impact the lives of people with bleeding disorders, the rich vein of innovation looks set to continue. We explore three domains and examples herein of innovation—technological, systemic and therapeutic—and describe how they can help to address unmet needs.

- **Domain 1: Technological innovations**
  Following the rise of smartphone apps and wearables such as smartwatches and their adoption in other areas of mobile health, a range of solutions are being developed to help manage treatment for bleeding disorders.
- **Domain 2: Systemic innovations**
  Care for people with bleeding disorders extends beyond symptomatic treatment. Patients require comprehensive care that incorporates psychosocial, psychiatric, physiotherapy, dental and orthopaedic care.
- **Domain 3: Therapeutic innovations**
  Existing treatments, while effective, have drawbacks. The advent of gene therapy for haemophilia A and B, alongside an increase in personalised therapy, looks set to revolutionise treatment for bleeding disorders.

Making it happen

To address the unmet needs facing people living with bleeding disorders, a range of approaches will need to be pursued. We describe five principles around which improved services and care can be designed:

#1: Commission integrated services
There remain inconsistencies in care, both in terms of access to treatment and in the provision of vital aspects of comprehensive care, including psychosocial, psychiatric and physiotherapy support. This care needs to be delivered in a patient-centric manner.

#2: Develop regulatory, HTA and payment models that support innovation
Neither regulatory approaches, value assessment practices in health technology assessment (HTA) appraisal, nor the reimbursement frameworks used to negotiate a price, are well suited to accommodate the combination of high up-front costs and long-term value potential for innovations like gene therapy. This is an issue that needs to be solved across the increasing range of therapeutic areas for which functionally "curative" therapies are available.

#3: Enable technology
Broader innovative tech trends have created space to develop the already encouraging offering of devices and platforms that exists in haemophilia care. Payers will have to develop funding and coverage frameworks that support tech that improves patients' lives.

#4: Aim for a functional cure
The potential impact of functionally "curative" therapies is huge, almost revolutionary. Current progress in gene therapy is found in haemophilia A and B, but there is the potential for similar developments in other bleeding disorders, including vWD.

#5: Amplify the patient voice
Underlying all the above is the need to amplify the patient voice. Patient organisations are already active—mainly in patient advocacy. Given the opportunity, and supported through systemic change, they can play a yet greater role in awareness, education, research prioritisation and HTA.

Glossary

Clotting factors
Proteins in the blood that help control bleeding

Haemophilia A
Deficiency of clotting factor VIII, an essential blood-clotting protein

Haemophilia B
Deficiency of clotting factor IX, an essential blood-clotting protein

Von Willebrand disease
Deficiency of the von Willebrand factor, which attracts platelets to clump together at a wound site and aid with blood clotting

Prophylaxis
The administration of clotting factor concentrate in anticipation of or to prevent bleeding

Replacement therapy
Injection (infusion) of clotting factor concentrates into a vein, to help blood to clot normally

Inhibitors
Antibodies that are developed due to an immune response to infused clotting factor and make exogenous factor replacement therapy ineffective

Recombinant factors
Lab-made (not from human blood) factors, which offer a safer option than plasma-derived products because they avoid potential blood-borne transmission of infectious diseases

Bypassing agents
Instead of replacing missing factors, these go around (or bypass) the factors that are blocked by inhibitors to help the body form a normal clot

Subcutaneous injection
An injection into the fatty tissues just beneath the skin

Introduction

Rare, hereditary bleeding disorders, such as haemophilia A, haemophilia B and vWD, are difficult conditions characterised by bleeding, pain and long-term complications. Severe cases can be fatal and sufferers experience a range of physical impacts (notably joint damage, caused by spontaneous and/or traumatic bleeding into joints) and treatment regimens can be arduous. More broadly, bleeding disorders, even if managed to the extent possible with existing treatment options, have profound impacts on quality of life, meaning that those affected also require—but do not always receive—psychiatric, psychosocial and physiotherapy assistance.[1] As bleeding disorders are usually diagnosed in childhood, the burden begins in early life and is faced by both parents and young children and continues throughout the life course.[2]

This report explores the role of innovation in rare, inherited bleeding disorders, a group of diseases that have a major impact on the people affected by them. Innovation can be defined as a novel treatment, product, service or care pathway that has clear benefits when compared to what is currently being done or what has been done in the past. While sometimes considered a buzzword of little value, innovation has played, and continues to play, an important role in improving the quality of life of people with bleeding disorders. Some have been incremental in nature, and some are better described as breakthrough innovations.[3]

As we will see, a potentially transformative innovation is waiting in the wings. We therefore see innovation not as something that starts anew now, but rather as an area in which existing momentum needs to be maintained.

Our report focuses on haemophilia A, haemophilia B and vWD as they are the most common of the rare bleeding disorders and have significant community and clinical impact.

Box 1: A note on von Willebrand disease

Despite its comparative prevalence, relatively little is known about vWD, and awareness is low even among healthcare professionals and in the medical community.[4] Historically, the focus has been on haemophilia, with less attention and research being provided to vWD and other bleeding disorders. We acknowledge that vWD gets relatively less coverage in our report compared to haemophilia A and B. However, where possible, we have attempted to cover the disease fairly, and we argue that more efforts should be made to improve the lives of sufferers.

We describe three "innovation domains" that have provided and continue to provide hope for people with bleeding disorders. We assess the unmet needs that these innovations can help to resolve, as well as looking at what is still outstanding.

Domain 1: Technological innovations

Following the rise of smartphone apps and wearables such as smartwatches and their adoption in other areas of mobile health, a range of solutions are being developed to help manage treatment for bleeding disorders. Such platforms face barriers to their adoption, but if these can be overcome, apps and wearables offer the potential to be part of a comprehensive approach stretching well beyond clinical treatment into a more holistic focus on quality of life and wellbeing.

Domain 2: Systemic innovations

Care for people with bleeding disorders extends beyond the various types of medical treatment designed to head off or counter direct symptoms. Patients require comprehensive care that incorporates psychosocial, psychiatric, physiotherapy, dental and orthopaedic care. Yet this level of support is not always available or as accessible as it should be, nor is there always a sufficient focus on shared decision-making.

Domain 3: Therapeutic innovations

Despite a range of advancements in recent years, existing treatments have drawbacks linked to limitations in the level or consistency of protection they offer and the impacts on the quality of life of people who have to take them. The advent of gene therapy for haemophilia A and B, alongside an increase in personalised therapy, looks set to revolutionise treatment for bleeding disorders.

How innovation saves and improves lives

Introducing haemophilia A, haemophilia B and von Willebrand disease

The three most common bleeding disorders are haemophilia A, haemophilia B and vWD, though many other bleeding disorders exist.[5] Haemophilia A is the deficiency of clotting factor VIII and haemophilia B is a deficiency of clotting factor IX. vWD is a deficiency of the von Willebrand factor (VWF), which attracts platelets to clump together at a wound site, helping to prevent excessive bleeding. VWF also prolongs the half-life of clotting factor VIII, meaning that people affected by vWD also suffer from deficiency of factor VIII. The most common form of treatment for these conditions is the replacement of the clotting factors via injections or infusions administered either on an on-demand or prophylactic basis. Managing these conditions is a lifelong endeavour.

Haemophilia, the best known grouping of clotting factor disorders, affects a significant amount of people (severe disease is seen almost always in males): according to a 2019 study, there are 24.6 cases (including 9.5 severe cases) of haemophilia A per 100,000 males and five cases (including 1.5 serious cases) of haemophilia B per 100,000 males at birth.[6] vWD, another lifelong disorder, which affects both men and women, affects up to 1% of the US population (although it is only clinically symptomatic in about 0.01% of the US population).[7,8]

Waves of innovation have transformed people's lives over the past few decades

While not a comprehensive history of innovation in bleeding disorders, we describe here some of the most significant breakthroughs in treatment.

Haemophilia

1960s: The arrival of concentrated and purified clotting factors for replacement therapy in the 1960s revolutionised treatment for bleeding disorders. Before then, blood transfusions had been the most common treatment (initially transfused fresh from a family member, as there was no way of storing blood at the time). But the disease was often left untreated and life expectancy was very low.[9]

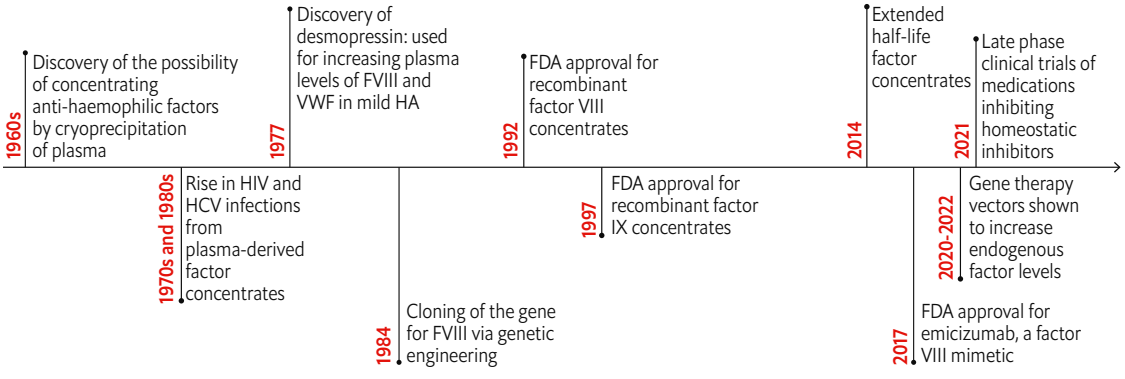
1960/70s: This period saw the discovery that residue left over from thawing frozen plasma (known as cryoprecipitate) contained enough clotting factor to treat haemophilia and vWD without requiring the transfusion of large amounts of plasma. This was followed by the arrival of clotting factor replacement therapy and desmopressin, an inexpensive, non-plasma-based treatment for mild haemophilia A and vWD.

1980/90s: The arrival of HIV/AIDS heralded another innovation drive, as researchers were pushed to find an alternative treatment to eliminate the threat of blood contamination from transfusions. In the early 1990s the first recombinant factor replacement treatments were introduced. Subsequently came the arrival of extended half-life factor replacement treatments, available for both haemophilia A and haemophilia B, which significantly decreased the frequency of treatment injections.

2010s: Due to factor replacement therapy having an inherent risk of developing inhibitors (antibodies that bind to factor concentrates and stop them from working; 20-30% of patients with haemophilia A develop inhibitors, as do a smaller portion of patients with haemophilia B and vWD[10,11]), treatments such as the bispecific antibody emicizumab and bypassing agents such as recombinant FVIIa were developed, which have revolutionised the care of people affected by inhibitors.[12]

2020s: Gene therapy offers the potential of a cure via endogenous production of factor VIII and factor IX in haemophilia A and B respectively, and has received considerable attention. Evidence from trials in gene therapy for both haemophilia A and B is promising despite some limitations. For haemophilia B, a gene therapy treatment (etranacogene dezaparvovec) is awaiting market authorisation,[13] and the European Commission has very recently granted authorisation for valoctocogene roxaparvovec gene therapy for the treatment of severe haemophilia A.[14]

Figure 1: The evolution of haemophilia treatment



Von Willebrand disease

Overall, vWD has not witnessed advances in therapeutic innovation to the same degree as has been seen in haemophilia. Although the first noted case dates to the 1920s, the disease was not fully understood, in a genetic sense, until the 1970s. Until early 2000, desmopressin and intermediate-purity factor concentrates were the mainstay of treatment of vWD.[15] A purer plasma-derived VWF concentrate, low in FVIII activity, was developed in 2005 and recombinant VWF concentrate first became available in 2015 in the US and in 2017 in Europe.[16] Alongside, and partly driven by, these therapeutic innovations, is the development of home treatment. Certainly, the onerousness of treatment for bleeding disorders has been eased by treatment at home, which reduces hospital visits, increases patient independence and drives a preventive approach. Several of the experts we spoke to highlighted the huge impact of home treatment in driving people's independence and limiting the time that they have to spend in hospital—both for planned and emergency treatment. "I think that was the biggest difference in the lives of people with [haemophilia], especially because it gave us the space to almost live a normal life," says Manon Degenaar-Dujardin of the European Haemophilia Consortium. "I think it's the biggest achievement in the past couple of decades."

Unmet needs remain

The therapeutic innovations described have improved the lives of people with bleeding disorders by reducing the frequency of treatment, the frequency of bleeding, and the occurrence of joint damage. These better outcomes and increased flexibility have given those affected the ability to lead a lifestyle that is closer to "normal". However, unmet needs still remain, which could be met through new therapeutic options and innovations. In addition, significant gaps still exist in the management of patients with bleeding disorders. We turn to these in the next section.

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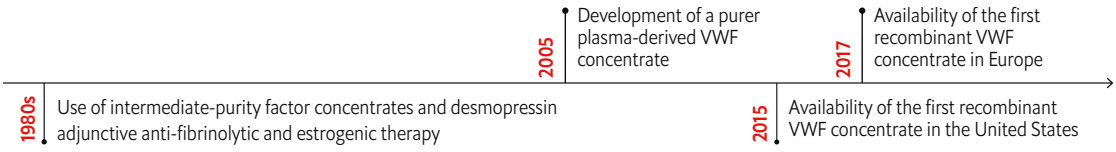
"I think it's the biggest achievement in the past couple of decades."

Manon Degenaar-Dujardin of the European Haemophilia Consortium.

Figure 2: The evolution of vWD management



Unmet needs and challenges for people with bleeding disorders

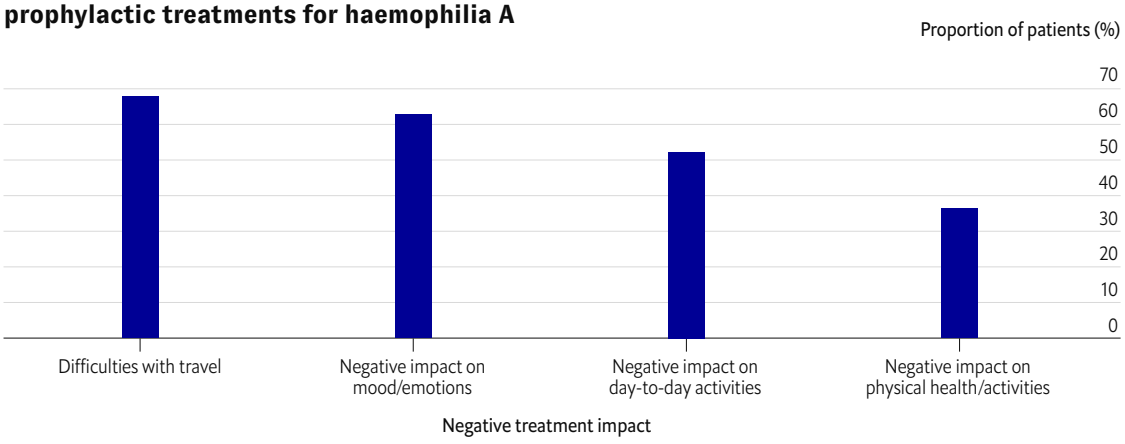
The ability to live a 'normal' life?

Haemophilia

Factor replacement, the current standard of care in haemophilia, has undergone significant improvements over the past few decades. However, patients continue to face challenges due to the need for lifelong administration imposing a significant physical, financial and psychosocial burden. Although prophylaxis is linked to some improvements in health-related quality of life, compared to the general population people with haemophilia have lower employment levels and lower productivity, and suffer from much higher levels of pain.[17] Even with newer agents that require fewer injections, more than 50% of patients identify issues that prevent them from living a "normal" life. These include difficulties with travel, negative impacts on mood and emotions, poor physical health, and a limit on physical activities, particularly when there is a need to be more cautious on non-treatment days (see figure 3).[18]

As well as difficulties in dealing with treatment, people with haemophilia also sometimes suffer from feelings of shame, guilt, fear and anxiety related to their condition, as they feel they are different from others.[19] This has been shown to affect relationships, with a risk of becoming socially isolated. Impacts have also been seen on education and work, with 94% of adults with haemophilia B reporting a negative effect on their ability to complete a formal education, often owing to an inability to attend or concentrate in school as a result of haemophilia-related bleeding or pain. Additionally, 95% of adults with haemophilia B, along with 89% of caregivers and 84% of partners, respectively, indicate that haemophilia has a negative impact on employment.[20]

Figure 3: Negative treatment impacts associated with current prophylactic treatments for haemophilia A



Source: Adapted from Sun et al. 2020

Von Willebrand disease

vWD has also been associated with a lower health-related quality of life, particularly for women with severe vWD, who are at high risk for bleeding-related complications.[21] In one study, very high rates of complications were reported due to heavy menstrual bleeding, including emergency department evaluation in 53% of patients, hospitalisation in 50%, blood transfusion in 48% and haemorrhagic ovarian cyst requiring treatment in 44%.[22] Evidence supports the rationale for ongoing efforts to increase awareness of vWD as a cause for heavy menstrual bleeding and to improve the quality of life in females with known vWD.

Management of the disease is challenging, owing to the wide variability of symptoms and clinical practice, and the lack of high-certainty evidence that is crucial for decision-making.[23] This can lead to patients feeling unsure of how to deal with their disease, which can affect their quality of life. Therefore there remains a need for accurate, rapid and feasible vWD diagnosis to allow selection of the most adequate treatment.[24]

Unmet needs for people with bleeding disorders

Impaired joint health and microbleeding

Haemophilia

The advent of recombinant factor products, extended half-life products and a bispecific antibody product in prophylactic treatment of haemophilia, has still not completely eliminated the risk of the haemophilia-related complications of spontaneous and trauma-related bleeding into joints, muscles and internal organs. Repeated episodes of bleeding continue to be the main cause of joint damage and subsequent chronic pain, arthropathy and arthritis, and morbidity and most complications are also associated with joint damage.[25]

Micro-bleeding in muscles and other organs also causes acute and chronic pain, and can lead to longer impairments in mobility and functional status owing to repeated episodes. Chronic pain can also lead to joint degeneration and other long-term complications, which may require orthopaedic surgery to alleviate the pain.[26] And even for patients on a regular prophylaxis regimen, breakthrough bleeds, particularly in the joints and muscles, can still occur.

"With any therapy we have, patients are still experiencing bleeding," says Barbara Konkle, professor of medicine at the University of Washington School of Medicine. "If we can really solve the issue of arthritis and synovitis and understand which trough level of protection is needed to eliminate the risk of joint bleed, that can make a huge difference to patients," says Flora Peyvandi, president of the International Society of Thrombosis and Haemostasis.

More research is needed to better understand the optimal levels of factor needed to prevent joint and other bleeding, how individuals vary in their response, and the use of imaging and biomarkers to detect early joint damage.[27]

Von Willebrand disease

Joint bleeding also occurs in a considerable number of patients with severe vWD, and the presence of bleeding is strongly associated with reduced energy and fatigue and a lower quality of life.[28,29] Many patients may also develop arthropathy after joint bleeds, which is associated with pain, radiological abnormalities, functional limitations and reduced social participation.[30] However, information on prevalence and severity is limited.

Burden of current treatment and adherence

Haemophilia

Treatments such as emicizumab have changed the landscape of prophylaxis for patients with haemophilia A, owing to the subcutaneous route of administration and less-frequent dosing. However, recombinant products, whether standard or extended half-life factor replacement treatments, are still associated with a high treatment burden, which can impact quality of life and reduce adherence. The threat of active bleeds continues to exist and patients need to use a different product for an active bleed.

"I think it would be great to have novel drugs that can be used for both prophylaxis and active bleeding with an easier administration," says Prof Peyvandi. Also, emicizumab still does not remove the need for injections, which patients find very burdensome. "It would be nice if patients didn't have to poke themselves in their veins or their stomach to have therapy," notes Prof Konkle.

It is therefore no surprise that poor adherence to treatment can be a problem. Studies suggest that the time-consuming nature of prophylaxis is the most important adherence barrier.[31] There is also the worry of causing harm, especially for parents of children with haemophilia, who may have difficulty with venous access or "sticking" their child.[32] Poor adherence to prophylaxis has economic consequences, both direct and indirect—due to missed days of work or school, for instance.[31] Crucially, non-adherence to prophylaxis regimens can lead to poor clinical outcomes.

Von Willebrand disease

Most people with vWD experience less frequent and less severe bleeding than people with haemophilia. Consequently, rather than prophylactic treatment, people with vWD usually receive treatment at the time of bleeding.[33] However, those with clinically severe forms of the disease may need long-term prophylactic therapy, particularly if they bleed repeatedly into the joints, nose or gastrointestinal tract.[34] There is growing interest in the long-term prophylactic management of selected vWD patients, and there is an important need to tailor these strategies for patients with severe vWD who suffer from recurrent spontaneous bleeding.[24] Although such an approach promises to improve quality of life, any prophylactic regime carries an element of burden to the patient, and hence the chance of poor adherence.[33,35]

Challenges in tailoring treatment to factor levels to minimise breakthrough bleeding

Haemophilia

To prevent breakthrough bleeds, factor trough levels need to be maintained above a certain level. However, this is difficult, even with prophylactic therapy, and people with haemophilia continue to have breakthrough bleeds due to fluctuating trough levels.[36] Dosage of prophylactic factor therapy is often adjusted based on in-person reviews with haematologists (themselves based on patient self-monitoring of bleeding episodes), and the frequency of these visits is usually limited to three to four per year.

Patients with haemophilia therefore often struggle with lack of clarity on whether their factor levels are in a "safe range" on a daily basis. This has a significant impact on mental health, especially when there is a need to be more cautious with physical activities on non-treatment days.[37] The routine measurement of individual factor levels to guide physical activity, and so reduce the risk of breakthrough bleeding, is impractical and cumbersome. Although methods to circumvent this problem using technology and statistical modelling have been developed, implementation is challenging owing to regulatory and financial issues.

Risk of inhibitors

Haemophilia

Using extended half-life recombinant products or emicizumab does not eliminate the risk of developing inhibitors. An inhibitor is a type of antibody that is developed due to an immune response to infused clotting factor and renders exogenous factor replacement therapy ineffective. Inhibitors greatly increase the burden on patients, impact the efficacy of treatment and lead to poorer health outcomes, such as significant morbidity related to bleeding, allergic and anaphylactic reactions, and nephrotic syndrome (mostly in patients with haemophilia B).[38,39]

"Patients with haemophilia and inhibitors have limited treatment options, and in such circumstances disease management is challenging" says Ester Zapotocka, a paediatric haematologist at the Charles University in Prague. This is an area of significant unmet need where new therapies are desperately required.

"Patients with haemophilia and inhibitors have limited treatment options, and in such circumstances disease management is extremely challenging."

Ester Zapotocka, Department of Pediatric Hematology/Oncology, University Hospital Motol

Challenges to care and management of bleeding disorders

Variable access and quality of care

Across the US and Europe there are dozens of treatment centres, but they are not always accessible to large swathes of the population. In Europe, coverage in some countries is better than others. This can have implications in terms of cost, if patients need to travel larger distances to reach these centres. Dr Zapotocka points to the example of a well-linked network of large, comprehensive treatment centres and smaller centres in the Czech Republic. "I am head of one of the complex, comprehensive centres, and we have very good co-operation with [the smaller] centres," she says. Yet whereas the Czech Republic, a country of just over 10m people and an area of 79,000 sq km, has five haemophilia centres, Spain—over six times as large and home to more than five times as many people—also has only five.[40]

Even within many higher-income countries, access to quality care is inconsistent, says Amanda Bok, chief executive officer of the European Haemophilia Consortium. "This is because patients navigate healthcare systems that are not [Europe-wide], they're not even always national; often they're sub-national, in many regards. And even under that we'll have different types of centres or clinics or hospitals that are private or public that receive funding directly or indirectly from companies, and it makes the whole constellation very complex." Beyond specialist treatment centres, there is also sometimes a lack of knowledge and experience of bleeding disorders among generalist healthcare workers, which means that they can be overlooked when people engage with the healthcare system.

Underdiagnosis and lack of access to care among women is also common in bleeding disorders.

Underdiagnosis and lack of access to care among women is also common in bleeding disorders. "[Women are] not even the poor relations. They are the relations we don't even talk about for many, many years," says Clive Smith, chair of the UK's Haemophilia Society and a member of the World Haemophilia Society's board. The limited focus on haemophilia in women can perhaps be explained by the fact that symptomatic cases are rare in women and girls. Less justifiable is the relatively larger focus placed on haemophilia (which primarily affects men and boys) in comparison to vWD, which is at least as prevalent as haemophilia A and is twice as prevalent among women as it is among men.

While these biases are in some ways dictated by the historical approach to bleeding disorders specifically, they also speak to an even broader stigmatisation of discussion about women and how their bodies function. For example, heavy menstrual bleeding is among the most common symptoms of vWD in women, yet discomfort and a lack of knowledge around the topic of periods result in fewer women seeking care, fewer healthcare providers addressing the issue and fewer women getting the care they need.[41]

Inconsistent execution of holistic care

People affected by bleeding disorders require co-ordinated comprehensive care that incorporates specialist haematology care alongside psychosocial, psychiatric, physiotherapy, dental and orthopaedic care. This is offered by the best haemophilia centres, but it cannot always be relied upon. "When comprehensive care works well, and you have a fantastic team, it's great," says Sonji Wilkes, vice-president of public affairs at the Hemophilia Federation of America. "But when it's a nightmare, it's a nightmare."

"I can speak quite accurately in terms of the UK position [regarding] comprehensive care," says Mr Smith. "We have 37 care centres across the UK; three years ago we carried out a peer review of them all, and 60% of them don't have, or have inadequate, psychosocial support, psychiatric support and physio." The situation is much the same in the EU, says Brian O'Mahony, CEO of the Irish Haemophilia Society, citing surveys carried out by the European Haemophilia Consortium between 2009 and 2018.[42] "When we looked at all the aspects of comprehensive care, psychosocial intervention, physiotherapy and pain management roles, there was a deficit in many centres in Europe—many comprehensive care centres do not have full-time physiotherapists, or adequate resources for psychosocial care or pain management."

Patients with vWD should similarly receive long-term, comprehensive care—currently the disease is often undertreated, with a reliance on on-demand, short-term prophylaxis treatments. People considering treatment ought to be receiving individualised advice on the risks and benefits of different therapeutic options from a multidisciplinary team that includes haematology professionals, cardiovascular medicine specialists and, if relevant, gynaecology professionals.[23]

A recent study in the US found that hospitalists and obstetrician-gynaecologists were the most common treating physicians both pre-and post-diagnosis of vWD. On the other hand, haematologist visits for bleeding management were documented for only 8% of patients who had continued bleeding after diagnosis.[43] Correct management of the disease, with the inclusion of a haematologist, is especially important when patients wish to undergo elective procedures. Personalised treatment plans should be implemented, in liaison with a comprehensive care tertiary referral centre, before any procedure.[44]

A lack of shared decision-making

Patient preference is crucial for understanding the value of treatments and their impact on patients' lives. Functional outcomes such as pain, anxiety and depression, and the impacts of disease and treatment regimens on daily life all massively affect careers, education, activity levels, and family and social life. This can be true to such an extent that patients' perception of their quality of life can shift so that they become more accepting of a day-to-day reality that is suboptimal for them—the so-called disability paradox. "It's this phenomenon that people with chronic disorders, disabilities, something that is always underlying, something that is always there—it gets normalised for them," says Ms Bok. "And so, they're 'fine', their quality of life is 'fine' in a way that would not be 'fine' for the standard population."

Shared decision-making, through which physicians explain treatment choices to patients and factor in patient preferences and goals when formulating treatment plans, improves patient engagement, treatment adherence and health outcomes, while also lowering costs.[45] In a survey conducted by the European Collaborative Haemophilia Network across 19 haemophilia treatment centres in 17 countries, 95% of respondents supported shared decision-making, with 74% allowing all patients to choose between products for factor replacement.[46] However, implementation of shared decision-making is variable across centres, and its effectiveness depends on many factors, including the knowledge of healthcare professionals regarding the pros and cons of various therapies and the level of patient empowerment.

"[When I was a child], my parents had only two questions they needed to answer: how much factor and how often. Whereas now patients have a multiplicity of questions they need to answer and it's a real burden making those decisions."

Clive Smith, chair of the Haemophilia Society

The rapidly changing landscape of treatment and emerging new innovations in care are exciting, but decision-making becomes increasingly complex. New sets of risk and benefit considerations will need to be evaluated during any treatment decision process, and discussion will be needed on what matters most to people with bleeding disorders and their families.[47] "[When I was a child], my parents had only two questions they needed to answer: how much factor and how often. Whereas now patients have a multiplicity of questions they need to answer and it's a real burden making those decisions," says Mr Smith.

Economic burden of care

Bleeding disorders are associated with high costs and impose a financial burden on people with bleeding disorders and their families, the healthcare system, and society. They are chronic conditions that require lifelong treatment, with costs increasing with several factors including the severity of the disease, the age and the weight of the patient.

Direct costs can include medication, clinician visits and hospitalisations, while indirect costs include reduced productivity and lost wages due to the disease.[48,49,50] This significant economic burden can be a challenge, particularly for those on lower incomes.

Table 1: summary of unmet needs in bleeding disorders

Unmet need	Description
Impaired joint health and muscle bleeds	**Haemophilia** • Persistent risk of joint and muscle bleeds with current therapies • Acute and chronic pain can lead to long-term complications • Lack of knowledge of what trough level of factor should be maintained to prevent joint bleeds **Von Willebrand disease** • Risk of arthropathy after joint bleeds
Treatment burden, adherence	**Haemophilia** • All currently available factor or non-factor products require injection for administration • People with haemophilia sometimes need to use different products for prophylaxis and treatment • The time-consuming nature of current treatment options for haemophilia can lead to low adherence **Von Willebrand disease** • Severe forms need long-term prophylactic therapy, which is a burden and can lead to poor adherence
Tailoring treatment, breakthrough bleeding	**Haemophilia** • Monitoring factor levels for each person with haemophilia on prophylaxis on a regular basis is cumbersome and impractical • People with haemophilia are often not sure whether it is safe to engage in physical activity on non-treatment days
Risk of inhibitors	**Haemophilia** • Monitoring factor levels for each person with haemophilia on prophylaxis on a regular basis is cumbersome and impractical • People with haemophilia are often not sure whether it is safe to engage in physical activity on non-treatment days

Table 2: summary of challenges in bleeding disorders

Unmet need	Description
Accessibility	• Remote areas have limited access to Haemophilia Treatment Centres (HTCs) • GPs and A&E/emergency room physicians have limited awareness of management of bleeding disorders • Limited integration between different specialties involved in caring for bleeding disorders • Limited attention is given to women with bleeding disorders • Less attention is given to vWD, even though it is more prevalent than some forms of haemophilia
Lack of holistic care	• Incomplete implementation of comprehensive care • Limited access to pain management and psychosocial support in HTCs
Shared decision-making	• Limitations in shared decision-making capability due to rapid expansion of therapeutic options and gaps in awareness and knowledge among patients and healthcare providers
Economic burden of care	• High costs (both direct and indirect) associated with current treatment options • Potential increased costs in relation to disease severity, age and weight.

The innovation landscape

A range of unmet needs continues to impact on the lives of people with bleeding disorders. Yet a rich vein of innovation—defined in this report as any novel treatment, product, service or care pathway that has clear benefits over what is currently being done or has been done in the past—is working to help meet these needs. New technologies, therapies and systems of care have the potential to both improve treatment outcomes and yield significant positive impacts on people's quality of life. Innovations in the treatment of bleeding disorders are a response to many of the unmet needs of patients. In this section we describe three "innovation domains" that have provided and continue to provide hope for people with bleeding disorders. We assess the innovations that have the potential to help resolve the unmet needs outlined in the previous section, as well as looking at what challenges (and potential solutions) are still outstanding.

A range of unmet needs continues to impact on the lives of people with bleeding disorders. Yet a rich vein of innovation is working to help meet these needs.

Box 2: ripples of innovation across bleeding disorders

As stated in Box 1, there is limited awareness of vWD, leading to challenges in both diagnosis and defining the optimal treatment approach for patients. However, some previous improvements in the treatment of haemophilia have later been applied to vWD. For instance, developments in prophylaxis in haemophilia helped to provide the rationale for long-term prophylaxis in patients with severe forms of vWD. The hope is therefore that improved knowledge and the development of innovations, such as those listed below, which at the moment are often focused on haemophilia, could in future be applied and translated to patients with other bleeding disorders, such as vWD.

Domain 1: Technological innovations

Over the past several years, smartphone apps and wearable devices such as smartwatches have revolutionised how people manage their health and wellness. Not only are people able to monitor specific metrics—such as the steps they have walked in a day or their blood glucose levels—they are also able to access detailed assessments of these metrics and share them with others, whether a healthcare provider or a personal trainer. Now, mobile health (mHealth) solutions are being developed to help with the management of bleeding disorders.

New app- and wearable tech-based pharmacokinetic innovations can help to eliminate the logistical and practical challenges that more regular factor dosage adjustment entails by tracking patient factor use and patients' stocks of replacement plasma factor.[51] App data, which can be tracked by both patients and physicians, can be combined with readings of patients' previous post-infusion blood test data and data from population-level pharmacokinetic databanks to predict plasma factor level and make real-time dosage adjustments.

Figure 4: App-based innovations allow patients and physicians to track haemophilia symptoms and treatment

One such platform is Web Accessible Population Pharmacokinetic Service—Haemophilia (WAPPS—Hemo), which pulls together patient data on the absorption and metabolism of drugs from 649 haemophilia treatment centres globally.[52,53] An accompanying app and dashboard provide patients and physicians with data and graphs on predicted plasma factor levels, and can be used to create a tailored treatment plan. Similarly, florioHAEMO, another app-based platform, enables patients to record factor infusion data and physical activity (which affects factor levels), as well as allowing doctors to access individual patient data on therapy compliance, plasma factor levels and annualised bleeding rates.[54]

In terms of the impact of such apps, studies demonstrate significant reductions in annualised joint bleeding rates among haemophilia A patients after use of both WAPPS-Hemo and myPKFit, an age- and factor-based platform that is FDA cleared.[55,56] However, the data are inconclusive on factor usage, with usage rising in one WAPPS-Hemo study while reducing in a slight minority of myPKFit study participants.[55,56] More conclusively, patient satisfaction levels are high—a study of florioHAEMO users found that 90% of users were satisfied or very satisfied and 97% found the platform easy to use. Interestingly, however, only 3% of patients reported using the app for discussions with doctors.[57]

How will technological innovation help to resolve ongoing unmet needs?

The use of technological advances for more nuanced tailoring of therapy and improving access to physicians for real-time care will become increasingly important and commonplace, as will the evolution, also technology-driven, of patient health libraries to facilitate patient education, sharing of experiences, and remote access to medical records and doctors.[58] Using an app to adjust prophylactic factor dosage between clinic visits could help to improve patients' symptoms, reduce joint damage, improve lifestyle and mental wellbeing, optimise factor utilisation, and potentially reduce care costs.

Beyond apps, further development and incorporation of hand-held ultrasounds into home care can also assist with early detection of joint bleeds. According to our experts, increasing in-home ultrasounds would help to differentiate acute joint bleeds from other conditions, such as arthritis. This, combined with pharmacokinetic apps, promises to improve joint health overall. An opportunity exists to use apps to shift their focus beyond purely clinical issues to broader aspects of care including psychosocial care and pain management.

Finally, the incorporation of specific settings in platforms—such as the WAPPS-Hemo app—that enable tracking factor replacement in relation to the menstrual cycle would also take considerations unique to women into account. There are already some specialised menstrual cycle tracking apps for women, such as the MyFlow Score app, but uptake has been low.

Where next?

The adoption of mHealth technology is not without barriers. In terms of patients, the uptake of apps and wearables is reliant on the digital skills and accessibility needs of each patient. Functionality of individual apps will need to be simple to understand and navigate. But regardless of individual tech knowhow, there are questions about whether people will remember or be inclined to update or access apps as regularly as they are required to. "They're great if you're using them," says Ms Wilkes, "I can speak from personal experience here, and in clinical trials, you were forced to use them. And so you were very consistent in using them. But [it was different] when it came time for real-world, practical use."

Patients with mild and moderate cases are not often suitably targeted by mHealth solutions. Not only does this directly impact on treatment, but it also means a lack of patient information for a group that is already underserved compared with those facing more severe cases. "We are lacking a lot of data on the mild and moderate cases of vWD especially," says Ms Degenaar-Dujardin. "And I think that's also a reason why treatment is still behind for those patients. Because we don't have the data, we don't know what to ask for. And we cannot make [treatment centres] see that these people really need treatment."

Beyond personal barriers to use, the next challenge is whether bleeding disorder mHealth platforms can be adopted on a systemic level. Co-ordinated, wide-scale tech adoption is often a challenge for health systems, and the relatively rare nature of even the most prevalent bleeding disorders means that hospitals and health services may feel mHealth is too expensive.

"If you want to implement a new technical solution, there can be a lot of resistance in terms of 'why should we add money to this, this is going to be more expensive, and what do we gain from it,' and the whole bureaucracy of implementing new things," says Ms Skouw-Rasmussen, referring to attempts that she has been involved in to drive the adoption of a bleeding disorder app in the Danish health system. "It's been really difficult to find any money for it, because we are not oncology, we are not diabetes."

Despite these challenges, the ability to monitor individual physical activity suggests a clear utility for wearable tech to boost the impact of app-based haemophilia management and plasma factor dosing. A wrist-worn device is already in development for use with the florioHEMO app, while another, HemMobile Striiv, which tracks activity levels and heart rate, can already be paired with its own app that records plasma factor use and bleeding events.[59] A broader push to correlate physical activity with plasma factor levels would significantly improve prophylactic treatment.

Domain 2: Systemic innovations

Given the day-to-day impact on people's lives, care for bleeding disorders goes well beyond the various types of medical treatment designed to counter the direct symptoms. Comprehensive Haemophilia Treatment Centres (HTCs; called Comprehensive Care Centres—CCCs—and Haemophilia Care Centres—HCCs—in Europe) tackle head-on the challenge of complex multidisciplinary needs in bleeding disorder management. They do so by delivering integrated care for all patients with inherited bleeding disorders in a patient-centric, shared decision-making model, shifting the focus from a purely clinical to a more holistic approach.

HTCs first came about as the result of a two-year campaign, starting in 1973, for a network of facilities in the US to provide comprehensive care for bleeding disorders. Nowadays there are about 141 federally funded HTCs in the US. They aim to provide consistent treatment across all centres through development and dissemination of unified guidelines, ongoing provider training, and specialised laboratory and pharmacy resources.[60,61] Similarly, in Europe there are 409 centres, established under the European Haemophilia Consortium, providing holistic care and home treatment plans for patients with bleeding disorders.[62]

Specialist treatment centres have consistently been shown to improve bleeding disorder care, self-care capability, morbidity and mortality.[63,64] In a 2021 survey of US HTC patients, over 90% of patients stated that they were always or usually satisfied with the care and services offered. However, there remain some barriers to care. The same survey revealed that about 15% of patients cited insurance-related barriers to access and 13% mentioned covid-19-related barriers.[65] In addition, integration, access and consistency are an issue for the networks of specialist treatment centres in Europe and the US. Efforts are being made to address these gaps in care.

How will systemic innovation meet unmet needs?

In both the US and Europe, discussions are turning towards the need for an even more unified system of treatment centres, especially with the institution of next-generation therapies, which calls for a re-evaluation and evolution of infrastructure and comprehensive care.. For example, trials of gene therapy for bleeding disorders are underway in just a small percentage of the 141 US haemophilia treatment centres.[61]

However, once treatments begin to roll out, these centres will need to take the lead in terms of knowledge of gene therapy protocol. "All the rest are going to need training from those centres," says Kim Phelan, chief operating officer of the Coalition for Haemophilia B.

More generally, the development of a "hub-and-spoke" model would improve access for all and the US and Europe are moving towards this model. The "hub-and-spoke" model offers patients the opportunity to receive gene therapy regardless of their location by centres of expertise working with a network of smaller, geographically dispersed, local centres. Elsewhere, the "carousel model" of care, piloted in the Netherlands, where patients are able to receive several aspects of their therapy in a single visit, is an innovation in process that reduces the problems of fragmented care.

Specialist centres can also support the training of general practitioners on how to, for example, differentiate between normal and abnormal bleeding. In the Netherlands, for instance, such training is in some cases being provided to local facilities by specialist treatment centres, demonstrating the opportunities for integrated care.

"We have some parts of the country where [centres train non-specialist clinic staff] very well," says Ms Degenaar-Dujardin—"where we don't see people ending up in places where they don't want or need to be."

Systemic innovation can also help to lower healthcare costs and improve collaboration between payers and HTC providers. For example, the Comprehensive Care Sustainability Collaborative, comprising ten HTC representatives and eight payer representatives in the US, has developed a set of standardised metrics to be used by providers and payers to assign value to the services provided. A pilot study is currently assessing the feasibility of utilising these metrics in the clinical setting.[66]

Finally, shared decision-making is an increasingly important tenet of the comprehensive care model provided by specialist treatments centres. Newer algorithms and approaches are exploring better and more accurate ways of integrating patient preferences into treatment plans in a more quantitative fashion. This can be through the assigning of ranks and weights to variables of importance to the patient so as to empower the patient to play a larger role in treatment decision-making. Together with patient characteristics and clinician choices, patient preferences will be integrated in this model to develop final treatment plans.[67]

Where next?

To ensure the sustainability of specialist centres such as HTCs, issues of staffing and financing will need to be ironed out. "At present, most HTCs are overburdened and staffing is inadequate", says Dr Zapotocka. Improved staffing of centres for both diagnostics and treatment is also crucial for equitable access to care.[68] "Sometimes it's about personnel—investment in staff to make everything work smoothly," says Dr Zapotocka. "For example, if you don't have enough [staff] to cover new innovations and to implement them into clinical practice … it can be a problem." There is significant disparity in laboratory capabilities between different HTCs. Some centres may need to send out laboratory tests due to lack of in-house facilities and this contributes to delays in diagnosis and treatment.

Financial sustainability also needs to be explored. HTCs require operating costs and their funding is not always assured. Ensuring the provision of holistic care alongside newer therapies, with potentially high up-front costs, will require adequate funding and education. Centres should ensure access to physiotherapy, psychosocial care and so on—some HTCs integrate these services well, others need assistance. There are also some clinics for women with bleeding disorders, which provide holistic and sensitive care, but these services can be expanded.

Finally, HTCs can work towards enabling home treatment and improving connectivity of patients with their treatment centre. Shared decision making is an integral part of making this model a success. Such patient partnerships will ensure that fewer patients will be lost to follow up in the system.

The delivery of care in haemophilia changes over time, sometimes due to outside events (such as covid-19) and sometimes due to novel and breakthrough therapies—which, as we will see in the next section, are expected to arrive soon. Care models and specialist treatment centres will therefore have to adapt to address these changes and be regularly re-evaluated.

Domain 3: Therapeutic innovations

One area ripe for future therapeutic innovation is personalised medicine. Given the heterogeneity of the clinical and day to day experiences of people with bleeding disorders, high hopes exist around the potential for advances in personalised medicine to improve treatment options. "I think it's the only [approach] that really works," says Glenn Mones, director of advocacy and public policy for the Coalition for Hemophilia B. "What some people would tolerate as a reasonable quality of life, other people might think was unbearable."

As bleeding disorders such as haemophilia and vWD are caused by single genetic defects, gene therapy offers significant potential for treatment. Gene therapy is a technique of using genetic material to treat or cure a disease. In the case of inherited monogenic bleeding disorders, countering genetic abnormalities with gene therapy yields increases in clotting factor levels that can significantly improve the bleeding phenotype over longer periods of time.

After a slow journey from trials in the late 1980s to regulatory approval for medical use 25-30 years later, a handful of gene therapies are approved for use in a range of diseases, including several forms of cancer and neurological disease. The dominant form of gene therapy used for inherited diseases caused by variation in a single gene are a family of viruses called adeno-associated viruses (AAV). AAV vectors act as a vehicle that can be engineered to deliver therapeutic genes to specific target tissues and cells—the goal of which is to achieve the durable expression of the therapeutic protein via a single administration. No replacement or editing is done at the genetic level. The clinical use of in vitro AAV-based gene therapy is well established, with a number of products already approved in lipoprotein lipase deficiency, retinal dystrophy, metachromatic leukodystrophy and spinal muscular atrophy.

AAV-based gene therapy is being investigated as a novel treatment option for both haemophilia A and B.

Although there has been great progress in gene therapy for haemophilia, many gene therapies still await regulatory approval. The first successful human clinical trial for gene therapy in bleeding disorders was for haemophilia B.[69] Currently, one gene therapy for haemophilia A (valoctocogene roxaparvovec) has received market authorisation in the European Union, and one gene therapy for haemophilia B (etranacogene dezaparvovec) is still pending approval.[13, 14] Gene therapies for haemophilia A and B have similar acceptable safety profiles, and five-year phase 1 and 2 follow-up studies have been published for both, with phase 3 studies completed and interim data published.[70,71] "It's likely that you are going to get some degree of durability [with gene therapy for haemophilia B] over time; whether that's ten years or more, remains to be seen," says Leonard Valentino, president and CEO of the National Hemophilia Foundation.

Several factors related to the disease and the AAV vector design involved make haemophilia B more likely to see enduring impact from gene therapy than haemophilia A. Although haemophilia A and B are characterised by similar clinical symptoms, they differ on a molecular basis. Additionally, there is a high level of similarity in vector design for haemophilia A and B gene therapies because they both use AAV-based vectors. The F8 gene (the gene that encodes Factor VIII protein), associated with haemophilia A, is larger and more structurally complex than the F9 gene (the gene that encodes the Factor IX protein) associated with haemophilia B. This means that the F8 gene needs to be truncated before delivery via gene therapy vectors.

Additionally, AAV vectors target liver cells, but factor VIII (unlike factor IX) is not naturally expressed in these cells. Initial data suggests a slow decline in factor VIII activity levels over time, while factor IX activity levels remain relatively stable over time. These characteristics make gene therapy for haemophilia A more challenging.[72]

Other non-factor therapies are also on the horizon that have demonstrated promise in clinical studies. These include efanesoctocog alfa, a novel fusion protein that, given once weekly, offers improved prevention of bleeding episodes in certain people.[73] There are also yet newer therapies, such as concizumab, marstacimab and fitusiran, which rebalance the coagulation pathway and may act as prophylactic therapies for haemophilia A and B. They can be given subcutaneously, are effective against inhibitors and could potentially be expanded to treat other rare bleeding disorders.[74,75]

How will therapeutic innovation meet unmet needs?

Gene therapy offers the potential of a cure for patients with haemophilia. This would, of course, be a game-changer. In terms of lifelong dependence on regular factor infusions and the risk of bleeding and its complications, such as joint damage, chronic pain and the need for surgery, clinical trials have shown that these would all be overcome to a great extent with gene therapy. Although whether, and for which individuals, gene therapy would be "curative" remains to be seen.

Nevertheless, it has been shown that a severe bleeding phenotype can be transformed into a mild one—with factor levels at the near-normal range. The majority of patients on clinical trials for gene therapy could stop prophylactic treatments without significant bleeds.[76]

This would alleviate problems that have been identified by patients as impairing their day-to-day lives: in a study that presented patients with hypothetical scenarios, all patients expressed preference for gene therapy over their current treatments (although several of them also mentioned that they would have questions about safety, efficacy and duration of protection from bleeds).[18] In addition, a one-year follow-up study of ten patients with haemophilia B who had received mediated gene therapy reported improved quality of life.[77]

"One of the big advancements is moving from survival to quality of life" says Ms Bok. "We're no longer just talking about stopping the bleed, we're talking about addressing microbleeds, improving normality, things like that. If you look at standard therapies in the general population, you're looking at therapies that dial down symptoms, dial down pain … but now [with gene therapy] we're really starting to look at therapeutic options that dial up, that create possibilities".

In anticipation of regulatory approval of gene therapy, there are plans to enhance the existing care models in HTCs with development of hub-and-spoke care. This strengthening of co-ordination and increased resource allocation will support the implementation gene therapies but will also have other effects: it will help to reduce fragmentation of care, improve communication and co-ordination between GPs and specialists, and provide more holistic care encompassing various disciplines—including social workers and genetic counsellors.

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Amanda Bok, chief executive officer of the European Haemophilia Consortium

Where next?

The acceptability of gene therapy among patients appears to be high. A Belgian study found that about 75% of patients were either very willing or willing to receive gene therapy for haemophilia, and that patients were more concerned about long-term safety than long-term efficacy.[78] Other studies show that the potential impact of gene therapy on daily life is important to patients. This information can be used by regulators, health technology assessment bodies and payers in their evaluation of gene therapies for haemophilia.

Integrating patient-reported outcome measures into assessment of treatment efficacy will help to foster innovation and improve the demonstration of true value to patients. Flexibility will also be needed in the evidence requirements of health technology assessments, as new therapies for rare diseases often come with limited evidence.[79] Indeed, the inability of current value assessment and payment frameworks to deal with gene therapies remains a concern. There are potentially high upfront costs with gene therapy, and many health systems and payers are not currently set up for this type of treatment. If left unaddressed, this could have an impact on the accessibility of gene therapy for some patients. Alternative payment models, such as risk-sharing arrangements and value- and performance-based outcomes are being explored.[80,81,82,83]

Short-term toxicities of gene therapy must also be addressed, and long-term outcomes monitored in a phase-4 trial setting. The development of harmonised and unified registries to track and record the usage, impact and complications of novel agents such as gene therapy would offer the chance to improve the collation of real-world data of importance to patients. There are examples of such initiatives—for example, the American Thrombosis and Hemostasis Network has begun to enroll patients receiving gene therapy for haemophilia A or B into a long-term cohort study.

Appropriate education is an often-overlooked aspect of many diseases and treatments, and gene therapy education is no exception. To enable more meaningful conversations about the risks and benefits of gene therapy—the knowns and unknowns—there is a requirement for ongoing education efforts targeting everyone that is part of the shared decision-making process – patients, caregivers and healthcare professionals. In addition, there is also a need for improved health literacy on gene therapy to patients, caregivers and the general public. Evidence of current knowledge levels of gene therapy remains mixed. Even with healthcare professionals, a recent survey across 55 countries showed that while over three-quarters of health workers directly involved in haemophilia care had a good understanding of gene therapy, there remained some important knowledge gaps and educational needs remained.[83]

Other studies have shown a lack of confidence among healthcare providers in their understanding of gene therapy, even among those who actively manage patients with haemophilia.[84] In a survey conducted by the World Federation of Hemophilia in 2018, among the 109 treating physicians from 76 countries, 44% had "basic" or "intermediate" understanding of gene therapy, with only 12% having an "advanced" understanding.[85] Education programmes and targeted dissemination of materials are needed for both healthcare professionals and patients to enhance knowledge and awareness.

This education could be supplied from a number of different sources, including patient advocacy groups. "[These organisations] need to be more actively involved in delivering unbiased education that's fair, balanced, and really provides consumers, health care professionals, and importantly, payers, the information needed to be able to embark on transformative therapies," says Dr Valentino.

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Conclusion

To solve the unmet needs facing people living with bleeding disorders, a range of approaches will need to be pursued. We describe here five principles—which emerged from the workshops and interviews that we conducted—around which improved services and care can be designed:

#1: Commission integrated services

There remain inconsistencies in care, both in terms of access to treatment and in the provision of vital aspects of comprehensive care. These include psychosocial, psychiatric and physiotherapy support, and the patient-centric delivery of these. While the promise of gene therapy may make some of these services redundant for some people with bleeding disorders, they will remain crucial for others.

There are many routes to improved service integration. Delivery of care could be co-ordinated through collaborations between states and provinces (in countries such as the US and Canada) and countries (in regions such as Europe) to develop a unified offering of treatment and treatment centres. Public-private partnerships may free-up resources to better support comprehensive care. Incentives could be developed to drive innovation in the treatment of haemophilia, vWD and other bleeding disorders. To support this goal of joined-up care, commissioning will need to consider the full care pathway, life course and unmet needs of people with bleeding disorders.

#2: Develop regulatory, HTA and payment models that support innovation

Neither regulatory approaches, the value assessment processes during HTA, nor the reimbursement frameworks used to negotiate prices, are well suited to accommodate innovative therapies. The combination of high up-front costs, clinical uncertainty and long-term value potential for treatment options such as gene therapy present a challenge. This is a challenge not only for bleeding disorders, but for the increasing range of therapeutic areas for which functionally "curative" therapies are becoming available.

Payers and providers will have to devise a way of enabling equity and affordability—and avoiding undue cost burdens on patients. Outcomes-based payments may be one option, as could the ability to spread treatment costs over a fixed period. The focus should be on the likely cost-effectiveness and future value of these treatments over existing therapies, and the clinical and quality-of-life benefits that they can deliver for the patient. Bleeding disorders are among the first therapeutic areas where gene therapy will enter a marketplace in which established and effective—yet burdensome—therapies already exist. What industry, payers and others learn here is likely to steer the development of value assessment processes for other gene therapies.

#3: Enable technology

An area where care for bleeding disorders is not completely reliant on specialist innovation is the fast-moving technology sector. Here, broader innovative trends have created space to develop the already-encouraging offering of devices and platforms that exists in haemophilia care. Examples of such technological development include the expanded role of artificial intelligence (AI) and wearables in research, and computing advancements that will improve the way that health services, payers, physicians and patients can collect, analyse and use data.

However, there is a need to drive wider adoption of tech offerings. Tech firms, health services and patient organisations should be incentivised to work together to devise and promote the adoption of tech solutions that patients are able and willing to use. Similarly, payers will have to develop funding and coverage frameworks that support technology that improves patients' lives.

#4: Aim for a functional cure

The potential impact of curative therapies in bleeding disorders is huge, almost revolutionary. The continued day-to-day impacts on quality of life—even with current treatment—faced by people affected by bleeding disorders means that a search for a functional cure, where possible, should be prioritised.

The momentum is there for treatments such as gene therapy. Current progress is found in haemophilia A and B, but there is the potential for similar developments in other bleeding disorders, including vWD. Long-term outcomes will need to be tracked, but the data seen so far is promising. Such "curative" treatment, it is hoped, would address the ultimate unmet clinical needs of patients—having to live with a bleeding disorder.

#5: Amplify the patient voice

Workshop participants agreed that patient organisations play a central role in helping their members make better-informed treatment decisions. Such organisations are already active, of course. In fact, the bleeding disorders patient community is a prime example of engagement with patients and healthcare providers—the work of the European Haemophilia Consortium in amplifying the patient voice to healthcare providers being one clear instance. But, given the opportunity and supported through systemic change, patient organisations could play an even greater role. They could partner with health systems to contribute to the training and education of healthcare professionals on the patient perspective, for example. And they could offer peer-to-peer support for people with bleeding disorders.

As the new waves of therapeutic innovation discussed in this report are in development, patient organisations should collaborate or partner with industry to ensure that patient-centric development strategies are implemented to address patient needs, wants and preferences for therapy. In order for patient-centred care to be successful, patients need to feel educated and empowered in order to have a voice throughout their journey with a bleeding disorder—education equals empowerment. Indeed, amplifying the patient voice underpins all of the above recommendations.

Our report has highlighted the unmet needs of people living with bleeding disorders, and the innovations that will help to meet those needs. But many of the barriers and enablers that we have discussed are applicable across healthcare. Building services around the principles outlined above—including empowering patients, education, enabling technology and working out how to reimburse a new generation of therapies—will not only help people with bleeding disorders, it will also improve healthcare services as a whole.

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