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REVIEW ARTICLE

Achieving the unimaginable: Health equity in haemophilia

Mark W. Skinner^{1,2}  | Diane Nugent³ | Pam Wilton⁴ | Brian O'Mahony^{5,6} |
 Gerry Dolan⁷ | Jamie O'Hara^{8,9} | Erik Berntorp¹⁰ 

¹Institute for Policy Advancement, Ltd., Washington, DC, USA

²McMaster University, Hamilton, ON, Canada

³Children's Hospital of Orange County, University of California at Irvine, Irvine, CA, USA

⁴Canadian Hemophilia Society, Montreal, QC, Canada

⁵Irish Haemophilia Society, Dublin, UK

⁶Trinity College, Dublin, UK

⁷Guy and St Thomas' Hospital, London, UK

⁸HCD Economics, Daresbury, UK

⁹University of Chester, Chester, UK

¹⁰Lund University, Skane University Hospital, Malmo, Sweden

Correspondence

Mark W. Skinner, Institute for Policy Advancement, Ltd., 1155 23rd St NW, #3A, Washington, DC 20037, USA.
 Email: mskinnerdc@gmail.com

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Abstract

Historically, treatment based on the availability of clotting factor replacement has resulted in an arcane guideline for the correction of factor deficiencies in people with haemophilia (PwH). While all other disease entities seek to restore function to a normal level, PwH are restricted to factor nadirs still equivalent to mild or moderate disease, resulting in continued risk of bleeding. A new treatment paradigm is needed based on the defined needs of PwH. A treatment model was developed by a panel of haemophilia providers, patient advocates and health economists to establish specific treatment milestones and targeted outcomes. The panel defined a series of treatment milestones to characterize the activity and outcomes linked to level of factor deficiency correction. All agreed that the ultimate goal should be 'functional cure' and 'health equity'. Seven levels to achieving a functional cure were identified, (a) Sustain life; (b) Minimal joint impairment; (c) Freedom from any spontaneous bleeds; (d) Attainment of 'normal' mobility; (e) Able to sustain minor trauma without additional intervention; (f) Ability to sustain major surgery or trauma; and (g) Normal haemostasis. A parallel set of patient-reported outcomes to achieve health equity was identified. These guidelines are now comparable with other disorders where the goal is to replace missing proteins to attain normal activity levels. As we are no longer limited by plasma supply due to the manufacture of recombinant factors, mimetics, and the early success of gene therapy, health equity is now achievable.

KEYWORDS

haemophilia, outcomes, prophylaxis, replacement factor

1 | INTRODUCTION

Current prophylaxis protocols for haemophilia A are designed conservatively, with a minimal goal of achieving factor VIII (FVIII) trough levels of $\geq 1\%$. This threshold was originally selected based on generally favourable outcomes from early cryoprecipitate studies that targeted trough FVIII levels of 1%-3%, supportive evidence that moderate haemophilia was associated with fewer bleeds and better preserved joint function than severe haemophilia, and limitations in plasma resources

at the time.¹⁻³ However, persons with haemophilia (PwH) who are maintained at 1% FVIII continue to experience spontaneous bleeding and remain at higher risk for injury with daily activities.⁴ Furthermore, current prophylaxis regimens do not prevent haemophilic arthropathy over a PwH's lifetime.⁵ With the growing availability of current therapies, the validity of the 1% threshold has come under scrutiny, accompanied by the proposal to target higher thresholds $\geq 15\%$.⁶

Recent success in clinical development of haemophilia therapies opens an era of new possibilities and holds great promise for people

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with haemophilia (PwH). PwH are now able to achieve previously unattainable life expectancy as a result of improved bleeding control and a reduction in complications. Prior to therapeutic clotting factor replacement, persons with severe haemophilia had a shorter life expectancy, with many dying in infancy and rarely surviving beyond the early teens. With access to prophylaxis and comprehensive care, PwH now have a life expectancy close to that of the general population.⁷ In parallel, treatment goals have evolved from simply preventing early death to decreasing spontaneous bleeding and associated morbidities.

Prolongation of life is admirable but without optimizing therapy, patients are living longer lives with chronic pain and disability. Recent advancements that could normalize haemostasis open up the possibility of attaining a lifestyle unimpacted by disease complications. The major barrier to meeting this goal is an absence of health equity for PwH (WHO defines equity as the 'absence of avoidable or remediable differences among groups of people').⁸ Overcoming this challenge requires that PwH and physicians align their aspirations to achieve equity in their health and healthcare goals, respectively.

Within this manuscript, we propose a structured framework providing a roadmap to attaining outcomes that equate to various levels of haemostasis. Regardless of an individual's personal situation or the health system within their country, each person can find their place along the proposed milestones. This paper may serve as a model for patients, clinicians, health systems and payers to advance care using a patient-focused approach with the goal of normal haemostasis and lifestyle.

2 | METHODS

The treatment model described herein was conceptualized through a collaboration between clinicians and patients. Panel members were selected based on their extensive and diverse experiences working in the field of bleeding disorders to achieve and advance access to treatment. At an initial face-to-face meeting in July 2017, the panel

discussed the need for new treatment models for haemophilia in the context of the current and anticipated future treatment landscape. Highlights from the discussion included agreement by the panel that a new paradigm was needed to replace the current 'minimal treatment approach', largely driven by product limitations and historical events that are no longer relevant. A new model was proposed that enables patients to achieve specific milestones in a stepwise fashion, culminating in a progressive definition of cure. Two global workshops including patient and clinician representatives from 24 countries were convened during which concepts from the model were presented for feedback (January 2018) and subsequently tested through a workshop exercise (January 2019). The model was refined and subsequently agreed upon by the panel. This paper builds on recent work by Iorio et al who published a Delphi consensus statement describing target plasma factor levels for tailoring treatment for PwH.⁹ Additional literature reviews were conducted to identify pertinent evidence for each clinical and patient-relevant outcome.

3 | RESULTS AND DISCUSSION

To advance the concept of patient care further and to ensure the inclusion of the patient voice, we developed a new treatment model that enables patients to achieve specific milestones in a stepwise fashion, resulting in a progressive definition of cure (Figure 1; Table 1). Here, we describe both clinical and patient-relevant goals of treatment in parallel with the medical approach to correct haemostasis, summarizing the current literature, proposed approaches and implications of achieving each milestone.

3.1 | Milestone 1. Survival/prevent premature death

Life expectancies for PwH have increased dramatically from 11 years in 1930 (among Swedish patients) to 78 years after 1950.⁷ However,

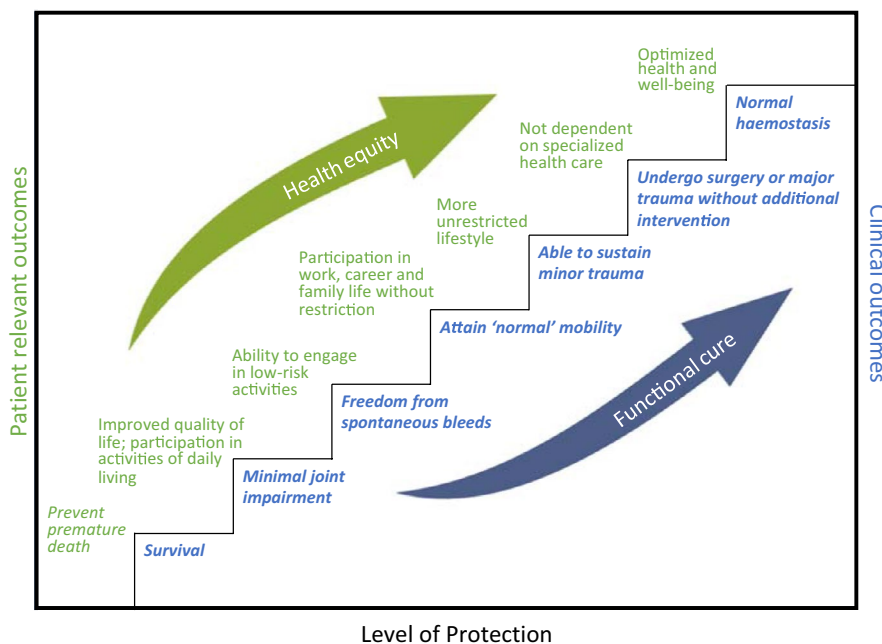


FIGURE 1 Model of Milestones towards normal haemostasis. Level of protection on horizontal access; Medical outcome on right vertical access; patient-relevant outcome on left vertical access [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Treatment model milestones

Step	Clinical outcome	Patient-relevant outcome	Status
1	Sustain life	Prevent premature death	Achievable with use of factor concentrates and home treatment/easy access to health care
2	Minimal joint impairment	Improved quality of life; participation in activities of daily living	Achievable in virtually all patients with prophylaxis started early in life
3	Freedom from spontaneous bleeds	Ability to engage in low-risk activities	Achievable in most patients with current prophylactic regimens
4	Attain 'normal' mobility	Participate in work, career and family life without restriction	Achievable in some patients with prophylaxis, but must be initiated at an early age
5	Able to sustain minor trauma	More unrestricted lifestyle	Current management is on-demand replacement factor and other local treatments to manage bleeds
6	Undergo surgery or major trauma without additional intervention	Not dependent on specialized health care	Managed in consultation with haemophilia treatment center and with laboratory support that can monitor and supply required replacement factor levels
7	Normal haemostasis	Optimized health and well-being	Would require treatment (prophylaxis, gene therapy or non-replacement factor therapy) almost immediately after birth, while avoiding immune tolerance/inhibitors; promising gene therapy trials

mortality remains higher for PwH than the general population. For example, from 1977 to 1999 in the UK, median life expectancy for persons with non-HIV, severe haemophilia was only 63 years, with mortality exceeding that of the general population by a factor of 2.69; bleeding and its consequences, along with liver disease and Hodgkin disease, were the primary causes of death in those patients.¹⁰ Recent studies have shown significant improvement in patient survival as a consequence of improved organization of healthcare resources (i.e. establishment of HTC, integrated care models, organization of blood banking resources, etc).^{11,12} Prophylaxis use has also led to significant reductions in mortality among severe PwH who experience intracranial haemorrhage (ICH; mortality risk is increased by 20% in the absence of prophylaxis following ICH).^{13,14} Even among non-severe PwH, risk for death from intracranial bleeding is 3.5-fold higher than in the general population¹⁵—further emphasizing the need for improved protection even among those with mild haemophilia.

Current regimens continue to target a level of haemostasis broadly equivalent to mild haemophilia, leaving these individuals at increased risk for bleeding. PwH—both mild and severe—will continue to benefit from greater levels of protection and greater access to health care, not only through prevention of premature death, but also by largely eliminating significant morbidity, disability and pain experienced by those without adequate treatment.¹⁶

3.2 | Milestone 2. Minimal joint impairment/ improved quality of life, participation in activities of daily living

PwH experience secondary complications to bleeding, most notably joint impairment due to long-term and recurrent hemarthrosis. While joint damage is less detrimental in mild cases of haemophilia vs severe, the risk of joint damage remains higher even with mild haemophilia, compared with the general population.^{4,16}

Presence of target joints has been associated with fatigue, loss of enjoyment, reduced leisure pursuits and particularly pain, with more than eight times as many patients reporting extreme pain or discomfort in the presence of a target joint.¹⁷ In the value equation, defined by Porter as outcomes relative to costs, outcomes are multidimensional and condition-specific and, for haemophilia, including objective measures of survival, ABR and joint impairment, as well as qualitative measures such as quality of life and participation in activities of daily living.^{18,19} Therefore, to properly evaluate the impact of joint impairment on patients with haemophilia, it is important to consider such qualitative outcomes that result directly from joint impairment,²⁰ for example, pain—an insidious outcome reported by the majority of PwH in the US and EU that impacts daily living by reducing range of motion, impairing mobility and limiting function and productivity.²¹ In the CHES study, patients with target joints had worse pain/discomfort, in addition to accompanying lower EQ-5D measures of mobility, self-care, usual activities and anxiety/depression.¹⁷

Participation in activities of daily living is considered achievable for PwH who start prophylaxis in early life, but less so for those exposed to joint bleeds that have resulted in chronic damage before starting prophylaxis.²¹ In a study by Mazepa et al, recent improvements in access to standard-of-care have correlated with prophylaxis use and reduced ABR, but bleeding-related complications including development of target joints have shown little improvement over time, suggesting that greater access and better therapeutics are still needed.⁴

3.3 | Milestone 3. Freedom from spontaneous bleeds/ability to engage in low-risk activities

The challenge with spontaneous bleeding is that it may occur without overt clinical signs. Subclinical microbleeds further contribute to the progressive development of target joints and subsequent complications, even among PwH on prophylaxis.^{22,23} While prevalence

of microbleeds is difficult to quantify, they are often suspected when joint abnormalities or damage is seen by MRI or ultrasound in the absence of clinically apparent bleeds. Strikingly, more than half of all asymptomatic joints show abnormal joint structure by MRI.^{22,24} In cases of cerebral microbleeds, detection methods are limited, and delays in diagnosis can lead to impaired cognition and hospitalization.²⁵

Spontaneous bleeding limits the ability of PwH to freely engage in even low-risk activities. While replacement factor therapy has been effective in treating spontaneous bleeding, effective control or prevention can only be achieved through routine prophylaxis. In studies comparing on-demand therapy vs either primary prophylaxis (ESPRIT and the Joint Outcomes Study^{26,27}) or secondary prophylaxis (SPINART, LEOPOLD II, POTTER and ADVATE²⁸⁻³¹), prophylaxis significantly reduced bleeding rates compared with on-demand therapy. Primary prophylaxis significantly reduced annualized bleeding events by three- to fivefold, and secondary prophylaxis by at least sevenfold, completely eliminating bleeding episodes in some patients. In further support of these studies, a longitudinal analysis of >600 patients treated at US HTCs (1999-2010) showed parallel decreases in bleeding rates with increased prophylaxis use ($P < .001$).³²

Therefore, as the third milestone on the journey to normal haemostasis, achieving control of spontaneous bleeding appears to be feasible with current therapies. Improved technology, both in fine-tuning the treatment regimens and in better understanding of the triggers for subclinical and overt bleeding, should enable patients to live without fear of spontaneous bleeding, even though at present, this success is likely to be accompanied by increased treatment burden with associated impact on the lives of PwH and their families.

3.4 | Milestone 4. Attain 'normal' mobility/ participation in work, school and family life without restriction

In defining normal mobility as the fourth milestone in our treatment model, achievement of this goal is demonstrated by showing no visible differences from the general population in terms of day-to-day activities, such as walking, cycling or working.

PwH and their caregivers often face issues in the workplace in terms of choosing a job, engaging with colleagues, job performance and job retention.²¹ Among PwH, 80% report a negative impact of haemophilia on working life, with more than half indicating the impact is moderate to very large.^{33,34} For parents of children with haemophilia, the negative impact remains high, at 59%.³³ In adult PwH, employment decreases with increasing disability or pain and mobility.³⁵ Among young adult PwH (ages 18-30), nearly a quarter have voluntarily left their jobs because of haemophilia, and 20% believe they were not hired or lost a job because of haemophilia.³⁶ Comparison between workers with vs without haemophilia has shown that PwH are more likely to retire early (48.1% vs 3.6%) or work part-time due to health (31.4% vs 3.8%); both early retirement and part-time work were associated with use of mobility aids, acute/

chronic pain, difficulties with daily activities and a history of joint surgery.³⁷

Studies of primary prophylaxis have shown that normal or near-normal activity with respect to joint motion and school or work attendance is achievable. Patients on prophylaxis maintain or improve physical activity levels, compared with pretreatment levels³⁸⁻⁴² and achieve similar activity levels as those with mild or moderate haemophilia.⁴³ Prophylaxis also enables sports participation, which in turn contributes to improved fitness, health satisfaction and psychosocial wellness.^{39,44} Early prophylaxis prior to development of target joints is associated with minimal joint changes and minimal functional disability in boys with severe haemophilia.^{45,46}

Secondary prophylaxis has also improved both clinical (ABR, joint health) and qualitative (HRQoL, pain, activity level) outcomes related to joint health, having shown associations with decreased bleeding and improved joint health, as well as substantial reductions in chronic pain and increased participation in physical activities and improved lifestyle—including unrestricted participation in work/school and recreational activities.⁴⁷

However, secondary prophylaxis (initiated post-target joint development) may not afford the same degree of benefit in terms of mobility. A prospective study of secondary prophylaxis vs episodic therapy showed that, despite significant improvements in rates of hemarthrosis, there were no differences in target joint development or in target joint range of motion, suggesting that late prophylaxis cannot prevent damage caused by bleeding prior to the initiation of early prophylaxis regimens.⁴⁸ Consistent with this observation, a longitudinal US HTC study also showed that although prophylaxis significantly predicted decreased bleeding at any age, only prophylaxis initiation prior to age 4 (and absent obesity) predicted preservation of joint motion.³² Likewise, work impairment has also been lowest among PwH receiving primary prophylaxis, and highest in those receiving on-demand treatment.⁴⁹

Thus, with proper management, achieving the milestone of normal mobility appears to be within reach, but timing of treatment initiation is critical, with early prophylaxis important for maintaining healthy joints. Furthermore, although effective treatment may lead to 'normal' physical mobility, mental constraints, including worry and anxiety, have a persistent negative impact.⁵⁰ PwH who successfully achieve a greater level of activity should expect to experience improved QoL without major safety considerations beyond that of the general population.

3.5 | Milestone 5. Able to sustain minor trauma/ more unrestricted lifestyle

Although studies have shown that PwH benefit from physical activity, including sports and physical labour,⁵¹ it is unclear how much increased risk is associated with increased activity, as findings have been somewhat variable and difficult to interpret with scientific vigour. Some studies have suggested a transient increase in relative risk for bleeding with physical activity or that trauma-related bleeds may be increased with strenuous exercise,^{52,53} whereas others have

shown no difference in risk for sports-related injuries or target joint development between PwH who are active vs. those who do not participate in sports or vs unaffected peers.^{54,55} In the HERO study, increased age was associated with lower-activity risk among adult patients, whereas in children, increased age is associated with higher-activity risk. For both adults and children, bleed frequency was not associated with activity risk level.⁵⁶ Nonetheless, in a cohort of US patients with haemophilia B in the HERO study, 98% of adult PwH and 90% of caregivers reported that haemophilia impacts their decisions whether to participate in recreational activities, with history or fear of bleeds being the driving reasons for not participating.⁵⁷ The global HemACTIVE survey showed ~90% of PwH wished to be more active, believing that increased activity could be enabled by greater bleed protection and less pain.⁵⁸ To facilitate participation in activities, NHF provides a scale from 1 to 3 on risk ratings, based on low-to-high risk, noting that even low-risk activities are not guaranteed to be injury-free, and highlighting the importance of working with a healthcare provider before engaging in any of the listed activities.⁵⁹

Current recommendations for minor trauma include increasing the PwH's factor level as soon as possible, for up to 5-7 days or longer if there is neurovascular compromise.¹ For routine dental procedures, local treatments (e.g. sutures, local haemostatic agents, antibiotics, antifibrinolytic agents) and replacement factor (as directed by an HTC) are recommended. For other wounds, such as soft tissue haemorrhage or lacerations and abrasions, the level of therapy depends on how superficial or the severity of bleeding is.¹ For patients undergoing minor surgery, the WFH recommends infusing to levels of 50-80 IU/dL FVIII pre-operation and maintaining levels of 30-80 IU/dL for 1-5 days postoperation, depending on the procedure.¹

Therefore, although rates of injuries and target joint development are similar between PwH who participate in physical activities and those who do not,⁵⁴ proper preventive treatment should enable PwH to experience a more unrestricted lifestyle—one that is accompanied by risk of mild trauma—in the same manner as those unaffected.

3.6 | Milestone 6. Undergo surgery or major trauma without additional intervention/not dependent on specialized health care

In the current landscape, PwH undergoing surgery require specialized health care, including greater levels of prophylactic replacement factor both pre- and postsurgery to accommodate loss of blood in the absence of clotting. For PwH undergoing major surgery, the WFH recommends infusing to levels of 80-100 IU/dL FVIII pre-operation and maintaining levels >30 IU/dL for up to 14 days postoperation (or higher levels for shorter durations).¹ Gene therapy products in clinical trials have shown substantial reductions in requirement for replacement factors, accompanied by fewer annual bleeding episodes, higher physical activities and sports and reaching a phenotype similar to that of mild haemophilia; such patients experience

few spontaneous bleeds, but remain at risk for haemorrhage after trauma or surgery.⁶⁰ In a phase 1/2 trial of an investigational gene therapy, severe haemophilia A patients receiving treatment had mean and median FVIII levels of 104% and 89%, respectively, over a 1-year period, eliminating the occurrence of spontaneous bleeds and need for replacement FVIII injections, even for major trauma and surgery.⁶¹ Long-term effects of this approach are not yet known.

With gene therapy on the horizon, new approaches to clinical evaluation are being developed to accommodate their greater potential to overcome limitations of existing treatment approaches. CoreHEM was an initiative of the NHF whose goal was to determine a set of outcome measures for evaluating efficacy, safety, comparative effectiveness and value of gene therapy in order to ensure that outcomes are meaningful and relevant, while supporting comparative assessments of efficacy and value.⁶²

In achieving milestones towards functional cure, the ability to undergo surgery or major trauma without additional intervention is a potential goal achievable with gene therapy, particularly meaningful to patients for whom haemophilia is no longer a consideration. This goal may be achievable for PwH who have had full access to health care from an early age, but for those without early access, comorbidities will continue to be a burden to some PwH, as well as to the healthcare system as a whole.

3.7 | Milestone 7. Normal haemostasis/optimized health and well-being

Achievement of cure entails a genetic correction (or 'genetic cure') such that there is no possibility of offspring inheriting the disorder. The idea of a cure for haemophilia is currently aspirational, but foreseeable with future technological advances. Until such a 'genetic cure' exists for PwH, a 'functional cure' that achieves the goal of normal haemostasis would be transformative, eliminating any consideration of haemophilia in planning life, medical or emergency care.

To achieve the final milestone of normal haemostasis, a PwH would have no joint problems and would be indistinguishable from a matched peer. To achieve this, that person would need to receive treatment in the form of early and intensive prophylaxis, gene therapy or non-replacement factor therapy, almost immediately after birth, while avoiding development of inhibitors or immune tolerance. If this was achieved, that person would have optimized their QoL because they would have normal haemostasis allied with the resilience and coping skills which living with haemophilia will have, in many cases, added to their psychological profile. Aspirations for better treatment up to this point in time have been stymied by economic considerations and a failure of imagination. Payers, clinicians and in many cases PwH themselves have been satisfied with very slow incremental improvement in access to treatment. The objective of a 1% trough level using prophylaxis has been seen as the holy grail for far too long. With newer treatments, novel products and gene therapy on the horizon, we must set our sights at a more ambitious goal—normal haemostasis and normal and optimized QoL.

4 | CONCLUSION

In summary, the treatment model presented herein intends to transform the current approach taken by healthcare providers, patients and other stakeholders towards treatment, from the outdated, conservative target of FVIII > 1% to a stepwise approach that allows freedom from both lifestyle and medical restrictions caused by haemophilia. This new treatment paradigm encompasses a shared vision by providers and patients alike, tracking clinical and patient-centric outcomes in parallel, such that value is not limited to efficacy endpoints alone, but rather provides a clear path towards normal haemostasis.

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ORCID

Mark W. Skinner  <https://orcid.org/0000-0002-0934-0680>

Erik Berntorp  <https://orcid.org/0000-0002-1337-7195>

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