The Swedish Institute for Health Economics
Institutet för Hälso- och Sjukvårdsekonomi

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IHE Report 2016: 10

ISSN: 1651-7628

IHE – The Swedish Institute for Health Economics

The report can be downloaded from IHE´s website.

Please cite this report as:
Persson U, Steen Carlsson K, Jönsson B. Alternative Payment Models in Haemophilia Treatment. IHE Report 2016:10, IHE: Lund.

This report was commissioned and funded by Bayer.

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Executive Summary

In this report, we review existing health care payment models and discuss the implications of applying new models in haemophilia A care. Current payment for factor VIII (FVIII) replacement treatments is usually based on price per international unit (IU), a model that has functioned well for factor products with shared safety and efficacy profiles.

Haemophilia A care is emerging from an era of relatively undifferentiated FVIII treatments that have delivered a 'standard' profile of treatment burden and expected outcomes and level of protection – as measured by annualized bleed rate (ABR). The entry of extended half-life (EHL), or other longer-acting FVIII products necessitates a departure from this one-size-fits-all payment paradigm. Longer-term, innovations such as monoclonal antibodies and gene therapy will not treat patients by replacing FVIII concentrations, supporting the need to move away from a per-IU-based payment mechanism.

If we focus on the near term, EHL factor concentrates are expected to increase the interval between infusions in prophylaxis regimens and/or reduce the risk of bleeding at current intervals of infusions. Thus, there is a need to explore payment models that support this exciting change in the haemophilia treatment landscape, and lay the groundwork to support future innovation.

The introduction of EHL FVIII products opens up for changes in the current treatment strategy on the aspects of reducing patient burden or improving patient outcomes:

- *Maintain patient outcomes while reducing patient burden*. Product consumption levels (IU/kg/week) would be lower for EHL products; patients would experience less burdensome treatment and yet achieve outcomes on par with current standards.
- *Improve patient outcomes while maintaining infusion frequency*. Consumption levels (IU/kg/week) would remain equal to that of standard-acting FVIII products yet patient outcomes could improve.

Both of these aspects could be implemented as new strategies in a given health care system, or as an individual mix according to patient preferences. The outcome will depend not only on the choice of treatment strategy by the health care provider, but also on the degree of benefit conferred by the new treatment options and patients' adherence to the prescribed strategy. Treatment adherence is influenced by patient preference, which means that outcomes in real-world settings will be empirical, and therefore may not be readily determined by the clinical trial results.

Imminent changes in treatment options with EHL products compel a need to consider the design of alternative payment models, including requirement for data collection, incentives and benefits to different stakeholders, and terms of payment. While financial risk-sharing models – an agreement between a payer and a manufacturer to share risk in order to advance patient access to the new therapy when the financial exposure is considered unpredictable but high – reduce uncertainty in population costs through budget restrictions and management of sales volumes, they do not explicitly include incentives for increasing patient benefit. They are also not linked to patient outcome, which means they do not require data collection or information beyond what is readily available in sales contracts.

And while a pay-per-patient model is also not outcomes-related, this paper shows such an approach can reduce uncertainty in population costs and increase payers' budget control. Importantly, this model does allow for patient choice. For example, an EHL product will make it possible for the patient to choose between achieving an improved outcome, a less burdensome treatment, or, to some extent, both.

Two additional models are also explored that are health outcomes-based schemes: one for actual outcomes and one for surrogate measures of outcomes using biomarkers. For these payment models, payment is tied to the value of treatment and requires the collection of real-world outcomes data. Annual outcomes need to be measured, and agreement on a definition of bleeding episode or risk level has to be reached. Requirements of real-world data and agreement on defining "response" could increase the administrative burden, and this needs to be weighed against the value of these tools for optimizing treatment. However, these payment models also include some favourable aspects, i.e., they are linked to performance, and the value includes incentives for health care providers to individualize and optimize dose and frequency of infusions, which could be expected to provide benefit for patients.

Finally, it may be possible to combine features of the proposed models; for instance, a model based on payment per patient could be combined with conditions of achieving a certain quality of the treatment, e.g., low risk for bleeding. The quality of the treatment may be defined as a minimum threshold FVIII level that should be attained, e.g., 1% FVIII. If the manufacturer and the payer agree on a fixed cost for FVIII, there is potential to provide patients with both health benefit and a less burdensome treatment regimen according to patient preference.

Conclusion

Payment per IU may not be an ideal payment model when the properties of factor concentrates for replacement therapy in haemophilia become more divergent. Therefore, it is essential to

explore alternative and feasible payment models from payer and manufacturer perspectives and, at the same time, elucidate expected implications for patients and their health care providers.

Summary table of two financial risk-sharing models and three new payment models for haemophilia developed in this report

Model	Payment terms	Example	Benefit to patients	Benefit to payers	Need for data collection
0.1. Financial Risk-Sharing	Budget cap. IU price fixed to an agreed-upon volume.	€1 per IU for the first 100 vials, €0.50 for the second 100 vials, etc.	None	Tight budget control	Utilization data only
0.2. Financial Risk-Sharing	Patient specific discount/cap: IU price is capped per patient per period of time	€1 per IU for the first IUs per kg weekly. Lower € per IU for subsequent use.	None	Controls for catastrophic cases (for ”outliers”)	None
1. Pay Per Patient	Payment fixed to a negotiated amount per patient such as the average cost of prophylaxis to achieve ABR = 1	€15,000 per patient for a pre-specified average use	Removes incentives for on demand, and inadequate doses / frequency	Moderate budget control	Real-world data on FVIII consumption required
2. Pay-Per-Actual Outcome	IU price adjusted for a rate of negative outcomes, e.g., bleeding rate, inhibitors	€1 per IU/kg/week for patients with less than 2 bleeds per year without inhibitors. €0.5 per IU/kg/week for those with negative outcome.	Incentives for good patient care	Payment tied to value	Real-world data collection on utilization & outcomes required
3. Pay-Per-Surrogate Measure	IU price adjusted for FVIII concentration achieved over time	€1 per IU/kg/week for patient-time with FVIII above 1%, 5%, 15%, etc. €0.5 for patients with lower FVIII concentration.	Incentives for good patient care	Payment tied to value	Real-world data collection on surrogate measure required

*ABR, annual bleeding rate; IU, international unit

1. Introduction

The introduction of FVIII replacement therapy, which began in the late 1950s, has dramatically changed prospects for people with haemophilia A. Treatment with FVIII concentrates was initially derived from blood plasma. Introduction of factor replacement therapy has increased the life expectancy for people with severe haemophilia from 17 years (median) before the 1960s to the near-population average in the 2010s [1, 2], while improving quality of life (QoL) (see [3] for instance). However, reliance on plasma as a source for FVIII resulted in exposure of patients to transfusion-associated viral diseases. The introduction of recombinant technology for manufacturing FVIII in the 1990s was a major step toward increasing the availability and quality of the anti-haemophilia treatment.

There are two main modes of therapy in the field of haemophilia: prophylaxis and on-demand. Prophylactic treatment involves regular infusions of FVIII concentrate to prevent bleeding episodes, whereas on-demand treatment is given to stop an ongoing bleed. Individualized treatment regimens can be provided where patients adapt their regimen depending on bleeding patterns. Such regimens consider the patient's clinical phenotype, as well as changes in age-related risk patterns, including both biological and behavioural aspects.

There are additional options to individualize treatment. One is to vary the dosing frequency of prophylactic treatment. For example, clinical practice in Sweden shows a range of prescribed intervals for prophylactic treatment from dosing to once every 5 to 7 days, with typical treatment intervals every other day or 3 times per week for severe haemophilia) (see [4] for instance).

The current payment system for haemophilia treatment is based on international units (IUs) and the price per unit. This system has worked well when physicians and patients could treat as clinically appropriate and there were incentives for manufacturers to continue to develop new treatments. However, concerns have been raised from payers about the optimal use of the product in the health care system, and individualization of treatment has increasingly been observed and discussed. There are significant variations in the treatment practices between countries that have resulted in part from health systems managing the consumption of IUs and vials.

The development of EHL or other longer-acting FVIII products provides opportunities for new treatment programs, both for on-demand and prophylactic treatments. To capture the potential benefits to patients in terms of less frequent dosing, increased protection against bleeds and the potential benefits to payers in terms of lower IU and vial consumption, there is a need to develop a payment system to meet new objectives for patient access to treatment, creating maximal value for patients and cost control and cost effectiveness for payers. Longer-term innovations, such as monoclonal antibodies and gene therapy, will use different mechanisms to supply the missing FVIII protein, or improve clotting ability, and thus also support the need to move away from a price-per-IU-based payment mechanism.

There is a general trend in health care systems away from payment for input or use of resources, i.e., volume, toward payment for the value of treatments and outcome. This development varies between systems and takes many forms. In the US, integrated care and bundled payment are important driving factors. In Europe, value-based reimbursement and payment based on assessment of cost effectiveness and follow-up studies of outcome in clinical practice are under development. Pay-for-performance and risk-sharing agreements are part of what is generally called “access agreements” or “managed entry agreements” for new technologies.

The purpose of this study is to discuss alternative payment models for haemophilia treatment that meet the objectives of providing incentives for the optimal use of new treatments in a health care system and for further innovation. Optimal use infers balancing the sometimes-conflicting goals of multiple stakeholders, including access for patients, value-based use according to data on relevant patient outcomes, control of total costs and incentives for innovation.

2. Rationale and objectives for a new payment system for haemophilia treatment

Nilsson and colleagues first introduced prophylactic treatment for haemophilia in Sweden in the late 1950s. They observed substantial reductions in bleeding rate and QoL and potential protection against haemophilic arthropathy in patients with severe haemophilia who maintained FVIII levels above 1% normal from an early age. Evidence of improved outcomes from prophylaxis compared to on-demand treatment resulted in an increase in prophylactic treatment in countries such as Sweden and the Netherlands, but disparity in treatment patterns remains worldwide.[1]

The World Federation of Hemophilia (WFH) reported in their 2014 annual global survey that there are large differences in average global FVIII use per capita (i.e., per inhabitant) between upper and lower income countries. This variation is attributable in part to differences in affordability across markets. In 2014, the actual mean FVIII use in upper income countries was 4.91 IU per capita, compared to 0.013 IU for the lower income countries [5]. Disparities in FVIII use can also be seen between different high-income countries; in 2012, the mean per capita FVIII use in Sweden was 10.54 IU, while it was only 5.10 IU in the US [6].

FVIII use measures the intensity of prophylactic or on-demand regimens prescribed.[2] For example, in Sweden, the average annual factor concentrate consumption per adult with haemophilia was reported in the 1990s to be 211,000 IU/year based on an 11-year panel of all patients nationwide [7]. Later reports indicate higher use of factor concentrates using data from 2009 with a median factor consumption of 312,000 IU/year [4]. In The Netherlands, annual prophylactic consumption has been measured at 105,000 IU/year [8]. Similar results have been found in a study of long-term resource use in young adults. Costs and outcomes for young adults born between 1970 and 1994 were compared for two prophylactic regimens used in real-world settings in Sweden (high-dose prophylaxis) and The Netherlands (intermediate-

[1] The median life expectancy before the introduction of replacement treatment was estimated to be 26 years for people with severe haemophilia (Larsson SA. Life expectancy of Swedish haemophiliacs, 1831-1980. Br J Haematol 1985; 59:593-602). The most recent estimate of the gap in life-expectancy from Sweden is 6 years for people with haemophilia (age at death 69.4 years vs 75.5 years for matched controls) [2, 21]

[2] The statistics reported focus on published results for people with haemophilia without inhibitors. The development of inhibitors changes the conditions for choosing replacement treatment regimens. Thus, separate analyses are required for this group, including the use of by-passing agents and immune tolerance induction therapy.

dose prophylaxis). A nearly two-fold difference in IU/kg was observed, though considerable variations also were documented within each prophylactic regimen. The same study also reported significant differences in bleeding and joint outcomes, but not in self-assessed QoL [8].

On-demand treatment has led to FVIII consumption with mean levels in France as high as 140,000 IU per patient per year [9]. A recent review found a notable variation in annual consumption of factor concentrates for patients treated with on-demand therapy, ranging from 711 to 2,871 IU/kg/year in 10 studies from Australia, the US, Turkey, Spain, France, Norway and Italy [10]. These dosages corresponded to a range of 50,000 to 215,000 IU per adult per year on average.

Differences in FVIII consumption can be explained by use of treatment strategy in terms of dose and frequency. For example, Sweden has a high-dose prophylactic regimen for patients with severe haemophilia, where 98% of such patients receive prophylactic regimens and 2% receive on-demand treatment [11]. Fischer *et al.* (2013) reported in a study in young adults that 96% in Sweden and 61% in The Netherlands were on full-time prophylaxis. While these two prophylactic regimens involved similar numbers of infusions per week, they differed significantly in the number of IU per infusion (resulting in median weekly dose of 88 IU/kg in Sweden and 46 IU/kg in The Netherlands). Finland uses less intensive FVIII treatments for patients with severe haemophilia, with less than 30% on prophylactic regimens [11].

Decades of progress in haemophilia treatment have greatly improved conditions for patients. However, there is no single score or measure that guides treatment choice appropriately and precisely for individual patients. Optimization of treatment strategies in clinical practice relies on determination of level of severity, treatment patterns and clinical experience subject to resource restrictions. In practice, uncertainty about underlying risks, budget limitations and under- and over-treatment may coexist.

The risk of bleeding varies by the amount of FVIII treatment and by an individual's characteristics. Patients with the same degree of severity could have different bleeding phenotypes and thus require differing doses of FVIII to maintain a low risk of bleeding. Children and adolescents require more factor concentrate per kg bodyweight to achieve the

same level of risk reduction as adults, due to biological factors that shorten FVIII half-life in young people.

To examine the challenges for payment models, it is useful to start by considering patients with the same degree of severity and same phenotype under different treatment regimens.[3] For these patients, the risk of bleeding and the associated costs of treatment and health care services vary with treatment regimen. As shown in Figure 1, the cost of bleeding can be significant for patients on on-demand treatment because of the higher expected number of bleeds per year. In contrast, the risk of bleeding approaches zero for patients on high-dose prophylactic treatment, and the associated health care costs are negligible. The upward sloping line (blue) illustrates the cost of FVIII treatment, while total cost – FVIII treatment plus other health care – is captured by the top line (black). This line is lowest between the on-demand treatment and high-dose prophylaxis paradigms, indicating that the optimal treatment pattern versus cost falls somewhere between these options.

Further, the figure illustrates that over- and under-treatment in prophylaxis can exist for any group with a particular severity and phenotype. To what extent these situations occur in different jurisdictions is an empirical question. Given that over- and under-treatment may coexist within each severity and phenotype, optimizing treatment strategies also requires choosing a treatment regimen suitable for patients depending on their phenotype.

[3] For this publication, haemophilia patients with an inhibitor, or other exceptional treatment need were excluded from analysis.

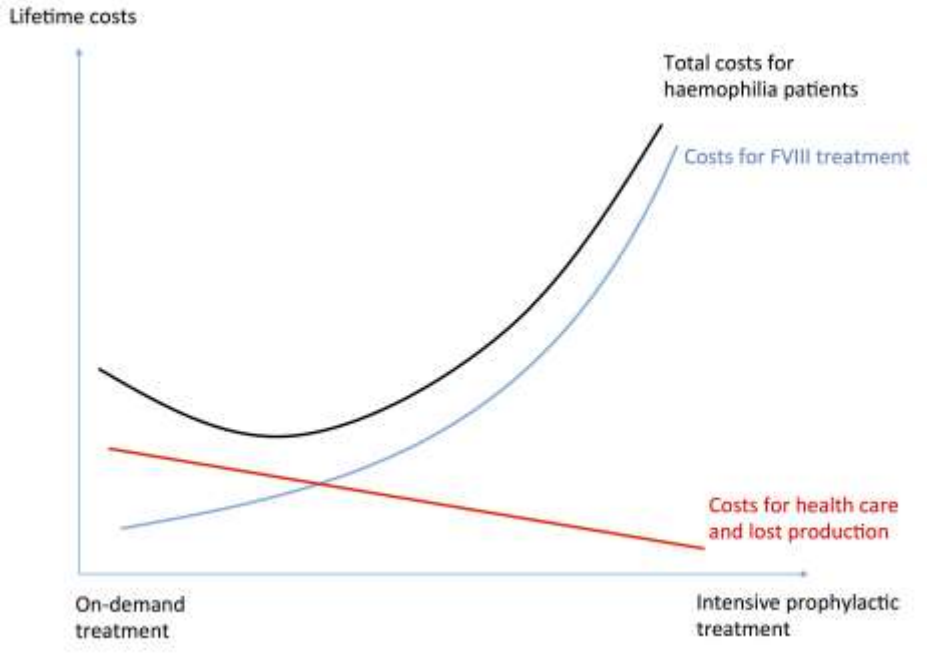

Figure 1. Haemophilia costs based on treatment strategy.

The introduction of EHL FVIII products opens up the following potential treatment strategies:

- *Maintain patient outcomes while reducing patient burden*. Product consumption levels (IU/kg/week) would be lower for EHL products; patients would experience less burdensome treatment and yet achieve outcomes on par with current standards.
- *Improve patient outcomes while maintaining infusion frequency*. Consumption levels (IU/kg/week) would remain equal to that of standard-acting FVIII products yet patient outcomes could improve.

Both of these aspects could be implemented as new strategies in a given health care system, or as an individual mix according to patient preferences. The outcome will depend not only on the choice of strategy, but also on the patient's adherence to the prescribed strategy. Treatment adherence is influenced by patient preference, which means that real-world outcomes are an empirical issue and will not readily be determined based on results from clinical trials.

Figure 2 provides an illustration of patient choice between treatment burden on one side and improved outcomes in terms of enhanced protection on the other. The upper curve (blue) illustrates the possible combination of outcomes with standard-acting FVIII products, and the lower curve (red) represents possible combinations with an EHL product. The introduction of new EHL products will enable the patient to select a new combination of outcome and treatment burden. The solid vertical arrow (*a*) illustrates the circumstance under which a

patient chooses a higher level of protection and a lower risk for bleeding while maintaining the same level of treatment burden. The dashed horizontal arrow (*b*) illustrates a patient choosing a less burdensome treatment while maintaining the original level of protection. The dotted arrow (*c*) in between illustrates a patient choosing both increased protection and less burdensome treatment.

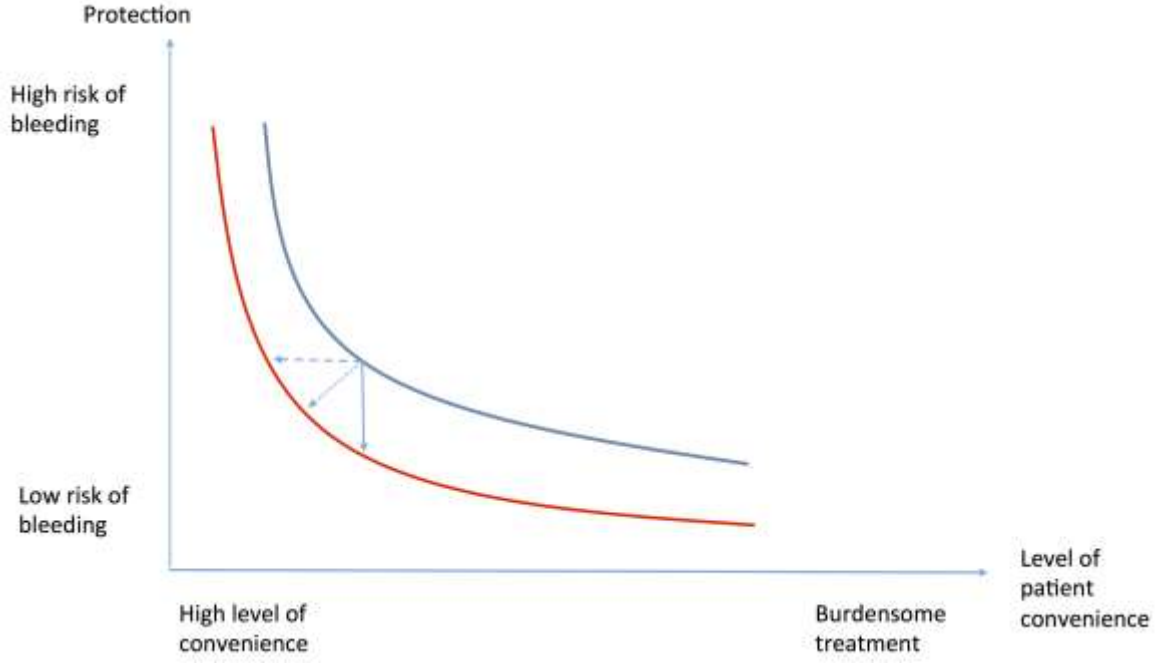

Figure 2. Protection and risk of bleeding episodes (*vertical axis*) versus treatment burden (*horizontal axis*).

It is important to note that the patient should be able to select the optimal combination of treatment burden and protection. Of course, the doctor's advice and family members' engagement may affect the patient's choice, and actual patient adherence to the chosen strategy will push the outcome in either direction. Similarly, the pharmacological attributes of the agent may influence the patient's choice of treatment regimen; being able to extend the infusion interval by one day may not be meaningful to a patient, whereas an agent that enables moving from three-times weekly to once weekly or even longer intervals may be quite attractive.

The different strategies can also be presented as the FVIII concentration throughout the patient week and infusion time points. Figure 3 illustrates FVIII levels following a prophylaxis regimen with a standard-acting product with an established infusion frequency. Use of an EHL

FVIII product leads to a higher level of protection against bleeds at all times, due to greater AUC and increased trough levels, which will not drop to 1% as with standard-acting FVIII concentrate.[4]

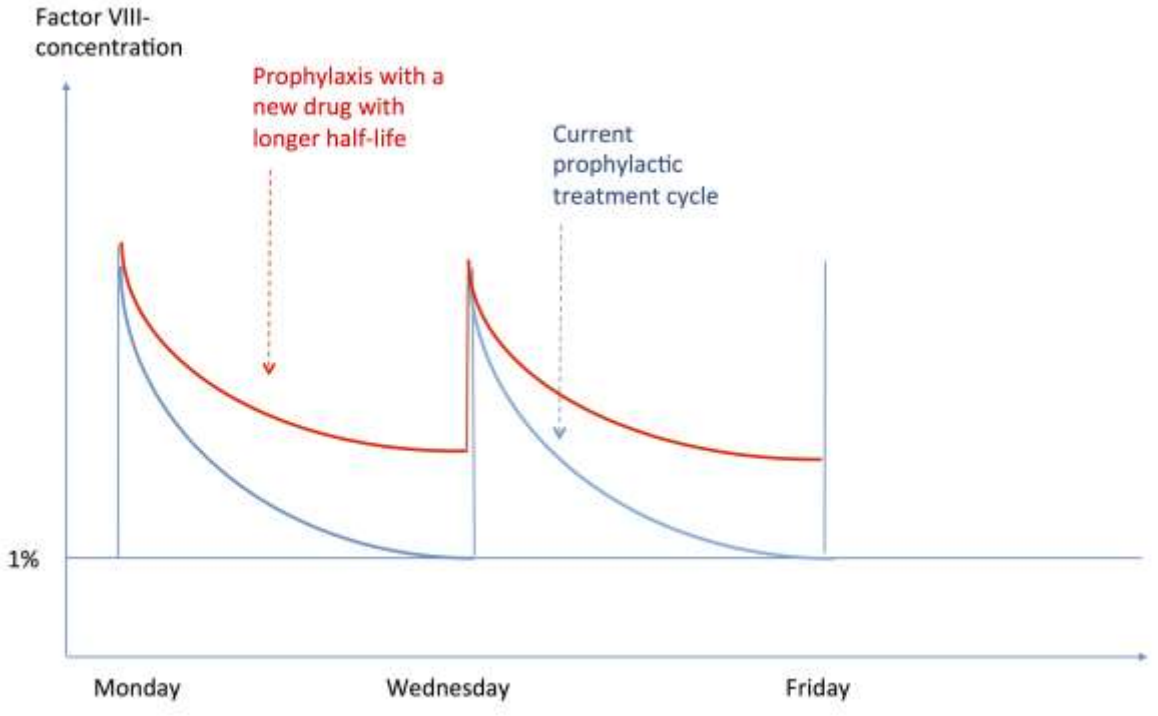

Figure 3. Higher protection against bleeds during a patient week.

An EHL FVIII concentrate could also enable patients to reduce the frequency of treatment and increase time between doses (Figure 4). Depending on the strategy selected, the benefits accrue differently. The latter enables less burdensome treatment, as the patient only needs to infuse every three-to-four days instead of two-to-three days, or, as in the example below, delaying the day of infusion from Wednesday to Thursday and the subsequent infusion to the following week. Instead of taking the infusion every three days, such a regimen would enable infusions less than twice weekly.

[4] FVIII concentration above 1% was an early a rule of thumb for prophylactic treatment [22]. Recent studies have advocated the use of pharmacokinetic measurement of factor levels to inform clinical decision making on adapt dosing and frequency of infusions [14].

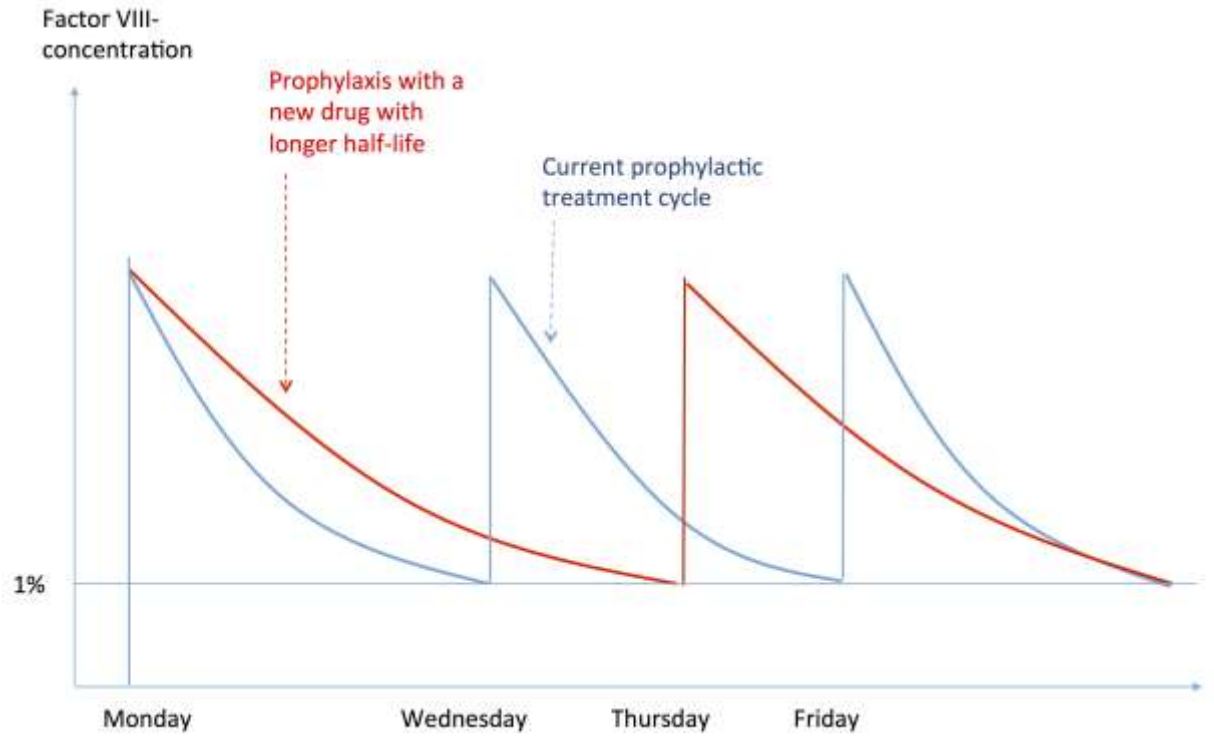

Figure 4. Improved patient treatment burden with a new, half-life Factor VIII product.

In a third possible alternative, the patients could combine these regimens, e.g., by choosing higher protection during some weeks (Figure 3) and less treatment burden during others (Figure 4).

Depending on the current treatment goals and treatment standards, as well as a particular purchasing type, a manufacturer may have greater or less incentive to develop and offer innovative treatment products. The incentives will be small or non-existent when the revenues either remain unchanged or decrease depending on payer/health provider/patient decisions on use of the new product. In such a case, any future innovation for haemophilia A treatments would be inhibited.

3. Objectives for new payment models

Giving patients access to innovative technologies that address unmet needs and provide value for money is a shared goal of payers, health care providers and manufacturers. For example, prompt access to proven, appropriate innovation for health care providers is important in their relationship with patients. Rapid access to innovation is important for manufacturers to recognize a return on their investment and to provide incentive to supply capital for further innovation. Payers seek to attract and retain beneficiaries to their health plans or to otherwise meet the needs and satisfy the covered populations in their jurisdiction. Confidence in the availability and timely and appropriate use of the best available medical technology benefits all stakeholders.

In order to ensure high quality treatment and avoid over- and under-treatment, payers and health care providers are now increasingly relying on information about real-world treatment outcomes. Further, this information is useful for all stakeholders to discern instances where health care services organization and delivery may be suboptimal for achieving the benefits to patients that could be realized from appropriate access to and use of these therapies.

Payers who are responsible for managing the costs of pharmaceuticals seek to reduce uncertainty in aggregate health care costs. Manufacturers seek to minimize uncertainty in the volume and stream of sales, so they can plan for the production and secure the delivery of their products.

Patterns of pricing schemes across countries can influence patient access, including in ways that have implications for health outcomes. Various forms of international reference pricing (IRP), international price comparison, external reference pricing and cross-reference pricing are applied in many countries, especially in Europe. These tend to result in limited price differences for the same products among countries [12]. Further, IRP provides incentives for stakeholders such as payers and manufacturers to take action to avoid similar prices across all jurisdictions because the willingness to pay for the treatment may vary by ability to pay and by incomes. IRP reduces the opportunities for differential pricing (Ramsey pricing), i.e., using the fact that the ability and willingness to pay differs between countries.

IRP that eliminates or minimizes differential pricing can pose challenges to access to innovative pharmaceuticals. Thus, payers, health care providers and manufacturers sometimes align around the same goal of limiting the unintended consequences of IRP. One approach is to use confidential agreements for discounts and rebates, i.e., different payment models. Most objectives are the same between payer/provider and manufacturer.

Individualized regimens based on the best available evidence and patient preferences are expected to provide the most cost-effective use of FVIII treatment products. Individualization of treatment is not only a question of selecting the optimal dose, dose frequency and treatment timing (e.g., when to initiate treatment and the duration of treatment), but also a choice of FVIII product because products have different pharmacokinetic (PK) properties, half-lives and provide variable protection from bleeds.

From a payer perspective, individualization and optimization of FVIII treatment is not a question of regulating physician behaviour. Payers normally have little information on an individual patient's response to treatment, their behaviours, or demands. Health care providers in direct contact with patients have a better understanding of those factors.

For payers, it would be more relevant to ensure high quality care for clinically appropriate therapeutic alternatives. Relationships between FVIII regimens and bleeds are well documented based on, for example, evidence from haemophilia quality registries from several countries, including France, The Netherlands and Sweden [13].

Quality of care reflects not only reducing the risk of (joint) bleeds, but also minimizing risk of blood-borne diseases and reducing a patient's treatment burden. Payers that want to enable individualized treatment and reduce the uncertainty of health care costs (e.g., FVIII treatment) can guide procurement by defining quality of care standards that should be achieved within a limited, predefined level of costs.

Quality of care can be assessed by a commonly used outcome measure, such as joint bleeds and the total number of bleeds (annual rate per patient). This measure would then focus on current expression of the disease. Quality of care could also be defined as consequences of joint bleeds measured by the degree of haemophilic arthropathy, or musculoskeletal health as assessed by radiological or clinical scores, as identified by MRI findings or radiological

Pettersson scores reflecting the degree of arthropathy. Such a measure captures the cumulative impact over time on joint health of smaller and larger bleeds.

Quality of care can also be defined by use of risk factors for a bleed, e.g., level of FVIII concentration (UI/dL). For example, it is possible to define a certain minimum level of FVIII concentration that patients should achieve, such as 1%, 5% or 15%. Tailoring of doses to avoid dropping below these minimum thresholds is achieved by today's treatment recommendations for patients with severe, moderate and mild haemophilia at the group level. Risk management could be further individualized by tailoring doses based on repeated PK measurement, as advocated by Collins et al [14].

Corresponding to each minimum level of FVIII are different levels of consumption per patient over time. The higher the plasma trough level, the greater the amount of FVIII required.

4. Review of new payment models in health care

In recent years, there has been an increasing interest in payment models for pharmaceuticals, driven partly by new innovations whose properties necessitate alternative arrangements (as discussed in this paper), as well as concerns from stakeholders of suboptimal payment schemes in the current landscape.

Such models may be more or less applicable to management of haemophilia depending on mode of action, goals of treatment and other factors. One common model is the pay-per-IU, which can be combined with discounts and rebates. Episode payment, also known as a bundled payment, is primarily used for health services, e.g., hip or knee replacement [15]. This type of payment includes a bundle of health care services, such as surgery and anticoagulation therapy. Moreover, it requires episodes that have an easily defined beginning and end, together with a well-defined clinical indication. If the cost of care during an episode is less than the pre-defined episode payment, then providers keep the difference, and vice versa. As for such orthopaedic procedures, there is a clear start and end within a limited time frame. In haemophilia care, this situation would be suitable for certain payment agreements and time periods for interventions such as surgery, where there is a defined beginning and end.

A recent idea is the so-called amortized payment of credit type. This has not yet been tried, but could be an option for high-cost cure treatments, e.g., gene therapy [16]. Manufacturers would provide a "credit," thus allowing the cost of treatment to be amortized over a period of time. This strategy would then offer an opportunity to enhance collaboration, with an aim of early access together with evidence development.

Managed-entry agreements, also called risk-sharing agreements, have been developed to handle uncertainty regarding the cost-effectiveness of health care technologies and aims to share the risk between payers and manufacturers [17]. Incentives might be structured to enable access to potentially beneficial medical products associated with unpredictable factors, such as the transferability between health outcomes observed in controlled clinical trials and outcomes in clinical practice. The solution can be coverage that is granted, provided that additional evidence is collected, which is then used to inform any further modification of coverage or payment level. This is an example of an agreement between payers and manufacturers where the price, level or nature of reimbursement is conditional on future measures of outcomes.

Managed-entry agreements can be divided into non-health outcome-based schemes and health outcome-based schemes (Figure 5), where the former are schemes that are cost-containing, but not contingent on a certain health outcome, while the reimbursement for the latter depends on health outcome.

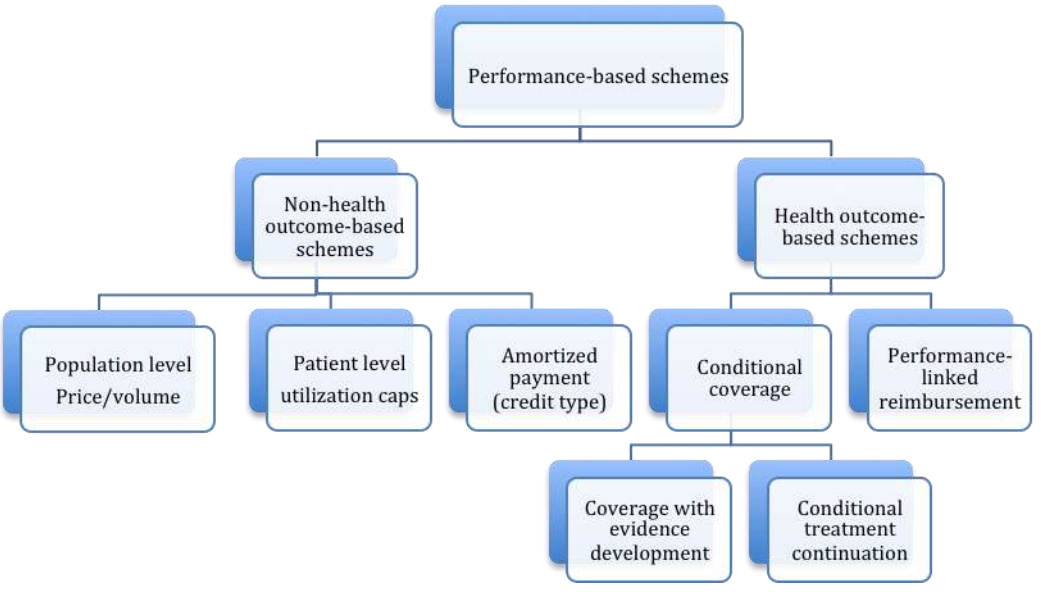

Figure 5. Overview of payment models for managed entry.

4.1. Health outcome-based schemes

Performance-linked reimbursement is a scheme with outcome guarantees in which the manufacturer provides rebates or price adjustments if the product does not meet the agreed-upon outcome target. By using rebates or refunds instead of price adjustment, the manufacturer can avoid alteration of list prices. This scheme can be recommended when the manufacturer is confident in the product, or when the outcome can be measured objectively, thus allowing no anticipation of loss.

Conditional coverage schemes are also dependent on outcome, either requiring more data to get reimbursement (coverage with evidence development [CED]) or providing the initial treatment for free, then getting reimbursed in the following period for those patients who meet the treatment goals, hence restricting treatment to patients who truly benefit (conditional treatment continuation [CTC]). CED provides an alternative approach for granting some degree of coverage for promising products for which evidence collected to date remains inconclusive. In these instances, outright rejection of reimbursement until sufficient evidence

is provided inhibits or delays opportunities for some patients to benefit, likely slows data collection on effectiveness and safety in different patient groups and delays returns to manufacturers [18].

4.2. Non-health outcome-based schemes

Among schemes that are not dependent on health outcome are price-volume agreements (PVAs) at the population level, where the unit cost is linked to the total volume purchased, often with different thresholds that further reduce price per unit [17]. At the patient level, utilization caps are an alternative, where manufacturers and payers agree on a certain level of consumption of the product per patient, and where any use above this level is provided free of charge by the manufacturer. This enables shifting the risk of over-utilization from the payer to the manufacturer, in which any additional, clinically appropriate consumption by the patient improves the cost-effectiveness of treatment.

5. Outline of alternative payment systems for haemophilia

We suggest three payment models with a focus on incentives to increase patient benefit in haemophilia care. One model anchors the payment strategy in the number of treated patients. The other two payment models relate payment to the outcome achieved for patients. For all three models, the purpose is to individualize and optimize treatment, i.e., avoid both over- and under-utilization and to avoid uncontrolled cost increase. The three suggested payment models focus on different aspects and have different pros and cons.

Each payment model will be illustrated in terms of patient (group) level data need and the basic principles for the payment schedule. This may entail an illustrative description of a patient population in terms of current treatment such as current annual average use of FVIII products for different age groups, or for the outcome-based payment models, more detailed information on the current regimens provided to patients.

5.1. Pay per patient

The first payment model is "**pay per patient**." Payment in this model is not related to the outcome of the treatment, but rather focuses on reducing uncertainty in treatment costs for FVIII consumption. The manufacturer offers a fixed payment per patient of FVIII consumption. The expected consumption of FVIII per patient may vary by degree of disease severity among the patient population. It will also vary by treatment strategy decided by the health care provider, in agreement with and as monitored by the payer in accordance to policy.

Variation of FVIII consumption also depends in part on the patient's choice of receiving the benefit of an EHL product by reduced burden via less frequent administration or in increased benefit in quality of care, i.e., reduced risk of bleeding. For example, in a country or other health care system in which a payer has a policy of providing a high level of FVIII consumption that reflects a high-dose prophylactic regimen, the payment-per-patient would be correspondingly high. In another country where a health care payer uses a less intensive prophylactic regimen or combines prophylactic with on-demand regimens, the price per patient will be lower for patients who are satisfied with the prescribed regimen.

Table 1 shows details for payment per patient for two products: a standard-acting FVIII product and an EHL product. In this example, the patient population is divided into three demographic groups – children, adolescents and adults. These groups differ in terms of expected factor concentrate requirements according to body weight and PK properties. Thus, a payment per patient schedule may require adaptation to each subgroup, taking into account the patient distribution between treatment centres and over time. Adaptation to specific clinical settings depends on payer preference for annual factor levels, thus may be adjusted according to the aims of prophylaxis between demographic groups. The example provided below assumes the same total annual FVIII measured in IU between adolescents and adults, allowing a slightly higher annual dose per kg bodyweight in adolescents on a group level.

Table 1. Payment model 1 – Payment per patient.

			Standard-Acting Product		EHL Product
Type of patient	Number of patients	Average IU per patient and year current treatment	Annual costs (€) for treating the patient population at €0.70 per IU	Payment per patient year for budget neutrality at €0.933 per IU	Payment per patient year with incremental value at €0.933 per IU
Children	10	100,000	700,000		
Adolescents	10	200,000	1,400,000		
Adults	10	200,000	1,400,000		
Total/ Average per year	30	5 million IU/ 166,667 IU	€3.5 million /€116,630 per patient	€3.5 million /€116,630 per patient	€4.67 million /€155,501 per patient
Average per patient		13,889 IU	€9,719	€9,719 (10,417 IU)	€12,958 (13,889 IU)

This method does not fix the frequency of dosing or the dose per infusion. Rather, the regimen is based on the level of costs for factor concentrate for each patient. If there is sound rationale for the appropriate payment per patient, then reaching a price-volume agreement is relatively straightforward, taking into account only the number of patients that will be treated in a given period.

The manufacturer promises to deliver up to a maximum amount of factor concentrate per patient. The advantages with this payment model are that the payer and manufacturer can plan for a certain expenditure and revenue, respectively, in advance. However, even though the manufacturer's income is fixed, the volume delivered is not. As such, some of the uncertainty that was formerly experienced by the payer will be transferred to the manufacturer. The resulting patient outcomes, especially the risk of bleeds, depends on the optimization of

treatment regimen per patient, but within the context of the vial distribution of vials, the dose per vial (in IU), and the frequency of infusions per patient.

It is the informed patient's choice to optimize the dosing in order to achieve the incremental benefit from the EHL product, either in terms of less burdensome treatment or higher level of quality, i.e., lower risk of bleeding. Under this payment model, it is unknown *a priori* the exact amount of FVIII consumption; however, the payment-per-patient treated will be known and fixed. Thus, the health care provider controls the costs for FVIII consumption. As the payment per patient is fixed, the provider has no incentive to under-treat to save on costs.

Assuming cost neutrality, the use of a standard-acting FVIII product implies an average of 13,889 IU per patient, and with the EHL product, an average of 10,417 IU per patient (***Table 1***). This example illustrates the situation in which FVIII consumption (IUs) with an EHL product is only 75% of that of a current FVIII product. These assumptions imply that patients who change from a standard-acting FVIII product to an EHL product benefit from less frequent infusions. However, if a patient chooses to minimize the risk for bleeding while maintaining the same frequency of infusions and the same dose, the average FVIII consumption with the EHL product will be similar to that of the standard-acting FVIII product, i.e., 13,889 IU. Because the cost to the payer will be fixed according to the agreement, the manufacturer will take the risk and have to deliver a similar amount of FVIII as before, and for the same cost, i.e., €9,719 per patient. As such, the manufacturer accepts the risk of paying for the increase in benefit for patients without additional compensation.

Assuming that the manufacturer is not willing to take this risk completely, the manufacturer and payer can modify this payment model by agreeing to deliver a maximum number of IUs per patient. Another option is to make an agreement of a higher fixed price per patient in order to compensate the manufacturer for taking all of the financial risk.

Yet another option is to make an *ex ante* agreement based on the best available information on physician and patient behaviour, fix the price per patient at an agreeable level, and start collecting data on actual volume consumption. When information on FVIII consumption becomes available, the average price per patient could be renegotiated upward or downward based on the data.

The number of IU per vial will depend on the current practice using standard-acting FVIII product for the demographic group and the improved PK properties for an EHL product. The volume cap in the price-volume agreement would be set at different levels for a standard-acting product and an EHL product. A higher volume cap for the former and a lower cap for the latter per patient will have a neutral impact on the budget and the manufacturer will deliver lower volumes of FVIII. Although the agreement could be understood as a premium per IU, it would not lead to a premium for innovation, as budget caps would be implemented with the aim of budget neutrality. Patients would benefit from fewer infusions and, if calibrated correctly, they would experience no increase in risk of bleeding.

Alternatively, the manufacturer may calibrate to vials of different sizes, which would reduce the dose per infusion of the EHL product, without changing the number of weekly infusions. For example, assuming vials contain 1,000 IU of product, if the same number of IU of the EHL product is infused as a standard-acting FVIII product, the longer half-life of the former will allow patients to experience a corresponding improvement in weekly FVIII concentration and lower risk of bleed than those receiving a current product. However, if the EHL product is only distributed in vials containing 750 IU, while the standard-acting product is distributed at 1,000 IU per vial, FVIII concentrations will not improve (assuming the same treatment interval). The payment per patient must fix different maximum volume agreements for products with different PK properties if the manufacturer expects to remain at the same level of revenue despite the improved properties of the EHL FVIII product.

5.2. Payment-per-actual outcome

The second payment model, "**payment-per-actual outcome**," aims to individualize and optimize treatment, i.e., avoid over- and under-utilization and to achieve budget neutrality.

In this payment model, the first step is to define the level of quality of care demanded in terms of maximum acceptable number of bleeds per patient per year. A reasonable point of departure is the current level of bleeds accepted by payers. Depending on the available reporting systems at the population level, a bleeding episode can be defined as bleeds in MRI findings, joint haemorrhages or total haemorrhages. It is important to note that this only requires group-level data for negotiations between payer and manufacturer. Providers or clinicians need not provide individual-level data, thereby maintaining patient privacy.

Measuring haemorrhages as joint bleeds or total number of bleeds will most likely rely on patient reports. In defining bleeds, two factors are important. First, there must exist some knowledge of the relationship between the frequency and dose of FVIII treatment and the anticipated annual number of bleeds per patient. Second, it must be possible to reach an agreement between payer, provider and patient in the definition of a bleed and how to measure the annual number of bleeds occurring in real-world treatment. Feasibility cost and potential for bias in patient reports are important considerations in such agreements, particularly when bleeding episodes are linked to health care system budgets. Payment for a maximum annual number of bleeding episodes could be defined to include payment for all health care treatment, including FVIII treatment throughout a bleeding episode, initiated at diagnosis and continued until the end of the bleeding episode.

As a special case, such a payment scheme could also be adapted for specific situations with typically short duration. Examples of such payments for a maximum level of bleeding episodes can also be defined as a combination of prophylactic treatment prior to a surgical procedure, a dentist or physiotherapist visit, or leisure activity associated with an elevated risk of bleed. In this case, the health care provider is responsible for all treatment until the end of the bleeding episode. Thus, there is an incentive for the health care provider to optimize prophylactic dosing to reduce total FVIII consumption costs. This is a type of bundled payment.

It should also be noted that the payer policy would address the maximum average number of bleeds per patient accepted. This decision is based on knowledge of FVIII consumption needed with currently available agents. Without this knowledge, it would be difficult to choose the affordable level of bleeds. For example, in countries that have adopted a treatment policy that results in a very low average number bleeds per patient per year likely reflects the choice of a high quality treatment that payers in that jurisdiction would like to continue. Another country could have selected a lower-quality treatment that is reflected in a higher annual number of bleeds per patient. Some data exist on the relationship between FVIII consumption and annual bleeds per patient.

Figure 6 is a schematic illustration of the principles of the expected relationship between the average number of bleeds per patient per year and annual FVIII consumption. It shows the commonly observed pattern that further reduction in the number of annual bleeds will require increasing amounts of factor concentrate, whose target levels may differ by country or jurisdiction.

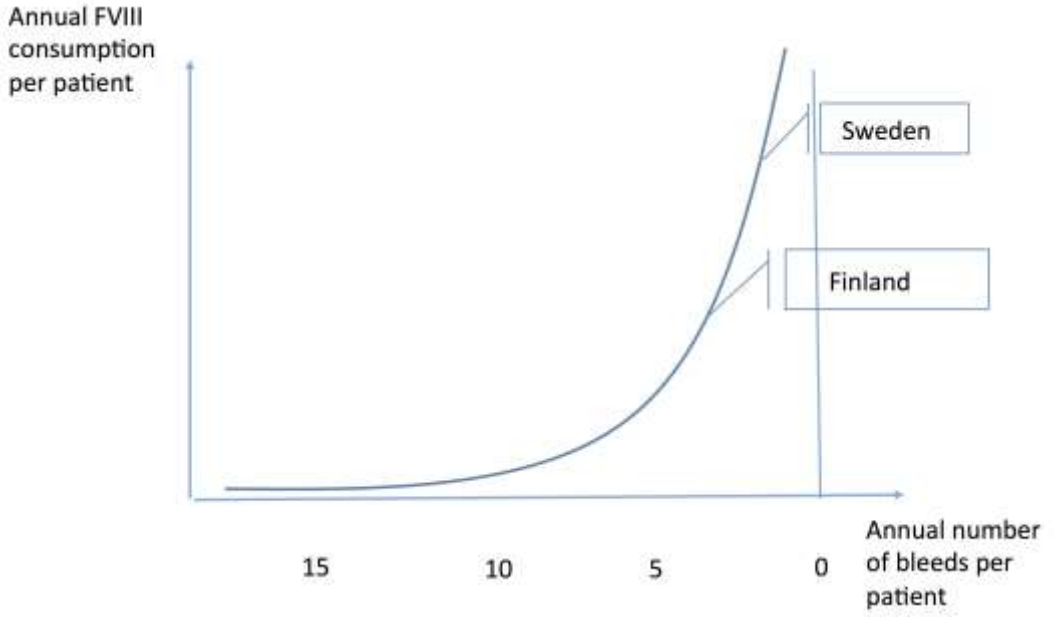

Figure 6. Annual number of bleeds per patient at different levels of FVIII consumption.

In Figure 7, a schematic relationship between annual number of bleeds per patient and consumption of a new FVIII agent with PK properties resulting in a longer half-life (red line) is presented together with that of currently available FVIII agents (blue line). It can be noted that with the EHL FVIII agent, the same quality of care, i.e., same annual number of bleeds (in this case, two bleeds per patient per year), can be maintained at a lower level of FVIII consumption than with the standard-acting FVIII product.

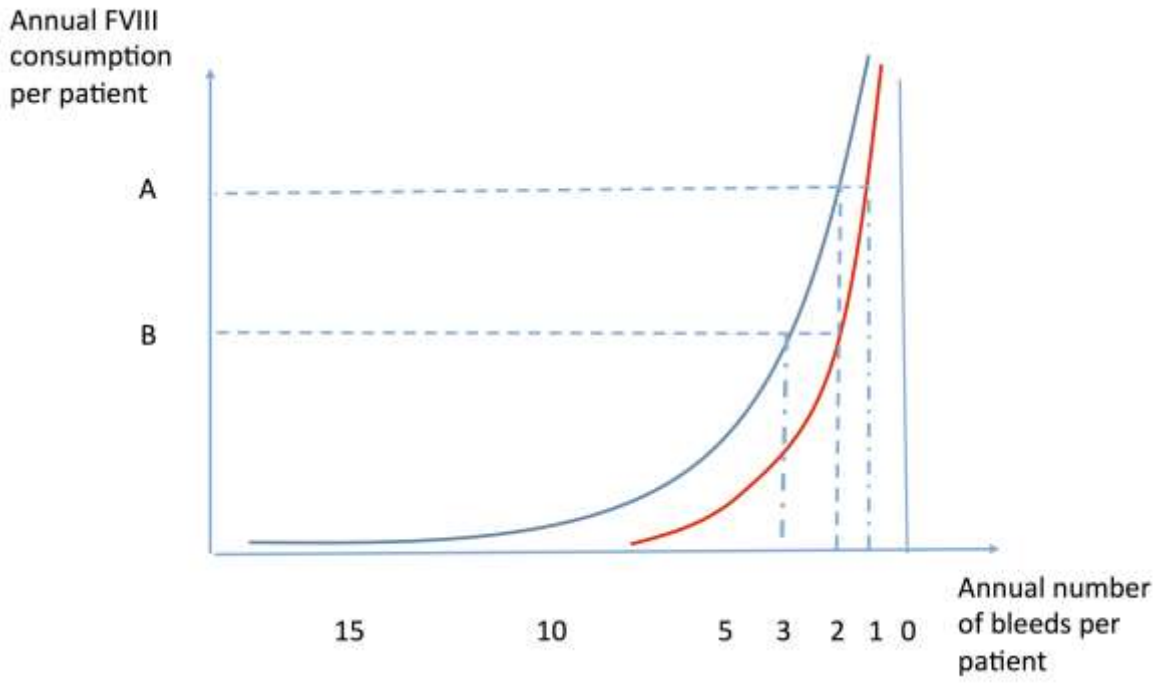

Figure 7. Schematic illustration of annual number of bleeds per patient with standard-acting FVIII agents (blue line) and with EHL FVIII agents with hypothetical PK resulting in longer half-lives (red line).

Figure 7 also illustrates that introduction of the EHL agent at the same level of consumption as the former standard-acting FVIII product could achieve an improvement in the quality of care, e.g., from three annual bleeds to two annual bleeds. Similarly, an improvement in quality of care is achievable for those currently practicing a treatment strategy corresponding to levels of FVIII consumption with the standard-acting FVIII product; with the EHL agent, they could improve their quality of care, e.g., from two annual bleeds to one annual bleed without increasing FVIII consumption.

Table 2. Payment model 2 – Pay-per-actual outcome.

Number of patients	Average IU per infusion	Number of infusions per week	Annual (52 weeks) costs (€) for treating the patient populations at €0.7 per IU	Treatment with standard-acting FVIII product	Treatment with extended half-life product
10	1,000	3	€1.092 million	Acceptable <2 bleeds per year	-
10	1,000	3	€1.092 million	Non-acceptable 2+ bleeds per year	-
Total all 20			€2.184 million (156,000 IU per patient)		
			With a price per IU of €0.884 per IU		
5	1,000	2	€0.460 million		Acceptable
5	750	3	€0.517 million		Acceptable
5	1,000	3	€0.690 million		Acceptable
5	750	3	€0.517 million		Acceptable
Total all 20			€2.184 million (123,500 IU per patient)		

Table 2 presents an illustrative example of a situation where the current treatment regimen of infusing 1,000 IU three times weekly leads acceptable bleed rates (< 2 per year) in 10 patients and non-acceptable quality of treatment (≥ 2 bleeds per year) in the other 10 patients.

With the suggested new payment model for an acceptable maximum number of bleeds per year, the manufacturer will deliver the EHL FVIII product in 1,000-IU or 750-IU infusions. The health care provider may use the product at 1,000 IU for two infusions per week for five of the patients who earlier received three infusions per week. These patients will have a less burdensome treatment, while maintaining the same FVIII concentration as with the standard-acting product. The other five patients can choose to maintain the same FVIII concentration, but using only 750-IU infusions.

For the 10 patients with non-acceptable bleed rates on the standard-acting product, it will not be possible to reduce the number of infusions. All 10 patients will continue to require 3 three infusions per week. Depending on patient heterogeneity in bleeding phenotype, however, there may be allowances for some patients to reach an acceptable level of prophylaxis by reducing IU per infusion from the 1,000-IU to 750-IU of the new EHL product.

Our hypothetical example also indicates that, using the same budget for different FVIII products, about €2.2-2.3 million, treatment goals for all 20 haemophilia patients can be reached. In addition, with the EHL product, 10 patients will receive better quality of care in

terms of reduced risk of bleeds. For some of the 10 patients who reached an acceptable level of care, the treatment will be less burdensome, e.g., with two instead of three infusions per week.

5.3. Pay-per-surrogate outcome

In the third suggested payment model, "**pay-per-surrogate outcome**," it is unnecessary to know the relationship between FVIII doses and outcomes in the annual number of bleeds. Instead, the payment is linked to a clinical measure of treatment efficacy, such as a biomarker that measures the level of FVIII concentration over time. Such PK testing is currently used in clinical practice to inform decisions on appropriate dosing and infusion frequency (see [4, 14, 19] for instance). For this payment model, it is only important to measure or estimate the patient's level of FVIII concentration over time. There are several methods for measuring PK properties in clinical practice.

With regard to applying the payment models, it is sufficient that the country or jurisdiction to decide its criteria for measurement and application of a particular method. The measurement of risk for a bleed is correlated with FVIII concentration levels of 0.1%, 0.5%, 1%, 1.5%, 2%, etc. Treatment strategies in Sweden, for example, aim to avoid FVIII levels below 1%.[5] This risk level results in a very low number of bleeds per patient. A treatment strategy that can secure a high level of FVIII concentration will result in a low risk for bleeds per patient. However, because of budgetary restrictions and affordability, these low-risk strategies are not frequently used in many countries, and many patients are unwilling to infuse more frequently.

In this payment model, the choice of trough level is important, as it correlates to the risk of bleeds, rather than the expected number of bleeds, *per se*. Monitoring individual FVIII concentration levels would be needed to manage an agreement for any given patient based on clinically/policy-defined risk of haemorrhages.

[5] In addition to pharmacokinetic measurement of FVIII concentration, the risk of haemorrhages also depends on the patient's bleeding phenotype. A patient with a severe phenotype may bleed in spite of keeping factor levels above 1%, whereas another patient with a mild phenotype may have few bleeds despite of factor levels sometimes falling below 1%.

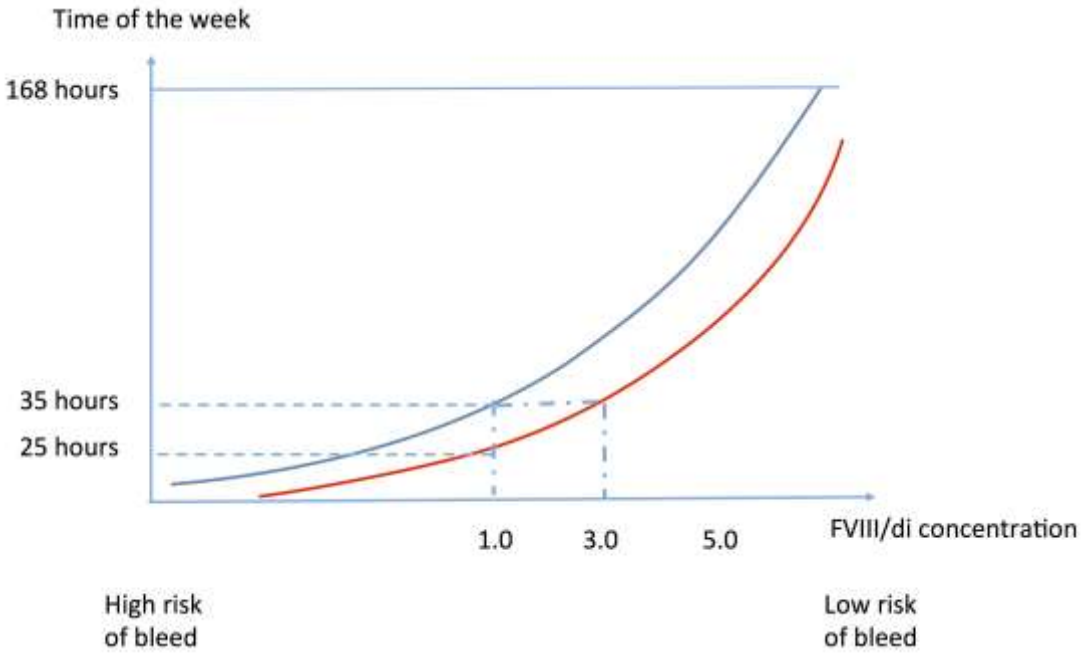

Figure 8. Duration of risk for bleed as a function of FVIII concentration with existing FVIII agents (blue line) and with new FVIII agents with longer half-lives (red line).

As shown in Figure 8, treatment with currently available FVIII agents in Sweden results in high FVIII concentration during most of the week (blue line). For only a few hours of the week do patients face the risk of declining below the < 1% FVIII threshold. A high FVIII concentration during most of the week means a low risk for bleeds, indicating a relatively high quality of care for haemophilia patients.

However, with a new agent with an EHL (red line), patients can reach and maintain a higher average FVIII concentration and a shorter relative amount of time when FVIII concentration drops below 1%, indicating increased quality of care.

The first step in this third suggested payment model is that the payer, in consultation with providers, has to set a policy for the acceptable level of risk for bleeds. For example, if the payer is not willing to accept that FVIII concentration will drop below 1% for some patients at certain hours during the week,[6] the payer will have to agree to payment for a high consumption of FVIII concentrate to maintain that level of security. If another payer has a policy that accepts that FVIII declines on average to < 1% for a large part of the week, that

[6] Or number of hours during some days – compare Figures 2 and 3.

payer will not need to pay as much for FVIII consumption to maintain this lower average level of protection against bleeds.

In the second step of this payment model, the health care provider will have the freedom to choose the FVIII agent that best satisfies this risk level. This decision has to be based on knowledge of FVIII consumption required with currently available agents to achieve that risk level.

The payment model shown in Table 3 assumes a population of 20 patients, in which half reach current treatment goals and half do not. Treatment decisions based on payment model 3 indicate that with a current treatment regimen, 10 patients reach acceptable bleed risk levels (< 35 hours per week at risk) when infusing 1,000 IU three times weekly with the standard-acting FVIII product. Using the same treatment regimen, the other 10 patients do not reach acceptable quality of treatment with that product.

Table 3. Payment model 3 – Pay-per-surrogate outcome.

Number of patients	Average IU per vial infusion	Number of infusions per week	Annual (52 weeks) costs (€) for treating the patient populations at €0.7 per IU	Treatment results with standard-acting FVIII product	Treatment results with EHL product
10	1,000	3	€1.092 million	Acceptable <35 hours/week below 1 % FVIII/dl	-
10	1,000	3	€1.092 million	Non-acceptable 35+hours per week below 1% FVIII/dl	-
Total all 20			€2.184 million (156,000 IU per patient)		
			With a price per IU of €0.884 per IU		
5	1,000	2	€0.0.460 million		Acceptable
5	750	3	€0.517 million		Acceptable
5	1,000	3	€0.690 million		Acceptable
5	750	3	€0.517 million		Acceptable
Total all 20			€2.184 million (123,500 IU per patient)		

With the suggested new payment model 3, in which the payer has to pay for an acceptable risk for bleeds, the manufacturer will deliver the EHL product in 1,000-IU and 750-IU infusions. The health care provider may use the product at 1,000 IU for two infusions per week for five of the patients who earlier received three infusions per week. These patients will have a less burdensome treatment regimen, while maintaining the same FVIII concentration as with the

standard-acting FVIII product. The other five patients can choose to maintain the same FVIII concentration, but using only 750-IU infusions.

For the 10 patients with a non-acceptable risk level on the standard-acting FVIII product, it will not be possible to reduce the number of infusions with the new EHL product. All 10 patients need to continue three infusions per week. However, some may be allowed to reduce the number of IU per infusion from 1,000 IU to 750 IU and still be able to reach the acceptable quality of prophylaxis.

The illustrative calculations for payment model 2 and payment model 3 are similar in all aspects, differing only according to the definition of outcome that anchors each payment model. They both indicate that payment for the risk of an acceptable maximum level of bleeds per patient can result in delivery of a different amount of IU per infusion with an EHL product and that the price per IU could increase from €0.7 to €0.884 for this product.

Our hypothetical examples also indicate that the treatment of the 20 haemophilia patients with the EHL product can be achieved at the same total cost of about €2.2-2.3 million as for the standard-acting FVIII product, except that half of the patients will receive better quality of care. For the other half of patients who reached an acceptable level of care, the treatment will be less burdensome with two instead of three infusions per week.

6. Discussion

The payer and health care providers' choice of payment model will influence timing of patient access to new therapies and the impact of such therapies on patient outcomes. The choice of a particular payment model will reflect the goals of payers, providers and other stakeholders, including some combination of enabling prompt access to new technologies that offer or promise improvements in patient outcomes, managing costs, willingness to proceed with uncertainty of evidence, and other factors.

One type of payment model for treatments that can cure a chronic disease is based on a credit. A payment model in which the manufacturer provides a technology for amortized payments over time, may enable rapid uptake by lowering the barrier to affordability. A credit repayment solution has been discussed in the U.S. for highly expensive drugs that cure hepatitis C infections.

Another reason for the growing interest in payment models is the increasing awareness of the disadvantages of the IRP. Persson and Jönsson (2015) have shown that payers who are subject to IRP and have the ambition to provide patients with care and early access to new therapies have an incentive to implement confidential rebate agreements, which reduce transparency [12].

A third reason is international awareness of a slow uptake of some new medical technologies and the pressure from patient advocacy groups and politicians to speed the regulatory process and the health technology appraisal (HTA) process, including decisions on coverage and prices. Such decisions are not enough to guarantee an uptake in clinical practice because of budgetary and affordability restrictions. New payment models offer means to overcome those issues. Sometimes the regulatory and HTA authorities decide that the new technology receives a conditional approval. Such an approval could be linked to a request for additional clinical evidence or proof of effectiveness in clinical practice in different settings and under different organizations of health care services.

Thus, there is a growing need for various payment models that can be used for different types of diseases at different stages of a product's life cycle across different countries and regions.

We have reviewed here existing payment models and suggested new payment systems that may be suitable for haemophilia treatment. Table 4 summarizes the three payment models presented in this paper (models 1-3) and contrasts them with two financial risk-sharing models (models 0.1 and 0.2). The financial risk-sharing models have a strict focus on the costs of treatment and budget control, but do not explicitly include incentives for increasing patient benefits. The three models developed in this report, i.e., the pay-per-patient model and two pay-per-outcome models, in which payment is linked to the number of bleeds and FVIII trough levels, respectively, allow for incentives that could improve patient benefits.

Table 4. Summary of three new payment models for haemophilia contrasted with two financial risk-sharing models where patient benefit is not explicitly included.

Model	Payment terms	Example	Benefit to patients	Benefits to payers	Need for data collection
0.1. Financial Risk Sharing	Budget cap. IU price fixed to an agreed upon volume	€1 per IU for the first 100 vials, €0.50 for the second 100 vials, etc.	None	Tight budget control	Utilization data only
0.2. Financial Risk Sharing	Patient specific discount/cap: IU price is capped per patient per period of time	€1 per IU for the first IUs per kg weekly. Lower € per IU for subsequent use.	None	Controls for catastrophic cases (for ”outliers”)	None
1. Pay Per Patient	Payment fixed to a negotiated amount per patient such as the average cost of prophylaxis to achieve ABR = 1	€15,000 for X IU per patient	Removes incentives for on demand, and inadequate doses/frequency	Moderate budget control	Real-world data on FVIII consumption required
2. Pay-Per-Actual Outcome	IU price adjusted for a rate of negative outcomes, e.g., bleeding rate, inhibitors	€1 per IU/kg/week for patients with less than 2 bleeds per year without inhibitors. €0.5 per IU/kg/week for those with negative outcome.	Incentives for good patient care	Payment tied to value	Real-world data collection on outcomes required
3. Pay-Per-Surrogate Outcome	IU price adjusted for a rate of FVIII concentration achieved as a proxy for bleeding rate	€1 per IU/kg/week for patients with FVIII above 1%, 3%, etc. €0.5 for patients with lower FVIII concentration.	Incentives for good patient care	Payment tied to value	Real-world data collection on outcomes required

The two financial risk-sharing models (models 0.1 and 0.2) use a total budget cap or a patient-specific discount/cap, respectively, to control costs. The agreement relates payments to the number of vials sold. Through agreements between manufacturers and payers on volumes per time period and price per IU, payers may exert tight budget control. Another advantage of

financial risk-sharing models is that they do not require additional data other than standard sales information automatically available for both manufacturer and payer. The limitation is that these payment models do not provide incentives for improving patient benefit, *per se*.

The new payment models (models 1-3) for haemophilia treatment discussed in this paper explore potentials for including incentives for improving patient benefit when EHL factor concentrates are introduced, while maintaining cost neutrality.

The pay-per-patient model is not linked to patient outcomes. The purpose of this model is to reduce uncertainty in population costs. With a fixed payment per patient, payers will have moderate budget control. It also provides an opening for discussion of patient choice as EHL products will make it possible for a patient to achieve either improved outcomes, reduce treatment burden, or, to some degree, both. Today, it is unclear what patients will choose in the real-world setting. Certainly, it is an empirical question to determine the exact outcome of the introduction of EHL products. Therefore, there is a need to collect data on real-world consumption of standard-acting FVIII products when EHL products are introduced. The result of this data collection will show the extent to which the manufacturer has received a price premium per IU with the new EHL product. Or, if patients remain at similar dosing and frequency of infusions, there will not be any price premium for the new products. In that case, patients will have realized all benefits as consumer surplus. In that instance, the payer will retain the same payment-per-patient and will not need to take any financial risks; all financial risk is transferred to the manufacturer.

Models 2 and 3 are health outcome-based schemes. For these payment models, payment is tied to value of treatment, and these payment models also require real-world data collection. Annual outcomes should be measured, and agreements on definition of bleeding episode or risk level have to be reached. A disadvantage of these payment models is that their transaction costs may be high if such data are not readily available or reliable. The availability and quality of such data will vary by country, health system and jurisdiction.

Pay-per-responder models also include some favourable aspects, i.e., that they are linked to performance and provide incentives for health care providers to individualize and optimize dose and frequency of infusions, which should improve patient outcomes and acceptability.

An EHL FVIII product offers value for patients and society in several ways. First, there is value to patients due to the less burdensome treatment and acceptability of fewer infusions per week, while maintaining the same quality of care. Second, there is value to society because it provides a new treatment option that enables additional health benefits by optimizing treatment (individualized treatment) using smaller doses of FVIII per patient. As long as it is packaged and delivered appropriately, any remaining FVIII can be allocated to other haemophilia patients who are not treated sufficiently, while maintaining the same total FVIII costs.

Finally, the three new payment models for haemophilia may, through various mechanisms, increase incentives for patient benefit. It may also be possible to combine features of the proposed models; for instance, a model based on payment-per-patient could be combined with the condition of achieving a certain quality of the treatment, e.g., low risk for bleeding. The quality of the treatment may be defined as a minimum threshold FVIII level that should be attained, which may range from 1% to reduce the risk of spontaneous bleeding for some patients to higher than 15% if the aim is to minimise the risk of bleeding for all patients [20]. If the manufacturer and the payer agree on a fixed cost for FVIII, there is potential to provide patients with health benefit as well as a less burdensome treatment regimen.

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