Received: 23 February 2024 | Revised: 19 April 2024 | Accepted: 24 April 2024

DOI: 10.1111/hae.15031

Haemophilia WFH WILEY

REVIEW ARTICLE

# Moving towards Normalization of haemostasis and health equity: Evolving treatment goals for haemophilia A

Pål André Holme[1] | Jan Blatný[2,3] | Pratima Chowdary[4] | Riitta Lassila[5] | Niamh O'Connell[6] | Cédric Hermans[7] | María Teresa Álvarez Román[8] | Claude Négrier[9] | Antonio Coppola[10] | Johannes Oldenburg[11]

[1]Department of Haematology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[2]Hospital Bory, Bratislava, Slovakia

[3]Masaryk University, Brno, Czech Republic

[4]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free London, London, UK

[5]Coagulation Disorders Unit, Department of Hematology, Comprehensive Cancer Center, Helsinki University Hospital, Research Program Unit in Systems Oncology, University of Helsinki, Helsinki, Finland

[6]National Coagulation Centre, St James's Hospital, Dublin, Ireland and Trinity College Dublin, Dublin, Ireland

[7]Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques universitaires Saint-Luc, Catholic University of Louvain (UCLouvain), Louvain, Belgium

[8]Department of Hematology, La Paz University Hospital-IdiPaz, Autonomous University, Madrid, Spain

[9]UR4609 Hémostase & Thrombose, University Lyon 1, Lyon, France

[10]Regional Reference Centre for Inherited Bleeding Disorders, University Hospital of Parma, Parma, Italy

[11]Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

**Correspondence**
Pål André Holme, Department of Haematology, Oslo University Hospital, Institute of Clinical Medicine, University of Oslo, Postbox 4950, N-0424 Oslo, Norway.
Email: pholme@ous-hf.no

## Abstract

**Background:** Treatment options for people with haemophilia are evolving at a rapid pace and a range of prophylactic treatment options using various technologies are currently available, each with their own distinct safety and efficacy profile.

**Treatment goals:** The access to replacement therapy and prophylaxis has driven a dramatic reduction in mortality and resultant increase in life expectancy. Beyond this, the abolition of bleeds and preservation of joint health represent the expected, but rarely attained, goals of haemophilia treatment and care. These outcomes also do not address the complexity of health-related quality of life impacted by haemophilia and its treatment.

**Conclusion:** Capitalizing on the major potential of therapeutic innovations, 'Normalization' of haemostasis, as a concept, should include the aspiration of enabling individuals to live as normal a life as possible, free from haemophilia-imposed limitations. To achieve this—being supported by the data reviewed in this manuscript—the concept of haemostatic and life Normalization needs to be explored and debated within the wider multidisciplinary teams and haemophilia community.

KEYWORDS
haemophilia A, haemostasis, health equity, Normalization, quality of life, treatment goals

## 1 | EVOLUTION OF HAEMOPHILIA TREATMENT

The advances in treatment options for haemophilia over the past 70 years have irrefutably changed the outlook and prognosis for this condition. Multiple recent developments (Table 1) justify and support a shift away from annualized bleed rates and factor consumption as the primary measures of treatment outcomes, to a new target of normal haemostasis and health equity.[1] This would enable people with haemophilia, irrespective of disease severity, to live a normal and stable life comparable to their non-haemophilic peers. Although advances in treatment are evident in both haemophilia A and B, haemophilia A serves as a model for the rationale and benefits of ambitious, new standards of care.

The advent of whole blood or plasma transfusions in the 1950s increased life expectancy from adolescence[2] to around 20–30 years.[3,4] The introduction of cryoprecipitate in 1964, followed by intermediate-purity factor concentrates (from plasma) increased life expectancy to over 60 years,[5] with treatments administered on-demand. Lyophilization and subsequent storage stability of factor concentrate in the early 1970s enabled prompt bleed treatment at home, along with the initiation of prophylactic treatment, one of the key pillars of modern haemophilia treatment.[5,6] Recombinant factor VIII (FVIII) was developed in the 1980s, with the first availability from 1992.[5] This innovation practically eliminated the risk of infectious disease transmission[5] and, combined with an increase in the use of prophylactic treatment rather than episodic factor replacement for bleeds, allowed individuals to achieve a life expectancy that became close to that of the general population.[1]

Prophylactic treatment for people with severe haemophilia A originally aimed to provide minimum FVIII trough levels of ≥1 IU/dL, which significantly reduced bleeds and the risk of intracranial haemorrhage.[1,7] This 1 IU/dL minimum threshold was the compromise between the ambition to convert severe haemophilia to moderate and the constraints imposed by the need for frequent intravenous administration of the deficient factor due to rapid clearance from the blood. However, this factor level did not provide sufficient protection, and the majority of people still experienced joint bleeds[7] and subsequent joint damage.[8,9] This meant that while prophylactic treatment was undoubtedly a milestone in the advancement of haemophilia care, it still left individuals with significant unmet needs. One route to achieving health equity would be to prolong the time spent with factor levels in the non-haemophilia range. However, people with haemophilia already experience a substantial treatment burden due to the need to repeat intravenous dosing every 2–4 days.[5,10,11] Therefore, increasing the frequency of treatment further would impair efforts to attain health equity, as well as increasing treatment costs.[8,9]

## 2 | INTRODUCTION OF NOVEL THERAPIES HAS REDUCED THE TREATMENT BURDEN

The introduction of extended half-life factor concentrates has reduced the treatment burden by extending dosing intervals and achieving higher trough levels.[12,13] This prompted both the World Federation of Haemophilia (WFH) and the European Directorate for Quality of Medicines and Healthcare to recommend a higher target FVIII trough level of 3–5 IU/dL on the basis of bleeding pattern, joint status and lifestyle, guided by an individual's pharmacokinetic (PK) profile.[14,15] The wide inter-individual variability in treatment PKs has meant that treatment needs to be tailored to the individual, taking into account their lifestyle.[16] While the motivation was the attainment of zero bleeds, this was not universally achieved.[17]

The reduction in treatment burden created the potential to improve adherence and minimize bleeding events, while also increasing willingness to switch from on-demand to prophylactic treatment.[13] Additionally, non-factor replacement therapy administered subcutaneously, as well as the recent progress made in gene therapy, have potential to improve bleed protection while reducing treatment burden. Moreover, a recent development in high-sustained factor therapy has permitted FVIII activity to be at, or close to, the non-haemophilia range for approximately 4 days of the week, and at 15 U/dL by day 7 with a single injection.[18,19] FVIII levels in excess of 40 IU/dL have been shown for up to 2 years in a proportion of people with haemophilia (18% [three out of seven individuals] in one study[20]) treated with gene therapy,[11,21] and improved thrombin generation (with the median peak falling within the lower end of the non-haemophilia range[22]) has been demonstrated with non-replacement therapies. These innovations should prompt a reconsideration of treatment goals for discussion with people with haemophilia.

Normalization of haemostasis, as achieved with these different treatment strategies, was not conceivable decades ago, not only because it was difficult to achieve, even with frequent injections, but also because it was considered too ambitious and unaffordable. Life expectancy may have increased, but quality of life has been unpredictable and lagged behind, with many people with haemophilia reporting persistent chronic pain secondary to joint damage, both of which limit participation in normal life activities. Longevity brings with it age-related joint deterioration and other comorbidities, including cardiovascular challenges. Ageing causes an increasing health equity deficit for people with haemophilia, when compared with their haemophilia-free peers.[1] Yet the focus continues to be on minimum factor activity levels and preventing or reducing bleeds,[12,13,23] while people with haemophilia still experience morbidity, haemophilic arthropathy, pain, mental distress and impaired health-related quality of life (HRQoL).[24]

**TABLE 1** The current and future options of haemophilia treatment.

| Treatment approaches | Treatment goals | Treatment limitations |
|---|---|---|
| **Factor replacement therapy** | | |
| SHL-FVIII[16] | Maintain FVIII trough levels ≥1 IU/dL[16]<br>Reduce ABR and preserve joint health[14] | IV access and high frequency of infusions[16,27]<br>Immunogenicity impacts[35]<br>Breakthrough and subclinical bleeds[16]<br>Activity peaks and troughs[11]<br>Inter-patient PK variability requires treatment individualization[16]<br>Deterioration of joint health[7,25,26]<br>Zero bleeds for all not achievable[14,16]<br>Poor HRQoL[8,24,32,33] |
| EHL-FVIII[16] | Maintain FVIII trough levels >3–5 IU/dL[14]<br>Reduce frequency of infusions[13]<br>Reduce ABR and preserve joint health[14] | IV access[16,27]<br>Immunogenicity impacts[35]<br>Breakthrough and subclinical bleeds[16]<br>Activity peaks and troughs[11]<br>Inter-patient PK variability requires treatment individualization[16]<br>Joint damage is not completely prevented[7,25,26]<br>Suboptimal HRQoL[8,24,32,33] |
| High-sustained-FVIII[16,19] | FVIII close to normal 4 days out of 7, with 15 IU/dL activity at day 7[11,18,19]<br>Independent of endogenous VWF levels[36]<br>Target zero bleeds[11,19]<br>Preserve joint health[19]<br>Simplified dosing regimen (fixed dose weekly IV administration)[19]<br>Simplified perioperative management with FVIII monotherapy[19]<br>Predictable and measurable FVIII levels[18] | IV access[19]<br>Unknown immunogenicity impacts in PUPs[35]<br>No long-term safety analyses<br>Long-term data on joint health and HRQoL not currently available |
| **Non-replacement therapy** | | |
| Bispecific Ab[11,16] | Equivalent FVIII: stable 9–15 IU/dL[16]<br>Reduce ABR[11,14,16]<br>Subcutaneous administration[14,16]<br>Prophylaxis possible, regardless of FVIII inhibitors[11,14] | Limited flexibility and, due to bioequivalence level, adjuvant FVIII required for trauma, surgery, and high-risk activity[37]<br>Injection site reactions[38]<br>Long-term data on joint health, and HRQoL not currently available<br>Limited long-term safety analyses |
| **Rebalancing therapy** | | |
| Antithrombin inhibition[11] | Reduced antithrombin activity[11]<br>Reduce ABR[11]<br>Subcutaneous dosing[11]<br>Prophylaxis possible, regardless of FVIII inhibitors[11] | AE burden, including risk of thrombotic events, injection site reaction and ALT elevation[11]<br>Long-term data on joint health, and HRQoL not currently available<br>Limited long-term safety analyses |
| Tissue factor pathway inhibitors[11] | Generate sufficient FVIIa to overcome lack of FVIII[11]<br>Reduce ABR[11]<br>Subcutaneous dosing[11]<br>Prophylaxis possible, regardless of FVIII inhibitors[11] | Risk of thrombotic events[11]<br>Long-term data on joint health, and HRQoL not currently available<br>No long-term safety analyses |
| APC inhibition[11] | Prevent inhibition of FVa, thereby rebalancing haemostasis[11]<br>Prophylaxis possible, regardless of FVIII inhibitors[11] | Waiting for data from initial clinical trials (NCT04073498) |
| **Gene therapy** | | |
| AAV5-based treatment[16] | Reduce treatment burden[11,16]<br>Target zero bleeds[11,21] | Unpredictable and variable level and duration of expression[21]<br>Many exclusion criteria[11,21]<br>Safety concerns including ALT elevation and need for immunosuppression[20]<br>Limited long-term safety analyses |

Abbreviations: AAV5, Adeno-associated virus serotype 5; ABR, annualized bleed rate; APC, activated protein C; AE, adverse event; ALT, alanine transferase; EHL, extended half-life; FVa, activated factor V; FVIII, factor VIII; FIX, factor IX; HRQoL, health-related quality of life; IV, intravenous; PUP, previously untreated patient; SHL, standard half-life; VWF, von Willebrand Factor.

## 3 | THE CONSEQUENCES OF JOINT BLEEDS ON HRQOL

The majority of people with severe haemophilia and nearly all individuals in the absence of prophylaxis, will, at some point, develop chronic haemophilic arthropathy.[7,25,26] Currently, people with haemophilia have to experience a long-term decline in joint health, which seems inevitable given that haemophilic arthropathy can evolve even in the absence of symptomatic joint bleeds[27] and regardless of the disease severity.[28] This is thought to be due to subclinical or microbleeds and early-stage asymptomatic synovitis, which progresses to predominantly symptomatic chronic synovitis and subsequent arthropathy.[16] This notion is supported by the observation that seemingly normal joints can reveal abnormal structures when assessed with magnetic resonance imaging.[1] This silent disease progression has historically confounded detection and treatment, resulting in a population with mobility limitations and a burden of joint pain.

People with haemophilia often consider pain as a marker for bleeding only and not arthropathy; therefore, experiencing pain results in anxiety around participating in physical activity and rehabilitation, leading to a vicious circle since successful physical activity and rehabilitation would improve HRQoL.[29] Pain, both anticipated and experienced, becomes a cognitive burden that impacts behaviours and physical activity choices.[30] It is evident that living with (or with the fear of) chronic pain can increase levels of depression and anxiety.[31] Every bleed has a cumulative effect, and the decrease in HRQoL has a measurable impact on both drug-related and non-drug-related direct costs.[31,32]

The complex interplay between joint disease, bleeding (including subclinical bleeding), and pain causes an economic burden driven by frequent hospitalizations (both in-patient and outpatient appointments), orthopaedic surgeries, rehabilitation treatments, reduced work productivity, decreased social participation, and poor mental health.[33] The vicious circle may lead to impaired adherence to treatment due to pain, depression and anxiety.[28] Consequently, reliance on healthcare professionals (HCPs), as well as direct medical costs, are increased[33]; a burden that may not substantially differ between people with moderate and severe haemophilia.[28] Recent advances in treatment increase protection from bleeding and thereby help promote health equity.

## 4 | NORMALIZATION AS A NEW STANDARD OF CARE

Normalization of haemostasis could begin to be targeted with the most recent factor replacement therapy or gene therapy, and possibly with non-factor therapy and rebalancing options (depending on their efficacy in clinical trials). These strategies offer different mechanisms of actions, characteristics and clinical implications. Regardless of how Normalization is achieved, it should allow people with haemophilia to withstand minor trauma without triggering even a subclinical bleed (annualized joint bleeding rate of zero), thus avoiding joint damage, synovitis and chronic haemophilic joint disease, (or preventing further haemophilia-related deterioration in individuals who already have impaired joint health) as well as other life-threatening or debilitating bleeds. This would give people with haemophilia the mental stability and security to pursue social and professional physical activities without any anxiety about the potential short- and long-term repercussions on their joints and general health. A therapy option that has a simple dosing schedule would result in simpler clinical decision-making, allowing HCPs and multidisciplinary teams (MDTs) more time to focus on the management of comorbidities, while increasing adherence by empowering people with haemophilia to proactively manage their haemophilia. Individuals should have the confidence to make unrestricted life choices, enabling them to achieve goals regardless of haemophilia. If people with haemophilia can live a life with similar aspirations to peers unaffected by haemophilia, then improved mental health and emotional and psychosocial well-being may be realized.

Achieving Normalization of haemostasis and HRQoL will require the haemophilia medical community to commit to making health equity a reality for all people with haemophilia. Central to this will be the role of the MDT facilitating a holistic approach to treatment and care. Normalization should be the aim for all people with haemophilia regardless of their disease severity, eligibility, financial resources or geographical restrictions of treatment, even if healthcare disparities result in an uneven playing field. This is highlighted by the WFH 2020 annual global survey, which reported that only 12.3% of the FVIII consumed was destined to treat 63% of the population living in low- and lower-middle-income countries.[34] Such global wealth inequalities will always confound those seeking health equity, but it is only through challenging standards of care that we can begin to effect change.

The benefits of Normalization, and the means by which it is achieved, are largely dependent on the individual's phase of life and individual status. In a young child, the advantage of Normalization would be to maintain pristine joint health, unlike an adult who may already have sustained irreversible joint damage. However, in the case of a child, not all treatment options are currently available. It is vital to look at the application of Normalization for those that already have multiple joint arthropathy, along with those who do not have joint health deterioration, as they can also benefit from reduced pain, prevention of further joint damage and improvements in HRQoL. Therefore, the path to Normalization of haemostasis will need to be adapted to each person with haemophilia, taking into account the phases of life, pathophysiology, treatment options, comorbidities and the individual's personal aspirations.

## 5 | CONCLUDING REMARKS

Although the concept of Normalization shared in this manuscript is aspirational, the time has come where health equity is an attainable goal in haemophilia (Supplementary video). Challenging the status quo will require those who believe that Normalization is possible to prepare

the path so that others may follow. To achieve health equity, treatment goals and clinical measures need to be re-framed in the context of the Normalization of haemostasis and its assessment. There is currently enough evidence and reasons that the concept of Normalization should represent the beginning of the journey to elevate standards of care and provide optimal treatment for all people with haemophilia—the conversation needs to continue with all stakeholders in the community as we explore how Normalization can become a clinical reality for all.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the analysis, the interpretation of data for the work, drafting the work or reviewing it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## ACKNOWLEDGEMENTS

Medical writing support was provided by Catherine Hoare, PhD, of Bioscript Group Ltd, funded by Sobi. Sobi and Sanofi received the article for courtesy review; however, they did not influence the content. The authors have authorized this support and approved the inclusion of all conflicting interests and funding disclosures. This commentary article is the outcome of the scientific project (Elev8) funded by Sobi.

## CONFLICT OF INTEREST STATEMENT

PH has received research grants and research support to institution from Bayer, Octapharma, Pfizer and Sobi and consultation fees/lecture honoraria from Bayer, Biomarin, BMS, CSL, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and Takeda. JB has received speakers fee and/or consultation fee from CSL Behring, Novo Nordisk, Roche, Sobi, and Takeda. PC has served on advisory boards for Apcintex, Bayer, Boehringer Ingelheim, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, Sobi and Takeda, and has received research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer, Takeda and Sobi. RL has received honoraria for consulting (advisory board) and lecturing from CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, Sobi and Takeda. NOC is a principal investigator for studies sponsored by CSL Behring, Freeline, Roche, Sobi, Spark, Takeda and UniQure and has received research support from Sobi, has received honoraria/speaker fees from AstraZeneca, Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, Sobi, and Takeda. CH has received research funding from Bayer, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi; honoraria and speaker's bureau from Bayer, BioMarin, CAF-DCF, CSL Behring, F. Hoffmann-La Roche Ltd, LFB, Novo Nordisk, Octapharma, Pfizer, Shire/Takeda, Sobi, and UniQure. MTAR has received honoraria for speaking and/or honoraria for consulting, and/or funds for research from, Amgen, Bayer, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Novartis, and Takeda. CN has received honoraria for speaking and/or honoraria for consulting from Novo Nordisk and Sobi. AC has received honoraria for speaking and/or for consulting from Bayer, Biomarin, Novo Nordisk, Sobi, Takeda, and Werfe. JO declares grants or contracts from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Sobi, and Takeda paid to the Medical Faculty University of Bonn; payment or honoraria from Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, Takeda; support for attending meetings/travel from Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, Takeda; has participated in data safety monitoring/advisory boards for Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, Takeda; leadership or fiduciary role in other board, society, committee or advocacy, paid or unpaid for the GTH, and foundation "Hämotherapie Forschung".

## DATA AVAILABILITY STATEMENT

All data referred to in this article are available for review as required.

## ETHICS STATEMENT

This commentary article complies with all ethical requirements for data review and analysis.

## ORCID

*Pratima Chowdary* https://orcid.org/0000-0002-0135-1051
*Riitta Lassila* https://orcid.org/0000-0002-1911-3094
*María Teresa Álvarez Román* https://orcid.org/0000-0003-3296-4288
*Claude Négrier* https://orcid.org/0000-0002-2905-055X
*Antonio Coppola* https://orcid.org/0000-0003-3697-706X
*Johannes Oldenburg* https://orcid.org/0000-0002-1585-4100

## REFERENCES

1. Skinner MW, Nugent D, Wilton P, et al. Achieving the unimaginable: health equity in haemophilia. *Haemophilia*. 2020;26(1):17-24.
2. Larsson SA. Life expectancy of Swedish haemophiliacs, 1831–1980. *Br J Haematol*. 1985;59(4):593-602.
3. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. *Nat Rev Dis Primers*. 2021;7(1):45.
4. Lewandowska M, Nasr S, Shapiro AD. Therapeutic and technological advancements in haemophilia care: quantum leaps forward. *Haemophilia*. 2022;28(Suppl. 4):77-92.
5. Oldenburg J, Dolan G, Lemm G. Haemophilia care then, now and in the future. *Haemophilia*. 2009;15(1):2-7.
6. Mannucci PM, Tuddenham EG. The hemophilias–from royal genes to gene therapy. *N Engl J Med*. 2001;344(23):1773-1779.
7. Ferri Grazzi E, Sun SX, Burke T, O'Hara J. The impact of pharmacokinetic-guided prophylaxis on clinical outcomes and healthcare resource utilization in hemophilia A patients: real-world evidence from the CHESS II study. *J Blood Med*. 2022;13:505-516.
8. O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes*. 2018;16(1):84.
9. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125(13):2038-2044.
10. Hermans C, Mancuso ME, Nolan B, Pasi KJ. Recombinant factor VIII Fc for the treatment of haemophilia A. *Eur J Haematol*. 2021;106(6):745-761.

11. Fassel H, McGuinn C. Haemophilia: factoring in new therapies. *Br J Haematol*. 2021;194(5):835-850.
12. Persson S, Berndt C, Engstrand S, Trinczek A, Carlsson KS, Berntorp E. Area under the curve: comparing the value of factor VIII replacement therapies in haemophilia A. *Haemophilia*. 2023;29(1):145-155.
13. Hermans C, Reding MT, Astermark J, Klamroth R, Mancuso ME. Clinical studies of extended-half-life recombinant FVIII products for prophylaxis in adults and children: a critical review from the physician's perspective. *Crit Rev Oncol Hematol*. 2022;174:103678.
14. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26(Suppl. 6):1-158.
15. Peyvandi F, Berger K, Seitz R, et al. Kreuth V initiative: European consensus proposals for treatment of hemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies. *Haematologica*. 2020;105(8):2038-2043.
16. Berntorp E, Hermans C, Solms A, Poulsen L, Mancuso ME. Optimising prophylaxis in haemophilia A: the ups and downs of treatment. *Blood Rev*. 2021;50:100852.
17. Srivastava A. Defining success in haemophilia care—are we doing it right? *Haemophilia*. 2024;30(Suppl. 3):52-59.
18. Lissitchkov T, Willemze A, Katragadda S, Rice K, Poloskey S, Benson C. Efanesoctocog alfa for hemophilia A: results from a phase 1 repeat-dose study. *Blood Adv*. 2022;6(4):1089-1094.
19. von Drygalski A, Chowdary P, Kulkarni R, et al. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. *N Engl J Med*. 2023;388(4):310-318.
20. Castaman G, Di Minno G, De Cristofaro R, Peyvandi F. The arrival of gene therapy for patients with hemophilia A. *Int J Mol Sci*. 2022;23(18):10228.
21. Hermans C, Gruel Y, Frenzel L, Krumb E. How to translate and implement the current science of gene therapy into haemophilia care? *Ther Adv Hematol*. 2023;14:20406207221145627.
22. Pasi KJ, Lissitchkov T, Mamonov V, et al. Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran—Results of the phase 1 inhibitor cohort. *J Thromb Haemost* . 2021;19(6):1436-1446.
23. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AKC. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. *Cochrane Database Syst Rev*. 2011;9:CD003429.
24. O'Hara S, Castro FA, Black J, et al. Disease burden and remaining unmet need in patients with haemophilia A treated with primary prophylaxis. *Haemophilia*. 2021;27(1):113-119.
25. O'Hara J, Hughes D, Camp C, Burke T, Carroll L, Diego DG. The cost of severe haemophilia in Europe: the CHESS study. *Orphanet J Rare Dis*. 2017;12(1):106.
26. Rayment R, Chalmers E, Forsyth K, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. *Br J Haematol*. 2020;190(5):684-695.
27. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of haemophilia. *Ther Adv Hematol*. 2018;9(9):295-308.
28. Rodriguez-Santana I, DasMahapatra P, Burke T, et al. Differential humanistic and economic burden of mild, moderate and severe haemophilia in european adults: a regression analysis of the CHESS II study. *Orphanet J Rare Dis*. 2022;17(1):148.
29. McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. The experiences and beliefs of people with severe haemophilia and healthcare professionals on pain management, and their views of using exercise as an aspect of intervention: a qualitative study. *Disabil Rehabil*. 2022;44(26):8420-8428.
30. McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study. *Disabil Rehabil*. 2022;44(26):8412-8419.
31. Steen Carlsson K, Winding B, Astermark J, et al. Pain, depression and anxiety in people with haemophilia from three Nordic countries: cross-sectional survey data from the MIND study. *Haemophilia*. 2022;28(4):557-567.
32. O'Hara J, Noone D, Watt M. Relationship between bleeding episodes, health-related quality of life and direct costs in adults with severe haemophilia A: secondary analyses from the CHESS study. *Haemophilia*. 2022;28(5):e117-e120.
33. O'Hara J, Walsh S, Camp C, et al. The relationship between target joints and direct resource use in severe haemophilia. *Health Econ Rev*. 2018;8(1):1.
34. Ozelo MC, Yamaguti-Hayakawa GG. Impact of novel hemophilia therapies around the world. *Res Pract Thromb Haemost*. 2022;6(3):e12695.
35. Lacroix-Desmazes S, Voorberg J, Lillicrap D, Scott DW, Pratt KP. Tolerating factor VIII: recent progress. *Front Immunol*. 2019;10:2991.
36. Seth Chhabra E, Liu T, Kulman J, et al. BIVV001, a new class of factor VIII replacement for hemophilia A that is independent of von Willebrand factor in primates and mice. *Blood*. 2020;135(17):1484-1496.
37. Castaman G, Di Minno G, De Cristofaro R, Peyvandi F. The arrival of gene therapy for patients with hemophilia A. *Int J Mol Sci*. 2022;23(18):10228.
38. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811-822.


## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Holme PA, Blatný J, Chowdary P, et al. Moving towards Normalization of haemostasis and health equity: Evolving treatment goals for haemophilia A. *Haemophilia*. 2024;1-6. https://doi.org/10.1111/hae.15031