Haemophilia B: impact on patients and economic burden of disease

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Summary
Worldwide, haemophilia is the most common hereditary bleeding disorder. The incidence of haemophilia B, however, is considerably less than haemophilia A and consequently appears to have received less attention in the research literature. This article aims to summarise the available evidence documenting the patient and economic burden associated with haemophilia B and current methods of disease management. Both the immediate and long-term clinical consequences of haemophilia B can have significant implications for patients in terms of functional limitations and diminished health-related quality of life (HRQOL). Evidence demonstrates that primary prophylaxis is the optimal strategy for replacing missing clotting factor IX (FIX) and managing haemophilia B. Use of recombinant FIX (rFIX) over plasma-derived FIX (pd-FIX) is also generally preferred for safety reasons. Prophylaxis using currently available rFIX products, however, requires a demanding regimen of intravenous infusions 2–3 times a week which may have significant implications for adherence and ultimately the long-term efficacy of such regimens. Only limited assessments of the cost-effectiveness of prophylactic versus on-demand FIX treatment regimens have been conducted to date. Prophylaxis, however, is generally more costly as greater quantities of FIX are consumed. Any reduction in FIX replacement dosing frequency is expected to improve patient adherence and contribute to improved clinical outcomes, further supporting the cost-effectiveness of such interventions. Although a rare disease, as economic constraints for healthcare increase, generating further information regarding the key clinical, patient and economic outcomes associated with haemophilia B will be essential for supporting improvements in care for people with haemophilia B.

Keywords
Burdens, cost-effectiveness, factor IX, haemophilia B, health-related quality of life

Introduction
Haemophilia is a hereditary bleeding disorder characterised by impaired blood coagulation as a result of deficiencies in the production or function of proteins involved in the haemostatic pathway of blood coagulation. Deficiencies in blood coagulation factors VIII (FVIII) and IX (FIX) are used to define the two most common forms of haemophilia; A and B, respectively (1). Haemophilia is the most common inherited bleeding disorder with estimates suggesting that, worldwide, there are more than 400,000 people currently living with haemophilia (2). In terms of incident cases, haemophilia A is the most common form of the disease, affecting approximately 1:5,000 males. By contrast, the incidence of haemophilia B is approximately 1:30,000 males (3). As an X-linked recessive chromosomal disorder, almost all people living with haemophilia are male.

Traditionally, haemophilia has been associated with significant morbidity and mortality. However, advances in haemophilia therapeutics over the past two decades mean that the condition can now be relatively well managed. To date, haemophilia A has been the primary focus of research activity and clinical investigation, while haemophilia B has remained largely overlooked (4). However, as potential therapeutic management strategies for the two conditions begin to differ, there is becoming a greater need to understand key clinical, patient and economic issues specific to haemophilia B. In order to facilitate understanding in this area, therefore, this article summarises currently available evidence regarding the clinical, patient-reported and economic impact of haemophilia B and evidence supporting the effectiveness of strategies for the management of this condition.

Impact of haemophilia B on patients
Haemophilia is a condition characterised by frequent and recurrent bleeding episodes. The frequent bleeding episodes experienced by patients with haemophilia B are associated with events that may be of immediate clinical importance. Soft tissue haemorrhages and intracranial bleeding, for example, whilst being acutely painful to patients, also have the potential to cause long-lasting damage to internal organs and can be life-threatening in some instances (5). Recurrent bleeding episodes are also associated with a range of longer-term clinical consequences, including musculo-skeletal problems, which have the potential to restrict functional impairment in later life (6). The degree of impact associated
with haemophilia, from a clinical perspective, is often determined by the severity of the condition as well as the extent to which the condition has been successfully managed (7). Patients with mild haemophilia (defined as clotting factor concentration 0.05–0.40 IU/ml), for example, tend to experience abnormal bleeding only in response to surgery, tooth extraction or injuries. Conversely, patients with moderate haemophilia (0.01–0.05 IU/ml) experience prolonged bleeding responses to relatively minor trauma and patients with severe haemophilia (<0.01 IU/ml) experience frequent spontaneous bleeds (8). The proportion of patients with mild, moderate and severe forms of haemophilia B is not well established but data from community studies suggests that approximately 60–70% of patients with haemophilia B have a moderate or severe form of the condition (9–11). Traditionally the clinical manifestation of haemophilia B has been considered identical to that of haemophilia A (12). Recent evidence, however, suggests a less severe bleeding phenotype (lower bleeding frequency) and better long-term outcomes (lower likelihood of joint arthroplasty) among patients with haemophilia B (13–15).

For a person living with haemophilia B the clinical consequences of their condition can have far reaching implications. For example, they may have to carefully consider their participation in particular activities (e.g. contact sports), in appreciation of the immediate consequences that may ensue (e.g. bleeding). Long-term impairments in mobility and functional status (as a result of recurrent bleeding episodes) may also limit the activities that people with haemophilia are able to engage in (9, 16). The inability to participate in certain activities can have implications in terms of social participation and peer integration, particularly when children are growing up. As people with haemophilia progress into adulthood, evidence suggests that they are also less likely to proceed into full-time employment and occupational disability is typically greater among haemophilia patients, when compared to the general population (17). Evidence also suggests that the collective experience of living with haemophilia can have a substantial effect on mental well-being, particularly among young people living with the condition, within whom signs of major depressive disorder are common (18).

Despite advances in the management of haemophilia in recent decades, the physical, mental and social consequences of living with haemophilia B serve to reduce the health-related quality of life (HRQOL) of individuals with haemophilia B, particularly those with severe disease (19–22). However, determining the exact HRQOL burden associated with haemophilia B is challenging, as cross-sectional studies collecting HRQOL data have seldom investigated haemophilia B in isolation, perhaps in part due to the low incidence of haemophilia B.

A further challenge in understanding the exact degree of burden associated with haemophilia B is the widespread implementation of generic assessments of HRQOL such as the 36-Item Short-Form Health Survey (SF-36) (23), the Euro-Qol 5-Dimensions (EQ-5D) (24), and the Child Health Questionnaire (CHQ) (25). Whilst these instruments can be useful for enabling norm-based comparisons of HRQOL among haemophilia patients, compared to the general population or patients with other chronic disorders, they may not provide a comprehensive assessment of haemophilia-associated burden. The lack of available haemophilia-specific HRQoL and wider patient-reported outcome (PRO) measures has been acknowledged previously (26). Recently, however, some progress has been made towards addressing this issue with the development of measures such as the: Canadian Haemophilia Outcomes Kids’ Life Assessment Tool (CHO KLAT) (27); Functional Independence Score in Haemophilia (FISH) (28, 29); Haemo-QoL (30, 31); Haem-A-Qol (32); Haemophilia Activity List (HAL) (33, 34); Hemofilia-QoL. (35, 36); Hemolatin-QoL (37); and Hemo-Sat (32). The main advantage of these haemophilia-specific measures is that they enable the measurement of specific issues of relevance to haemophilia patients, thus (theoretically) providing a more accurate assessment of PROs in these patients. Of particular note, the Haemo-QoL, Haem-A-Qol and Hemo-SAT are available in up to 32 languages, thus helping to facilitate the assessment of burden of haemophilia, worldwide (38).

Alleviating patient burden: management of haemophilia B

Plasma-derived FIX (pd-FIX) versus recombinant FIX (rFIX)

The aim of treatment for haemophilia is to prevent or control bleeding episodes via the replacement of missing blood coagulation factors. Currently available FIX replacement therapies include intermediate-purity plasma-derived FIX (Konyne-80 & Bebulin®); high-purity plasma-derived products (AlphaNine® SD); ultra-high-purity monoclonal-purified, plasma-derived FIX (Mononine®, Nonacofix®); and recombinant FIX (Benefix®). All currently available therapies are administered by intravenous infusion.

Traditionally, products derived from human plasma carried with them the risk of transmission of blood-borne diseases and infections. The use of contaminated plasma-derived clotting factors, for example, is held to be responsible for the widespread transmission of the human immunodeficiency virus (HIV) in haemophilia patients in the early 1980s and the subsequent increased mortality rates from acquired immune deficiency syndrome (AIDS) which ensued (39, 40). Advances in plasma screening, purification and pathogen inactivation technologies have improved the safety of modern-day plasma-derived products. However, theoretical risk of disease transmission via plasma-derived products still exists in relation to prion diseases such as variant Creutzfeldt-Jakob disease (vCJD) and emerging diseases that may cross the interspecies barrier or may be resistant to viral inactivation processes (e.g. avian influenza A [H5N1]) (41, 42). For these reasons the use of rFIX products, which are produced using recombinant DNA technology, is widely recommended and some countries (England, Ireland, Denmark, Scotland, Canada) have even allocated extra financial support and provided all haemophilia patients with access to recombinant factors (43–47). Unlike for haemophilia A, where
there are multiple recombinant products licensed for treatment, there is only one rFIX product currently available for haemophilia B (BeneFix®).

In addition to improvements in safety, modern-day factor concentrates also offer significant advantages over traditional factor concentrates as they are easier to store, reconstitute and administer, which means that it is possible for infusions to be delivered by the patient themselves or a carer in the home as opposed to delivery by a healthcare professional in a hospital setting (48). Children with haemophilia become increasingly more experienced in the management of their condition as they age, with many able to self-infuse by eight years of age and most being fully self-sufficient by the age of 14 years (49, 50). Such opportunities for self-management have increased the convenience of factor replacement therapy for people living with haemophilia and helped to reduce the impact of haemophilia on patients’ daily lives (51, 52).

**On demand versus prophylaxis**

Management of haemophilia B using factor replacement therapies centres on two distinct approaches: on-demand treatment and prophylaxis. The main objective of on-demand treatment is to offer short-term and immediate compensation of FIX to stop further haemorrhaging and minimise the impact of a bleeding episode on survival or longer-term cumulative damage. Conversely, prophylaxis centres upon the principal of maintaining acceptable levels of baseline FIX to address the FIX deficiency and prevent bleeding episodes from occurring in the first place. Quantifying the benefit of either approach, from a clinical and wider patient perspective, has been a major focus of research in haemophilia over the past two decades.

Research to date suggests that prophylaxis is an effective strategy for the management of haemophilia in general (53–57). The frequency of acute haemorrhage and life-threatening bleeding episodes is significantly less among people with haemophilia receiving primary prophylaxis, compared with those receiving on-demand treatment (58–63). In addition to the short-term benefits of prophylaxis, evidence suggests that treatment via prophylaxis is also associated with better long-term outcomes in people with haemophilia. For example, primary prophylaxis (introduced before joint haemorrhages have occurred), may prevent joint damage and decrease the likelihood of arthropathy and other long-term morbidities (54, 56, 60). Evidence also suggests that while secondary prophylaxis (introduced following the onset of joint haemorrhage) does not reverse joint damage, it slows the progression of damage by decreasing the frequency of haemarthrosis (64, 65). Conversely, studies have repeatedly shown that on-demand therapy, even at high doses is ineffective in preventing arthropathy (51). As a result, prophylaxis is now also widely considered to be the optimal therapy for individuals with severe haemophilia, as evident within treatment recommendations and guidelines issued by leading health organisations (61).

By reducing the frequency of bleeding episodes and preventing long-term morbidity, prophylaxis is associated with improved HRQOL among people with haemophilia (66). Furthermore, by maintaining acceptable levels of factor concentrate in the blood, prophylactic regimens may also allow adolescents and young men with haemophilia to participate in many activities that may not have otherwise been possible, facilitating social integration among their peers (16, 17). Rates of absence from school or work and rates of unemployment are also significantly lower among those treated with prophylaxis as opposed to on-demand treatment (67). In light of such evidence it is therefore not surprising that people with haemophilia demonstrate a clear preference for prophylactic therapeutic regimens over on-demand regimens (68, 69).

Ettinghausen and Kreuz (2004) previously reviewed the body of evidence available in support of prophylaxis, specifically from a haemophilia B perspective (62). It was reported that whilst the benefits of prophylaxis over on-demand treatment had been widely reported in the literature, there had been only a limited focus on haemophilia B specifically and limited assessment of the benefits of prophylaxis using recombinant clotting factors. While subsequent prospective research has demonstrated the efficacy of rFIX in preventing bleeding episodes among haemophilia B patients treated via prophylaxis (55, 70, 71), there has been limited assessment of the short-term or long-term benefits of prophylaxis over on-demand treatment in these patients.

**Challenges for haemophilia care: adherence**

Ensuring adherence to prophylaxis regimens is an issue of particular importance because as little as one or two bleeds can trigger progressive, irreversible joint disease and subsequent impairments in HRQOL among people with haemophilia – the very outcome that prophylaxis is designed to prevent (72). However, despite the consequences of non-adherence, as many as 41% of patients report that they do not always take factor replacement therapy in accordance with their prescribed regimen and experimenting with stopping prophylaxis is particularly common in adults with haemophilia (72, 73).

Maintenance of adequate FIX plasma levels to protect against breakthrough bleeds, using currently available products, requires a demanding regimen of frequent re-administration of factor concentrates (2–3 times per week), due to the relatively short half-life of FIX in circulation (15, 74). The time commitment associated with prophylaxis has been highlighted as the predominant reason among parents, carers and patients for missing scheduled infusions, even when the benefits of prophylaxis are understood (52). Patients have demonstrated a preference for factor replacement regimens which require only a weekly infusion and evidence suggests that haemophilia patients would be willing to make a trade-off between a slightly higher bleeding frequency and a lower frequency of factor administration (68, 69).

There is limited evidence at present in relation to actual levels of adherence to current FIX replacement therapies among patients...
with haemophilia B and the consequences of non-adherence to such regimens. Evidence suggests, however, that a longer acting FIX product, resulting in reduced infusion frequency for treatment via prophylaxis, would be more convenient for patients with haemophilia and could potentially promote treatment adherence (75).

Economic burden

Although an uncommon disease, haemophilia is a life-long condition that places a considerable burden not only on patients themselves, but also on healthcare systems and wider society from an economics perspective (76). Haemophilia patients, for example, are accredited with requiring 2–3 times the health resources per inhabitant in developed countries – a figure which rises to 500–700 times per inhabitant in developing countries (77).

Direct costs

In comparison with other lifelong diseases where hospitalisation and institutionalisation comprise the main drivers of healthcare expenditure, estimates suggest that clotting factors can account for up to 98% of the total cost of haemophilia care (21, 78). This has significant implications for the allocation of financial resources by healthcare authorities. Indeed, figures from the World Federation of Hemophilia (WHF) show that average FIX usage per country varies considerably according to gross product per capita (GNP): 0.39 IU for countries with a GNP > $10,000 (US) per capita; 0.06 IU in countries with a GNP between $2000–$10,000; and 0.001 IU in countries with a GNP < $2000 (79). Due to heterogeneity of the standard of care employed, in terms of implementation of primary prophylaxis and prescribed dosage of clotting factor, factor usage and subsequent healthcare costs can vary dramatically even among countries with similar economic, social and cultural profiles (79). This can have implications on the total costs for haemophilia care. Lippert et al. (2005), for example, reported mean annual direct medical costs for on-demand treatment of haemophilia (A and B) ranging from €24,771 in the United Kingdom to €92,918 in Germany, with direct costs for prophylaxis ranging from €112,727 in the Netherlands to €182,075 in Germany (80).

There are a number of factors which can impact on the direct medical costs (i.e. factor usage) associated with the management of haemophilia B at both institutional and individual levels, including the type of factor prescribed (pd-FIX vs. rFIX), age of the patient and presence of co-morbid conditions (e.g. HIV or HCV). Acquisition costs for rFIX were previously quoted to be approximately 56–83% higher than for pd-FIX (58); however, more recent estimates suggest that costs for rFIX and pd-FIX are now approximately similar (11). Despite similarities in acquisition costs, however, the costs associated with treating haemophilia B patients with rFIX via prophylaxis are consistently reported to be higher than for treating patients with pd-FIX (81). This is largely due to the diminished in vivo recovery (IVR) associated with the one rFIX product currently available, which means that higher volumes of FIX concentrate are needed to achieve and maintain prophylactic levels of FIX (81–84).

Age is also an important factor in understanding the direct medical costs associated with haemophilia as children have been found to consume significantly more factor concentrate at a greater cost than adults (11). Studies investigating response to treatment via rFIX or pd-FIX also support this as subjects of 15 years or younger have lower incremental recovery rates than those over the age of 15 (70, 85). In addition, outpatient costs following a bleeding episode may also be expected to be higher in children as they require more extensive monitoring.

Development of factor concentrate inhibitors is relatively rare in haemophilia B (1.5% to 3%) (86), particularly in comparison to haemophilia A where rates can be as high as 25% (87). Nonetheless, the presence of inhibitors can significantly increase the cost of treating haemophilia B patients with estimates suggesting that costs can be approximately double that of treating a patient without inhibitors (11, 88). The increased use of factor concentrate is predominantly responsible for associated increased expenditure in treating these patients; however, the need to use immune tolerance induction (ITI) and/or by passing agents, such as recombinant activated factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrates (pd-aPCCs), can also escalate costs (86, 89).

The increased prevalence of HIV among haemophilia populations also has implications for the cost of haemophilia care with evidence suggesting the presence of HIV and decreasing CD4+ cell counts to be associated with increased clotting factor use and subsequent increases in costs in provision of care (90).

Indirect costs

Indirect costs associated with haemophilia are difficult to quantify and depend primarily on patient absenteeism, ability to work, amount of care needed and level of disability. Compared with the general population, for example, patients with haemophilia are absent from work for a greater number of days annually and have higher rates of early retirement and disability allowance (91). The clinical impact of haemophilia and hospitalisations and clinic visits associated with management of the condition may also result in time lost from work, education or social activities (7). Furthermore, the general deficits in HRQOL observed among haemophilia patients (19–22), may also amount to significant intangible costs that are difficult to truly quantify in monetary terms (76).
Cost-effectiveness

Due to limits on health-care resources, consideration of the cost of therapeutic regimens in relation to expected treatment benefits is essential for guiding resource-allocation decisions (92). However, to date, only a handful of studies have attempted to establish the cost-effectiveness of treatment strategies for haemophilia B (prophylaxis versus on-demand treatment) with reference to treatment outcomes.

Lippert et al. (2005) investigated the incremental cost-effectiveness of on-demand versus prophylaxis treatment in patients with severe haemophilia A or B (80). Cost-effectiveness was determined with reference to annual direct medical costs in terms of cost per avoided bleed and cost per quality-adjusted life year (QALY) gained. Findings from this study revealed that, when the prevention of joint bleeds was considered, prophylaxis demonstrated superior incremental cost-effectiveness compared with on-demand treatment with the cost-per-avoided bleed being approximately €6,650 and €14,410, respectively. When costs per QALYs were considered, however, findings revealed that prophylaxis was associated with better outcomes but at extremely high cost, with incremental cost-effectiveness ratios (ICERs) per QALY gained ranging from €2.21m to €5.7m among HIV-negative patients.

Since all prophylactic measures are investments for the future, long-term economic consequences have to be considered (77). Miners et al. (2002) attempted to assess the life-time cost-effectiveness of severe haemophilia B by simulated long-term consequences of treatment using a decision-analytic Markov model that incorporated a range of direct and indirect costs (93). The lifetime costs of on-demand treatment (£280,000) were estimated as being less than for infrequent prophylaxis (every 84 hours – £408,000; every 56 hours – £292,000) but greater than for frequent prophylaxis (every 48 hours – £272,000; every 24 hours – £250,000) and continuous infusion (£123,000). Estimates of incremental cost-effectiveness were considerably lower than reported by Lippert et al. with baseline ICERs for individuals receiving prophylaxis estimated at £8,600 per QALY gained and varying depending on prophylactic dosing schedule employed. From this perspective, therefore, prophylaxis is seen as a far more attractive therapeutic option for the treatment of haemophilia B.

From these studies alone only limited conclusions can be drawn regarding the cost-effectiveness of prophylaxis versus on-demand therapy for the treatment of haemophilia B. The disparity among the ICER estimates reported by Lippert et al. and Miners et al., for example, may be largely attributable to the utility values employed. In the absence of information regarding suitable data, the utility values employed by Miners et al. (11.79 per QALY) were based on the assumption that patients treated via prophylaxis had equal utilities as patients with mild/moderate haemophilia. Conversely, Lippert et al. estimated utility values based on assessment of HRQOL over a short period of time. As a result, differences in incremental effectiveness of prophylaxis and on-demand treatment were small (0.76 vs. 0.73). ICERs are heavily influenced by utility values employed and as such it is essential that more be done to establish accurate, robust and believable utility values for use in cost-effectiveness evaluations in haemophilia B (94).

Furthermore, most published guidelines for pharmaco-economic evaluations highlight the importance of taking a broad perspective including both direct and potential indirect costs and outcomes associated with a particular condition and its management. Evidence suggests that haemophilia can have considerable impact and economic implications for parents and carers of children with haemophilia, in terms of HRQOL deficits and time lost from work (95). Such factors, however, have yet to be considered in economic evaluations for haemophilia B. In order to determine the true cost-effectiveness of haemophilia B therapies, therefore, establishing reliable information regarding these costs is essential. Finally, despite evidence of the greater costs associated with rFIX compared to pd-FIX, there has been little or no assessment, to date, of the cost-effectiveness of prophylaxis using rFIX products.

Conclusions

Consideration of the available literature demonstrates that haemophilia is a condition associated with considerable burden to patients and the economy. Consistent with recent assertions, a bias towards research in haemophilia A or unspecified haemophilia is evident, with only a limited number of articles focussing specifically on haemophilia B or presenting findings for haemophilia B separately.

The scientific literature and recommendations from leading healthcare societies support the benefits of rFIX products over pd-FIX clotting factor concentrates from an improved safety perspective. Primary prophylaxis is also considered the optimal treatment regimen for the treatment of haemophilia B given the success of such regimens in reducing the immediate and long-term clinical consequences of recurrent bleeding associated with poorly controlled haemophilia. Such regimens are, however, based on the demanding administration of factor concentrates by intravenous infusions up to 2–3 times per week which may have important implications for adherence and ultimately the success and cost-effectiveness of such therapies.

To date there have been only limited assessments of the cost-effectiveness of haemophilia B treatment regimens, none of which offer a complete model of all the factors associated with the treatment of these patients. As the life expectancy of those with haemophilia approaches that of the general population, the challenges faced by the haemophilia community will undoubtedly increase in coming years. This is particularly true in terms of the treatment and prevention of age-associated diseases, previously uncommon in the haemophilia population (96). It is therefore essential that more work be done to generate further information regarding the key clinical, patient and economic outcomes associated with haemophilia B. This will be integral for supporting improvements in care for people with haemophilia B both now and in the future.
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Conflict of interest
Mapi Values were commissioned to conduct this review on behalf of Novo Nordisk. A. Gater and T. A. Thomson are employees of Mapi Values and have been paid consultants for this research work. M. Strandberg-Larsen is an employee of Novo Nordisk A/S.

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