The first Team Haemophilia Education meeting, 2015, Amsterdam, The Netherlands

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Abstract

Haemophilia remains a complex disorder to diagnose and manage, requiring close cooperation between multidisciplinary healthcare professionals. There are still many unmet challenges in haemophilia care. The first Team Haemophilia Education (THE) meeting, held on 7–8 May 2015 in Amsterdam, The Netherlands, aimed to promote the optimal care of haemophilia patients through education of the multidisciplinary treatment team. This was achieved by reviewing the latest developments in haemophilia management, considering how these can be implemented in the clinic to improve patient care and providing a platform for networking and debate for all haemophilia treatment team members. Haemophilia treatment centres from several countries were asked to complete a premeeting online questionnaire to establish the biggest challenges that they face when managing patients. The concerns expressed were used to develop the agenda, which comprised a combination of formal presentations, case studies and informal workshops covering such topics as pharmacokinetics, laboratory assays and tailoring of treatment to individual patients. This report is a summary of the key developments in haemophilia care presented by various investigators and healthcare professionals at THE meeting 2015.

Key words haemophilia; pharmacokinetics; pharmacoeconomics; laboratory assays; clotting factor concentrates; multidisciplinary

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Introduction

David Perry (Cambridge, UK)

The first Team Haemophilia Education (THE) Meeting was held on 7–8 May 2015, in Amsterdam, The Netherlands. The aim of the THE Meeting was to promote optimal and seamless care of haemophilia patients through education of the multidisciplinary treatment teams. This was achieved by reviewing the latest scientific developments in haemophilia management, then considering how these novel updates can be implemented in the clinic to improve the care of patients, providing an inclusive platform for networking and debate.
An insight into the management of haemophilia across Europe

Daniel Hart (London, UK), Elizabete Cehura (Riga, Latvia), Nanda Uitslager (Utrecht, The Netherlands), Mehdi Osouli (Malmö, Sweden), Daniela Janeckova (Prague, Czech Republic), Rosie Haldon (London, UK), Brian O’Mahony (Irish Haemophilia Society, Ireland), Radoslaw Kaczmarek (Polish Haemophilia Society, Poland), Miguel Crato (Portuguese Haemophilia Society, Portugal)

The aim of this first session was to find out how haemophilia is treated across Europe and to understand the challenges faced by haemophilia treaters. A total of 15 centres responded to the premeeting online survey about unmet needs in haemophilia care, representing 11 countries. Delegates and patient representatives were invited to give presentations on this topic, a summary of which is provided below and in Table 1.

Latvia

In Latvia, decision-making regarding haemophilia care is organised by the government, state reimbursement agencies and clinicians. The main challenges are a lack of staff specialised in coagulation pathology, diagnostic and monitoring challenges and issues with poor treatment compliance.

The Netherlands

There are seven haemophilia treatment centres (HTCs) in The Netherlands which are coordinated by the Dutch Association of Haemophilia Treaters (NVHB). Patients can choose which centre to attend. Decision-making regarding haemophilia care is agreed upon between the government, clinicians and patient organisations. Key challenges for the future include reimbursement of clotting factors; keeping HTCs independent from the larger academic/political scene; patient compliance with treatment and visit frequency; teaching elderly patients the difference between bleed pain and arthropathy pain; and teaching young children what a bleed feels like.

Sweden

In Sweden, haemophilia care is coordinated by three comprehensive HTCs in collaboration with the Swedish Haemophilia Society (FBIS). All patients with bleeding disorders in Sweden are cared for by one of the three centres. The government, clinicians and patient organisations are responsible for decision-making regarding haemophilia care. The main management challenges are inhibitor eradication, cost of care and monitoring patients’ adherence to therapy.

Czech Republic

In the Czech Republic, haemophilia care is coordinated by the Czech National Haemophilia Program. The government, reimbursement agencies, clinicians and patient organisations are all involved in decision-making about haemophilia care. Lack of financial resources is the main problem, so not all patients have access to recombinant products.

UK

Haemophilia care in the UK is coordinated by the United Kingdom Haemophilia Centre Doctors’ Organisation (UKHCDO), the Haemophilia Alliance, the Clinical Reference Group (CRG) and also the government. Clinicians and patient organisations are involved in haemophilia care decision-making. The main challenges are patient education, to ensure collection of accurate data on a regular basis; managing expectations of patients/carers in relation to musculoskeletal outcomes; and the increasing needs of an ageing population with multiple comorbidities. Another consideration is whether high-dose prophylaxis for all patients is financially sustainable.

Ireland

In Ireland, it is easy to coordinate haemophilia care, as the country is small and has three, very well-organised comprehensive care centres. There is a good home treatment service and prophylaxis is available for children and adults. The HTCs, the Irish Haemophilia Society and the health ministry work together on a Statutory National Haemophilia Council which coordinates policy and sets priorities.

Poland

Geographically, haemophilia care is a bigger challenge in Poland. There are 17 HTCs, but they differ in expertise
<table>
<thead>
<tr>
<th>Country</th>
<th>No. of HTCs</th>
<th>Access to prophylaxis?</th>
<th>Are patients’ organisations involved?</th>
<th>Which additional services do the centres provide?</th>
<th>Which additional services are not provided by the centres?</th>
<th>Main problem(s)</th>
</tr>
</thead>
</table>
| Latvia           | 3          | Children < 18 yr: 26–50%; adults ≥ 18 yr: 0–25% | No                                     | Sometimes paediatric, physiotherapy, genetic, emergency care/acute surgery, general surgery and orthopaedic services | Rheumatology, dentistry, hepatology, obstetrics/gynaecology, urology, pain management, infectious disease or social/psychological support | • Lack of specialised staff  
• Diagnostic and monitoring challenges  
• Poor compliance to treatment |
| The Netherlands  | 15         | Children < 18 yr: 26–50%; adults ≥ 18 yr: 0–25% | Yes                                    | Paediatrics, physiotherapy, rheumatology, orthopaedics, dentistry, hepatology, infectious diseases, genetics, obstetrics & gynaecology, urology, emergency care and acute surgery, general surgery, pain management, social and psychological support | Rheumatology – | • Reimbursement of clotting factors in the future  
• Keeping independence of the clinic for rare diseases within a large academic political scene  
• Maintaining scientific output with decreasing money  
• Patient compliance to treatment and to visit frequency  
• Teaching elderly patients the difference between pain caused by a bleed and arthrosis  
• Teaching young children what a bleed feels like |
| Sweden           | 3          | Children < 18 yr: 26–50%; adults ≥ 18 yr: 51–75% | Yes                                     | Orthopaedics, dentistry, infectious diseases, genetics, pain management and social/psychological care are sometimes available | Rheumatology – | Inhibitor eradication, cost of care and monitoring patients’ adherence to therapy |
| Czech Republic   | 18         | Children < 18 yr: 51–75%; adults ≥ 18 yr: 0–25% | No                                     | Genetics, obstetrics & gynaecology, urology, emergency care and acute surgery, general surgery, pain management, social and psychological support | – | Financial resources |
| UK               | 87         | Children < 18 yr: 76–100%; adults ≥ 18 yr: 51–75% | Yes                                     | Paediatrics, physiotherapy, rheumatology, orthopaedics, dentistry, hepatology, infectious disease specialists, genetics, obstetrics & gynaecology, urology, emergency care and acute surgery, general surgery, pain management, social and psychological support | – | • Patient education to ensure collection of regularly reported and accurate outcome data  
• Managing expectations of patients/carers in relation to musculoskeletal outcomes  
• Managing the increasing needs of an ageing population with multiple disabilities and comorbidities  
• Is high-dose prophylaxis for all patients financially sustainable, even in developed countries? |
(none of them is certified by EUHANET), meaning that patients requiring special services often need to visit a comprehensive care centre in the capital. Although prophylaxis is free for all patients, good prophylactic care (including close monitoring and home delivery of CFCs) is provided almost exclusively to children. When a patient reaches 18 yr of age, a decision is made between patient and doctor about whether prophylaxis should be continued.

Portugal

There are five major haemophilia centres in Portugal: two of these are certified by EUHANET as European Haemophilia Comprehensive Care Centres (EHCCCs) and two as European Haemophilia Treatment Centres (EHTCs). The economic situation in Portugal is very stressful and doctors often have to act as budget managers.

Summary of the session

Half of the treatment centres that responded to the survey were certified by EUHANET. The average number of patients in each centre was 504 (range 30–1900), with approximately half of patients having severe haemophilia. Comorbidities were commonly reported. Centres that were part of large teaching hospitals usually had good access to all services. The main treatment challenges identified were patient education, how to individualise prophylaxis to different patients, cost of care (therapy reimbursement issues), problems associated with an ageing patient population, lack of specialised staff, monitoring treatment outcomes and managing inhibitors. Fewer than a quarter of the delegates present at the meeting knew whether their centre was accredited. Some thought that there are too many HTCs, making it difficult to have specialists in all of them, and leading to a situation where haemophilia treaters are not able to acquire enough expertise as there are too few patients in their care. A futuristic scenario would be to have fewer centres but with improved care, involving a multidisciplinary care team.

Pharmacokinetics in clinical practice

John Pasi (London, UK), Erik Berntorp (Malmö, Sweden) and Daniel Hart (London, UK)

Pharmacokinetics (PK) describes how a drug is handled in the body and its fate. In the case of haemophilia, PK data are used to describe the behaviour of factor VIII and IX that is infused as replacement therapy. PK describes a number of mathematical parameters, such as how long the product lasts in the circulation (half-life), how quickly it is removed (clearance) and the volume the drug is distributed (volume at steady state) aside from many more. Every individual will handle infused factor VIII and IX differently – PK allows one to quantitate and evaluate these differences and describe for that individual how factor VIII or IX is handled. Given that this is not a new ‘science’ why is there so much interest in it now?

Let us consider prophylaxis. The primary target for prophylactic treatment in patients with haemophilia is to prevent or delay arthropathy development by maintaining a detectable trough level of FVIII:C of, traditionally, at least 1 IU/dL, essentially converting severe to moderate disease. Moreover, prophylaxis is also aimed at reducing the bleeding frequency and improving quality of life (QoL). Based on the broad assumption that in the vast majority of individuals factor VIII concentrates all behaved in the same way, with a half-life of approximately 12 h, standard regimens have evolved for haemophilia A prophylaxis of 25–40 IU/kg FVIII which is given on alternate days or at least three times per week.

However, it is now more widely appreciated that there is considerable interindividual variation in factor concentrate half-life. Allied to the fact that individuals have different levels of activity, it is now increasingly being appreciated that a standard ‘one size fits all’ approach to prophylaxis is not going to provide optimal care for all. Let us consider two extremes – a very sporty adolescent who finds it easy to regularly infuse and an older patient who finds venepuncture very difficult and leads a far more sedentary lifestyle. The needs and demands for optimal prophylaxis regimens for each will be considerably different – peak levels potentially being of much greater importance in the sporty individual while trough level protection and interval between infusions being the more important aspect in the older sedentary individual with poor venous access. If we then consider that the half-life of factor VIII may be different in these individuals, we can start to see how one blanket approach to prophylaxis is not going to be providing optimal care.

Figure 1 schematically demonstrates the impact of a 25% variation in half-life around the mean. Such a variation would be a 9-h half-life (−25%) or a 15-h half-life (+25%) based on a mean of, say, 12 h. It can be seen that such a variation will significantly affect when an individual hits 1 U/dL and requires further infusion. For an individual who has problems with venepuncture, knowing when one has to infuse to maintain a trough of >1 U/dL is clearly of major importance.

Understanding the variation that exists in our patient populations and that optimal prophylaxis requires individualisation of prophylaxis regimens, one can start to identify both patient-specific and product-specific factors that will influence the choice of the optimal regimens for any individual. Patient-specific variables would include age, personal choices, activity levels, comorbidities, venous access, individual PK and how much bleeding is acceptable to that individual. Product-related variables would include the half-life (1), PK, how the product is manufactured (recombinant or plasma derived) and costs. Taking all these factors into consideration, the ideal regimen for an individual patient will be a combination of dosing interval and dose, tailored to the
individuals’ PK, that keeps the annual bleed rate (ABR) as low as possible which fits in with the individual’s activity levels and personal choices (Fig. 1).

Aside from addressing optimising regimens to maintain levels >1 U/dL, increasingly it is questioned as to whether this is the optimal approached for haemophilia prophylaxis management. A study by den Uijl et al. (2), investigating the annual number of joint bleeds in haemophilia patients and FVIII activity, demonstrated a significant change in the bleeding phenotype at ~3 U/dL. It is also well accepted that the more time an individual spends below the minimum FVIII trough level of 1 U/dL, the greater the risk of a breakthrough bleed, a risk that increases with time (3). It has been shown that patients can have subclinical bleeds which cause deterioration of joints without evidence of haemarthroses, but prophylaxis is not able to prevent these in all individuals (4).

Currently, dosing is based on the observed bleeding pattern and clinical response to treatment and adjusted according to the patient’s daily activities and after spontaneous bleeds. However, this is, at the end of the day, empirical. Having specific PK data from individuals will allow us to be reassured that we can keep factor levels above 1 U/dL at all times. Moreover, it will also allow us, should we wish, to specifically work out and develop regimens that will keep levels at a higher level, say 3 U/dL for those individuals who we may have additional concerns about joint disease progression and recurrent microbleeding.

The trend therefore is now to move away from fixed outcome-based thinking to individualised dosing in order to optimise therapy and reduce costs (5). Individual PK data facilitate this new approach and provide a rational basis for individual dose regimens.

The difficulty and problems with calculation of PK data for individuals have historically detracted from more widespread use. Following an infusion of factor VIII, a patient’s individual PK can be calculated by taking 8–10 separate measurements of FVIII levels over a 48-h period. Undoubtedly, this provides the best-fit model (1 compartment or 2-compartment) but clearly is cumbersome, time-consuming and inconvenient to perform, particularly for the patient. An alternative approach, increasingly popular, is the use of population PK modelling. Population PK uses a large pool of population data to develop a single model to describe the behaviour of drug in that population. It is inevitably an approximation but with large data sets used to develop it, it can describe drug behaviour well. Similar models have been described for FVIII concentrates given to patients with haemophilia. The advantage of the population PK model is that if the time of infusion is known, the FVIII level can be fitted to the model and, based on the variation away for the model, can be used to derive PK parameters such as half-life. Robust data for half-life can therefore be obtained from only 2–3 samples taken after infusion. It is, however, an approximation, estimation for an individual based on the population average, and one must always bear in mind the confidence intervals for that prediction. Whether one model would suffice for all concentrates or each individual concentrate requires an individual model is not clear yet and currently the subject of considerable investigation. Nonetheless, the simplicity of the approach is very attractive.

With all PK-based approaches, the most valuable benefit is to be able to identify ‘outlying’ patients, that is those with a very long or very short half-life, which is significantly different to the average. As discussed above, in such patients the variation in half-life will have a significant impact on dosing requirements. Today, this is becoming more relevant with the advent of extended half-life products EHLs (6) as potentially the range of half-life distribution across a population could be significantly larger. Understanding PK will also allow a much broader approach to the optimal use of EHLs, rather than simply extending treatment interval. Knowledge of PK for an individual will allow one to discuss with the patient the optimal approach for that individual to maximise the theoretical benefits of a longer half-life. Options, aside from simply increasing the interval to maintain the same trough level, that could be outlined include continuing at the same dose and frequency but achieving a higher trough and reduce the dose and frequency of injections while still maintaining an adequate trough level or even hybrid regimen such as more frequent dosing at lower dosage with a higher trough. Knowing an individuals’ PK allows these options to be discussed and for the patient to choose with the treater the best regimen that is tailored truly to their needs.

However, translating the PK into clinical practice is not simple, not least collecting the individual PK data in significant numbers of patients. The idea of individual PK (cf population PK) for many treaters and patients alike could be a major impediment. Introducing a new concept to people who have lived with haemophilia for decades is similarly not easy.
Looking forward, four broad groups of patients can be considered:

- Bleeding with low levels of FVIII:C.
- Bleeding with high levels of FVIII:C.
- Minimal bleeding with low levels of FVIII:C.
- Minimal bleeding with high levels of FVIII:C.

Currently, PK studies are often carried out for patients in the first group. There may be pressure to drive down dosing as a result of payers understanding the potential application of PK studies. For those in group 4, it will be particularly challenging to modify treatment in patients who trough at high levels and who have had the benefit of excellent prophylaxis over the years. However, clear data demonstrating to patients that even at a lower dose they would be adequately protected may help reduce treatment usage. Overall though, the benefits of PK-based dosing remain positive – by individualising dosing, the case can be made for an individual patient based on their circumstances.

For the future, understanding PK profiles will allow the opportunity for highly individualised and optimised regimens, with improved QoL and outcomes. Tailoring prophylaxis allows the opportunity for the clinician to engage actively with the patient. Understanding how the available products behave in the individual patient will enable therapy to be tailored rationally for the first time. This future scenario can in a simple way be summarised as: if you do not know, you will neither see.

Pharmacoeconomics and the cost of haemophilia care

Alec Miners (London, UK) and Katarina Steen Carlsson (Land, Sweden)

Efficacy and safety of treatment remains a big issue today especially when considering new treatments. In addition, effectiveness and cost-effectiveness of when treatments are used in daily life and over long time are increasingly important from decision-makers in the health sector.

Decision-makers in health care, and elsewhere, are constantly facing the fundamental problem of balancing between limited resources and unlimited patient needs. Health economic tools are used increasingly used, inter alia as part of health technology assessments. The aim of the economic analysis is to help the decision-maker in health care by systematically comparing two or more alternative healthcare programmes in terms of costs and consequences, especially in terms of benefits to the patient.

There are four methods used for economic evaluations:

- Cost-effectiveness analysis (CEA) – measures effects in physical quantities such as life years gained and joint bleeds avoided.
- Cost-utility analysis (CUA) – measures effects by quality-adjusted life years (QALYs).
- Cost-benefit analysis (CBA) – measures patient benefits in monetary terms.
- Cost-minimisation analysis (CMA) – health benefits are identical. This might be used, for example, to compare two different generic products but is usually difficult to use.

The choice of method for the evaluation in a specific situation will depend on, for instance, the perspective of the analysis, for example the hospital, the healthcare sector or a broader societal perspective, the data available for analysis, but also on the question to be addressed and the specific characteristics of the health condition and its treatments. For a lifelong disease such as haemophilia where treatment today can be expected to have both short- and longer-term consequences, it is generally preferable adopt a long-term perspective for the analysis as well in order to reflect all consequences.

The results from CEA and CUA are expressed in terms of cost per unit gained. For example, in haemophilia care, the number of bleeds avoided could be considered as a relevant outcome measure when comparing alternative strategies for replacement treatment with factor concentrates. Analyses reported by Fischer et al. (7) estimated that people with severe haemophilia on on-demand treatment had a median of 11.5 bleeds/yr, whereas prophylaxis was associated with 2.8 bleeds/yr. Using these data, the question for a CEA could then be how much extra would the payer be prepared to pay for avoiding eight bleeds a year? However, this may be considered a too narrow perspective on outcome of treatment as it does not directly reflect other patient values including consequences for quality life, for example from the risk of developing joint arthropathy. A CUA may then be considered more appropriate.

Since both CEA and CUA compare differences in costs between treatment alternatives to difference in patient outcome, the results are expressed as the incremental cost-effectiveness ratio (ICER). The ICER is thus a measure of the additional costs of treatment A over treatment B, compared to the additional health gains expected from treatment A versus treatment B. The results of a CEA might then show, for example, that treatment A costs €10,000 per life year gained compared to treatment B and the result of a CUA treatment A costs €12,000 per QALY (quality-adjusted life year) gained compared to treatment B.

In some cases, patient benefits may not be adequately reflected with measures such as life years gained, bleeds avoided or even quality-adjusted life years gained. CBA is an alternative where patient or population values can be appropriately expressed in monetary terms. In CBA, the willingness to pay for treatment A will be compared to its cost. Finally, in the special case where two treatments have
been evaluated as equally effective, for instance in the case of two product brands with identical generic drugs, the analysis may reduce to a CMA. The treatment recommendation from a CMA may then be expressed as treatment A is less costly and equally effective as treatment B.

Health economic analyses require data and information to describe resource use and outcome of the treatments in the analysis. Such data can be obtained from several sources. Analytical strategies employed are within trial analyses, that is well-designed studies that give high internal validity, or registry-based analyses, that is well-designed studies that give high external validity. Often the latter are to be preferred, as clinical trials tend to provide data only on carefully selected patients in sometimes small samples and may thus fail to be representative of the whole patient cohort. On the other hand, register-based analyses need to be carefully designed to address issues of confounding and selection bias when estimating treatment effects. Alternatively, simulation models synthesising data from multiple sources can be used to give a long-term or lifelong perspective. Simulation techniques can be very a useful tool to explore consequences of alternative policies when data are limited and where clinical trial data only partly reflect heterogeneous patient populations.

Economic evaluations of prophylaxis for severe haemophilia: Why do the results vary so much?

In order to investigate why the costs of prophylaxis with clotting factor concentrates vary so much for patients with severe haemophilia, a non-systematic literature search was performed. Eleven studies were identified: CUA – five studies; CBA – four studies; CBA – one study; and CMA – one study (8). The studies reported incremental cost-effectiveness ratios for prophylaxis ranging from ‘cost saving and clinically beneficial’ (i.e. ‘dominant’) to over €1 million per additional QALY if prophylaxis replaced treatment following a bleed. All 11 studies compared prophylaxis with on-demand treatment but none described the exact regimen used. Studies have shown that 90–95% of total severe haemophilia costs are attributable to FVIII consumption. However, four of the 11 studies did not state the price of the FVIII concentrates used; as the unit cost of concentrates varies widely, this would have led to a difference of around 270% in the cost of the concentrates. Furthermore, the length of time the studies were conducted for also varied considerably – ideally the studies should have been lifelong to capture all relevant costs and outcomes, but in four studies the time period was ≤1 yr.

Adjustments also need to be made for event timing, that is discounting. It is generally accepted that events that happen in the future have a lower value than if they occurred today. This has a huge effect on cost-effectiveness. A study showed that the choice of discount rate alone could determine cost-effectiveness (9). In the identified studies, the differences in cost were large, meaning that more precision is required about relative treatment effect. How health consequences of the different treatments were valued in terms of QALY’s also impacts on the final results.

In the future, economic evaluation could be improved by better reporting and structural considerations, for example better descriptions of prophylaxis. In addition, epidemiological evidence linking bleeding to progression of joint disease would improve modelling effects. Non-healthcare outcomes should also be evaluated, such as fewer infusions per week. Factors other than economics need to be considered too, such as equity/fairness in healthcare provision (10).

In summary, prophylaxis is effective but cost-effectiveness estimates are generally unfavourable unless the unit cost is low and/or the discount rate for health outcomes is low, and protection against inhibitors is included. In the future, the role and impact of longer-acting FVIII concentrates needs to be examined and individualised dosing schedules should be based on PK analysis.

Clotting factor concentrates: current options and future perspectives

Maria Elisa Mancuso (Milan, Italy)

The primary aim of care in haemophilia is to prevent and treat bleeding episodes by replacement therapy. Acute bleeds should be treated as soon as possible (within 2 h). Continuous prophylaxis (primary, secondary and tertiary) is the gold standard treatment and treatment should begin at a young age while the joints are still healthy.

The European Association for Haemophilia and Allied Disorders (EAHAD) is a multidisciplinary association of healthcare professionals who provide care for individuals with haemophilia and other bleeding disorders. Its aim is to promote clinical care, education and research for these patients across the continent. It developed from the activities of the European Interdisciplinary Working Group (IDWG) who published a paper in 2008 outlining European principles of haemophilia care (11). These principles are as follows:

- A central haemophilia care organisation with supporting local groups.
- National registries.
- Comprehensive Care Centres and Haemophilia Treatment Centres.
- Partnership in the delivery of haemophilia care.
- Safe and effective concentrates at optimum treatment levels.
- Home treatment and delivery.
- Prophylactic treatment.
- Specialist services and emergency care.
- Management of inhibitors.
- Education and research.
Prophylaxis was originally developed in Sweden using a high-dose regimen (12). The Dutch experience of a lower dose tailored prophylaxis regimen is also very important (13), and in Canada, the concept of a standardised stepwise approach was developed (14). There are several issues with the current treatment of haemophilia: prophylaxis should be started at a very young age, repeated intravenous injections can be a problem even in some adults, and there is no universal treatment regimen – while individualised treatment is the best option, if the patient is not compliant it will fail (15). New products are needed for various reasons, such as to decrease costs – with more competitors it is hoped that prices will fall. Over the last few years, several new longer-acting bioengineered recombinant products have been developed, which are hoped to improve patient adherence as they may not need to be administered as frequently as current products.

The half-life of clotting factors can be extended by various technologies, including Fc fusion, albumin fusion, glycoPEGylation and site-specific PEGylation. Such technologies result in approximately 1.6- and fivefold increase in the half-life of FVIII and FIX, respectively, compared to standard factor concentrates (16). Some of these new products have received regulatory approval, while others are still undergoing clinical trials. For patients with haemophilia A switching to one of the new FIX products, it is expected that the number of annual injections needed will decrease from 150–180 to 80–100; for haemophilia B patients switching to one of the new FIX products, the reduction is estimated to be from 100–120 to 30–40, representing a substantial difference to patients’ QoL.

Of the three new products for the treatment of haemophilia B (none of which are yet approved by the European Medicines Agency [EMA] at time when THE meeting was held), rFIXFc fusion protein has a half-life of approximately 60 h and is commercially available in the USA/Canada. A phase 3 study in previously treated patients (PTPs) showed that individualised prophylactic rFIXFc administered every 1–2 wk resulted in a low annualised bleeding rate (ABR, 1.4 bleeds/yr) in patients with haemophilia B; no inhibitors were detected (17). N9-GP is a glycoPEGylated FIX product with a half-life of 93 h. A multinational randomised phase 3 study in 74 PTPs revealed that once-weekly N9-GP prophylaxis with 40 IU/kg resolved target joints in 66.7% of affected patients and improved QoL (18). In addition, 91.7% of bleeds were successfully treated with a single dose and no inhibitors developed. A third product, rIX-FP, a recombinant albumin fusion product, has undergone a safety and PK study in 25 PTPs (19). Results showed that the product has a mean half-life of 92 h and no inhibitors have been observed. A phase 3 study is underway comparing on-demand versus prophylactic treatment.

Among the modified FVIII molecules described below, none was yet approved by EMA at the time when THE meeting was held.

rFVIIIIFc is a recombinant B-domain deleted FVIII Fc fusion product for the treatment of haemophilia A already licensed in the United States, Canada and Japan. A phase 3 study in PTPs showed that it has a half-life of 18.8 h, with 30% of patients achieving a 5-d dosing interval; no inhibitor was detected (6). The ABR in 117 patients on tailored prophylaxis was 1.6 bleeds/yr (Fig. 2).

BAY 94-9027 is a PEGylated BDD-FVIII product with a half-life of 18.7 h. Results of a phase 2/3 study showed that the ABR in patients given treatment (45–60 IU/kg) every 5 d was 1.9 bleeds/yr, compared to an ABR of 3.9 in patients given 60 IU/kg every 7 d. Patients treated on-demand had an ABR of 23.4 bleeds/yr.

N8-GP, a glycoPEGylated B-domain truncated FVIII protein has a half-life of 18.4 h. A phase 3 study revealed that prophylactic treatment with 50 IU/kg every 4 d resulted in an ABR of 1.3 bleeds/yr, compared with 30.9 for on-demand treatment. One patient developed an inhibitor, although the rate of inhibitor development was in line with that expected for PTPs. Finally, BAX-855, a PEGylated FVIII product, is undergoing a phase 2/3 study in 146 patients comparing prophylaxis with on-demand treatment (20). The primary efficacy endpoint is the ABR.

All these new products could potentially lead to fewer infusions and higher trough levels. Studies have so far been conducted in PTPs, the best model to assess immunogenicity. Studies in previously untreated patients (PUPs) are awaited.

Non-replacement therapies are also being developed. ACE910 is a bispecific antibody to FIXa and FX that mimics the cofactor function of FVIII. A study showed that it had haemostatic potency against ongoing bleeds in a haemophilia A model offering the possibility of routine once-weekly subcutaneous supplementation also in patients with high-titre inhibitors (21). Another non-replacement therapy shown to be safe in a phase 1 study is concizumab.
(anti-tissue factor pathway inhibitor), but additional efficacy data are awaited (22). Also, this product can be administered subcutaneously.

All these new products provide an exciting new horizon in haemophilia care. However, all have potential risks and their real benefits are still to be proven in clinical practice, where patients are often very different to those taking part in trials. Safety concerns and difficulties with laboratory monitoring may limit the introduction of new therapies in clinical practice.

A potential caveat of trials with long-acting products is the fact that they were not designed to achieve zero ABR. An ABR of just over 1 looks very good compared to on-demand treatment but this translates into about 15 bleeds/10 yr, which is not an acceptable outcome. When prophylaxis is started at a very young age, a target of zero bleeds is possible. However, patients recruited to these clinical studies were older and some had been on on-demand treatment or had come from countries where prophylaxis is not the standard of care, so they already had target joints. In this situation, it is probably reasonable to have a non-zero ABR as the primary endpoint of clinical trials.

Pharmacoconomic profiling of new therapies may become a strong factor influencing their introduction in specific subsets of patients, but there may be savings in the long term as they do not need to be administered as frequently as standard treatments.

The challenges of monitoring clotting factor therapies

Steve Kitchen (Sheffield, UK) and David Perry (Cambridge, UK)

Factor assays are useful for diagnosis, classification of the severity of haemophilia and monitoring of treatment. There are two main types: immunological and functional, of which there are three types of the latter (one-stage clotting assay, two-stage clotting assay and the chromogenic assay). Immunological assays measure concentrations but not function and cannot establish the presence of a dysfunctional molecule. The one-stage assay measures functional activity and is based on the ability of a plasma sample to shorten the prolonged activated partial thromboplastin time, aPTT (or prothrombin time, PT) of a factor-deficient plasma sample. Single point assays should be avoided; three points (i.e. three different dilutions of test sample) are recommended (23).

The chromogenic assay measures functional FVIII activity. Factor X, factor IXa, calcium and phospholipids are added to the plasmas well as either thrombin or a mix of prothrombin and factor V. The rate-limiting step is the FVIII concentration. The FXa that is generated is measured using a chromogenic substrate. A reference curve is created using a reference plasma of known FVIII concentration.

In the laboratory, a method needs to be selected that gives the same answer as the method used for potency assignment. In the USA, until recently, regulatory authorities had only approved concentrates with FVIII or FIX potency assigned by the one-stage assay. By contrast, in Europe, the EMA requires manufacturers to use the chromogenic assay to assign potency to FVIII products and the one-stage assay for FIX. The method used to assign potency has an important influence on the results obtained in samples collected postinfusion. The values for chromogenic and one-stage assays are not interchangeable in all settings. In a study by Lusher et al., FVIII results run by each of four different methods following infusion of rFVIII were compared. Results showed a consistent difference in FVIII values, with chromogenic assays being considerably higher than results from one-stage assays (24). There were also differences between the various one-stage assays (Fig. 3).

In a study looking at two different full-length rFVIII concentrates, it was found that potencies by the chromogenic method were significantly higher (53% and 45%) than potencies by the one-stage clotting method when a plasma standard was used. The different behaviour of rFVIII and plasma-derived FVIII in the chromogenic method was proposed as the main cause of the method-based potency discrepancy. The results support the use of a concentrate standard to measure rFVIII in postinfusion plasma (25). Many of the studies that have been published in this area have used artificial samples in the laboratory, but it is advisable to use samples from patients wherever possible.

A UK National External Quality Assessment Scheme (NEQAS) study in April 2011 aimed to investigate postinfusion of FVIII (unpublished data). Results showed that when one-stage and chromogenic assays were compared, the difference in FVIII concentration between assays was 11% post-ReFacto AF, 32% post-Kogenate and 3% post-Advate. Thus, different assay results can be seen with B-domain deleted products and full-length concentrates. Differences
between one-stage assay reagent sets can also have an impact on the results. Another important factor is that
rFVIII-deficient plasma may sometimes not contain VWF, whereas in other samples it might be essentially normal.
Ultimately, it is important to be aware of which assay is used in each laboratory.

Looking at FIX, the UK NEQAS carried out a postinfusion study of FIX using both the one-stage and chromogenic
assays. Results showed a lower FIX:C level with the chromogenic assay for BeneFIX, but similar results using the
two types of assay for Replene. Thus for BeneFIX, a chromogenic assay should not be used (26).

Gritsch et al. looked at potency results using one-stage FIX assays for full-length recombinant FIX concentrates. Recoveries varied between agents, up to 40% in some cases (27).

There is already useful guidance on potency labelling from the Science and Standardisation Committee of the
International Society for Thrombosis and Haemostasis. They state that the optimal approach is to use a product-specific
standard, but recognise that this may be difficult to implement. Part of the concern about this recommendation is how
the laboratories will cope with patients on different products requiring a different standard to calibrate the assay. Routine
assays can be used, provided that the method/reference material is included in the manufacturer’s guidance. The manufac-
turer may recommend the use of a product reference when valid assays are not possible using conventional/local standards (28).

A comparative field study in the USA showed that plasma
rFVIIIFc levels can be monitored by either the one-stage or the chromogenic substrate assay routinely performed in clinical
laboratories, without the need for a product-specific rFVIIIFc laboratory standard (note: rFVIIIFc is currently licensed in the USA, Canada, Australia and Japan) (29). In a similar study, using the one-stage assay to measure plasma
rFIXFc levels led to an underestimation of FIX activity, just half the value expected. By contrast, the chromogenic assay
results were very close to those expected (note: rFIXFc is currently licensed in the USA, Canada, Australia and Japan) (29).

Regulatory authorities are very aware of these issues. A workshop on seven recombinant FVIII and four recombinant
FIX products run by the EMA concluded that, for most products, both one-stage and chromogenic assays are valid
against WHO (IU) (30). However, one-stage clotting assay methods can result in different potencies depending on the
aPTT reagent used. Based on the evidence available, chromogenic assays do not require specific product standards,
while one-stage assays may need specific standards for some longer-acting products.

How to monitor haemophilia outcomes

_Françoise Boehlen (Geneva, Switzerland) and Roseline d’Oiron (Le Kremlin-Bicêtre, France)_

Traditionally, outcomes in persons with haemophilia have been assessed using laboratory evaluation, bleeding fre-
quency, morbidity and mortality. However, it is also important to detect and quantify early signs of joint damage and
evaluate health-related QoL. Various techniques can be used, including physical [Gilbert score and Haemophilia Joint
Health Score (HJHS)], functional and imaging scores, bone mineral density, QoL measurements and economic data.

The Gilbert score can be performed in 30–45 min, but it is not very sensitive and not well adjusted for patients on
prophylaxis with low joint damage. In addition, it has not been validated in formal studies. In contrast, the HJHS is
performed in 45–60 min and is more sensitive than the Gilbert score, enough to detect early signs of joint damage.
There are three versions of the score and it has been tested in children; the results of the score are interpreted according
to reference values and their age-related variation. However, the HJHS requires a multidisciplinary approach by trained
professionals, such as physiotherapists.

Functional scores available are the Functional Independence Score in Haemophilia (FISH) and the Haemophilia
Activities List [HAL and paediatric HAL (PedHAL)]. The FISH score can be completed in 15 min and comprises eight
dquestions divided into self-care, transfers and locomotion. Scores range from 1 to 4 depending on the degree of inde-
pendence. It is an objective performance-based instrument that measures the functional ability of a person with
haemophilia. While it takes into consideration daily life activities, it is not designed to assess challenging activities
or consider activities such as education and employment. The FISH was developed and validated in patients with sig-
nificant arthropathy and although there is a modest correla-
tion with the Gilbert score, Pettersson’s radiological score
and MRI score, there is quite a good correlation with other
functional ability tests. The HAL score is a self-assessment
questionnaire that quantifies the functional abilities of adult
patients. The test covers seven domains, including lying, sit-
ting, kneeling, standing, functions of the legs, self-care and
leisure activities and sports. However, it is not very sensitive
or well validated. The paediatric version of the score, Ped-
HAL, comprises 53 items and there is a parent as well as a
child version.

Radiological scores are X-ray (Arnold-Hilgartner system,
Pettersson score), MRI (Denver MRI score, European MRI
score) and ultrasound [Haemophilia Early Arthropathy
Detection with Ultrasound (HEAD-US)]. X-ray is useful to
monitor advanced stages of arthropathy (bone lesions), but is
insensitive for early changes involving soft tissues or the
first steps of cartilage destruction. There is a well-known
discrepancy between physical status and radiology. MRI
gives better visualisation of soft tissue and cartilage changes
and involves no ionising radiation. However, it is expensive,
not easily available and young children usually have to be
given sedation. Ultrasound is dedicated to the examination
of soft tissues and cartilage interfaces. There are many advantages such as accessibility, lower costs and the absence of radiation, but also some disadvantages such as operator dependence and lack of standardisation. In addition, protocols for HEAD-US still require validation.

QoL measurements are of two types: generic instruments, that is EQ-5D, SF-36 and SF-12, (not specific to haemophilia) and those specifically developed for people with haemophilia. The generic instruments are very useful to compare QoL in persons with haemophilia versus other diseases, and there is significant correlation between EQ-5D and SF-36 with the orthopaedic joint score. The instruments specifically developed for persons with haemophilia are the Haemo-QoL, for adults and children. This comprises 36 questions and there is good correlation between the adult version and the SF-36.

To conclude, scores are helpful to monitor treatment change and to raise awareness in the family when treatment is not optimal. It is important to be clear about what kind of information the different outcome measures provide. Most haematologists do not have the skills to perform ultrasound, as the technique is very operator dependent. In addition, the equipment is expensive and not all hospitals can afford it. Joint pain is often misinterpreted by clinicians and patients and it is important to establish the difference between arthropathy and a bleeding episode.

**Haemophilia care: the patient’s perspective**

Brian O’Mahony (Ireland), Miguel Crato (Portugal) and Radoslaw Kaczmarek (Poland)

In Europe, current and future challenges are access to sufficient replacement therapy, access to all aspects of comprehensive care and access to new hepatitis C therapies. In recent years, hepatitis C has been a major cause of mortality. It is important to understand and integrate therapeutic advances into treatment regimens and look at adherence/confluence to treatment. Lifestyle challenges include the transition from paediatric to adult services and the consequences of ageing in the haemophilia population.

The amount of FVIII per capita varies widely from country to country, with a 17-fold difference between Romania and Sweden, the highest user. For some of the non-EU countries, treatment is very variable and cryoprecipitate and plasma are still used in some countries (31). Throughout Europe, the availability of comprehensive care for haemophilia patients also varies widely. While most centres have good access to paediatric, orthopaedic and emergency care, services such as social and psychological support, pain management and rheumatology care are not so widely available (31).

Patient organisations are very important in haemophilia care. They work in partnership and collaboration with healthcare professionals to optimise patient care. They collaborate on the collection of outcome data to prove that a particular treatment is successful, and they educate patients and their families and ensure that haemophilia is recognised within the healthcare system. They also have a crucial role in formally participating in national decision-making processes. In a survey of factor concentrates tender and procurement procedures in 38 European countries, it was found that lower prices were associated with tender boards that included both haemophilia clinicians and patient organisation representatives (32).

To people with haemophilia, what matters most is access to treatment and care of a standard that enables each individual to achieve their full potential in life. Good communication with haemophilia care teams is also important, as well as the opportunity to participate in decision-making. It is important in haemophilia care to build a wider community involving patients and their families and to give informed consent when switching products. One of the biggest fears among haemophilia patients is the perception that clinicians are under pressure to make treatment decisions based on increasingly limited healthcare budgets.

Education is increasingly important to make the most of and defend the benefits of prophylaxis, as well as stress how haemophilia, formerly a severe condition with a short life expectancy, is now in countries where optimum treatment and care are available a very manageable condition with near-normal life expectancy. It is important to educate patients about the difference between good and bad quality of care, and to inform people about available therapy options. With adequate treatment, patients can expect a dramatic change in their QoL.

Patient organisations have an important role in promoting good understanding among key stakeholders. Communication between patient and patient expert, between patient and clinician, and between patient expert and clinician is paramount to promote understanding and improved care. All stakeholders should avoid the dangers of complacency and poor knowledge.

**The future of haemophilia management: care in 2020**

Paul Giangrande (Oxford, UK)

Even within Europe, there are major differences in the availability of treatment and care between countries. During the Kreuth III meeting in 2013, experts from 36 European countries discussed recommendations relating to haemophilia care. It was proposed that a formal haemophilia body should be established in each country, the minimum FVIII consumption per capita should be 3 IU and approval of new therapeutic products should not be based solely on cost (33).
Earlier, in 2000, the Haemophilia Surveillance System Project Investigators published a paper which looked at the relationship between mortality in haemophilia patients and the medical care that they had received. They found that survival was significantly greater among haemophiliacs who receive medical care in a HTC (34). Another study within the framework of the EUHANET project published guidelines for the certification of haemophilia centres with the aim of setting quality standards (35). The guidelines define the standards and criteria for the designation of two levels of care delivery: EHTCs, providing local routine care, and EHCCCs, providing specialised and multidisciplinary care and functioning as tertiary referral centres. Additionally, they define standards about general requirements, patient care, provision of an advisory service and establishment of a network of clinical and specialised services.

In terms of the global burden of haemophilia, the WFH estimates that there are approximately 450 000 people with haemophilia worldwide, of whom 75% receive little or no treatment, and many patients are still not even correctly diagnosed. On the other hand, the switch to recombinant products in affluent countries is leading to a greater availability of plasma products in other parts of the world. Addressing the global burden of haemophilia is a daunting task, which in practice often involves the avoidance of replacement therapy for all but the most severe bleeding episodes, and the use of non-factor replacement interventions such as anti-fibrinolytic agents. While the gap in care between the different nations is expected to diminish in the future, not everything will improve; patient groups are particularly vulnerable. In addition, super-specialisation of healthcare professionals is being actively discouraged in favour of generalism – clinicians have to spend more time being general haematologists rather than haemophilia specialists. The growing trend for national tenders saves money but can have negative consequences, such as a permanent loss of money from allocated budgets.

Two future scenarios are possible: either the number of patients with haemophilia will rise due to increased longevity and QoL, or there will be a decline in patient numbers with the advent of preimplantation diagnosis. Furthermore, there will be fewer, but larger dedicated treatment centres, with merged adult and paediatric treatment services, but there will be a reduction in the number of haematologists devoted solely or mainly to haemophilia care. The migration of haemophilia patients within the EU to countries where better treatment is available may discourage improvements in haemophilia care in the patients’ home countries. Many older haemophilia patients have comorbidities such as type 2 diabetes mellitus, cardiac arrhythmias, chronic lung disease, dementia and malignancy which are not linked to the underlying haemophilia. They also have more chronic viral infections and hypertension, but fewer cardiovascular diseases (Fig. 4) (36).

Several studies have suggested that the prevalence of hypertension is increased in patients with haemophilia, although there is no obvious underlying cause for this (37). In view of this, regular blood pressure measurements should be part of standard care in haemophilia patients aged 30 yr or older. A relationship between haemophilia and osteoporosis has also been suggested: in a study of 62 patients with severe haemophilia A, a reduced bone mineral density (BMD) defined as osteopenia and osteoporosis by World Health Organization criteria was detected in 27/62 (43.5%) and 16/62 (25.8%) patients, respectively. Fifty-five of 62 (88.7%) patients suffered from haemophilic arthropathy (38). The authors also found that hepatitis C, low body mass index (BMI) and age were additional risk factors for reduced BMD in patients with haemophilia. Patients with haemophilia should be encouraged to exercise, in order to reduce the risk of developing osteoporosis; bisphosphonates can also be given to enhance bone density.

Older patients may have problems with self-injection because of problems associated with ageing, such as tremor, impaired vision, memory loss and limited movement in the upper limbs. For all haemophilia patients, care from a multidisciplinary team is particularly important.

There will be a greater emphasis on the cost-effectiveness of therapies in the future. This will result in novel products not necessarily being adopted for routine use, closer monitoring of factor usage by patients, and there might even be rationing of individual annual factor allowances. The role of nurses will become increasingly important, and patients will become more involved in their care. Industry will become more involved in patient care through the development of home care companies. Nurses are an extremely valuable resource in the care of haemophilia patients and they increasingly take on more responsibilities, including treatment of acute bleeds, organising outpatient review clinics, training parents and children in venepuncture and prophylaxis, and prescribing factor concentrates and other medicines.

In recent years, companies that deliver concentrates directly to patients have proliferated and prospered, but this
has led to a decline in the number of HTCs, with all their expertise. In the future, centres need to survive financially, otherwise they will close and this valuable resource will be lost, but it is likely that commercial companies will become more involved in delivery of care and not just provision of products.

Gene therapy is a proven technology but it will probably not be in place even in 20 yr of time. A landmark study has been published demonstrating the successful conversion of haemophilia B to mild or moderate disease in six patients who underwent infusion of an adeno-associated viral (AAV) vector expressing FIX (39). However, this is not an established treatment and postmarketing surveillance of gene therapy will be very important to assess the potential risk of malignancy, particularly if young children are going to be treated.

Sharing best practice in haemophilia care

Erik Berntorp (Malmö, Sweden)

Treatment centres were invited to submit an abstract ahead of THE Meeting sharing their experience of haemophilia care and their efforts to overcome challenging situations in their region. The Review Committee awarded THE Meeting Best Practice Award to Gianna Franca Rivolta, representing the Haemophilia Comprehensive Care Centre in Parma, Italy.

A network for inherited bleeding disorders: the experience of Parma Haemophilia Centre

Gianna Franca Rivolta (Parma, Italy)

Emilia Romagna is a region in the north of Italy where there are eight haemophilia centres, one in each province. In 2002, the Emilia Romagna Health Authority defined a new way to improve the care of haemophilia patients, based on a ‘hub and spoke’ model. The hub – the haemophilia centre in Parma – is the reference centre and coordinates a network of ‘spokes’. This model was chosen to ensure a consistently high level of haemophilia care throughout the region, with the aim of balancing two usually opposing requirements: a near-to-home distribution of services and the highly specialised services available in a few qualified centres.

To create this network, three websites were designed and developed by the hub centre. The whole project was supported by the Emilia Romagna Health Authority. The first tool, developed in 2003, was the registry, which not only provides epidemiological data, but also collects detailed information on the clinical and therapeutic follow-up, health costs and socioeconomic status of patients (40). The main purposes were to improve the performance of the healthcare system and to monitor the level of care offered in different centres, the registry helped to motivate all centres to improve their standards of care.

Figure 5 The number of patients in the Emilia Romagna Health Authority registry 2003–2014.

Knowledge of patients’ health status and healthcare costs is now more accurate.

• Shared guidelines, produced by the hub centre, have been adopted by all centres, covering the organisation of periodic patient check-ups.

• All centres have adopted the same therapeutic plan. This facilitates the monitoring of prescriptions and factor consumption.

• Areas for improvement revealed by the registry have stimulated the region to define the objectives for the hub and spoke centres.

The molecular laboratory located in Parma has performed genetic diagnoses since 2002 for all patients in the region, and these results are recorded in the Registry. 95% of patients with severe haemophilia, more than 80% of the patients with moderate and mild haemophilia A and more than 50% of patients with rare bleeding disorders have undergone genetic diagnosis (41).

In order to improve the organisation further, a project called ‘Web Connections of the Haemophilia Centres of the Region of Emilia Romagna’ was developed in 2006. This project aimed to fill some of the gaps in the previous system, namely:

• Enabling shared access to the databases from each haemophilia centre in the region.
Develop outpatient clinical records better suited to the centres’ needs.
- The possibility of accessing clinically relevant data anywhere.
- The possibility for patients to access part of their clinical records.

To meet these goals, the hub centre designed a new, computerised outpatient clinical recording system called ‘x1’Emofilia’: this is a web application that has a single database located in a regional server (42). It can be used by any computer connected to the Internet within each of the hospitals of the region. It has a clinical layout and can be used during outpatient visits and also by collaborating specialists in other fields. Web identity (a USB device) enables patients to access their clinical data and, independently of where they live, they can go to any of the centres in the region where their records can be accessed by the doctors and updated directly. The data entered by patients are available in real time and the haematologist in the haemophilia centre can follow the patient’s treatment and bleed history closely.

Treatment of patients with inherited bleeding disorders in the emergency department is challenging, because bleedings can be underestimated and their adequate management is not well known by emergency physicians. In 2010, all eight haemophilia centres and all 44 emergency departments in the region came together to improve this situation. The aim was to ensure that patients with an inherited bleeding disorder admitted to emergency departments are provided the fastest triage and given infusion as soon as possible before the haemophilia centre is called. Guidelines for emergency treatment, containing practical instructions for managing patients, were developed and shared by haemophilia centres and emergency departments and published on a dedicated website (www.emofiliarer.it) in February 2011; additionally, a pocket guide for all emergency department physicians was developed in June 2011. The website, which has a private area for doctors and a simplified public area, enables easy access to descriptions of diseases and drugs. Furthermore, the website contains the addresses and facilities of all haemophilia centres and emergency departments in the region of Emilia Romagna. An algorithm suggests the first dose of concentrates to use for every type and severity of bleed and trauma, according to the severity and type of bleeding disorder.

The ultimate aim of this project, which started in 2002 and is still ongoing, is to improve the quality of care offered to patients, by providing global care. Thus, in the region of Emilia Romagna, all the specialists involved in the management of inherited bleeding disorders are connected in a web-based network. The haematologists coordinate this network but the patients are at its centre, in order to ensure the best possible quality of treatment and QoL for all patients.

Concluding remarks

Erik Berntorp (Malmö, Sweden)

The aim of the first THE Meeting was to promote the optimal and seamless care of haemophilia patients through education of the multidisciplinary care team. This was achieved by reviewing the latest scientific developments in haemophilia management, discussing how these novel updates can be implemented in the clinic to improve patient care, and by providing an inclusive platform for networking and debate, open to all haemophilia treatment team members. Unmet educational needs and the biggest challenges faced by HTCs were identified as tailoring treatment to individual patients, compliance of patients to prophylaxis, treating the ageing haemophilia patient, lack of resources to educate and treat patients, ensuring hospital centres provide treatment to haemophilia patients throughout their lives, and recruiting and training a multidisciplinary care team.

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