Delivery of Treatment for Haemophilia

Report of a Joint WHO/WFH/ISTH Meeting
London, United Kingdom, 11 - 13 February 2002

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Delivery of Treatment for Haemophilia

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1 Introduction

The treatment of haemophilia is both costly and complex. The complexity is due to the rarity, the life-long nature and the variable severity of the condition and the fact that patients do not appear ill in the conventional sense. The lack of prompt, appropriate treatment may lead to prolonged hospitalization and the misuse or wastage of expensive blood products.

Although it is established that the deficiency of the clotting factor determines the severity and frequency of bleeding, the precise level required to prevent haemarthrosis is still unknown. Since the 1990s the treatment has been more unified but there is still no consensus on dosing.

This report on the delivery of treatment for hemophilia is one of a series of reports published since 1990 by the World Health Organization (WHO) and the World Federation of Haemophilia (WFH) on the control of haemophilia. ‘Dosing’ has become an increasingly important issue. The International Society of Thrombosis & Haemostasis (ISTH) joined WHO and WFH to add their already developed projects, particularly in laboratory diagnosis and quality control, and immune tolerance. It is hoped that this meeting will help direct future research in order to develop cost-effective strategies for the treatment of haemophilia, not only in the developed world but also in less well-resourced countries.

2 The delivery of treatment for haemophilia

2.1 The assay of factor VIII: new methodology designed to detect very low levels

The assays in current use are chromogenic depending on the generation of factor Xa or APTT based and dependent on the generation of thrombin. It has been shown that following initiation of coagulation thrombin activity peaks and with the action of antithrombin the thrombin generation lasts about 20 minutes.

Thromboelastography (TEG) has been used since 1946. The clotting time (CT) is the time taken to double the amplitude, and the clot formation time (CFT) is the time until the amplitude reaches 20mm. The first derivative of the TEG represents velocity. Thus, maximum velocity, time to reach maximum velocity, and area under the curve (AUC) can all be measured.

The rotating TEG (roTEG) is an adaptation of this methodology used to generate similar curves. In the untreated patient with haemophilia, the clot develops later and there is no burst. With as little as 1U/dl factor VIII (FVIII) there is a peak and the clot develops slightly earlier. Only a small amount of FVIII is required.

In applying this methodology to patients with severe haemophilia, there was individual variability between patients, both in the maximum velocity and the time to reach maximum velocity. It is possible that this methodology could be applied to correlate with the phenotypic behaviour of patients – do patients with fewer bleeds actually have very small amounts of FVIII currently undetectable by present assay methods? It might also be a way of achieving the minimal effective dose. It is also possible that this method might be useful for bedside monitoring.

2.2 The pharmacokinetics of clotting factor therapy

The pharmacokinetic properties of clotting factor concentrate are important to maximize efficacy and minimize cost. Clotting factor therapy is expensive and not readily available in all parts of the world.
There may be shortages due to limited production. Therefore the use of clotting factor should be optimized and pharmacokinetics is fundamental to dosing.

The different biochemical assays used to measure both potency of concentrate and plasma samples may yield variable results. The one-stage and chromogenic assay are particularly disparate in the assay of B-domain deleted FVIII where it has been recommended that infused concentrate diluted in haemophilic plasma should be used as a standard.

Traditionally dosing of FVIII or IX in haemophilia has been based on in vivo recovery (IVR) and biological half-life (T½).

IVR is calculated as observed peak FVIII or IX divided by expected peak activity. The expected activity is the dose divided by the plasma volume of the patient. However the clotting factor is not only distributed in plasma – although this can be approximated for FVIII, it is very difficult for FIX. The in vivo decline in FVIIIC and FIXC is characterized by several half-lives (T1/2). These can be estimated as the ‘terminal’ or longest observed in contrast to the ‘elimination’ or shorter distribution half-life. It is important that for FIX if the sampling is too short the estimated terminal half-life becomes too short.(1) Although the pharmacokinetics of FVIII are well-established in adults, these are less well described for FIX where the half-life is longer, there is a reluctance to test further out in time, and FIX deficiency is more rare. In general, the pharmacokinetics of both FVIII and FIX are far less studied in children.

The FVIII concentrates in common usage result in a rise of 2.0-2.5 U/dl per U/kg infused. The peak rise occurs 10-15 minutes after infusion.(2) The B-domain deleted FVIII has shown a similar clearance to the two full-length recombinant products and plasma derived FVIII.(3)

The von Willebrand factor (VWF) is important in the pharmacokinetics of FVIII because it has a stabilizing effect on the FVIII molecule. A correlation can be shown between pre-infusion VWF levels and the kinetics of FVIII.(4) It is possible that the VWF may explain the progressive reduction in clearance using continuous infusion after surgery.(56) The age dependent variable may be related to the increase of VWF with age.(7) It has also been found that patients with blood group O have a shorter half-life than those with blood group A.(8) This could also be related to VWF because blood group O is associated with a lower VWF.(7) It is unclear whether the VWF content of clotting factor concentrates influences, per se, the half-life.

When FIX is infused the average rise is 1.0-1.4u/dl per U/kg infused. Factor IX has a much larger volume of distribution than factor VIII because of rapid binding to the vascular endothelium.(910) Also FIX has a low molecular weight which allows diffusion into interstitial fluid. Although recombinant FIX has similar functional properties to plasma derived FIX there are biochemical dissimilarities.(11) The in vivo recovery was only 0.8 iu/dl compared to 1.2 iu/dl per iu/kg infused for plasma derived FIX.(12) Variations are observed in the pharmacokinetics of FIX with age.(1213) A correlation of the in vivo recovery has also been demonstrated with weight(14) and this is related to the decreasing fraction of plasma volume as weight increases.

Thus, in considering pharmacokinetics age and recombinant versus plasma, derived concentrate should be taken into account. Ideally, for each individual patient a pre-treatment measurement and two post treatment samples should be taken. These data can be used for computer simulation in order to establish person specific pharmacokinetics.
2.3  Treatment on demand – in vivo dose finding studies

Although it is clear that the severity and frequency of haemarthrosis is directly related to the degree of deficiency of the clotting factor, the precise level needed to prevent haemarthrosis is still unknown. Brinkhouse performed experiments in dogs in the early 1950’s and found that a dose of plasma 3.7ml/kg every four hours could produce a level of antihaemophilic factor of 5% (15). In 1964 Roberts described surgery using a priming dose of 15-20ml/kg and then 3-6ml/kg every four hours using plasma (16). However there was a high rate of complications.

In 1964, cryoprecipitate was described as a source of FVIII (17). In 1979, Allain described experience in the treatment of 70 children with severe haemophilia and determined the correlation between different doses of lyophilised and frozen cryoprecipitates (18). It was found that to achieve a 99% success rate for the resolution of a bleed, a mean plasma factor VIII of 53% was necessary and was achieved by a dose of 31U/kg.

With the advent of clotting factor concentrates, different levels of clotting factor were advocated depending on the severity of bleed: 12-35% for major bleeding episodes (16(19); 12-17% for minor bleeding (19); 40-50% for severe trauma and 30% for minor bleeds (20); and 10-20% for spontaneous bleeding episodes (21). A variety of studies have been performed between 1967 and 1982 and these are summarized in Table 1.

Since the 1990s, the treatment of haemophilia has been more unified although there is still no consensus on dosing. There is agreement that dosing regimens should be based on the pharmacologic properties of clotting factors including the half life and recovery. The type of bleed and minimal haemostatic level should also be considered. Guidelines for the treatment of haemophilia A and B for a variety of haemostatic events have been published. (Table 2). However, such guidelines are not based on randomized trials and vary worldwide. Whether these levels represent optimal values under all conditions is questionable. Evolution has resulted in humans having factor VIII levels of 100% or 100U/dl. Although bleeding can be arrested with levels less than 100%, levels of 100% factor VIII are required to cover all haemostatic challenges.

2.4  Continuous infusion

The evidence is anecdotal as there is a lack of randomized studies and no currently used clotting factor concentrates are licensed for this purpose. The concept of continuous infusion was developed by Brinkhouse in 1954 (15) before clotting factor concentrate became available. Although McMillan (32) used glycine precipitated concentrates in 1970, there was little further interest for the next two decades. It is likely that the majority of haemophilia treaters in North America and Europe now routinely use continuous infusion. There is an economic benefit of continuous infusion – there is a linear correlation between the dose of factor required to keep a set level and interval between boluses. The dose reaches a minimum as the interval reaches zero i.e. continuous infusion. There are no randomized trials comparing continuous infusion with bolus injections of concentrate. Various studies have reported a reduction in the amount of concentrate used in small series of patients (33)(5)(6)(34)(35)(36). A prospective study in which continuous infusion was used for 25 operations and whenever minipumps were unavailable bolus injections were used for another 18 operations, resulted in a postoperative total dose of 467U/kg and 733U/kg, respectively (p0.01) (37). The reduction in haemoglobin was less in the continuous infusion group (37). It has been estimated that a cost saving of 35% is achieved over a 5-day course of therapy (38). For factor IX there is at least one prospective study on continuous infusion (39) and with historical controls on bolus injection in another (40). In summary, it is clear from the published data that continuous infusion requires less concentrate and it is no less safe than conventional bolus dosing.
<table>
<thead>
<tr>
<th>Dose U/kg BW</th>
<th>Factor plasma level %</th>
<th># Treated episodes</th>
<th>Success rate %</th>
<th>Therapeutic material</th>
<th>Type of bleed</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>23</td>
<td>24 - 33</td>
<td>25</td>
<td>56- 64</td>
<td>Cryo</td>
<td>Hemarthrosis</td>
<td>(22)</td>
</tr>
<tr>
<td>20-30</td>
<td>40 - 50</td>
<td>51</td>
<td>92</td>
<td>FVIII, other</td>
<td>Hemarthrosis</td>
<td>(23)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>51</td>
<td>96</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(24)</td>
</tr>
<tr>
<td>7-9</td>
<td></td>
<td>106</td>
<td>90</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(25)</td>
</tr>
<tr>
<td>11-13</td>
<td></td>
<td>173</td>
<td>79</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(25)</td>
</tr>
<tr>
<td>15-17</td>
<td></td>
<td>64</td>
<td>94</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(25)</td>
</tr>
<tr>
<td>3-7</td>
<td></td>
<td>60</td>
<td>100</td>
<td>FVIII, other</td>
<td>Hemarthrosis, other</td>
<td>(26)</td>
</tr>
<tr>
<td>7.5-12.5</td>
<td></td>
<td>196</td>
<td>89</td>
<td>FVIII</td>
<td>Hemarthrosis, other</td>
<td>(27)</td>
</tr>
<tr>
<td>12.5-20</td>
<td></td>
<td>349</td>
<td>94</td>
<td>FVIII</td>
<td>Hemarthrosis, other</td>
<td>(27)</td>
</tr>
<tr>
<td>3-7</td>
<td></td>
<td>60</td>
<td>100</td>
<td>FVIII/FIX</td>
<td>Hemarthrosis</td>
<td>(28)</td>
</tr>
<tr>
<td>31</td>
<td></td>
<td>53</td>
<td>99</td>
<td>Cryo</td>
<td>Hemarthrosis, other</td>
<td>(18)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>119</td>
<td>73</td>
<td>FVIII, OTHER</td>
<td>Hemarthrosis</td>
<td>(29)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>134</td>
<td>75</td>
<td>FVIII, OTHER</td>
<td>Hemarthrosis</td>
<td>(29)</td>
</tr>
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<td>86</td>
<td>64</td>
<td>FVIII, OTHER</td>
<td>Hemarthrosis</td>
<td>(29)</td>
</tr>
<tr>
<td>11-16</td>
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<td>144</td>
<td>78</td>
<td>FVIII, other</td>
<td>Hemarthrosis</td>
<td>(30)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>95</td>
<td>89</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(30)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>106</td>
<td>77</td>
<td>FVIII</td>
<td>Hemarthrosis</td>
<td>(31)</td>
</tr>
</tbody>
</table>
Table 2. Indications and guidelines for factor replacement in Hemophilia A and B

<table>
<thead>
<tr>
<th>Site of hemorrhage</th>
<th>Optimal factor level (%)</th>
<th>Dose (U/kg BW)</th>
<th>Duration in days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Factor VIII</td>
<td>Factor IX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-30</td>
<td>30-50</td>
</tr>
<tr>
<td>Joint</td>
<td>30-50</td>
<td>20-30</td>
<td>30-50</td>
</tr>
<tr>
<td>Muscle</td>
<td>30-50</td>
<td>20-30</td>
<td>30-40</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>40-60</td>
<td>30-40</td>
<td>40-60</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>30-50</td>
<td>20-30</td>
<td>30-40</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>30-50</td>
<td>20-30</td>
<td>40-60</td>
</tr>
<tr>
<td>Hematuria</td>
<td>30-100</td>
<td>25-50</td>
<td>70-100</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>60-100</td>
<td>50</td>
<td>80-100</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>50-100</td>
<td>30-50</td>
<td>60-100</td>
</tr>
<tr>
<td>Trauma or surgery</td>
<td>50-100</td>
<td>30-50</td>
<td>60-100</td>
</tr>
</tbody>
</table>

The simultaneous use of antifibrinolytics will help conserve the use of concentrate. Conventional thromboprophylaxis should be given.

There are complications associated with continuous infusion – there may be a reduced stability after reconstitution, although most of the concentrates of intermediate, high or very high purity have stability for at least 24 hours and, in some cases, for several weeks. There may be superficial inflammation due to thrombophlebitis and this can be overcome by small amounts of unfractionated heparin or using a parallel saline infusion.

Although there have been concerns about infection and inhibitor formation, there is no evidence of either of these complications.

2.5 Prophylaxis

The rationale of prophylactic treatment is to maintain clotting factor activity above 1% and thus to convert the bleeding pattern of severe haemophilia into that of the milder bleeding pattern of moderate haemophilia.

The treatment strategies for the severe haemophilia include primarily "on demand" when patients are only treated in case of bleeding episodes and there are short courses of prophylactic treatment at the time of synovitis or after orthopaedic surgery\(^{(41)}\). Intermediate dose prophylaxis has been used in the Netherlands since the early 1970s. Prophylaxis begins at an early age according to the patient’s bleeding pattern but mostly after the occurrence of at least one joint bleed\(^{(42)}\). The doses used are 15-25IU/kg two or three times weekly for haemophilia A and 30-50 IU/kg twice weekly for haemophilia B. High dose prophylaxis has been used in Sweden since the early 1960s and children now begin around the age of one year at the
time of the first joint bleed with a dose 25-40IU/kg three times a week for haemophilia A and 25-40IU/kg twice a week for haemophilia B.

A comparison has been made between treatment history, orthopaedic outcome, and clotting factor consumption for three cohorts of patients: for on demand therapy, the cohort of Molho et al which included 106 patients treated in 35 haemophilia treatment centres in France; 49 patients treated with intermediate dose prophylaxis at the Van Creveld centre in the Netherlands; and a group of 24 boys treated at the Malmo centre with high dose prophylaxis. The outcome measures included the number of joint bleeds and the Pettersson radiological scores. The number of joint bleeds was 11.5, 2.8 and 0.5 each year for the French, Netherlands and Swedish group respectively. This was inversely correlated to the U/kg/y clotting factor used, which was 1260 (French), 1550 (Netherlands), and 4301 (Sweden) respectively. The outcome from this study confirms previous studies: Aledort reported a mean number of 16.5/year joint bleeds in 411 children treated on demand compared to 5.7/year in 66 children on prophylaxis. Szucs found 8.8 bleeds/year in 399 adults on demand compared to 3.1/year in 145 adults on prophylaxis.

The comparison of long-term outcome shows that prophylaxis can delay and even prevent haemophilic arthropathy. However, since 90% of treatment costs for haemophilia comprises the clotting factor concentrate, the cost for prophylaxis are clearly greater than for on demand therapy. Longitudinal studies from both Sweden and the Netherlands have shown that the annual consumption in U/kg/year of clotting factor is very high in childhood but decreases in adulthood. Various long term studies of on demand therapy have shown that clotting factor consumption increases with age. Thus it could be that intermediate dose prophylaxis would be equally or even less costly after two decades.

There are a number of unanswered questions. When to start? How to start - should the dose be individualized? What is the minimum effective dose - should the dose be low at first or should it be very high allowing the child to grow into the dose? When should the prophylaxis be stopped?

2.6 Immune tolerance

The incidence of inhibitors in haemophilia A has been estimated to be 33% (47). Inhibitor incidence in Haemophilia B is less frequent and between 1-6% (48). If an inhibitor can be cleared, it can actually save money but there are very few data and the studies are mostly small. The largest study is from Bonn with 41 patients using a dosage regimen of 200U/kg/day and from the Netherlands with 18 patients using a dosage regimen of 50U/kg three times weekly. There are several registries of immune tolerance including the international, German and the North American. Together, these have analysed 485 ITT courses in haemophilia A and 13 ITT courses in patients with haemophilia B. There is agreement that a low pre-induction titre of <10BU and a low peak titre are predictors of success. However, there are a number of controversial parameters including patient age at ITT induction, interval between inhibitor diagnosis and ITT induction, and the dose of clotting factor required to induce tolerance. Thus the role of dose and the dosing regimen in determining successful ITT remains unclear. For these reasons the International Immune Tolerance Study will compare both overall outcome and time to success in a good risk cohort. Patients will be randomized to receive ITT with a high dose 200U/kg/day or a low dose regimen of 50U/kg three times weekly.

There is limited experience with immune tolerance in haemophilia B. Although no adverse events have been shown using a dose of FIX concentrate ≤ 50U/kg, the very serious complication of nephrotic syndrome has been reported with doses > 100U/kg/day (53).

It has been shown that ITT is cost effective with an increased life expectancy of 4.5 years at a lifetime cost saving of $1.6 million compared to lifetime APCC therapy. However, it is probably inappropriate for
less resourced countries to use this approach and clearly it is most important to establish the most cost-effective dose.

2.7 The delivery of treatment in the developing world

In general, in developing countries the majority of patients affected with haemophilia are younger because such individuals die at a younger age. Treatment per se is probably less of a priority than education and having a good healthcare infrastructure. In order to achieve education, haemophilia should be contained in the standard textbooks of haematology and in the curricula of students, dentists and all healthcare teams. Thus, in Thailand, there is a primary care centre, a treatment centre, a comprehensive care centre and a reference centre. Moreover, it is considered important to start education at the antenatal stage.

Reagents are expensive for those working in the developing world and cheap adaptation of reagents is sometimes possible without compromising the standard of care. Thus, in Thailand, a whole blood clotting test depending on lyophilised FVIII or FIX deficient plasma as a standard has been developed. Good therapeutic products may be manufactured locally - in Thailand, cryoprecipitate is made from three donors and the plasma is quarantined three months with heating at 60°C for 72 hours. This is used in combination with DDAVP and tranexamic acid. Fibrin glue is manufactured locally adding thrombin to cryoprecipitate. Dental extractions are performed using fibrin glue together with dental splinting. In this way replacement clotting factor therapy is only used for major bleeding because patients have to pay for this. Thus, the minimal treatment is to have treatment on demand. In order to achieve home treatment locally produced blood product, local personnel, patient, and parent monitoring are required. Emla cream is an important adjuvant for the delivery of treatment in children. Thus, there needs to be a step by step approach with minimal provision of diagnosis and establishing a registry leading toward state of the art treatment.

2.8 Models of factor replacement therapy in haemophilia for the developing world

Factor replacement therapy for haemophilia has evolved much over the last three decades. The ability to infuse large quantities of concentrate has transformed the outlook for patients with haemophilia who can now lead a normal life without the fear of bleeding into joints. However, these benefits are largely limited to those in the developed world because haemophilia has become one of the most expensive diseases to treat.

WHO comprises 191 Member States and, of these, 26 may be considered as developed countries while 22 are in transition. Developed nations spend 5-10% of their GDP on health, whereas the 143 developing countries spend < 2% of their GDP on health.

The aim of therapy in the developed world is to preserve joint integrity and this costs some US $50-100,000/person, which is difficult for even countries with developed economies to sustain. In countries where the spending on health care may be as little as 1$ per person annually, perhaps the aim of therapy should shift from maintaining joint integrity to reasonable joint function that will allow the person to remain functionally independent.

Factor replacement therapy is given for the prevention of haemarthrosis, surgery and immune tolerance treatment. The factor replacement given for joint bleeding in developing countries is variable. The total quantity of clotting factor used varies from 2-30,000 IU/person annually. Some centres which use concentrate in an intermediate range report preservation of joint function and functional independence. It is not known whether there is a linear relationship between joint function and the amount of concentrate used. Carefully documented data on orthopaedic outcome using less than usually recommended dosing in developing countries may help identify the level at which the cost-benefit ratio is the highest. Such data would also help to obtain support from governments or insurance agencies for haemophilia care.
Large quantities of concentrate are utilized for surgery although the recommended doses are empirical\(^\text{(56)}\). It has been possible to explore the reduction of conventional dosing in the developing world. In Vellore, India, a low dose protocol for surgery has been developed aimed at maintaining 20-40% levels in the first 3-5 postoperative days followed by 10-20% levels in subsequent days. In this way the factor usage can be reduced by 300IU/kg\(^\text{(55)}\). Thus, although minor bleeding may occur, the lower dose of clotting factor results in a saving of 300U/kg per person and thus allows more patients to benefit from the limited resources available.

Most centres in developing countries do not have the luxury of attempting immune tolerance. Very little data are available\(^\text{(57)(58)}\). However, in Turkey, four out of seven patients underwent successful immune tolerance with 25U/kg factor VIII three times weekly over 1-4 months\(^\text{(57)}\). Although this is encouraging, a larger number of patients need studying.

### 2.9 Standardization of FVIII and FIX assays

There are three issues dependent on the standardization of assays: labeling, diagnosis of patients, and the assessment of post treatment dosing. There are three methods available for the measurement of FVIII: one-stage clotting, two-stage clotting, and the two stage chromogenic method. At present, the one stage clotting assay is the method preferred by most clinical laboratories, whilst the chromogenic assay is used to label most concentrates and is used in some clinical laboratories. Potencies of concentrates are measured in international units (IU) which are defined by the relevant standard established by WHO; there is one standard for measurement in plasma and one standard for measurement in concentrate. The introduction of high purity products in the late 1980s led to substantial discrepancies between laboratories and between assay methods. A number of technical factors were identified which needed to be standardized and these recommendations, published by ISTH\(^\text{(59)}\), were shown to give good agreement between laboratories on high purity plasma derived and recombinant concentrates. In particular, FVIII deficient plasma should be haemophilic plasma or a deficient plasma with a normal VWF which is essential to give full potency in 1-stage assays; assay buffers need to contain 1% albumin; pre-dilution of concentrates with haemophilic plasma or deficient plasma with normal vWF is necessary for all recombinant and high purity products.

The establishment of plasma standards has been more straightforward. The link between the international unit and the ‘normal plasma unit’ has been achieved by incorporating samples of normal plasma pools in calibration studies.

In a study of different factor VIII methods for measuring potency in the newer high purity and recombinant products, potencies were compared in 10 different concentrates by the one-stage and chromogenic method\(^\text{(60)}\). The largest discrepancies were associated with a plasma derived immuno-purified concentrate where the mean one-stage potency exceeded the chromogenic potency by 33% and with the B-domainless recombinant product where the chromogenic potency exceeded the one-stage potency by 28%. Overall, if the SSC recommended methodology is used, differences in potency for the two full-length recombinant products using the one-stage and chromogenic methods are clinically insignificant. However for the B-domain deleted product, even when the SSC methodology is used there are still discrepancies according to phospholipid used and, therefore, it is best to use the chromogenic method is used for potency labeling.

It was first found in 1978\(^\text{(61)}\) that when concentrates were assayed against plasma, potencies were higher with two-stage compared to one stage. In recent years, the chromogenic assay has largely replaced the two-stage method, on which it is based, and some laboratories have begun to use the chromogenic assay for the measurement of factor VIII in post infusion samples. Higher results are given by the chromogenic method compared to the one stage method. The reasons for this discrepancy are ill understood but a
practical solution is to use as a standard concentrate diluted in haemophilic plasma. The concentrate used as standard should be as close as possible to the injected concentrate. This approach has been tested on ex vivo samples and the difference between the two methods was abolished\(^{(62)}\).

Standardization of FIX assays has presented fewer problems than FVIII. WHO established a concentrate standard and there have not been problems with the introduction of high purity factor IX products. There is also a WHO plasma standard for FIX.

It is not clear, however, whether the measure of the level of FVIII of FIX in the blood of the patient is a measure of the haemostatic potential. For this reason, there has been an interest in the thrombin generation test, which was first developed by Biggs in 1953 and has been recently developed in a more sophisticated version\(^{(63)}\). The advantage of this test is that it can be performed with relatively simple reagents and instrumentation.

### 3 Conclusions and recommendations

Haemophilia is an inherited bleeding disorder, which is characterized by recurrent, spontaneous bleeding into joints and muscles. Without treatment, most people with haemophilia die in childhood or early adult life. Treatment with clotting factor can result in the control of bleeding, prevention of chronic arthropathy and premature death. However, such therapy is extremely expensive and it is therefore important that dosing is cost effective and based on good evidence.

**Guidelines:** It is recommended that national guidelines should be developed. It is recognized that these may be different in various economic settings. It may, therefore, be necessary to develop minimal and optimal guidelines. Guidelines should include:

- Aim of treatment.
- Product.
- Diagnostic tests.

**The assay of factor VIII: new technology to detect low levels:** The ISTH definition for severe haemophilia A is a level of <1U/dl. However, it is recognized that there is heterogeneity of phenotype. This heterogeneity has become unmasked by new laboratory tests, which may be more discriminatory. It is recommended that more studies be performed to correlate phenotypic behaviour and laboratory tests.

**Surgery:** Continuous infusion is the most cost effective method for surgical prophylaxis. The infusion is started with a bolus to reach the intended maintenance plasma level of clotting factor. The optimal level in the first 48 hours after surgery is 70-100U/dl in countries with unlimited resource and thereafter there can be a progressive reduction. In those countries with minimal resources, the level may be reduced to 50-70U/dl in the first 48 hours and, in such settings, it may be acceptable to accept risk in order that surgery is possible.

It is recommended that (1) a survey of major surgery cases should be set up with the aim of comparing outcomes with bolus injections or continuous infusion, particularly with regard to inhibitor formation; and (2) a randomized study of bolus injection or continuous infusion for total hip or knee replacement in the haemophilic patient should be performed. In this way the minimal trough levels and steady state levels that prevent bleeding could be established.
Prophylaxis: It is concluded that prophylactic treatment for patients with severe haemophilia reduces the number of bleeds. As a consequence, there is a reduction in arthropathy and thus an improved quality of life. It is recommended that the dose for prophylaxis is individualized: for high dose prophylaxis, pharmacokinetic studies should be used to establish the dose required to maintain a trough level of 1%, and for intermediate dose prophylaxis, the dose is aimed at preventing joint bleeds. Whereas the high dose regimen results in less joint bleeds, the intermediate dose regimen may be more cost effective. It is recommended conducting research into:

- The effect of arthropathy on disability and quality of life.
- The benefit of prophylaxis in adult patients with and without haemophilic arthropathy.
- The development of delivery systems which will increase convenience and make tailored dosing and more frequent treatment possible - ideally a device to allow continuous infusion.

Treatment on demand: Although the severity and frequency of haemarthrosis is known to be directly related to the degree of deficiency, the precise level to prevent haemarthrosis is unknown. Many studies have shown a dose of 30U/kg to be efficacious but it is likely that a sliding scale depending on severity of bleed can be used. Although the aim of therapy in the developed world is joint integrity, in the less well-resourced world an aim of maintaining ‘functional independence’ for the patient might be more realistic. It is recommended that individual pharmacokinetics should be established but in order to use such findings it is recommended that there should be variety of vial size and an improvement of delivery systems to make constant delivery of clotting factor possible. It is also recommended that a multidose vial be developed. It is recommended that there is co-comitant use of antifibrinolytics eg tranexamic acid.

Immune tolerance: Immune tolerance is cost effective but it is recommended that the effective dose and dosing regimen be established through the international immune tolerance study. It is inappropriate for less well-resourced countries to use this approach.

Standardization of FVIII and FIX assays: This is essential for diagnosis, potency labeling of clotting factor in order to achieve accurate dosing, and for monitoring of post infusion samples. It is recommended that WHO, WFH, and ISTH work together in order to achieve participation in EQAS schemes throughout the world.

The delivery of treatment for haemophilia: It is recommended that all treatment be dispensed from a haemophilia centre that is integrated into the existing healthcare system. The diagnosis should be made and the patient should be listed on a registry. There should be a protocol for dosing and follow up and this information should be entered on the registry together with clinical details of progress. It is recommended that regular audit and research and development should be conducted in order to establish optimal treatment guidelines, which are quality assessed. It is recommended that home treatment is the treatment of choice for patients with severe haemophilia.

4 List of participants

Trevor Barrowcliffe, MD, Head, Division of Haematology, NIBSC, Blanche Lane, South Mimms, Potters Bar, Herts EN6 3QG, United Kingdom.
Tel: +44 (0) 1707 654 753. Fax: +44 (0) 1707 647227. Email: tbarrowcliffe@nibsc.ac.uk

Professor Erik Berntorp, Lund University, Malmo University Hospital, Dept for Coagulation Disorders, Malmo S-20502, Sweden.
Tel: +46 40 33 23 92. Fax: +46 40 33 62 55. Email: erik.berntorp@medforsk.mas.lu.se
Ampaiwan Chuansumrit, MD, Bangkok IHTC, Faculty of Medicine & Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.
Tel: +66 2 201 1748 9. Fax: +66 2 201 1850. Email: raajs@mahidol.ac.th

Miguel A Escobar, MD, Associate Medical Director, Gulf States Hemophilia & Thrombophilia Center, 6655, Travis Street, Suite 400, Houston, TX 77030, United States of America
Tel: +919 843 0527. Fax: +919 962-8224. Email: miguel.escobar@uth.tmc.edu

Kathelijn Fischer, MD, Paediatric Haematologist, Universitair Medisch Centrum, Dept of Paediatrics, Utrecht, Van Creveldkliniek, National Haemophilia Centre, HP. C 01.425, University Medical Centre, PO Box 85500 3508 GA Utrecht, The Netherlands.
Tel: +31-30250400. Fax: +31 30 2505349. Email: K.Fischer@digd.azu.nl

Jørgen Ingerslev, MD, Dept of Clinical Immunology, Haemophilia Centre, University Hospital of Skejby, Aarhus DK-8200, Denmark.
Tel: +45 8949 5180. Fax: +45 8 949 5192. Email: j-ing@post3.tele.dk

Sam Schulman, MD, Coagulation Unit, Department of Haematology, Karolinska Hospital, S-171 76 Stockholm, Sweden.
Tel: +468-5177 3373. Fax: +468-5177 5084. E-mail: sam.schulman@ks.se

Alok Srivastava, MD, Christian Medical College Hospital, Department of Haematology, Ida Scudder Road, Vellore, Tamil Nadu 632004, India.
Tel: +91 416 222102 / 223603. Fax: +91 416 232035 / 232 054. E-mail: alok@hemato.cmc.ernet.in

WHO Secretariat

Dr Victor Boulyjenkov, Responsible Officer, Human Genetics Programme, Management of Noncommunicable Diseases Department, World Health Organization, CH-1211 Geneva 27, Switzerland
Tel: 00 41 22 791 3442. Fax: 00 41 22 791 4769. Email: boulyjenkovv@who.ch

Dr Jean Emmanuel, Director, Blood Safety and Clinical Technology Department, World Health Organization, CH-1211 Geneva 27, Switzerland
Tel: 0041 22 791 43 87. Fax: 0041 22 791 4836. Email: marambad@who.ch

WFH Secretariat

Professor Christine Lee, Haemophilia Centre & Haemostasis Unit, Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom (Chairperson and Rapporteur)

Ms Melanie Prentice, Haemophilia Centre & Haemostasis Unit, Royal Free Hospital, London, United Kingdom

Ms Line Robillard, World Federation of Haemophilia, 1425 Rene-Levesque Blvd. West, Suite 1010, Montreal, Quebec H3G 1T7, Canada
Tel: +1 514 875 7944. Fax: 001 514 875 8916. Email: line@wfh.org
5. References


