Patient-centred value framework for haemophilia

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Introduction: Growing budgetary demands have led to increased scrutiny of healthcare spending for rare diseases, leading to a unified goal within the haemophilia community to define objectively patient-centred value in haemophilia care.

Aim: To develop a patient-centred outcomes framework with global applicability for assessing value in haemophilia healthcare.

Methods: An international, multidisciplinary panel of experts convened to identify the range of patient impacts of haemophilia health care and organize these into a three-tiered, patient-centred outcomes framework based on Porter’s model for assessing value.

Results: In addition to measures common to other chronic diseases (eg survival and quality of life), Tier 1, health status achieved or retained, includes haemophilia-specific outcomes of bleeding frequency, musculoskeletal complications and life-threatening bleeds, as well as measures of function or activity. Tier 2, process of recovery, includes such outcomes as time to initial treatment, time to recovery and time missed at education/work; also included are disutility of care, measured by inhibitor development, pathogen transmission/infections, orthopaedic intervention and difficult venous access. Tier 3, sustainability of health, is measured by bleed avoidance, maintenance of productive lives and good health over time; potential long-term negative consequences include insufficient or inappropriate therapy and age-related complications. The applicability of the outcomes framework for different types of haemophilia healthcare interventions is described.

Conclusion: Haemophilia health care can affect multiple patient-centred outcomes across diverse patient types and healthcare systems. This framework organizes those outcomes for informing value-based decision making by multiple stakeholders and provides the basis for further refinement and development of a standardized outcomes set.

Keywords: haemophilia, outcomes, quality of life, value

1 Introduction

Budget constraints in health care have increased scrutiny of spending on pharmaceuticals and other interventions and the methods and policies for funding decisions. With increased focus on optimizing resource allocation, the goal is to maximize value. Haemophilia is a rare disease requiring consideration of multiple factors when determining value of a healthcare intervention. Decision-makers who must allocate resources across many healthcare priorities will benefit from an objective understanding of how interventions for haemophilia affect outcomes of importance to patients.
Assessment of value must be patient-centred, while accounting for treater perspective. In haemophilia, this starts with survival and extends to reduction in joint bleeds and arthropathy, avoidance of hospitalization/surgery, pain management, improvement in mobility, contribution to society and achieving expected lifespan. On the cost side are direct healthcare expenses, such as for medications, comprehensive healthcare services, hospitalization and emergency department visits, and inpatient and outpatient procedures. Direct non-healthcare costs include patient time, unpaid family member or volunteer time, and transportation; indirect costs include lost/impaired productivity.

Health care can have extended impacts on patient health and health system costs. Reflecting survival gains from decades of safe factor replacement therapy, prophylaxis and comprehensive care in mostly wealthier nations, persons with haemophilia (PWH) are now living to advanced age, acquiring common age-related chronic conditions and generating accompanying costs. Access to treatment is neither universal nor guaranteed; globally, 70% of PWH have no access to treatment. PWH are variably affected by changes in cost conditions and generating accompanying costs. Access to treatment is evidence of value. It is therefore essential that tools for assessment (HTA) agencies and policymakers will universally seek.

Value is commonly defined as health outcomes achieved per incremental cost. Most value frameworks incorporate aspects of health outcomes, including benefits and harms, and costs, although patients often regard with economic terms as less important. Some value frameworks are intended primarily to support population-based decisions and policies, while others primarily support individual patient care decisions. Porter notes that outcomes, the numerator of the value equation, are condition-specific and multidimensional. He proposes three tiers of outcome measures: (i) health status achieved or retained; (ii) process of recovery; and (iii) sustainability of health. Within each tier, Porter suggests beginning measurement efforts with at least one outcome dimension per level, then expanding the number of dimensions and measures as feasible subject to availability of relevant data. His approach to assessing value has been applied to breast cancer, knee osteoarthritis and type 2 diabetes. Others have provided further perspectives on the patient-centredness and practical challenges of implementing Porter’s framework.

Conventional approaches to assessing the impact of haemophilia health care have several limitations, including quantifying impacts on a narrow set of outcomes (eg number of joint bleeds) yet not their impact on, for example, overall patient health, family members or productivity. For example, they inadequately account for different impacts of prophylaxis vs. on-demand therapy in children and adults. Towards capturing this broader set of impacts, we adapted Porter’s three-tiered outcomes hierarchy, designating outcomes within that hierarchy that are more likely to capture the range of patient experience across diverse patient subgroups and healthcare systems.

A multidimensional framework of haemophilia-specific outcomes was developed to better convey patient experience in haemophilia and enable decision-makers—from advocates to healthcare providers to national health authorities—to assess value of haemophilia care. With the objective of identifying and organizing patient-centred haemophilia outcomes, and recognizing that different decision-makers would use and weight outcomes differently subject to their respective remits, the framework does not assign relative weights. Emphasizing the patient experience, this framework currently accounts only for the numerator (outcomes) of the value equation, although it can be incorporated into value assessments with economic denominators.
3.1.1 Tier 1—Health status achieved or retained

Tier 1 of Porter’s model represents health status achieved or retained and includes measures of survival and degree of health or recovery. Survival and life expectancy are presented as distinct outcome dimensions; increase in survival is a cohort-based variable used to evaluate the impact of a therapy or other healthcare intervention, whereas increase in life expectancy is a population-based variable for modelling progress in haemophilia care across a lifetime or across generations. For haemophilia, survival and life expectancy are the most tangible outcomes that can be measured, particularly given the leaps in these outcomes that have accompanied widespread availability of replacement factor in high-income and some middle-income countries. With available treatments, life expectancy of PWH can now approach or equal that of their non-haemophilic peers.

Tier 1 also encompasses outcomes that relate to the degree of health or recovery, not only in the short term, but also in the context of a lifelong condition. For haemophilia, bleeding frequency (or annual bleeding rates [ABR]) may serve as a marker of health, and the musculoskeletal complications that result from bleeding episodes may be quantified using clinical or radiological joint scores. There are, however, limitations to using ABR as an outcome measure, as absence of overt or patient-reported bleeding is not necessarily indicative of good health. Also, individuals with advanced haemophilic arthropathy may no longer experience significant bleeding because of joint destruction/fusion, yet may be severely disabled. Serious (i.e., life- or limb-threatening) bleeds are included as a separate measure due to their severe impact on health. Concepts of function/activity and health-related quality of life (HRQL) provide distinct measures with wide
implications for haemophilia, given its lifelong and life-altering nature. Ongoing efforts with gene therapy and other novel interventions are pursuing cures or sustained remissions that would register in Tier 1.

3.1.2 | Tier 2—Process of recovery

Porter defines Tier 2 as the time required to achieve recovery and return to normal function, and by disutility of care or treatment in terms of discomfort, retreatment, short-term complications, and errors and their consequences. For haemophilia, time to recovery includes improving outcomes by minimizing overall time to diagnosis (ie earlier in life), time to initial treatment of a bleeding episode and time to recovery from bleeding episodes. For example, prompt treatment of bleeding episodes or at-home administration of prophylaxis can prevent or limit the sequelae of bleeds and minimize negative outcomes. Time to recovery can also include duration of pain and disability caused by bleeds, time between consecutive bleeds, and rate of recurrence in the same joint or muscle.

Disutility of care or treatment can be measured by development of inhibitors, pathogen transmission from blood products, need for orthopaedic intervention (ie joint surgery), local infection caused by accessing drug delivery ports and problems associated with long-term venous access (eg needle phobia, complications with arteriovenous shunts or scar tissue).

3.1.3 | Tier 3—Sustainability of health

Sustainability of health refers to sustainability of overall health and recovery, including avoidance of recurrence of the original disease or longer-term complications and later-onset health problems that occur as a consequence of treatment. In haemophilia, this tier embraces limiting breakthrough bleeding, joint preservation, lifelong productivity in the workplace, other contributions to society, and sustained good health based on high quality of life (QOL) and health utility. Long-term negative consequences may include long-term disutility of insufficient/inappropriate therapy and haemophilia-related complications associated with age-related comorbidities and other conditions that may arise with increased longevity.

Outcomes within and across the three tiers are not independent and are not intended to be combined into a quantitative index. Consistent with Porter’s description, improvement in an outcome in one dimension can benefit others. For example, reduction in serious bleeds can affect survival and HRQL in Tier 1, the risk of joint replacement in Tier 2 and lifelong productivity in Tier 3.

3.1.4 | Applicability for diverse scenarios

Applicability of the haemophilia outcomes framework, ie its ability to account for relevant patient-related outcomes, was examined in three highly relevant clinical scenarios: a healthcare delivery model (HTC vs non-HTC), a treatment regimen (prophylaxis vs. on-demand therapy) and an innovative therapy (EHL vs standard therapy) (Figure 2).

3.2 | Healthcare delivery: HTC vs Non-HTC

With multidisciplinary teams of physicians, nurses, social workers, physical therapists and other haemophilia specialists, HTCs are designed to provide individualized health care to meet the physical and psychosocial needs of clinically diverse haemophilia patients, including many with serious risk factors and comorbidities. Applying the outcomes framework using evidence derived from comparisons of patients who receive treatment at HTCs to those who do not shows its sensitivity to various outcomes across the framework’s three tiers. Among the impacts for which HTCs have been evaluated are such patient-centred outcomes as survival, life expectancy, functional status, QOL, joint damage, absenteeism/days lost from work and school, unemployment and overall health. Most notably, clinical studies have demonstrated that survival and life expectancy improved significantly among those who received care at an HTC, vs. those who did not. Surveillance data collected by the US Centers for Disease Control and Prevention have shown that treatment at an HTC was significantly associated with reduced risk of death.

Outcomes related to degree of health or recovery (eg bleeding, musculoskeletal complications or pain) are managed at HTCs. In measures of sustainability of health (eg QOL over time and age-related comorbidities) and return to normal activities, HTC users have also reported a reduction in healthcare resource utilization and improvements in employment status.

3.3 | Treatment regimen: primary prophylaxis vs on-demand therapy

Primary prophylaxis in haemophilia care refers to the use of regularly scheduled clotting factor infusions prior to bleeding episodes for an indefinite or otherwise prolonged duration in order to prevent bleeding and related joint damage. On-demand therapy refers to provision of clotting factor infusions on an as-needed basis, typically in response to a bleeding episode. Patient-centred outcomes used to compare primary prophylaxis to on-demand therapy have included survival, joint bleeding, other bleeding (eg intracranial haemorrhage), joint damage/arthropathy, joint function/motion, inhibitor development, complications (eg infection and need for central venous catheter) and QOL. Evidence of clinical benefit of prophylaxis compared to on-demand treatment has led to its support by haemophilia organizations worldwide. While increased use of factor for prophylaxis raises per-patient product costs compared to on-demand treatment, its impact on joint function preservation also reduces disability and non-factor healthcare costs among prophylaxis users. In assessing prophylaxis vs. on-demand treatment, the most prominent and evaluable outcome measures are under Tier 1, degree of health or recovery, and Tier 3, sustainability of health. Children with haemophilia receiving primary prophylaxis (vs on-demand) experience lower rates of joint bleeds and arthropathy and higher rates of normal index-joint structure, as well as less limitation of work or leisure, improvements in HRQL, improvements in school performance and reduced pain. No formal head-to-head comparisons of
prophylaxis and on-demand therapy have been made for survival or life expectancy. Indirect evidence suggests that survival gains may accrue as a secondary effect of the primary outcome measure of reductions in serious bleeds. For example, primary prophylaxis is associated with reduced incidence of intracranial haemorrhage, which is associated with a 20% mortality rate and accounts for the greatest number of deaths from bleeding.28,29

3.4 | Innovative therapies: EHL products vs standard therapy

Due to the relatively short half-life of standard replacement clotting factor VIII (~12 hours on average), patients on prophylaxis generally require infusions every other day or three times weekly to maintain plasma levels sufficient to reduce bleeding events. For patients and caregivers, the requirement for frequent infusions represents a significant burden that can compromise adherence to prescribed treatment, especially for younger patients and those with poor venous access or busy lifestyles.30 EHL products requiring only once- or twice-weekly dosing have been developed to reduce the burden of frequent infusions for patients and their families, increase treatment adherence, facilitate higher trough levels and provide improved protection from bleeding and improve HRQL. In addition to addressing various pharmacokinetic parameters, studies of EHL products have addressed certain patient-centred outcomes, including breakthrough bleeds and ABR, while tracking inhibitor development, hypersensitivity reactions and other adverse reactions. In particular, approved EHL products and those in late-phase clinical trials have shown reductions in median ABRs and breakthrough bleeds compared to standard replacement factor and regimen-responsive differences in ABRs.30 Also, based on analyses of participants in early clinical trials, patients with severe haemophilia A or B showed improvements in HRQL when changing to EHLs, whether from episodic treatment or from conventional prophylaxis,31 although head-to-head comparisons against standard therapies have not been conducted. EHLs are anticipated to have secondary effects better than, or at least as good as those of standard replacement therapy, such as for degree of health or recovery and sustainability of health.

![Figure 2](https://wileyonlinelibrary.com) Conceptual application of the value framework to three relevant applications: Healthcare delivery (HTC vs non-HTC), treatment regimen (primary prophylaxis vs on-demand treatment) and innovative therapies (standard vs EHL products). Differentiating measures are those that have shown differences between treatment approaches, whereas non-differentiating measures have not shown substantial differences. Secondary effects are those that indirectly result from primary effects [Colour figure can be viewed at wileyonlinelibrary.com]
Today’s healthcare environment increasingly emphasizes the need to demonstrate value, with particular scrutiny on costly new therapies. The haemophilia community cannot rely on others to set the parameters of value for haemophilia health care. Key stakeholders, including government and private sector payers and other health authorities, must make resource allocation and other decisions involving many diseases and disorders, and cannot be expected to discern the many ways in which haemophilia health care can affect patients’ lives without guidance from the haemophilia community. The impacts of advances in care are not limited to the great strides made in survival, but also encompass the decline in serious, sometimes life-threatening bleeding events, joint bleeds, deterioration in joint function and eventual joint replacement. These collectively lead to gains in HRQL and functional status, including patient satisfaction, diminished pain, ability to return to work and other normal activities, and other contributions to society. A patient-centred haemophilia healthcare outcomes framework that captures the evidence of diverse impacts on haemophilia patients offers wide-ranging utility for healthcare decision-makers and other stakeholders in haemophilia healthcare.

The three comparative scenarios described here—HTC vs non-HTC use, primary prophylaxis vs. on-demand therapy, and EHL vs standard-acting products—illustrate how the three-tiered framework is sensitive to patient-centred outcomes that may be affected by diverse haemophilia healthcare interventions. The framework has the scope to reflect impacts on patient-centred outcomes in countries with currently low as well as high access to haemophilia health care. For example, in a low-access country, expanded use of factor products, whether plasma-derived or recombinant, could have a large impact on survival, serious bleeds, arthropathies and other important outcomes, while allocating resources to prophylaxis for most adults or to EHLs may be lower priorities. In contrast, in a country with broad access to haemophilia care, there may be limited remaining potential to improve survival, but ensuring access to adult prophylaxis and EHLs may have meaningful impacts on bleeding and joint damage.

For healthcare providers and payers, evidence of these impacts will help to assess any added value of haemophilia healthcare interventions and to inform efforts to reduce low-value services considered discretionary, unnecessary or harmful—thus freeing up budget for higher-value interventions. Further, an outcomes framework that is widely accepted in the haemophilia community will assist industry to develop therapies and other interventions that are most meaningful to patients and substantiate their value to HTA agencies, payers, clinicians and patients. For example, this framework can serve as a source of potential primary and secondary endpoints when designing clinical trials and other studies of haemophilia interventions.

Implementation of the framework will require (i) further review and validation by patient groups, (ii) development of data sources to support the evaluation of interventions’ impact on outcomes in the framework and (iii) application of the framework to clinical trial design and other evaluations. Further, this initial framework could provide the basis for development of a standardized outcomes set for haemophilia, such as have been developed for various chronic and acute conditions. Use of the framework for assessing the impacts of an intervention on a given patient group in a particular healthcare system depends on the availability and quality of relevant data. This includes findings from the carefully managed clinical trials that are typically used to gain regulatory approval of new therapies as well as from real-world data on outcomes and costs of these interventions in community settings. Based on available relevant health outcomes and economic evidence, decision-makers can apply their own methodologies, eg using incremental cost-effectiveness ratios, to assess value. The haemophilia community must take the initiative to ensure that such evidence is generated and continually evaluate the need for adding or modifying outcomes in the framework.

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