OHE

Investing in Innovation

A SPOTLIGHT ON HAEMOPHILIA THERAPIES

CONTRACT RESEARCH REPORT
OCTOBER 2024

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The individuals' participation in the roundtable was as subject experts rather than representatives of their respective organisations.

Table of Contents

Executive Summary

Pharmaceutical innovation is a key driver of improvements in health outcomes, quality of life and productivity for people with acute and chronic conditions. This progress has been exemplified in the context of haemophilia, where iterative and incremental innovation has added significant value for patients and health systems. New treatments have transformed the lives of people living with haemophilia from a life expectancy of around 30 years in the 1960s to a life expectancy at present comparable to the general population in developed countries (Mannucci, 2020).

THE IMPACT OF INNOVATION ON HAEMOPHILIA

In haemophilia, continued investment in research and development has led to the development of a number of new innovations, each with unique benefits to patients. These include reduced treatment burden, improved adherence, and improved quality of life, including greater ability to partake in physical activities and to achieve major life goals. Further, new treatments provide patients with multiple options, meaning they can make treatment decisions based on their clinical needs, physical activity level, and lifestyle. These benefits also have spillover effects on carers, family members and wider society. Haemophilia thus provides an exemplary case study of how continued investment in pharmaceutical innovation can transform the lives of patients and carers.

Yet, despite an impressive array of treatments, there is a remaining unmet need that requires further innovation (**Figure 1**). People with haemophilia still experience pain, joint damage, and mental burden due to their condition. Indeed, the aspiration for many people with haemophilia is to live with a haemophilia-free mind.

WHERE NEXT?

All stakeholders have a part to play in ensuring a healthy innovation ecosystem, allowing innovation to continue transforming patient lives. For example:

- Developers, manufacturers, and researchers must continue to invest in R&D, leveraging feedback loops of return on investment and scientific spillovers. R&D should be directed towards innovation that is of the highest value to society, as signalled by pricing and reimbursement policy.

- Governments, regulators, and HTA bodies must foster a supportive policy environment that recognises and rewards innovation, including intellectual property protection, transparent approval requirements and processes, and pricing and reimbursement policies that incentivise and reward the types of innovation that are of greatest value to society.

- All stakeholders should facilitate patient involvement throughout the development and assessment processes to ensure that unmet need and patient voice are appropriately considered.

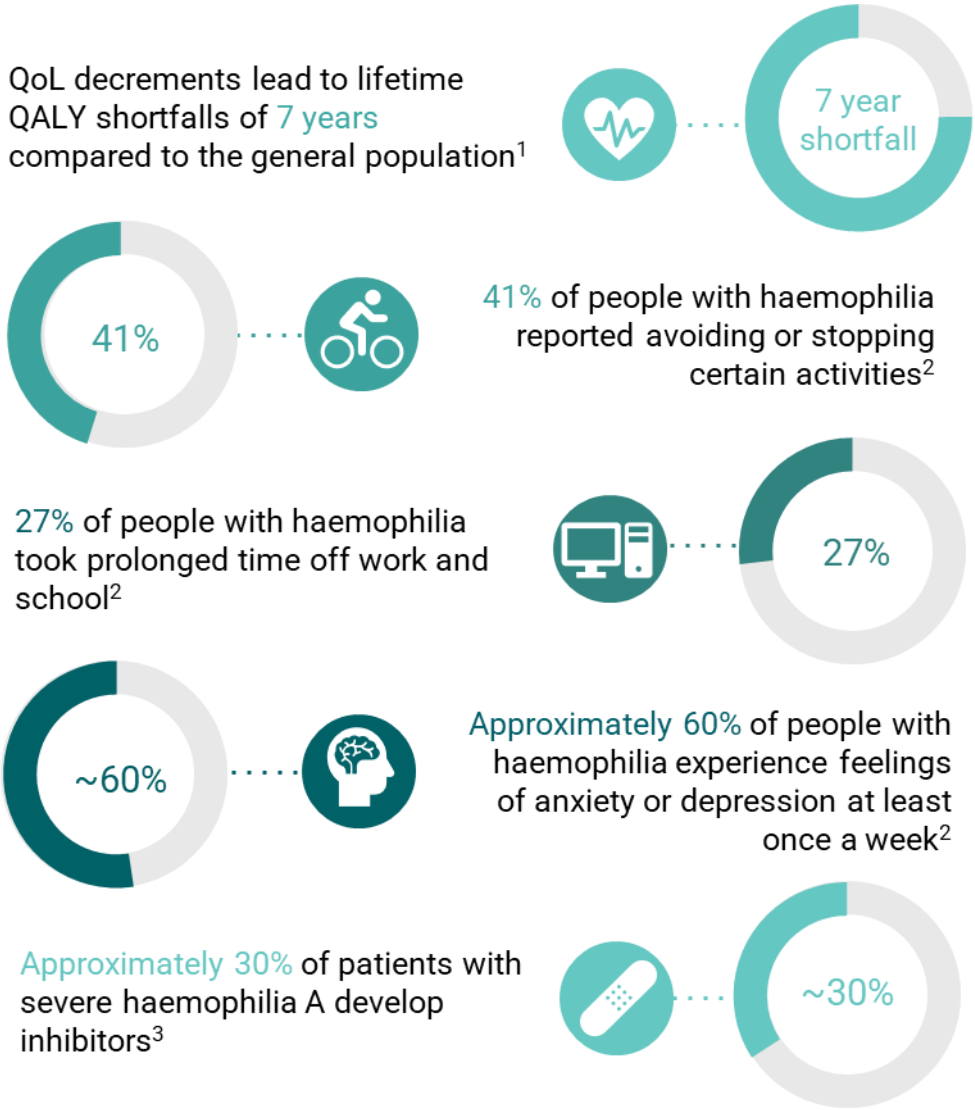
Within haemophilia, pharmaceutical innovation has significantly improved care, but considerable unmet need remains. To further advance the research agenda in the haemophilia space:

- Patient advocacy groups should leverage their unique position to package and communicate information about innovative treatments to overcome the knowledge gap experienced by health care professionals and patients, thereby removing education and understanding as barriers to access to innovation.

- Health economics and outcomes researchers should explore the depth and complexity of the factors that contribute to remaining unmet need in this space to enable innovation to target the aspects of unmet need that are most important to patients.

- Policymakers, including HTA bodies, should continue to improve and refine their polices to provide appropriate incentives and rewards for innovative haemophilia care.

FIGURE 1: UNMET NEED IN HAEMOPHILIA



[1] Based on an ICER report estimating the expected years of life and lifetime QALYs associated with factor IX treatment, non-factor treatment and gene therapies for haemophilia A and B. When comparing lifetime QALYs to expected years of life, all treatments are associated with a QALY loss equivalent to at least 7 full years of life loss indicating a substantial unmet need due to morbidity (ICER, 2022)
[2] Based on a 2023 global survey of people with haemophilia (The Harris Poll and Sanofi, 2023)
[3] Approximately ~30% of patients with severe haemophilia A will develop inhibitors, in addition to 5% of patients with mild and moderate haemophilia A and 3% of patients with haemophilia B (Meeks and Batsuli, 2016).

1. Background

Pharmaceutical innovation has revolutionised care for people living with haemophilia in recent decades. Numerous innovative therapies have been approved in recent years, made possible by pharmaceutical research and development (R&D), building on advances in clinical and scientific knowledge and targeting unmet needs. Many of these have offered the potential for further improvements in health outcomes and patient experience amongst eligible populations. Haemophilia thus provides an exemplary case study of how iterative and incremental investment in pharmaceutical innovation can transform the lives of patients and carers.

1.1. Disease background

Haemophilia A and B are hereditary haemorrhagic disorders characterised by the deficiency or dysfunction of coagulation protein factors VIII and IX, respectively (Peyvandi, Garagiola and Young, 2016). The gene that causes haemophilia is located on the X chromosome, and given that males only have one X chromosome, if a male has a haemophilia allele, he will exhibit the disorder (CDC, 2024a) Therefore, symptoms of haemophilia primarily affect males, but female carriers of the disease-causing mutations may also manifest milder forms of the disease. Despite being a genetic disease typically passed from parents to children, about one-third of cases are caused by a spontaneous mutation (CDC, 2024b).

Around 60% of those diagnosed with haemophilia A have a severe form of the disease; moderate cases represent around 15% of all patients, and mild cases represent around 25% of all patients (NBDF, 2024b). Haemophilia A is estimated to have a prevalence of approximately 0.7 in 10,000 people(EMA, 2022a). Haemophilia B is less common, with a prevalence of 0.2 in 10,000 people or around 10,000 people in the European Union (EMA, 2018a). The estimated prevalence of haemophilia in the United States is 12 cases per 100,000 U.S. males for haemophilia A and 3.7 cases per 100,000 U.S. males for haemophilia B (Soucie et al., 2020). As such, haemophilia A and B are designated as "rare" diseases according to both the European Medicines Agency (EMA) (affects fewer than 5 in 10,000) and the Food and Drug Administration (FDA) (affects fewer than 200,000 people in the US) definitions (Institute of Medicine (US) Forum on Drug Discovery, 2009).

Individuals with severe haemophilia will experience recurrent, spontaneous bleeds, often in the absence of any trauma event (NBDF, 2024b). Approximately 90% of people with severe haemophilia experience chronic haemophilic joint disease, characterised by chronic inflammation and progressive joint deformity, in one or more major joints by the age of 30 (O'Hara et al., 2017). As well as joint stiffness and diminished range of motion, individuals with haemophilia experience significant acute pain during bleed events and chronic pain due to arthropathy, leading to disability and impaired quality of life in more than half of cases (Franchini and Mannucci, 2017). The total "economic burden" (reflecting unmet need and taking into account costs to patients, carers, and the health system) of severe haemophilia across the largest five European countries (France, Germany, Italy, Spain and the UK) for 2014 was estimated at EUR 1.4 billion, or just under EUR 200,000 per patient annually (O'Hara et al., 2017). In the US, for individuals with haemophilia B, the average annual per-patient factor costs were $611,971, annual non-medical direct costs were $2,371, and annual indirect costs were $6,931 (Burke et al., 2021).

1.2. Treatment and unmet need

There are a number of treatment options available for those with haemophilia A and B (see Section 3). However, despite the existence of treatments, there is still considerable unmet need.[4] Shima (2020) indicated that several unmet needs remain, including reducing the need for repeated intravenous infusions, the development of inhibitors (where an autoimmune response reduces treatment effectiveness), and fluctuations together with low trough levels of clotting factor activity. The frequency of the clotting factor injections requires patients to make regular hospital visits, which creates a significant burden in terms of time and cost for patients and caregivers (Krumb and Hermans, 2021). Another unresolved challenge is preventing the progression of haemophilic arthropathy, a permanent joint disease that occurs in older adults with severe haemophilia as a consequence of repeated haemarthrosis (joint bleeds) (ibid.).

In this report, we focus on the available treatment options and remaining unmet needs from a developed country perspective. However, it's important to acknowledge that there are significant challenges in managing haemophilia in developing countries, ranging from financial to organisational and government commitments (Ndoumba-Mintya et al., 2023). We discuss these issues further in Section 4.

1.3. This report

The objectives of this report are to:

- Showcase the significant potential of pharmaceutical innovation by highlighting key step-changes in haemophilia treatment, the profound impacts these innovative new treatments have had on patients and health systems, and how pharmaceutical innovation has made these impacts possible.
- Explore the extent and nature of the remaining unmet need in the haemophilia space to shine a spotlight on the continued need for innovation to address the remaining gaps for patients and health systems.
- Demonstrate the importance of how and why policymakers and healthcare decision-makers recognition of the value of innovation is critical for supporting continued investment in innovation.

To achieve these objectives, we conducted two targeted literature reviews on the topics of (i) value of innovation in haemophilia and (ii) the broader value of pharmaceutical innovation. We also synthesised available data on step-changes in haemophilia care and remaining unmet need to form case studies. Finally, we hosted a roundtable with key stakeholders, including patient advocates, healthcare professionals, and value assessment/policy experts to gather primary insights and validate our earlier findings. Further details on the methods are given in Appendix A1.

The remainder of the report is structured as follows: Section 2 explores how innovation occurs and why it matters. Section 3 describes historic and innovative haemophilia treatments, assesses which attributes of innovation are present in each group of therapies and provides case studies quantifying the impact of innovation in haemophilia. Section 4 discusses the remaining unmet need in the context of haemophilia, barriers to uptake and value assessment challenges. Finally, Section 5 discusses the role of policy in incentivising innovation, and Section 6 provides conclusions and recommendations.

[4] There are various definitions of the concept of unmet need (sometimes referred to as unmet medical need) in the health economics literature; see Box 6 of Appendix A2 for a brief definition (Zhang, Kumar and Skedgel, 2021).

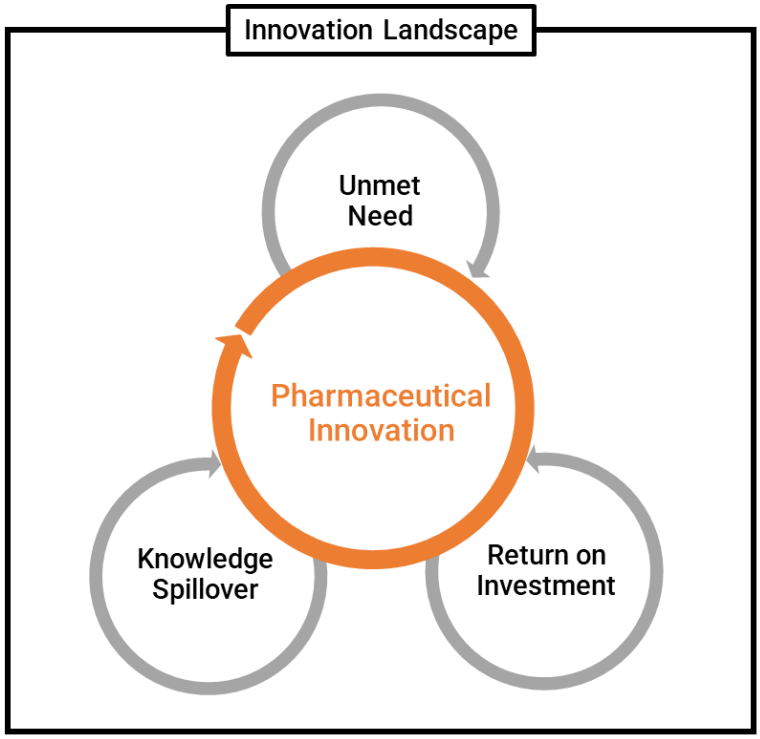
2. Pharmaceutical innovation

Innovation in haemophilia treatment is brought about via pharmaceutical innovation[5], rooted in pharmaceutical R&D.

2.1. How does pharmaceutical innovation occur?

Innovation is a collective societal process where innovators build upon prior work and adapt their scientific and commercial approaches according to prior knowledge, unmet needs, and return on investment (Hofmann et al., 2021; Bruen et al., 2016; Lakdawalla, 2018). Figure 2 and the subsequent paragraphs provide an overview of the pharmaceutical innovation feedback cycle, indicating the three main drivers of product innovation.

FIGURE 2: PHARMACEUTICAL INNOVATION FEEDBACK CYCLE



SOURCE: OHE SYNTHESIS OF HOFMAN ET AL. (2021), BRUEN ET AL. (2016) & NIJHUIS, GUAN AND TEWARY (2019)

From a **technical perspective**, pharmaceutical innovation is cumulative as new inventions and innovations critically depend on prior knowledge and efforts, i.e. **scientific (knowledge) spillove**r (or economic "externality") (Bruen et al., 2016; Lakdawalla, 2018). Pharmaceutical development therefore not only drives product innovation but also generates information that is of benefit to all innovators.

[5] *For more on what is meant by 'pharmaceutical innovation' see appendix A2.*

This generates a feedback loop whereby innovation generates scientific spillovers, which can promote further innovation.

From a **therapeutic perspective**, cumulative therapeutic innovations drive continuous improvements in healthcare and healthcare management, especially in areas of **unmet need**. When a new innovation targets or solves an area of unmet need, this sets a higher bar for subsequent innovation, whilst clarifying and highlighting areas of unmet need that remain. Collectively, this approach has the potential to bring about significant advancements in patient care (Nijhuis, Guan and Tewary, 2019).

From an **investment standpoint**, both current and prospective innovators carefully consider the anticipated impact of existing and future reimbursement policies and practices when making decisions about investing in R&D and directing their investments toward specific products. A positive **return on investment** serves as a reward for successful innovators and encourages subsequent rounds of investment (Bruen et al., 2016). This is, therefore, another feedback loop whereby innovation generates a return on investment, which can promote further innovation.

As part of this cumulative innovation process, pharmaceutical innovators weigh various factors in their R&D investment decisions such as the policy environment (e.g. Intellectual property protection, regulation, pricing and reimbursement, and specific incentives to support in certain areas, such as rare diseases), as well as demand-side (market size, disease characteristics) and supply-side (e.g. competition, technology) factors (Barrenho, 2014; Bruen et al., 2016). These factors create the **landscape for innovation**, within which these feedback loops can occur.

2.2. Why does innovation matter?

In line with the characteristics of pharmaceutical innovation outlined above, the introduction of new pharmaceutical innovation can deliver improvements in health outcomes, convenience, and broader health system benefits. Pharmaceutical innovation has been estimated to improve patient longevity (Lichtenberg, 2019; Buxbaum et al., 2020), quality of life (Lichtenberg and Virabhak, 2007), and productivity (Lichtenberg, 2001, 2005). In addition, patients who are treated with new medicines require fewer healthcare system resources leading to cost savings for healthcare systems which can offset the costs of new pharmaceutical innovation, as summarised by Zozaya, Alcalá and Galindo (2019).

Section 3 sets out the benefits of innovation using haemophilia as an example of how pharmaceutical innovation can revolutionise patient care.

3. Innovation in haemophilia

Continued investment in R&D by the global pharmaceutical industry, national research grant bodies, and haemophilia patient advocacy groups has revolutionised the lives of people living with haemophilia (The Haemophilia Society, 2024). Over the past two decades, the treatment landscape in haemophilia has evolved substantially with the introduction of extended half-life products, FVIII-activity mimicking agents, gene therapies, and rebalancing agents (Mannucci, 2020).

These iterative treatment advances have been driven largely by unmet need in haemophilia and the opportunity for pharmaceutical innovation to leverage scientific spillovers and previous returns on investment to address these gaps (Kusynová et al., 2022). Breakthroughs have built on previous pharmaceutical innovations, as well as general scientific advances and discoveries in fields such as molecular biology, genetics and biochemistry.

Prior to the introduction of recombinant therapies, life expectancy for people with haemophilia was low compared to the general population (Mannucci, 2020). A short description of older treatments (labelled 'historic treatment options') available from the mid-20th century up until the 2000s is provided in Box 1.

Historical Treatment Landscape

Until the mid-20th century, there was no effective treatment for haemophilia. Whole blood was the only treatment approach available, and this was of such limited clinical efficacy that the life expectancy of people with haemophilia was only 10-15 years (Mannucci, 2020). The first wave of innovation was largely driven by the events of the Second World War and related combat causalities. This external technological shock triggered the improved preparation of plasma, but this form of replacement therapy was not widely available and of limited clinical efficacy (ibid.). Up to the 1960s, the life expectancy of patients with haemophilia was still only around 30 years (ibid.).

Haemophilia treatment experienced a major breakthrough in the 1970s due to the ability to fractionate and concentrate FVIII or FIX from plasma and to lyophilize (freeze-dry) for later reconstitution when needed. Factor concentrate was produced by pooling human blood plasma from donors and concentrating it to extract the required clotting factor. Initially, the clotting factor concentrates obtained from plasma lacked measures to inactivate blood-borne viruses during the production process ((McClure et al., 2024). It was not until 1985 that these procedures were introduced, along with tighter screening methods, significantly lowering the potential for blood-borne infections (Lee, 2009). The diffusion of these procedures led to improvements in safety in the 1990s.

BOX 1: HISTORIC TREATMENT LANDSCAPE

3.1. This chapter

In this chapter, we provide an overview of the recent innovations in haemophilia treatment and highlight case studies of the impact of some of these therapies on patients and health systems. Each section follows the same structure where applicable: an overview of the new treatment, a description of how pharmacological innovation has enabled this progress, an analysis of elements of value or innovation added, and remaining challenges (including remaining unmet need).

When discussing how pharmacological innovation has enabled progress, we categorise these according to the three feedback loops/drivers of innovation as outlined in Section 2:

 technical (via scientific spillovers),

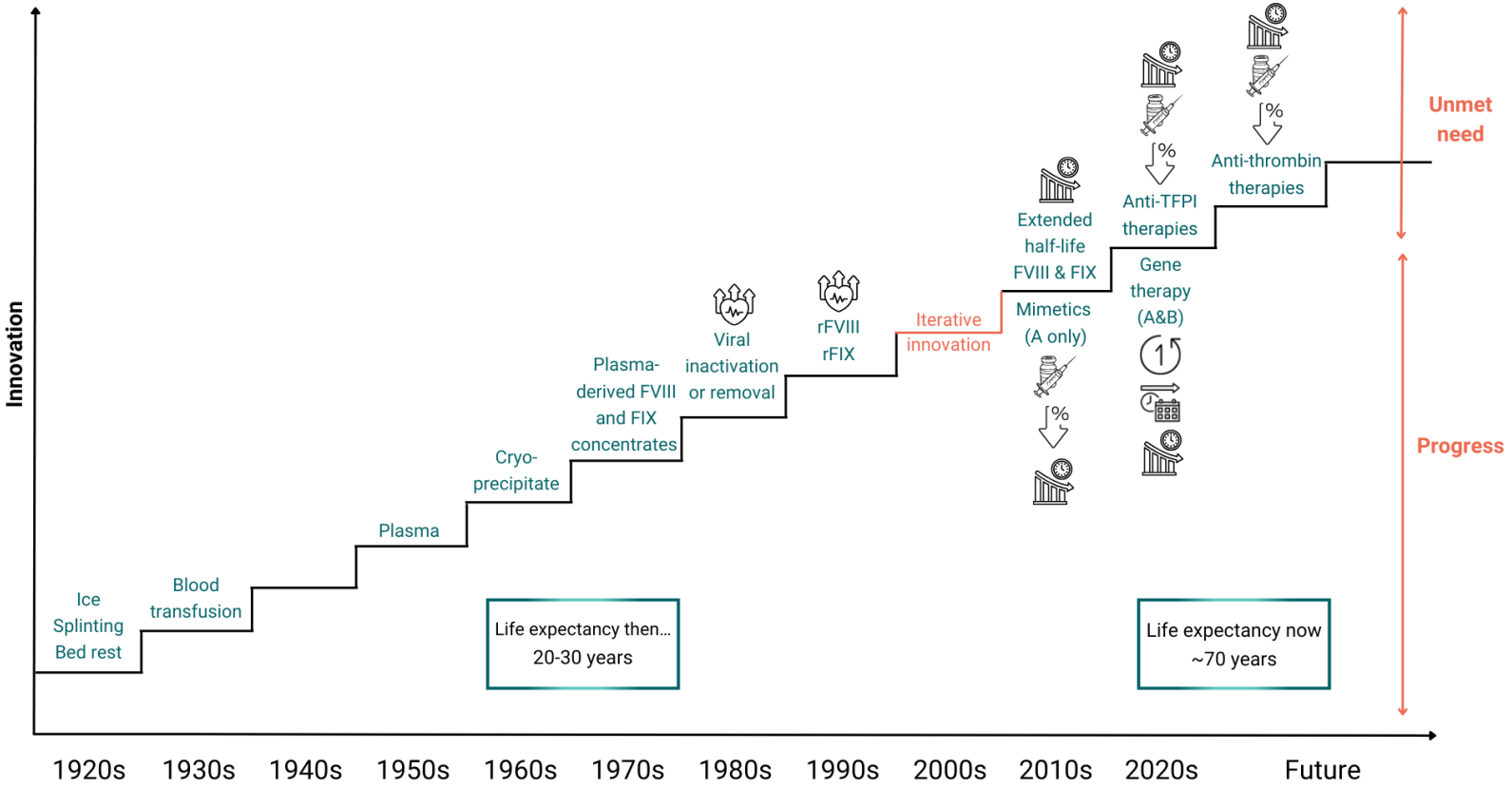
 therapeutic (driven by unmet need)

 return on investment.

Not all of these are addressed for each therapy due to a lack of evidence, usually regarding the technical origin of the new innovation. The return on investment is the same for each therapy as R&D is a dynamic process based on pooled returns: a share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of adding value via further innovation that will generate future returns.

Figure 3 provides a summary, illustrating the added value of the iterative innovations that have taken place from the 1920s to the near future. The key value improvements associated with these innovative treatments are noted in the legend box below. These innovations mean that people with haemophilia now have a similar life expectancy to the general population. However, unmet need remains in terms of quality of life and treatment burden; this is discussed in Chapter 4.

FIGURE 3: A CENTURY OF TREATMENT INNOVATIONS IN HAEMOPHILIA



SOURCE: OHE SYNTHESIS BASED ON MANNUCCI (2020);
Additional information sources: Extended half-life FVIII & FIX (Ar, Balkan and Kavaklı, 2019), Mimetics (Mannucci, 2020), Gene therapy (Leebeek and Miesbach, 2021), Anti-TFPI & Anti-thrombin (Mancuso, Croteau and Klamroth, 2024), Life expectancy then (Mannucci, 2020), life expectancy now (ICER, 2022; Hassan et al., 2021).
Acronyms: rFVIII = recombinant FVIII, rFIX = recombinant FIX; Anti -TFPI = Anti tissue factor pathway inhibitor

3.2. A New Wave of Innovation

3.2.1. Recombinants

Overview

Recombinant coagulation FVIII and IX are synthetic factor products (not derived from plasma).

How has pharmaceutical innovation enabled this progress?

Therapeutic (driven by unmet need): The previous risk of infection from historical treatment options represented an unmet need of crucial importance to the haemophilia community (Franchini, 2010).

Technical (via scientific spillovers): Scientific innovation led to rapid progress in molecular medicine, clarifying the genetic basis of coagulation defects. The cloning of FIX and FVIII genes in 1982 and 1984, respectively, paved the way for the creation of safer virus-free recombinant FVIII and FIX concentrates (Pipe, 2008).

This led to the therapeutic production and commercialisation in the 1990s of recombinant coagulation FVIII and IX. In 1992, the first recombinant factor VIII (8) was approved by the FDA (CDC, 2023). The first recombinant factor IX (9) product was granted FDA approval in 1997 (Swiech, Picanço-Castro and Covas, 2017). Additionally, synthetic drugs, such as desmopressin acetate were introduced to treat mild to moderate haemophilia A and von Willebrand disease (CDC, 2023; Mannucci, 2012).

Return on investment: A share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation (Berdud, Drummond and Towse, 2020; PhRMA, 2019)

Elements of innovation/value added

The major benefit of recombinant products is the improved safety profile, as they now have no added albumin (Schiavoni et al., 2019). This led to the conversion of many patients from plasma-derived to recombinant therapy (Franchini, 2010). Another benefit arising from recombinants was their increased availability given that they are not dependent on starting material i.e. plasma for their production (Coppola et al., 2014). Evidence of improved efficacy when compared to plasma products is mixed, depending on the type of study performed. Box 2 summarises the quantitative evidence of health and health system impacts of recombinants compared to previous plasma therapies. Further details are provided in Appendix A1.

On-demand recombinant therapies vs on-demand plasma-derived therapies

The literature indicates notable benefits on the health and cost-saving impact of recombinants compared to plasma-derived therapies. Evidence shows recombinant therapies lead to swifter bleed resolution compared to plasma therapies, leading to benefits for patients in terms of quality of life and benefits to health systems in terms of reduced costs.

Whilst randomised trials did not find significant efficacy differences between the recombinant therapy and plasma therapy arm, when using dosages approved by the FDA (Astermark et al., 2007;

Young et al., 2008), only two have been conducted for this comparison. Much of the evidence comes from non-randomized studies due to the difficulty of sourcing sufficiently sized representative samples for randomised controlled studies. This is due to a combination haemophilia's rarity (which leads to small sample sizes in studies), as well as the clinical variability among patients and subsequent unpredictability of bleeds. In particular patient populations, non-randomised evidence suggests superior efficacy for recombinant therapies. For example, a typical rFVIIa regimen was shown to be more effective than a typical activated prothrombin complex concentrate (aPCC) regimen in the management of acute bleeds (Treur et al., 2009).

Knight, Danø and Kennedy-Martin's (2009) systematic review found that 8 out of 11 studies indicated recombinant factor therapy to be the preferred treatment option, suggesting that recombinant therapy is cost-effective when compared to plasma factor therapy in the treatment of mild-to-moderate bleeds for haemophilia patients with inhibitors. However, studies that used efficacy estimates based on the clinical trial results found that the recombinant therapy was more costly overall (Kim et al., 2019; Hay and Zhou, 2011).

There is also some limited evidence on the beneficial impact of using recombinants on quality of life though the estimated magnitude varies. Ekert et al. (2001) performed a before-and-after cost-effectiveness analysis, where 6 children were observed for 6 months with their usual treatments for on-demand bleeding episodes before changing to a recombinant therapy for one year, collecting quality of life estimates using the EQ-5D. A substantial gain was seen in terms of quality of life, where the incremental quality-adjusted life years (QALYs) gained over the course of one year was 0.58. Kim et al. (2019) found contrasting results using quality-adjusted life days (QALDs) as an outcome measure. Over the course of 5 days, a plasma-derived therapy was associated with 4.09 QALDs on average compared to 4.08 QALDs for a recombinant therapy. Again, these widely contrasting results can be explained by the choice of randomised and non-randomised efficacy estimates.

BOX 2: CASE STUDY: ON-DEMAND RECOMBINANT THERAPIES VS ON-DEMAND PLASMA-DERIVED THERAPIES

Remaining challenges

Regular injections of octocog alfa, which is an engineered version of clotting factor VIII, remains one of the most widely available prophylactic treatment for haemophilia A (NHS, 2017). Injections every 48 hours are typically required (ibid.). Prophylactic treatment of haemophilia B is very similar, where injections of nonacog alfa (clotting factor IX) are recommended twice a week (ibid.). A potential side effect of replacement factors is that patients may develop an autoimmune response to the factor concentrate over time, which makes the treatment less effective (NHS, 2017). These neutralising antibodies, known as inhibitors, can develop against the infused factors; around 30% of haemophilia A and 3% of haemophilia B patients develop inhibitors (Meeks and Batsuli, 2016). Depending on the severity of haemophilia, these patients may be required to have additional treatment, such as immune tolerance induction, bypass therapy, or immunosuppressants (NHS, 2017).

Furthermore, frequent factor administration is not only disruptive to daily life, it can also lead to vein damage and scarring, potentially decreasing compliance to treatment (Wells et al., 2019). Another consideration for those on conventional factor replacement therapy is that prophylaxis with standard recombinants requires fore planning, particularly for individuals partaking in physical activities, because factor levels—and therefore treatment effectiveness—wane over time (Thornburg and Duncan, 2017; Berntorp et al., 2021; Krumb and Hermans, 2021).

3.2.2. Extended half-life factors

Overview

From around 2014, extended half-life recombinants became available to haemophilia B patients (Graf, 2018). These factors meant that many people required fewer infusions per week (Ar, Balkan and Kavaklı, 2019).

How has pharmaceutical innovation enabled this progress?

Therapeutic (driven by unmet need): Factor VIII and factor IX are proteins with relatively short half-lives, meaning that frequent doses had previously been required to maintain therapeutic levels (Graf, 2018). This high treatment burden represented an unmet need for patients.

Technical (via scientific spillovers): Advanced protein engineering gave rise to blood clotting factors that stay in circulation for much longer than previous treatments, extending the time of increased factor activity levels, thereby targeting this unmet need. The development of extended half-life factors utilised various strategies including PEGylation, Fusion Protein Technology and Single Chain Technology, among others (Mannucci, 2015; Graf, 2018).

Return on investment: A share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation (Berdud, Drummond and Towse, 2020; PhRMA, 2019)

Elements of value/innovation added

Extended half-life recombinants meant that many people with haemophilia required fewer infusions per week, thereby, reducing the burden and increasing compliance (Ar, Balkan and Kavaklı, 2019).

Remaining challenges

One of the drawbacks of extended half-life therapies is that they still rely upon intravenous administration and thus still incur the complications related to this route (Okaygoun et al., 2021). Furthermore, there is a disparity in the extent of extended half-lives of FVIII products for haemophilia A (1.2- to 1.5- fold compared to standard half-life) compared to FIX products for haemophilia B (3- to 5- fold)(Ar, Balkan and Kavaklı, 2019); signalling the need for further innovation, particularly in the haemophilia B treatment space.

3.2.3. Non-factor agent: Mimetics

Overview

The first nonfactor therapy for haemophilia A received marketing authorisation in the USA in November 2017 with breakthrough therapy designation and in Europe in February 2018 under an accelerated assessment pathway (FDA, 2017; EMA, 2018b). It is a monoclonal antibody used for routine prophylaxis in people with Haemophilia A, with or without inhibitors (Genentech, 2024) .

How has pharmaceutical innovation enabled this progress?

Therapeutic (driven by unmet need): Non-factor treatments specifically address elements of remaining unmet need associated with factor replacement treatments. For example, this class of therapy is administered subcutaneously and can be self-administered, which offers

advantages over current treatments by simplifying prophylaxis, e.g. in children with poor venous access. Mimetics are usually administered at weekly intervals, or in some cases every two weeks, going some way to alleviate the burden of frequent and uncomfortable treatment.

In addition, the probability of developing inhibitors against mimetics is low, as humanised antibodies have low immunogenicity (Sampei et al., 2013). If inhibitors develop, they are unlikely to cross-react with FVIII and compromise treatment, which allows the use of mimetics in patients with and without inhibitors.

Return on investment: A share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation.

Elements of value/innovation added

In addition to increased convenience and lower treatment burden, prophylaxis via mimetics can lead to a considerable reduction in annualised bleeding rates (ABR); results from the CHESS II study found that among severe haemophilia A participants previously on prophylaxis, mean ABR decreased from 3.49 to 1.40 after switching to this class of therapy (Mancuso et al., 2022).

Remaining challenges

Mimetics do not normalise haemostasis[6] so continued access to FVIII concentrate or bypassing agents for bleed management may still be necessary (Mancuso, Croteau and Klamroth, 2024). Although mimetics are generally well-tolerated, the most common adverse reaction is injection site reaction (ibid.). Another unknown is whether mimetics provide the same functional benefits as conventional coagulation factors, such as the long-term preservation of joint health and wound healing (Samuelson Bannow et al., 2019).

3.2.4. Non-factor agent: Anti-tissue factor pathway inhibitor (TFPI) therapies

Overview

Anti-TFPI therapies are a novel treatment class that reduces bleeding by targeting the system that prevents too much clotting (Chowdary, 2020). Anti-TFPI therapies seek to restore haemostatic balance by blocking TFPI, an anticoagulant, and preventing it from working normally (NBDF, 2024a). Because anti-coagulants decrease clotting, interfering with the way they work allows clotting to occur, anti-TFPI therapies do not rely on replacing a specific clotting protein, like factor VIII or factor IX, and thus can be used to prevent bleeding episodes in both haemophilia A and haemophilia B (ibid.).

How has pharmaceutical innovation enabled this progress?

Therapeutic (driven by unmet need): As with mimetics, anti-TFPIs target the drawbacks of previous therapies, such as the need for intravenous infusion, treatment burden, and treatment of patients with inhibitors.

Return on investment: A share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation.

[6] *Haemostasis is the mechanism via which a clot is formed, leading to cessation of bleeding (LaPelusa and Dave, 2024)*

Elements of innovation/value added

One of the anti-TFPIs only require once-weekly subcutaneous administration, which offers the potential to significantly decrease treatment burden for patients with B without inhibitors (Acharya et al., 2023; NBDF, 2023). Flat-dosing may have benefits compared to weight-based dosing, making the cost more predictable and reducing product waste. One anti-TFPI is especially encouraging for haemophilia B patients with inhibitors as it is the first subcutaneous prophylactic option for these patients in countries in which it has been approved (Keam, 2023).

In addition, anti-TFPIs may also be more effective than previous therapies at reducing bleeds and improving quality of life. Box 3 summarises the quantitative evidence of health and health system impacts of anti-TFPIs compared to recombinants.

Anti-TFPI therapies vs factor therapies

The evidence base for anti-TFPIs is still emerging, but early clinical trials suggest anti-TFPIs reduce bleed rates compared to previous treatments (Matsushita et al., 2023; Pfizer, 2023). One of these trials estimated that the group receiving an anti-TFPI had a significantly lower ABR compared to a group receiving on-demand bypassing agents, at 1.7 (95% CI: 1.0 to 2.9) compared to 11.8 (95% CI: 7.0 to 19.9) (Matsushita et al., 2023). Another trial found the group receiving a different anti-TFPI had an ABR 35.2% lower than a group receiving routine prophylaxis (7.85 (95% CI; 5.09-10.6) compared to 5.08 (95% CI: 3.40-6.77)) and 91.6% lower compared to on-demand therapy (38.00 (95% CI; 31.03-46.54) compared to 3.18 (95% CI: 2.09-4.85)) over a 12-month time horizon (Pfizer, 2023).

Anti-TFPIs may also improve important dimensions of patients' quality of life. Patient-reported outcomes were collected using the 36-Item Short-Form Health Survey, version 2 (SF-36v2), with bodily pain and physical functioning dimensions included as key secondary endpoints in one trial (Matsushita et al., 2023). There were no significant differences in either of these dimensions between the anti-TFPI and on-demand bypassing agents, although on other scores that were not selected as secondary endpoints, such as mental health and vitality, the anti-TFPI scores were significantly higher (ibid.). The trial also found that 93% of patients preferred the anti-TFPI compared to their previous treatment (ibid.).

Results for the economic modelling of anti-TFPIs are not yet available. In the UK, the National Institute for Health and Care Excellence (NICE) is currently conducting technology appraisals on the clinical and cost-effectiveness of these therapies (NICE, 2024b).

BOX 3: CASE STUDY: ANTI-TFPI THERAPIES COMPARED TO FACTOR THERAPIES

Remaining challenges

Rebalancing the haemostatic system has been associated with the risk of thrombosis especially in cases where additional clotting factors are required to treat bleeds (Mancuso, Croteau and Klamroth, 2024). This was identified in early clinical trials of some anti-TFPI therapies and necessitated further monitoring in later stages. Continuous monitoring of the benefits and risks in people with haemophilia will be essential, as with any novel medicine.

3.2.5. Non-factor agent: Antithrombin therapy

Overview

An alternative mechanism of action is targeting natural anticoagulants, such as antithrombin (AT) with AT reduction leading to increased thrombin (a procoagulant) (Fassel and McGuinn, 2021). These therapies make use of RNA interference technology to target AT and are administered

subcutaneously. There are no AT therapies with marketing authorisation at the time of publication, but there are products in the pipeline with promising results from clinical trials (Srivastava et al., 2023).

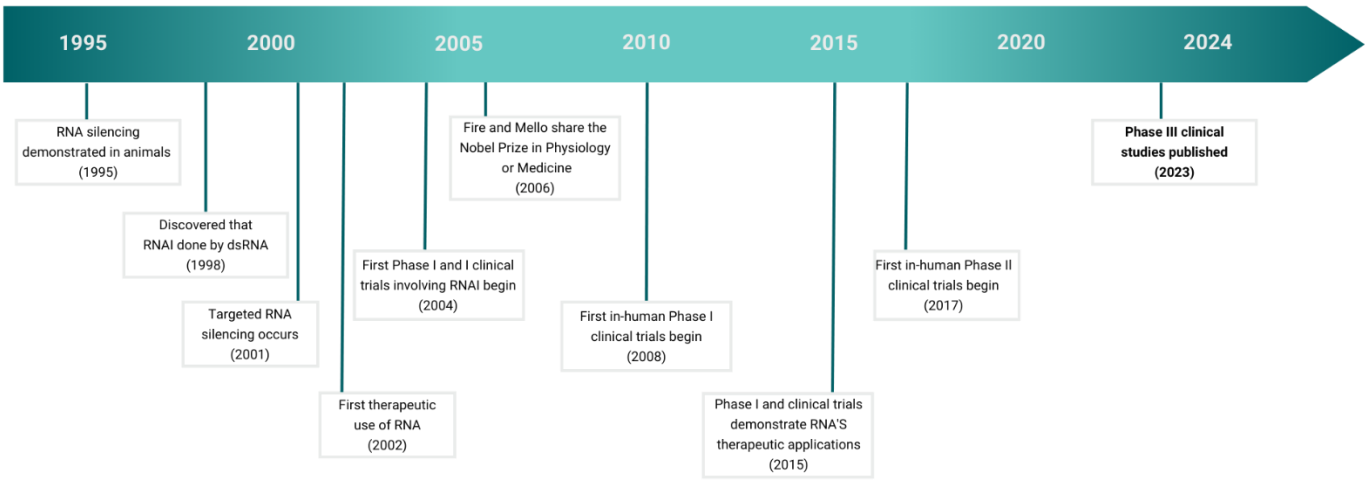
How has pharmaceutical innovation enabled this progress?

Technical (via scientific spillovers): The first demonstration that double-stranded RNA triggers the gene-silencing technique now known as RNA interference was conducted by Fire and Mello in 1998, for which they later won the Nobel Prize in Medicine in 2006 (Fire et al., 1998; Zamore, 2006). They were investigating how gene expression is regulated in the nematode worm, yet this work ultimately paved the way for a new research field, when it was proven that RNA interference is used to regulate gene expression in humans as well. In addition to haemophilia, RNA interference has been utilised in therapies across disease types such as oncology, cardiovascular disease, and viral infections (Chen et al., 2018). The timeline of events from research to clinical trials can be seen in Figure 4.

Therapeutic (driven by unmet need): As with other non-factor therapies, AT therapy targets the drawbacks of factor therapy, such as the need for intravenous infusion, treatment burden, and treatment of patients with inhibitors.

Return on investment: A share of returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation.

FIGURE 4: KEY MILESTONES IN RNA INTERFERENCE IN MEDICINE: THE TIMELINE OF A SCIENTIFIC SPILLOVER



SOURCE: OHE SYNTHESIS BASED ON (GUO AND KEMPHUES, 1995; FIRE ET AL., 1998; ZAMORE, 2006; CHEN ET AL., 2018; CORYDON ET AL., 2023; YOUNG ET AL., 2023)

Elements of innovation/value added

As with many of the recent treatment advances, AT therapy has the potential to decrease treatment burden; clinical trials have indicated that once monthly subcutaneous administration may be feasible (Peyvandi, Garagiola and Abbattista, 2023). Furthermore, clinical trial results are promising for patients with both severe haemophilia A and B with inhibitors (ibid).

Remaining challenges

As with other non-factor therapies, it's unclear whether they provide the same functional benefits as conventional coagulation factor, such as the long-term preservation of joint health and wound healing (Samuelson Bannow et al., 2019). Similarly to anti-TFPI therapies, there are some concerns about thrombotic risk (Sidonio et al., 2022).

3.2.6. Gene therapies

Overview

Gene therapy supplements a dysfunctional gene in haemophilia (Kumar et al., 2016). Strategies for gene therapy in haemophilia involve direct intravenous administration of a viral vector carrying a therapeutic gene in vivo. Several relevant virus vectors have been developed, and in most current clinical trials in haemophilia, adeno-associated virus (AAV) has been used to transduce FVIII or FIX genes directly into liver cells (Shima, 2020).

The first gene therapy for severe haemophilia A without inhibitors was approved by the FDA in June 2023 and gained conditional approval by EMA in August 2022 (FDA, 2023; EMA, 2022b). Despite regulatory schemes in the USA and Europe including FDA's Orphan, Breakthrough Therapy, Regenerative Medicines Advanced Therapy and Priority Review designation and EMA's PRIority MEdicines (PRIME) scheme and orphan medicine designation, respectively, the path to approval was not straightforward.

In August 2020, the FDA rejected the first gene therapy for severe haemophilia A with a requirement for further data that was expected to take an additional year to collect (Pierce, 2020). Similarly, the another manufacturer withdrew its initial application of its haemophilia A gene therapy in November 2020, after the EMA had concerns around safety and durability (EMA, 2020). This reflects a need for earlier and more transparent dialogue between the regulator and manufacturer regarding the evidence requirements for approval, as well as further consideration of the degree of flexibility around these requirements in specific cases.

In November 2022, the first and only one-time gene therapy for haemophilia B received FDA approval (FDA, 2022). The therapy was granted conditional approval by EMA in February 2023 (EMA, 2023).

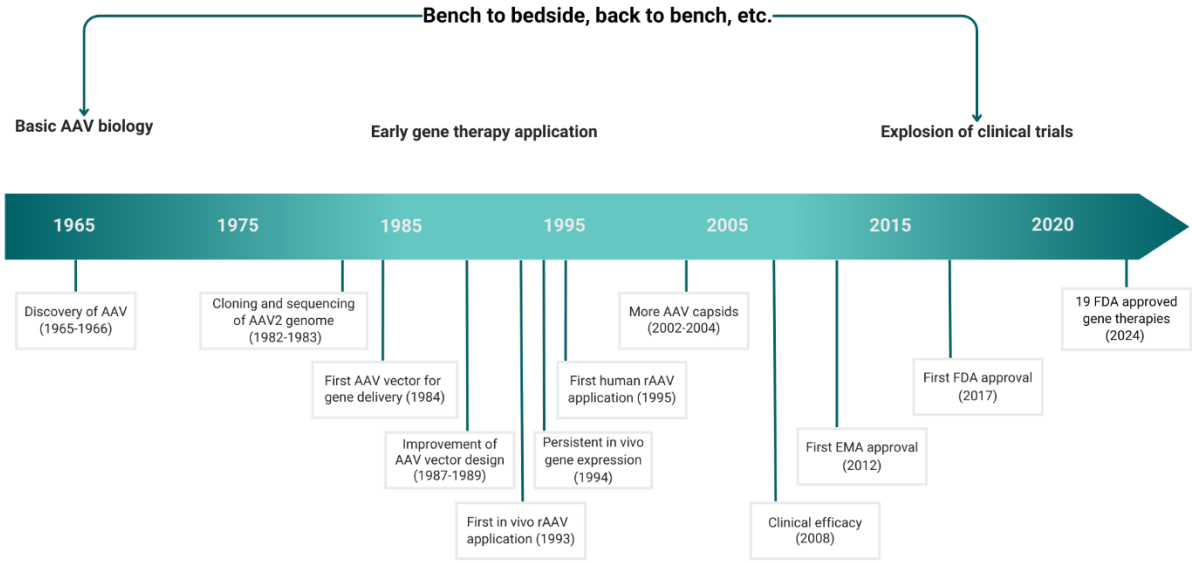
How has pharmaceutical innovation enabled this progress?

Technical (via scientific spillovers): AAV vectors are one of the platforms for gene delivery for the treatment of a variety of human diseases. Following the first reports on the discovery of AAV in 1965 and 1966, the next 15–20 years of basic biology research culminated in the cloning and sequencing of the AAV2 genome (Wang, Tai and Gao, 2019). It is generally acknowledged that these early studies of the basic biology of AAV laid the foundation for vector development and therapeutic applications. Key milestones within this process are illustrated in Figure 5.

Therapeutic (driven by unmet need): In terms of unmet need, gene therapies seek to supplement a dysfunctional gene with one-time infusion, thereby, potentially reducing the remaining treatment burden as well as the mental health (Leebeek and Miesbach, 2021).

Return on investment: A share of the returns from marketing of previous innovations are reinvested in R&D with the expectation of future returns from further innovation.

FIGURE 5: KEY MILESTONES IN AAV GENE THERAPY DEVELOPMENT



SOURCE: ADAPTED FROM (WANG, TAI AND GAO, 2019) AND UPDATED BY OHE (FDA, 2024)

Elements of innovation/value added

The results of the clinical trials of gene therapies for haemophilia A and B have been promising. Box 4 summarises the quantitative evidence of health and health system impacts of gene therapies compared to factor therapies.

Remaining challenges

Several difficulties remain to be addressed, however, including the presence of neutralising antibodies against the AAV capsid (Shima, 2020). Patients with such antibodies are currently ineligible for some gene therapies. In addition, the long-term durability of many of these gene therapies is yet to be established due to their novelty. There is evidence to suggest that waning of gene expression may occur in some haemophilia A and haemophilia B patients who have received gene therapy and that some may require immunosuppression with corticosteroids (Thornburg, Simmons and von Drygalski, 2023; Anguela and High, 2024).

Gene therapies compared to prophylactic factor therapies

The available clinical and economic evidence supports the superior effectiveness of gene therapies in improving health and reducing lifetime costs compared to prophylactic factor therapies (Tice et al., 2022; CADTH, 2024a; b).

Clinical trials have demonstrated that gene therapies lead to substantial reductions in bleeding for patients, with additional benefits in terms of reducing treatment burden. One trial showed that treatment with a gene therapy reduced the mean annualised rates of factor concentrate use and treated bleeding by 98.6% and 83.8% relative to prophylaxis with factor VIII, respectively (Ozelo et al., 2022). A second trial exploring another gene therapy showed adjusted annualised bleeding rates

reduced from 4.18 during a lead in period to 1.51 during the 24-month follow-up, with 96% of participants remaining free of factor IX prophylaxis at 24 months (Coppens et al., 2024).

Gene therapies in haemophilia may also lead to significant cost-savings for health systems. Economic models find that gene therapies eliminate the need for prophylactic treatments for a number of years after receipt, substantially reducing treatment costs that would otherwise occur with regular prophylaxis. For example, Cook et al. (2020) estimated a per patient mean reduction of 1,808 factor infusions over the course of a lifetime for those receiving a gene therapy compared to those who only received factor therapies. Additional savings also arose due to reduced need for on-demand treatment of bleeds. The reduction in treatment costs translates into lifetime savings of USD $6.8 million per patients compared to standard FVIII prophylaxis (ibid.).

Cost-effectiveness analyses have therefore unanimously found gene therapies to be dominant (health improving and cost-saving) compared to prophylactic factor therapies (Tice et al., 2022; Rind et al., 2020; NICE, 2024a).

There is limited data on long-term durability of gene therapies meaning that economic models must utilise short-term estimates alongside assumptions about persistence of effectiveness, increasing uncertainty about the longer-term costs and benefits. Indeed, NICE decided to recommend a particular gene therapy in their guidance under the conditions that further evidence must be collected on its long-term effects. This is due to uncertainty surrounding its long term clinical benefits and the resulting uncertainty for cost-effectiveness (NICE, 2024a). For this reason, it is critical that evidence continues to be collected to robustly evaluate the long-term effectiveness of gene therapies, and that economic models are updated to reflect these results.

BOX 4: CASE STUDY: GENE THERAPIES COMPARED TO PROPHYLACTIC FACTOR THERAPIES

3.3. Iterative Innovation in Haemophilia Summary

TABLE 1: SUMMARY OF ITERATIVE INNOVATION IN HAEMOPHILIA AND ITS VALUE ACCUMULATION

Therapy Class	Drivers of Innovation			Value added by innovation
	Therapeutic Innovation (unmet needs)	Technical (via scientific spillovers)	Return on Investment	
Recombinants	Driven by need to overcome infection risks associated with previous treatment (Franchini, 2010)	Molecular medicine advances enabled the cloning of FVIII and FIX genes, leading to therapeutic production and commercialisation	A share of the returns from marketing of previous innovation are reinvested in R&D with the expectation of future returns from further innovation (Berdud, Drummond and Towse, 2020; PhRMA, 2019)	▪ Improved safety profile. ▪ Increased availability as they are not dependent on plasma as starting material
Extended half-life factors	Factor VIII and IX are proteins with relatively short half-lives, necessitating frequent doses (Graf, 2018)	Advanced protein engineering gave rise to blood clotting factors that stay in circulation for longer compared to previous treatments		▪ Fewer infusions required, reducing burden and increasing compliance
Non-factor agent: Mimetics	Has the potential to address key remaining unmet needs including the need for intravenous infusion, high treatment burden from frequent administration and the development of inhibitors	No specific scientific spillover identified		▪ Increased convenience and lower treatment burden (Subcutaneous administration) ▪ May lead to a reduction in annualised bleeding rates (Mancuso et al., 2022) ▪ Use in haemophilia A with & without inhibitors
Non-factor agents: Anti-TFPI therapies				▪ Weekly subcutaneous administration ▪ Decreased treatment burden ▪ Use in haemophilia A & B with & without inhibitors
Non-factor agent: Antithrombin therapy		Utilises a gene silencing technique known as RNA interference		▪ Potential for monthly subcutaneous administration ▪ Decreased treatment burden ▪ Use in haemophilia A & B with & without inhibitors
Gene therapies	Has the potential to reduce treatment burden with a one-time infusion.	Utilises AAV vectors which are the leading platform for gene delivery		▪ One-time administration ▪ Potential for long-term health benefits and cost-savings ▪ Available for haemophilia A and B

4. Remaining unmet need

Despite the approval of a number of innovative therapies in the last 10 years, substantial unmet need in haemophilia remains (Shima, 2020). The unmet need manifests in the gaps in clinical outcomes and quality of life that remain between people living with haemophilia and the general population, in patient preferences across the pros and cons of different treatment options, and in access to innovative therapies (Shima, 2020; O'Hara et al., 2021b; Ozelo and Yamaguti-Hayakawa, 2022). There are also stark geographical differences; a brief discussion of haemophilia management in developing countries can be found in Box 5.

Further pharmaceutical innovation should aim to resolve remaining unmet needs and allow patients and their haematologists to tailor treatments to an individual's needs and preferences. Further research into the breadth and depth of unmet needs as seen by patients would be beneficial in shaping this future innovation. (Pierce et al., 2022)

4.1. Can we quantify the remaining unmet need?

Conventional cost-effectiveness analysis suggests a useful metric for quantifying unmet need though it is not fully comprehensive. The Institute of Clinical and Economic Review (ICER) published an evidence report on the effectiveness and value of gene therapies in haemophilia (ICER, 2022). In this report, they estimate the expected years of life and lifetime QALYs associated with factor IX treatment, non-factor treatment and gene therapies for haemophilia A and B. When comparing lifetime QALYs to expected years of life, all treatments are associated with a QALY loss equivalent to at least 7 full years of life loss indicating a substantial unmet need due to morbidity. The authors assume life years are the same for each treatment (27.13 years) citing that mortality with haemophilia is similar to the US average and there were no mortality impacts across treatments. Thus, there is clearly significant remaining unmet need.

4.2. Where is the remaining unmet need?

PHYSICAL MORBIDITY

One of the primary areas of unmet need in haemophilia is the ability to allow patients to live their lives with a 'haemophilia-free mindset'. There is evidence to suggest that people with haemophilia still experience morbidity and functional limitation due to joint damage despite prophylaxis and the recent advances in treatment. For example, O'Hara et al. (2021b) find that pain is commonly reported by haemophilia A patients using prophylaxis and is accompanied by presenteeism—diminished productivity at work— at a level comparable to that reported by people with osteoarthritis, an older population with more joint diseases.

Furthermore, in a 2018 study of patients with severe haemophilia A and B, it was found that only two-thirds of children and one-third of adults were bleed-free, even in a UK cohort selected for high compliance with prophylaxis (Wilkins et al., 2022). Haemarthrosis prevalence in HA/HB children was 33% and 47%, respectively, and 60% and 42%, respectively, in adults (ibid.). This was echoed during the roundtable, with a clinical attendee suggesting no patients make the transition from paediatric care to adult care without some level of joint damage despite prophylaxis being the current standard of care.

MENTAL BURDEN

Unmet need may also manifest as a mental burden associated with their condition, treatments, and effects on daily activities. A recent global survey of haemophilia patients found that more than half experience feelings of anxiety or depression once a week or more (The Harris Poll and Sanofi, 2023). 41% of patients reported that they had avoided or stopped participating in certain activities, 34% had avoided travelling or cancelled a trip, and 27% had taken prolonged time off work or school (ibid.). People living with haemophilia often worry about passing their haemophilia on to their children or may influence their decision to have children (Punt et al., 2020).

As with physical morbidity, the depth and complexity of the factors that contribute to this mental burden have not been well-researched to date. By implication, the patient voice is often buried under conversations of ABR and quality of life (as measured by specific tools), obscuring the details that really matter to patients.

INHIBITORS

While the non-factor therapy offers a lower probability of inhibitor development, not all patients take non-factors, so managing treatment for patients with inhibitors represents another unmet need (Mancuso, Croteau and Klamroth, 2024).

Immune tolerance induction (ITI) is a clinical approach that may be beneficial for haemophilia A patients with anti-FVIII inhibitor; ITI involves the administration of a high dose of factor VIII intensively for a long period of time, which could eliminate the inhibitor for a substantial fraction of such patients (Nakar et al., 2015; Hay and DiMichele, 2012). ITI is rarely attempted in patients with haemophilia B due to a lack of experience of its use and the risk of adverse effects such as severe allergic reactions and nephrotic syndrome (DiMichele et al., 2007).

Haemophilia patients with inhibitors or a history of inhibitors were generally excluded from initial gene therapy trials, but there are some gene therapy treatments for haemophilia A where investigations for the potential for use in patients with inhibitors are ongoing (Chou, Hsu and Lin, 2023).

FAMILIES AND CAREGIVERS

Improvements in treatment regimens are likely to also benefit patients' caregivers and wider family; parents of children with haemophilia may not have to teach their child to give themselves intravenous injections or experience the mental burden of treating their child every day.

ACCESS

Differences in access and uptake of innovative therapies are present within and between countries. Health systems may need to invest in activities to facilitate uptake. This could be achieved through community services, better signposting and education.

REMAINING UNMET NEED

All of the above suggests that the EQ5D-based measure of QALY loss, while very useful, may not reflect the full nature or extent of the remaining unmet need.

Unmet need in developing countries

In this report, we describe innovative haemophilia therapies and issues relating to unmet need and uptake in high-income countries; however, it's important to acknowledge that this is not reflective of the outlook for many people living with haemophilia in low- and middle-income countries. It is estimated that around 75% of people with haemophilia, primarily in low- to lower middle- income countries, have limited or no access to therapy with underdiagnosis also being a major issue (Ndoumba-Mintya et al., 2023).

The WFH Path to Access to Care and Treatment (PACT) program is an initiative designed to improve outreach and diagnosis to sustainable care for people with inherited bleeding disorders (WFH, 2023). Established in 2021, the program aims to identify 20,000 new people with inherited bleeding disorders, improve access to care through training and education, and increase government support to establish or expand national bleeding care programs by 2025 (ibid.). There are 20 lower middle and higher middle-income countries participating across Asia, Africa, and central and south America (ibid,).

Another two steps to improve the management of haemophilia in resource-limited countries are to establish i) a patient society and ii) a bleeding disorder registry (Ndoumba-Mintya et al., 2023). . This is also supported in many countries by the World Federation of Haemophilia Humanitarian Aid Program, which is the largest distributor of donated treatment products in the world (Pierce et al., 2022). In response to this program, some partnering governments increased their haemophilia care investment; however, there is still significant scope for improvement in management of haemophilia in developing countries.

BOX 5: UNMET NEED IN DEVELOPING COUNTRIES

4.3. Barriers to uptake of innovative therapies

Further unmet need arises from barriers to the uptake of innovative therapies. Not all uptake barriers are related to the reimbursement of therapies; barriers also relate to organisations, direct and indirect costs of switching therapies for patients, and concerns around the safety of new therapies as discussed below. Barriers relating to the uptake of gene therapies were most apparent based on the literature and roundtable; however, this does not mean that other therapy classes are without potential barriers. Value assessment and reimbursement challenges are discussed in section 5.2.

In the roundtable, patient representatives and clinicians indicated that given the treatment options already available, patients may have seen their symptoms and standard of care improve substantially and may be satisfied with their quality of life. They may not be willing to accept the burden of switching to a new treatment, which typically requires monitoring to ensure sufficient factor activity levels. This is especially true of people receiving gene therapy as patients experience a significant time and out-of-pocket cost burden of follow-up appointments in the year after administration (Pipe et al., 2023). This may be of particular concern to people from a low socioeconomic background who may have less access to flexible working arrangements or be less able to afford time off work, thereby raising equity concerns (ibid.).

Fletcher et al. (2021) explored reasons why men with severe haemophilia may not choose to have gene therapy: reasons included safety concerns (particularly for those who had a history of blood-borne viral infections), perceived lack of/immaturity of efficacy data, perceived lack of treatment burden, and perceived loss of identity as a haemophiliac. Concerns around safety and efficacy may be alleviated in due course, as uptake increases and more data is published. The authors also found

that younger people were less concerned about the perceived loss of identity, potentially indicating that uptake may continue to grow.

Roundtable participants raised that people with haemophilia may have concerns that receiving gene therapy may preclude them from receiving future innovations. Similarly, patients in the US may have concerns about their health insurance coverage in case gene therapy is unsuccessful. A subset of patients may be concerned about a perceived withdrawal of support mechanisms available to them if they receive gene therapy, in that they will be assumed to be 'cured' by health systems or other social welfare systems.

Another barrier and potential equity concern is the geographical location of specialist haemophilia centres which may be inaccessible to some people due to travel and accommodation requirements. This is particularly true for gene therapy given the infrastructure required for administration and monitoring. A survey of European Collaborative Haemophilia Network (ECHN) centres conducted in 2021 found that only 58% of centres were ready to implement gene therapies outside of clinical trials (Windyga et al., 2022).

5. The role of policy in incentivising innovation

5.1. Is innovation recognised and rewarded by health systems?

In the market for pharmaceutical innovation, healthcare systems and policymakers are presumed to have the aim of maximising population health (which includes facilitating patient access to the latest innovations) subject to their budget constraints.

As part of this, they are responsible for encouraging a sustainable stream of investment in pharmaceuticals. By rewarding innovation sufficiently, they send signals that stimulate and channel further R&D efforts. This highlights the importance of the policy environment for the emergence of innovation, and suggests a trade-off between maximising health subject to budget constraints in the short term (known as static efficiency) and maximising health (and well-being) achievable in the long run, which requires an optimal amount of R&D investment for future innovation (dynamic efficiency) (Bell et al., 2023; Woods et al., 2024; Garrison et al., 2010).

Decision making for the long term

Intellectual property protection and pricing and reimbursement models are used in combination to achieve a balance between maximum health subject to current budget constraints and incentivising further investment in pharmaceutical innovation.

Intellectual property protection: innovators are guaranteed a period during which they may be able to exert some monopoly power and thereby garner a premium for the innovation.

Pricing and reimbursement models: ensure innovation can be accessed in an affordable way by healthcare systems and patients.

Within pricing and reimbursement models, value-based pricing has been highlighted as an option to facilitate 1) patient access to the latest innovations, 2) sustainability for health systems, and 3) incentives to stimulate ongoing investment in the R&D of new treatments society values the most (Bell et al., 2023; Towse, Cole and Zamora, 2018; Danzon and Towse, 2003).

Value-based pricing can be effective in aligning price signals to investors and industry with patients' and citizens' priorities and therefore maximises the expected value of innovation for a given level of investment. In theory, well-designed value-based pricing would probably be the best tool for pricing innovation during intellectual property protection to ensure an optimal share of the total value of the innovation is captured by healthcare systems, patients and innovators, thereby supporting dynamic efficiency.

Problems with decision-making for the short term

In contrast, non-value-based approaches such as price regulations help maximise static efficiency for healthcare systems by lowering prices, but negatively affect dynamic efficiency by lowering incentives for R&D investment. This is because price regulations can lead to a decrease in market size and reduced return on investment for the innovator (Lakdawalla, 2018). Consequently, firms may reduce R&D investment and the development of new medicines (thereby reducing the potential for

health gain in the future) when rewards from pharmaceutical innovation are constrained in the present (Lakdawalla, 2018; Shaikh, Del Giudice and Kourouklis, 2021). Indeed, evidence supports that increases in market size led to increases in the number of new pharmaceuticals in that category (Acemoglu and Linn, 2004; Dubois et al., 2015).

Recognition of innovation within value-based approaches

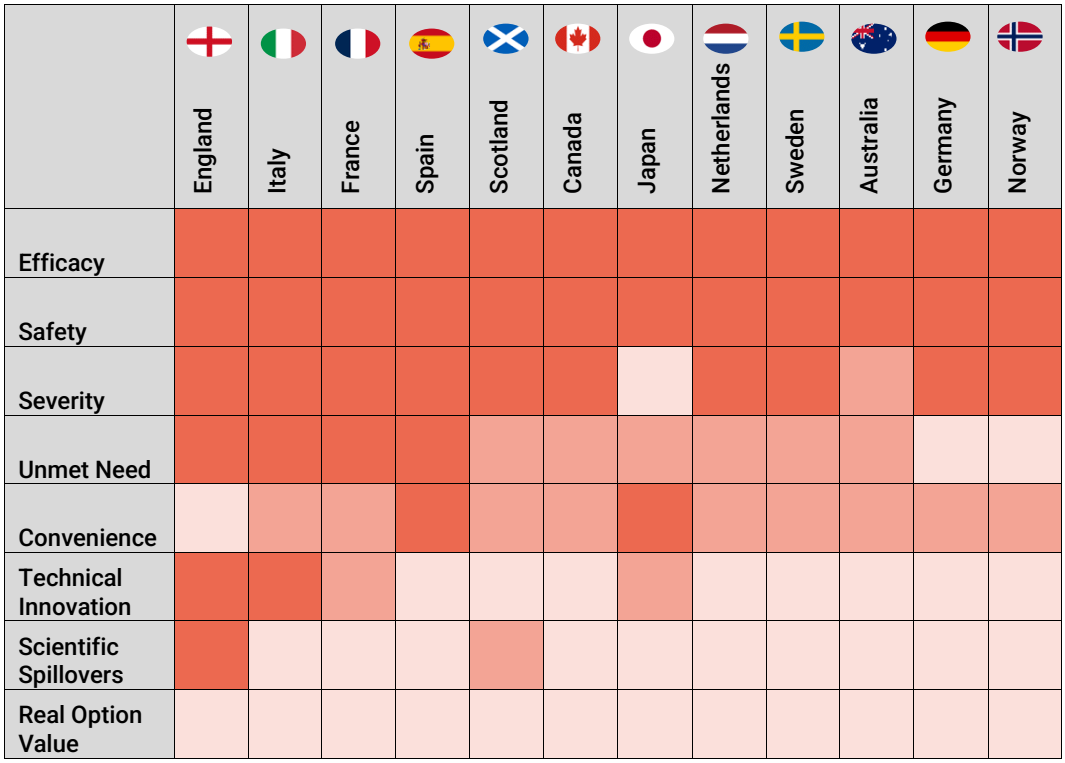
Many aspects of innovation (a full list with definitions is provided in Box 6, Appendix A2) can be considered as value elements in value-based approaches to pricing and reimbursement, especially from a societal perspective. Their inclusion signifies the perceived value of these aspects of innovation to decision-makers.

In Figure 6, we synthesise the findings from recent literature studies that examine how innovation characteristics are recognised in assessment reports or guidelines by twelve national payment and reimbursement policymakers (Breslau et al., 2023; Drummond et al., 2023; Hofmann et al., 2021; Rejon-Parrilla, Espin and Epstein, 2022; Bell et al., 2023). The results show that the therapeutic components of innovation (e.g. efficacy, safety, severity, unmet need) are the most significant criteria for payment and reimbursement decision-making. In contrast, technical aspects of innovation (such as type of technology and novelty) and knowledge spillovers are only recognised in a handful of countries.

Even where there is recognition of specific innovation attributes or broader value elements in guidelines, there is often a lack of guidance with respect to methodology for measurement. As a result, it remains unclear whether recognition of certain innovation attributes in guidance documents will lead to their practical incorporation into decision-making (Hofmann et al., 2021; Avşar, Yang and Lorgelly, 2023).

In order to achieve dynamic efficiency for healthcare systems, whereby R&D is sufficiently incentivised without compromising the sustainability of healthcare systems, decision-makers and payers must clearly communicate the values they wish to recognise and reward to manufacturers through reimbursement practices and policies (Garrison and Towse, 2017). This includes, where relevant, the explicit recognition of elements of innovation within value-based pricing and reimbursement models to incentivise optimal levels of R&D and generate further advances in health.

FIGURE 6: RECOGNITION OF INNOVATION ATTRIBUTES BY NATIONAL DECISION-MAKERS



OHE SYNTHESIS OF BRESLAU ET AL., 2023; DRUMMOND ET AL., 2023; HOFMANN ET AL., 2021; REJON-PARRILLA, ESPIN AND EPSTEIN, 2022; BELL ET AL., 2023; SCHURER ET AL., 2022. FOR METHODS, PLEASE SEE APPENDIX A1.

Legend

Recognition	No	Yes	Yes
Level of evidence	Recognition not reported in any study	Recognition reported in one study	Recognition reported in >one study

5.2. Value assessment challenges in haemophilia

The pricing and reimbursement landscape is critical in determining return on investment, and therefore, in promoting future innovation. This section explores challenges in value assessment (a key component of this landscape) relating to haemophilia therapies, which may ultimately mean the full value of innovation is not rewarded.

MEASURING PATIENT-REPORTED OUTCOMES

Generic measures of quality of life preferred by health technology assessment (HTA) agencies (such as EQ-5D) may not fully capture the wider benefits of innovative therapies, including reduced burden and higher adherence. This is exacerbated by a problem known as the "disability paradox", whereby people living with chronic conditions or disabilities often report a higher quality of life compared to population norms. Empirical evidence has indicated the presence of the disability paradox in the context of haemophilia; patients with haemophilia reported higher health states than the general population (O'Hara et al., 2021a).

There is also the notion of adaptation to their condition; patients may be satisfied by their current standard of care and have adapted their usual activities and aspirations based on what they believe to be possible with their condition. Yet, if they choose to switch to a new therapy that has a substantial impact on their ability to do physical activity or return to education or employment, this benefit may not be reflected in QoL questionnaires due to the relative ceiling effect. Furthermore, roundtable participants suggested that some people may assess their circumstances relative to older family members who would have had treatment with plasma therapies or recombinants.

As mentioned, people with haemophilia still experience arthropathy (joint damage) to some extent; however, roundtable participants discussed difficulties around the clinical measurement of joint damage. As a result, joint damage is not typically considered explicitly in economic models, meaning that the impact on health and healthcare utilisation may not be fully captured.

In part to overcome some of these difficulties, the multi-national PROBE (Patient Reported Outcomes Burdens and Experiences) study collects detailed information about the health and treatment experiences of people with haemophilia(PROBE, 2024). PROBE includes the EQ-5D alongside other data points such as history of joint surgery, joint range of motion, underlining the concern that EQ-5D does not fully capture all relevant elements (PROBE, 2024).

RECOGNITION OF BROADER VALUE ELEMENTS

Other broader value elements are sometimes considered by HTA decision-makers, such as improvements in convenience and adherence to treatment and the impact on the patient's and caregiver's ability to achieve major life goals related to education, work, or family life. However, consideration varies among HTA bodies and the extent to which these aspects may impact decisions is unclear.

The access and uptake of innovations such as extended half-life factors and mimetics have meant that haemophilia is generally well-managed in terms of bleeds: most patients can treat themselves at home. Clinical and health system representatives at the roundtable indicated that this has created additional capacity and allowed resources in haemophilia centres to be reallocated towards other previously lower-priority support activities, including by community nurses and multi-disciplinary teams. Capacity is a critical issue for many policymakers, yet the effect of such a constraint is generally not incorporated in cost-effectiveness analysis.

Similarly, impacts on other sectors and society more broadly (such as impacts on social care, education, and benefit transfers) are not usually considered in value assessments as decision-makers are focused on health system impact, and these effects are difficult to quantify. As a consequence, these impacts of innovation are ignored.

APPROPRIATENESS OF HTA METHODOLOGY

Gene therapies are considered to be a paradigm shift in our approach to health care, and for this reason, along with the uncertainty of long-term outcomes, traditional HTA methodology may not be appropriate for assessing these therapies (Besley et al., 2022). Garrison et al. (2021) identify six key methodological challenges regarding the assessment of gene therapies for haemophilia, namely immaturity of evidence and cure definition, assessment of comparative effectiveness based on single-arm trials, important clinical and patient-centric outcomes, valuation of cost offsets, addressing value uncertainties and perspectives of evaluation. Once again, this demonstrates limitations to current value assessment processes, which may adversely impact the pricing and reimbursement landscape and, thus, the incentives for further innovation in this space.

Finally, given the pace and quantity of approvals of new haemophilia treatments, the most appropriate comparator when clinical trials begin may not be the most appropriate comparator when

evidence is submitted to HTA or payers. In these cases, indirect or historical comparisons may be necessary but are generally less accepted by decision-makers (Macabeo et al., 2024). When paired with other uncertainties in terms of safety and efficacy, value assessment is likely to be more challenging. Manufacturers and HTA bodies should engage in early dialogue to align on appropriate evidence packages to help alleviate issues during assessment.

6. Conclusions and Recommendations

Haemophilia treatment is an exemplar of medical progress, demonstrating how the development of new and more effective drugs can play a pivotal role in advancing both health and healthcare (Hofmann et al., 2021).

Recognising and rewarding innovation is crucial for incentivising further innovation. As highlighted above, studies have demonstrated that where innovation is not sufficiently rewarded, this may have adverse effects on future innovation and scientific progress (Dubois et al., 2015; Acemoglu and Linn, 2004; Lakdawalla, 2018; Shaikh, Del Giudice and Kourouklis, 2021; Kourouklis and Gandjour, 2022).

All stakeholders have a part to play in ensuring a healthy innovation ecosystem, thereby channelling innovation to continue to improve the lives of patients and their carers. For example:

- Developers, manufacturers and researchers must continue to positively re-invest in R&D, leveraging feedback loops of return on investment and scientific spillovers. R&D should be directed towards innovation that is of the highest value to society, as signalled by pricing and reimbursement policy.

- Governments, regulators and HTA bodies must foster a supportive policy environment that recognises and rewards innovation, including intellectual property protection, transparent approval requirements and processes, and pricing and reimbursement policies that incentivise and reward the types of innovation that are of greatest value to society. In some cases, this may require research to develop or improve methodologies for measuring and evidencing relevant value elements and attributes of innovation.

- All stakeholders should facilitate patient involvement throughout the development and assessment processes to ensure that unmet need and patient voice are appropriately considered.

Within haemophilia, pharmaceutical innovation has significantly improved care, but considerable unmet need remains. New treatments provide patients with multiple options, meaning they can make treatment decisions based on their clinical needs, physical activity level, and lifestyle. However, the aspiration for many people with haemophilia is to live with a haemophilia-free mind; recent innovations have gone some way to making this a reality, but unmet need remains. To further advance the research agenda in the haemophilia space:

- Patient advocacy groups should leverage their unique position to package and communicate information about innovative treatments to overcome the knowledge gap experienced by healthcare professionals and patients, thereby removing education and understanding as barriers to access to innovation.

- Health economics and outcomes researchers should explore the depth and complexity of the factors that contribute to remaining unmet need in this space to enable innovation to target the aspects of unmet need that are most important to patients.

- Policymakers, including HTA bodies, should continue to improve and refine their polices to provide appropriate incentives and rewards for innovative haemophilia care.

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Appendix

A1. Methodology

Literature review on "innovation in haemophilia"

We conducted a targeted review of the literature to identify major innovations in the treatment of haemophilia. We filtered the articles that were shown on the first five pages of Google Scholar after employing our search criteria. The following search string was used:

(innovation AND (haemophilia OR hemophilia) AND (therapy OR therapies OR treatment)

This included publications published between December 2013 and December 2023 in journals indexed in Web of Science, Medline, Scopus, and EconLit, among others. This involves the identification of the primary articles in a field of study and then applying citation searching to find other relevant research. The Background and Innovative Haemophilia Therapies sections were supplemented by therapy specific literature once relevant therapies and classes were identified.

Literature review on "pharmaceutical innovation"

We conducted a targeted review of the literature to define pharmaceutical innovation in several aspects and document how the value of innovation has been used in the policy debates in addition to providing definitions of value.

We filtered the articles that were shown on the first five pages of Google Scholar after employing our search criteria. The following search string was used:

(broader value of innovation (AND (defining pharmaceutical innovation OR value frameworks OR policy frameworks OR life-cycle OR price evolution OR profits OR investment or R&D))
AND
(unmet need OR severity OR novelty OR therapeutic benefit OR scientific spillover effects OR real option value OR ease of administration OR anti-TFPIs OR gene therapies OR component of value OR haemophilia OR flow of innovation)

This included publications published between December 2013 and December 2023 in journals indexed in Web of Science, Medline, Scopus, and EconLit, among others. We also applied the snowballing technique to do searches. This involves the identification of the primary articles in a field of study and then applying citation searching to find other relevant research. In addition, we conducted a targeted review of expert authors and literature to supplement on particular aspects of interest including the R&D investment in light of regulatory restrictions on pricing and reimbursement, or unmet need in clinical development.

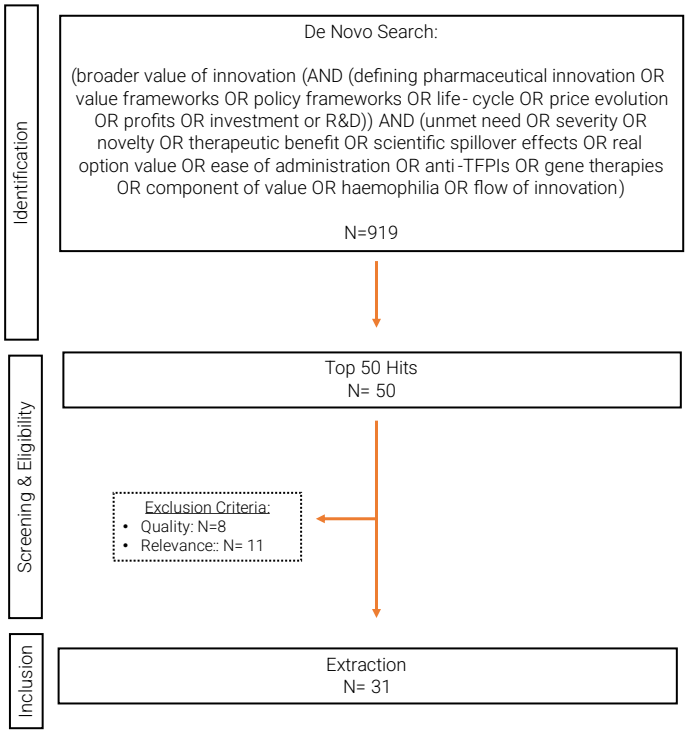


FIGURE A1: FLOW DIAGRAM FOR THE ELECTION AND EXTRACTION OF THE TARGETED LITERATURE REVIEW ON "INNOVATION"

TABLE A2: LITERATURE SOURCES AND CHARACTERISTICS

Technology Scope	Analysis scope	Countries	Reference
All therapies	Guidelines	Australia, Canada, England, France, Germany, Norway, Scotland, Spain	(Breslau et al., 2023)
Cell and gene therapy	Assessment Reports	England, Canada, Scotland, Italy, France, Germany	(Drummond et al., 2023)
All therapies	Guidelines	Australia, Canada, England, France, Germany, Italy, Japan, Netherlands, Norway, Sweden	(Hofmann et al., 2021)
All therapies	Guidelines	England, France, Italy, Japan, Spain	(Rejon-Parrilla, Espin and Epstein, 2022)
All therapies	Guidelines	England, France, Germany, Italy, Norway, Spain, Sweden	(Bell et al., 2023)
All therapies	Guideline	Netherlands	(Schurer et al., 2022)

TABLE A3: COUNTRIES AND DECISION MAKERS

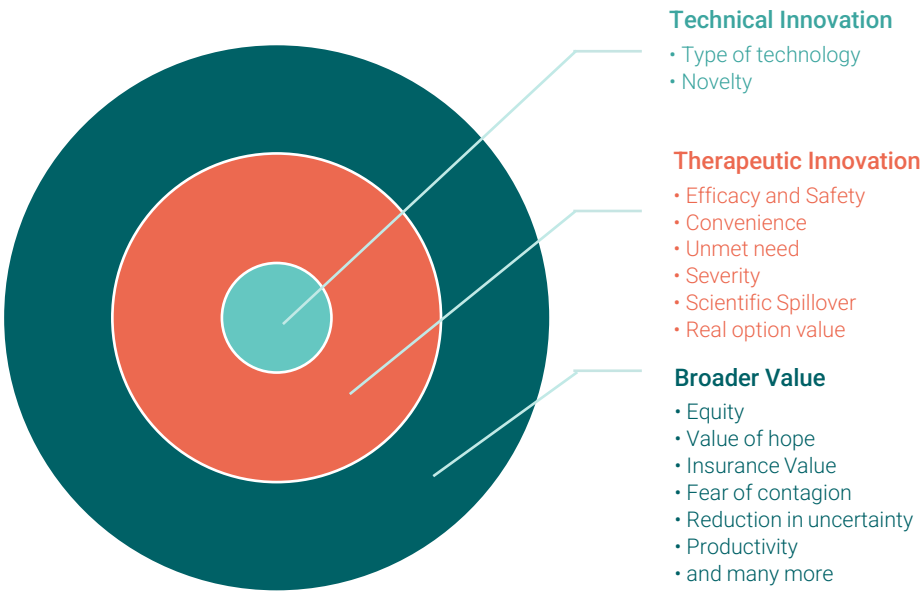
Country	Decision Maker
Australia	Pharmaceutical Benefits Advisory Committee
Canada	The Canadian Agency for Drugs and Technologies in Health
England	NICE
France	French National Authority for Health (Haute Autorité de santé (HAS))
Germany	Institute for Quality and Efficiency in Health Care (IQWiG), Foundation for Quality and Efficiency in Health Care
Italy	Italian Pharmaceutical Agency AIFA
Japan	Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health
Netherlands	Zorginstituut Nederland (National Health Care Institute)
Norway	Statens Legemiddelverk (The Norwegian Medicines Agency)
Scotland	Scottish Medicines Consortium
Spain	Spanish Ministry of Health and Social Policy
Sweden	The Swedish Dental and Pharmaceutical Benefits Agency TLV

A2. What do we mean by pharmaceutical innovation?

Pharmaceutical innovation falls under the category of product innovation. Product innovation is defined as a new or improved good or service that diverges from previous offerings in terms of quality, technical specifications, reliability, durability, economic efficiency, affordability, convenience, usability, and user-friendliness (OECD and Eurostat, 2018).

While commonly used, there exists no universally accepted definition for 'pharmaceutical innovation' itself (Hofmann et al., 2021; Kesselheim, Wang and Avorn, 2013; Rejon-Parrilla, Espin and Epstein, 2022; Syeed et al., 2022; Bruen et al., 2016; Barrenho, 2014; Arnold et al., 2022; Stiller, 2021; Nijhuis, Guan and Tewary, 2019). Instead, the literature describes and distinguishes various attributes of technical and therapeutic innovation, as well as value elements associated with pharmaceuticals (Hofmann et al., 2021) (Figure A2).

FIGURE A2: DEFINITION OF PHARMACEUTICAL INNOVATION – INNOVATION ATTRIBUTES AND VALUE ELEMENTS FOR CONSIDERATION
SOURCE: OHE SYNTHESIS



Technical innovation: Pharmaceutical innovation can be defined through its technological aspects (e.g. type of technology/medicine, like gene therapy) and novelty (e.g. new class/type of medicine, new mechanism of action, new formulation). In this context, pharmaceutical innovation is described as the 'introduction of new medicines' or the 'modification of existing medicines', encompassing structural, pharmacological, pharmaceutical, pharmacokinetic, and clinical features (Aronson, 2008).

Therapeutic innovation: Pharmaceutical innovation can also be defined through recognising various benefits to patients via healthcare, including efficacy, safety, administration, convenience, scientific spillover, and addressing unmet medical need (Hofmann et al., 2021; Rejon-Parrilla, Espin and Epstein, 2022; Syeed et al., 2022; Kesselheim, Wang and Avorn, 2013; Sanders et al., 2016). Scientific

spillover pertains to the knowledge generated during innovation development, which can be harnessed by all innovators within a marketplace (as discussed in section 2.1).

Broader value of pharmaceuticals: Alongside definitions of pharmaceutical innovation in the literature, there are so-called novel elements of value of pharmaceuticals that have been described in the context of cost-effectiveness studies and health technology assessments (Lakdawalla et al., 2018). For instance, the ISPOR Value Framework captures the additional value of pharmaceuticals in terms of productivity, adherence-improving factors, reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real-option value, equity, and scientific spillover (Lakdawalla et al., 2018).

For our interpretation of definitions of different elements of innovation and value elements based on the literature reviewed, see Box 6.

Definitions of elements of innovation and value elements

Technical innovation

Type of technology	The different scientific and technological characteristics of medicines (Aronson, 2008).
Novelty	The introduction of new medicines' or the 'modification of existing medicines', encompassing structural, pharmacological, pharmaceutical, pharmacokinetic, and clinical features (Aronson, 2008).

Therapeutic innovation

Efficacy	Clinical health outcomes capturing the treatment effect of health interventions (Hofmann et al., 2021).
Safety	Clinical health outcomes capturing safety of health interventions (Hofmann et al., 2021).
Convenience or adherence-improving factors	Enabling improved patient adherence to treatment, e.g., higher convenience like simpler dosing schedules, alternative routes of administration, or combination treatments (Lakdawalla et al., 2018).
Scientific Spillover	The scientific and medical knowledge gained by the development and adoption of a treatment (Bruen et al., 2016; Lakdawalla et al., 2018).
Severity of disease	The treatment of conditions causing severe health loss (Lakdawalla et al., 2018).
Real-option value	Enabling patients to have the option of receiving future innovative treatments by extending life (Lakdawalla et al., 2018).
Unmet need	The gap between the amount of healthcare received by the affected individual and the healthcare deemed necessary based on an objective medical opinion, or subjective preferences needs (Rejon-Parrilla, Espin and Epstein, 2022; Bruen et al., 2016; Pochopień et al., 2021).

Broader value of pharmaceuticals

Productivity	The value of treatments improving work-related productivity of the patient (or carer) that was lost as a result of their condition (Lakdawalla et al., 2018; Sanders et al., 2016).
Reduction in uncertainty (due to a new diagnostic)	The value that patients derive from knowing what their diagnosis is or how they may respond to certain therapies. This value is usually associated with diagnostics and companion diagnostics (Lakdawalla et al., 2018).
Fear of contagion	The value derived by the general population due to a reduction in the spread of disease. This is only related to anti-infective technologies (Lakdawalla et al., 2018).
Insurance Value	The value placed by a wider population of knowing that therapies will be available in the future, even if they are unlikely to need them (Lakdawalla et al., 2018).
Value of Hope	The value of a chance at greater health, even if that also means a chance of worse outcomes, e.g. the value patients place on the option of undertaking a risky procedure for the small probability of a cure (Lakdawalla et al., 2018).
Equity	The value of a treatment in improving or reducing health inequity (Lakdawalla et al., 2018).

BOX 6: OHE SYNTHESIS OF DEFINITIONS OF ELEMENTS OF INNOVATION AND VALUE ELEMENTS

About us

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- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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