Coagulation factor usage guideline for UHL haemophilia centre. CHUGGS CMG	University Hospitals of Leicester NHS NHS Trust Trust Reference: C6/2020

1. Introduction and Who Guideline applies to

This guideline is for use by those treating haemophilia and other inherited and acquired bleeding disorders, when coagulation factor replacement is being considered for the control of haemostasis.

2. Guideline Standards and Procedures

General recommendations

Patient information and consent

Good practice dictates that the necessity for treatment is appropriately explained to the patient and/or parent and family members.

This should include the advantages and risks of different therapies to allow an informed decision to be made. When consent has been obtained this should be recorded in the case notes.

Vaccination against hepatitis A and B

Hepatitis A and B vaccination is highly effective in preventing infection. All patients who currently receive, or have a high likelihood of requiring , blood products should be counselled about risks and offered vaccination.

Carers who are preparing and/or injecting blood products should also be offered vaccination.

Hepatitis A vaccine is not licensed for those less than one year of age.

In patients with more severe bleeding disorders, the vaccines should be given subcutaneously, not intramuscularly, to reduce the risk of haematoma at the injection site.

Choosing a therapeutic product

The key issues in selecting a product are its efficacy and safety. Other features such as cost, volume and ease of reconstitution, storage conditions, shelf-life, and the possibility of use by continuous infusion and the security of supply should also be considered.

Efficacy

Before a licence is granted a product will have to have demonstrated pharmacokinetic equivalence to other licensed concentrates, as well as safety and efficacy in the clinical setting.

The extent of clinical studies will depend on the novelty of the manufacturing process, but some concentrates prepared by well-established processes may not be required to demonstrate efficacy in a large number of patients.

Safety

When selecting a plasma-derived or recombinant concentrate, the two most important safety issues are transmission of infectious agents and inhibitor formation.

Clinical trials of new products are usually undertaken on relatively few patients and are therefore not large enough to assess the incidence of rare complications.

Safety from rare complications is usually assessed from vigilant follow-up of treated patients in formal post-marketing surveillance studies.

To minimize infectious risk, it is essential to consider the whole manufacturing process for both plasma-derived and recombinant concentrates. If the process contains any human or animal component, the epidemiology of known, and potential, transfusion transmissible infectious agents need to be considered.

Thus, for plasma products, the country of origin of the plasma, donor selection, viral screening by antibody, antigen and nucleic acid amplification testing, virus removal and inactivation processes (usually demonstrated with model viruses) and the extent of clinical experience with the concentrate should be taken into account.

For recombinant concentrates those manufactured and formulated with the least addition of human or animal protein will reduce the risk of exposure to infective agents as will virus removal and inactivation processes. However, it is noted that none of the currently available recombinant concentrates have ever been shown to have transmitted an infective agent.

The risk and consequence of inhibitor development in patients with haemophilia is the greatest safety concern in patients using recombinant products.

Avoidance of exposure to concentrates, blood products and animal proteins

Mild haemophilia A and von Willebrand disease (VWD) should be treated with desmopressin (and tranexamic acid) in preference to coagulation factor concentrates whenever possible. See also Desmopressin for bleeding disorders guideline.

Licensed products

Licensed products used within their product licence should be preferred to unlicensed products or products used outside their product licence unless there are clear advantages to an alternative treatment.

Unlicensed products should be used, if possible, under formal clinical trial rather than on a named patient basis.

UKHCDO Specific recommendations

Patients with congenital haemophilia should be treated with recombinant products, particularly, if they have never been exposed to plasma products

- **Haemophilia A (HA)** - Recombinant FVIII (SHL or EHL) or Emicizumab are treatment options for prophylaxis
- **Haemophilia B (HB)** - Recombinant FIX (SHL or EHL) is the treatment of choice for prophylaxis

HA and HB patients with inhibitors: Patients presenting with acute bleeds should be managed with bypassing agents including rFVIIa (NovoSeven) and FEIBA. Prophyalxis should be considered with an alternative agent such as Emicizumab.

- **N.B. CONCOMITANT USE OF EMICIZUMAB AND FEIBA SHOULD BE AVOIDED BECAUSE OF RISKS OF THROMBOTIC MICROANGIOPATHY**

von Willebrand disease: A concentrate containing von Willebrand factor (VWF) is the treatment of choice if desmopressin is not likely to be effective or is contra-indicated . When choosing a product, the VWF.RCo:VWF.Ag ratio, multimeric structure, and the ratio of FVIII to VWF, and proven response to DDAVP may influence choice

Factor XI deficiency: Patients with FXI:C levels <20 units dL/L may suffer excessive bleeding following trauma or surgery and should be managed with infusions of FXI concentrate unless there is a clear history of haemostatic challenge without bleeding. In those with milder deficiency of FXI (20–70 units dL/L), bleeding is difficult to predict and may not be excessive even in the context of surgery. Where there is a clear history of abnormal bleeding and treatment is required to secure haemostasis, the use of FXI concentrate or virally inactivated fresh frozen plasma (FFP, 15–20 mL/ kg) is reasonable, though for minor procedures and dental extractions tranexamic acid alone may suffice. If FXI concentrate is used, the dose should not raise the level of FXI:C above 70 units dL−1 (maximum dose 30 units/ kg) and tranexamic acid should not be given concurrently because of the risk of thrombosis. In the context of dental surgery, tranexamic acid mouthwash may be used. Patients should be assessed for pre-existing risk of thrombosis and the concentrate

should be avoided if possible, especially in those with a history of cardiovascular/vascular/stroke disease.

Factor VII deficiency: Recombinant VIIa is the treatment of choice. If not available, a specific pdFVII concentrate should be favoured over a FVII containing prothrombin complex concentrate because of the potential thrombogenicity of the latter.

Factor II or X deficiency: No specific concentrates are available, and prothrombin complex concentrates are the treatment of choice

Factor V deficiency: Factor V containing concentrates are not available and plasma is the only available treatment. Virally inactivated plasma ("SD FFP e.g. Octaplas) is recommended.

Factor XIII deficiency: Factor XIII concentrate is the treatment of choice.

Fibrinogen deficiency: Fibrinogen concentrate is the treatment of choice. If not available, then virally inactivated FFP or cryoprecipitate is recommended.

Replacement therapy – General principles

Deficiency or absence of coagulation factors results in impaired thrombin generation and resultant clot is unstable. The unstable clot is susceptible to lysis and break down. This can result in excess bleeding at the time of the injury on subsequently during wound healing. The net outcome is either unexpected bleeding during procedure and after trauma and poor wound healing resulting in either death of the patient or infections and open wounds.

Episodes of bleeding in patients with deficiency of coagulation factors require replacement therapy.

Bleeding episodes should be treated as early as possible.

An accurate diagnosis of the type of bleeding disorder and knowledge of the baseline levels is essential. Most patients with bleeding disorder carry a card that specifies the diagnosis and the baseline levels, which help the treater in acute treatment decisions

Two broad approaches are used in the management of bleeding disorders secondary to a decrease or defective coagulation factor protein:

On demand treatment

This includes replacing the missing factor as needed to stop bleeding in trauma related or spontaneous bleeds or replace prior to events that are associated with bleeding in normal subjects, including surgery and dental work.

The aim is to arrest bleeding and prevent rebleeding when the clot is acting as temporary barrier. In addition, bleeding can also happen during the tissue repair and wound healing when clot undergoes fibrinolytic breakdown.

Factor therapy must be administered promptly in doses adequate to control bleeding and continued for sufficient duration to ensure haemostasis and wound healing.

Prophylaxis

In patients with severe bleeding disorders, bleeding can be spontaneous and recurrent into any anatomical area, with weight-bearing and force-transmitting areas being most typically affected. Internal bleeding including cerebral bleeds can be fatal, and recurrent bleeding into joints and muscles can result in permanent damage with secondary disability.

To prevent recurrent and spontaneous bleeding, prophylaxis can be instituted. This consists of administration of the missing factor on a regular basis. This partial restoration of thrombin generation seems to be adequate for prevention of fatal bleeds and reduction in long term joint damage.

The frequency of infusion is related to the half life of the factor and the minimum levels that need to be maintained in between the infusions to prevent spontaneous bleeds.

Coagulation factors for use in Clinical practice

CFCs available can be either recombinant or plasma Deri reived. They can consist of one factor or more than one factor.

Recombinant Factor VIII – Standard half life

- Advate
- Novo Eight
- Refacto AF

Recombinant FVIII – Extended half life

- Elocta
- Esperoct

Plasma derived Intermediate purity factor VIII

VWF containing cocentrates

- Voncento

Factor IX - recombinant , SHL

- BENEFIX

Factor IX - Plasma derieved, SHL

Replenine-VF

Factor IX - recombinant , EHL

- Idelvion
- Alproxlix
- Refixia

Pure VWF containing concentrate

- Veyvondi

Prothrombin complex concentrates

- OCTAPLEX

Activated prothrombin complex concentrates

- FEIBA

Fibrinogen concentrate

- RIASTAP (Fibronogen)

Factor XI - Plasma derived

- BPL FXI
- LFB FXI

Protein C concentrate

- Ceprotonin

Anti-thrombin concentrate

- KYBERNINE-P

Recombinant activated factor VII

- NOVOSEVEN

Recombinant Porcine Factor VIII

- Obizur

Factor X Concentrate

- Coagadex

Factor XIII concentrate

- Fibrogammin P

Monoclonal antibody therapy – listed for completeness but see separate guideline

- **Emicizumab – N.B. CONCOMITANT USE OF EMICIZUMAB AND FEIBA SHOULD BE AVOIDED BECAUSE OF RISKS OF THROMBOTIC MICROANGIOPATHY**

Storage:

The factor concentrates that are listed in this document are all kept in the Haemophilia Centre fridge.

This is located on level 2 in the Osborne Building.

The stock levels and maintenance are the responsibility of the Lead Haemophilia Nurse.

The fridge temperature (both Minimum and Maximum) is recorded and documented every 24 hours Monday to Friday by the Haemophilia CNS team as per UHL guidance holidays. Excluding Weekends and Bank holidays.

The fridge has an internal thermometer as well as an external minimum/maximum thermometer.

The Fridge is connected to an alarm system that is located on the Haematology Inpatient Ward. This is a 24 hour clinical area.

If the fridge deviates outside of the normal range (2-8 degree centigrade) it will alarm on the ward.

During working hours the staff on duty in the Haemophilia Centre would liaise with the Duty Manager and Pharmacy to arrange the transfer of the products to an alternative fridge within the LRI site until the issue is resolved.

If the deviation occurs outside of the Centre working hours the nurse in charge on Ward 41 should then alert the Haematology SPR on call.

The Haematology SPR on call would need to contact the duty manager and make arrangements for the fridge stock to be transferred to an alternative fridge within LRI site until the issue can be resolved.

The Fridge has a yearly service contract with phcbi and these documents are held locally.

DISPENSING:

The factor concentrates are dispensed to patients if needed for home administration by HCP's working within the Haemophilia Centre.

There is a robust recording system in place whereby all factor concentrates dispensed are recorded in a Ledger as well as the patient's individual treatment record and the National Haemophilia Data Base. The product is labelled with a patient sticker identifying that it has been supplied by University Hospitals Leicester.

Principles of coagulation factor use

Factor activity measurements

Fibrinogen is the only clotting factor commonly measured by weight (mg/dL or g/L). The others are commonly measured in functional (biological) assays as plasma concentrations of these proteins are difficult to measure and may not be relevant as molar concentrations may not always directly translate into biologic activity.

Clotting factor "concentration" in plasma is determined by bioassays and expressed as coagulant activities in international units(u) per millilitre or decilitre in comparison to normal plasma. The word concentration is inappropriate to refer to coagulant activity and the word '**level**' is used to describe this activity.

A **unit of factor** is the amount of activity present in one millilitre (ml) of AVERAGE fresh normal plasma separated from blood anti-coagulated with sodium citrate solution in a 9:1 volume ratio.

Average pooled normal plasma contains 100% of each factor, which is the same as 1U or iu / millilitre (mL) or 100 U or iu /decilitre (dL).

An average normal person (70kg) with a plasma volume of 3000 ml has 3000 units of circulating factor of any type and the total factor in the body is function of the volume of distribution

Pharmacology of clotting factors

The science of the use and effects of drugs and may be subdivided broadly into pharmacokinetics and pharmacodynamics.

Pharmacokinetics (PK)

Process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body over a period and the study of such processes. (Drug disposition – **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion)

Important PK parameters in routine clinical practice

- Half- life (t ½)
- In vivo recovery (IVR) or Incremental recovery (IR) or Recovery
- Volume of distribution
- Clearance
- Time to trough (e.g. 3%, 1% factor…)

Pharmacodynamics

Process of interaction of pharmacologically active substances with target sites in living systems, and the biochemical and physiological consequences leading to therapeutic or adverse effects.

Dose →[PK]→ concentration (plasma and/or site of action) →[PD]→ effect

PK parameters

Pharmacokinetics properly deals with drug concentration and applying pharmacokinetic calculations to coagulant activities may be questionable but nevertheless convenient and valuable.

Of the below parameters, the **in vivo recovery or IR** is unique to clotting factors and is routinely used for dosing in clinical practice.

Volume of distribution

Distribution of the drug in the various body tissues is known as the volume of distribution and it is defined as the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration.

Thus, it represents the apparent volume of plasma in which a drug is considered distributed (or diluted) in the body. This is calculated as the amount of drug in the body divided by the plasma concentration and is ypically reported in (ml or litre)/kg body weight.

Since drugs in general diffuse gradually from the circulation into various organs and tissues, V normally increases over time after the injection. At distribution equilibrium, V is the volume of distribution at steady state (Vdss). The higher the Vdss, the more extensive is the distribution of the drug away from the plasma space.

Volume of distribution may be increased by renal failure (due to fluid retention) and liver failure (due to altered body fluid and plasma protein binding). Conversely it may be decreased in dehydration.

Of the coagulation factors, factor VIII and VWF are typically restricted to the intravascular space and their volume of distribution would be the plasma volume. Other coagulation factors, particularly the serine proteases distribute to extravascular spaces.

Clearance (CL)

CL is the capacity of the body to eliminate a substance and is defined as the volume of plasma from which a substance is completely removed per unit time; either mL/min or mL/hr.

However, the concept can be applied to any substance, either endogenous or exogenous. The CL of a drug is normally calculated as dose divided by the area under the plasma concentration curve (AUC).

During a constant rate infusion this corresponds to rate of infusion divided by plasma concentration at steady rate.

Half- life (t ½)

The half-life of a drug is the time it takes to decrease the plasma concentration to half of its initial value.

The processes of distribution and elimination govern the half-life of a drug and plasma half-life is also related to distribution to other body fluid compartments.

However, the plasma concentration curve of a drug normally shows several half-lives (or phases), at least one early phase owing to distribution and the “terminal” phasing representing elimination. Half-lives are determined by fitting an exponential equation to the plasma concentration versus time values (or in simple cases a linear function to log plasma concentration versus time values, which is equivalent).

Mean residence time (MRT)

This represents the average life time of the drug molecules in the body. The MRT depends on both distribution and elimination and can be calculated very simply as Vdss divided by CL.

In vivo recovery (IVR) or Incremental recovery (IR) or Recovery

This parameter has been used only for coagulation factors and is an estimate of the amount of coagulation factor ‘recovered’ in the circulation and is inversely related to the volume of distribution.

It is calculated as the rise in factor activity in iu/dL for every unit/kg administered.

The presence of "post infusion activation" makes the IVR dependent on the early blood sampling schedule in the pharmacokinetics study

IVR [U/dL per U/kg] = observed rise in U/dL / dose administered in U per Kg

Thus pharmacokinetic parameters are useful to describe the in vivo behavior of coagulation factors and help compare different preparations of coagulation factors but of greater clinical interest, is the ability to calculate the plasma levels of coagulation factors at any time during a treatment and to calculate the dose required to achieve a desired level.

IVR is dependent on the

- Clotting factor
- Inter individual variability
- Intra individual variability, especially in acute illness

IVR is applicable to factors in plasma, prothrombin complex concentrates, and single concentrates.

PK parameters of various clotting factors

Factor	**Median IVR (% or IU/dL)**	**Median IVR (IU/mL)**	**Half – life (Median; in hrs (range if avail))**
rFVIII	2.0 (1.5 to 2.5)		12 to 14 (8 to 16)
rFVIII:FC			
rFIX	0.8 (0.28 to 1.38)		16 to 18 (10 to 42)
Idelvion	1.30		Median 104 to 118
Refixia	0.023		Median 83 to 115
Alprolix	0.92		Median 82.12 (71.39-94.46)
pdFVII	1.7	0.017 IU/ml	Median 3.2 to 6.8
pdFII (Kcentra)	1.9 %	0.019 IU/ml	59.7
pdFX	1.9 %	0.019 IU/ml	29.4
pdFIX	1.3 %	0.013 IU/ml	16.6
Fibrinogen	1.7 mg /dL per mg/kg (range 1.30-2.73)		77.1 (55.73-117.26)

r – recombinant; pd- plasma derived; t1/2 – Fibrinogen – if level not known 70mg/kg

Calculation of factor doses – Principles

The appropriate dose of factor for replacement therapy is an amount of the relevant clotting factor that will provide satisfactory haemostasis to control a bleeding episode. It needs to take into account a number of parameters including;

- severity of the bleeding episode
- underlying severity of the bleeding disorder
- planned procedure and associated bleeding risk.

- pharmacologic properties of the clotting factors, including volume of distribution, t 1/2 , IVR

Regardless of the product used dose used is calculated in terms of units per kilogram of body weight

Dosing Principles

As factors are administered in bolus infusion, this will necessarily result in peak level immediately after the infusion and trough level that is lowest level before the next infusion.

The two questions that need addressing when designing a treatment regimen are (a) dose – how much and how frequent (b) the duration of treatment.

Dose – how much to give? The dose must be adequate to restore thrombin generation for arresting the bleed and must also maintain enough thrombin generation to prevent rebleeding. The dose and frequency of infusion are determined by the factor levels desired immediately, i.e. peak and what levels are desired before the next infusion i.e. trough.

Generally, peak levels must be within normal range as they are expected to be associated with normal thrombin generation. In addition, the peak is determined by known half life of the factor, desired frequency of infusion and desired trough level. For example, it is possible to achieve a lower peak and higher trough if factor VIII is administered three times a day compared to once a day as the desired trough level will dictate the dose of infusion and the achieved peak.

Duration of treatment is determined by the timeline for completion of tissue repair. This is particularly to address the breakdown of clot and presence of fragile blood vessels during tissue repair.

Factor VIII, IX and other clotting factors

Empiric calculation based on IVR (recommened method)

Where the IVR for a factor is known the dose needed per kg can be calculated as follows

Bolus dosing

- Rise required (IU/dL) = desired level of factor - baseline factor level or pre level
- Dose required (IU) = (Rise required in IU/dL/ IVR) X weight(kg)

Example

- For example a 50kg patient with a FVIII:C<1 iu/dl who needs a factor level of 100 iu/dl will require 2500 units FVIII concentrate
- Rise required (IU/dL) = 100 % – 0% = 100 %
- Dose required = (100/2) x 50 kg = 50 x 50 kg = 2500 IU or 100 x 50 / 2 = 5000/2 = 2500
- In patient with FIX deficiency instead of 2, a value of 1.0 is typically used.

Calculation of dosage based on plasma volume using FVIII as an example (theoretical consideration)

If whole plasma is given (fresh, fresh-frozen or freeze-dried), as was common before 1970 for all patients and is still used for rare clotting factor deficiencies, it expands the patient's plasma volume. Restrictions on volume expansion limit the plasma factor levels attained, as follows:

For example, in patient with haemophilia A being treated with plasma, the following need to taken into account to predict the factor VIII level.

- For factor VIII the volume of distribution is limited to the plasma volume.
- 70 kg patient with severe haemophilia A, factor VIII < 1iu/dl and plasma volume of approximately 3000 ml.
- For other factors the apparent plasma volume is higher as this accounts for the extravascular distribution.

If FFP is considered, then 1000 ml of FFP will have 1000 units of factor VIII

- Final concentration of Factor VIII with FFP
- = dose / volume of distribution (patients plasma volume + infused volume)
- = 1000 / 4000 ml (3000+1000) i.e .25 units/ ml or 25 %

For a concentrate, 1000 units/10 ml

- Final concentration of Factor VIII with concentrate
- = dose / volume of distribution (patients plasma volume only)
- = 1000/3000 ml i.e 0.33 units /ml or 33 %

To reach a desired plasma factor VIII level, e.g. 50%, in severe hemophilia, multiply that desired level, 0.5 units/ml, by the plasma volume [41 x 70 = 2870] ml, to get the needed dose, 1435 units.

To reach a desired plasma factor VIII level, e.g. 50%, in mild hemophilia, subtract the patient's own factor level, e.g. 10%, from the desired level: 50 -10 = 40 or 0.4 units/ml, and multiply by the plasma volume.

The doses calculated by the two different methods are slightly different, and indeed there is range for plasma volume, and unless truly measured the calculation of doses is approximate.

Fibrinogen

PK study following 70 mg/kg of fibrinogen concentrate demonstrated a median peak (g/L) - 1.3 (1.00-2.10) and median incremental IVR was 1.7 mg/dL per mg/kg body weight.

Normal values **(units)**	1.5 to 4 **g/L** or 150 to 400 **mg/dL**
Dose of Fibrinogen **(mg/kg)**	desired level – measured level **(g/L)** / 0.017 (g/L per mg/kg)
Dose in fibrinogen **(mg/Kg)**	Desired level – measured level **(mg/dL)** / 1.7 (mg/dL per mg/kg)

Pharmacokinetics of Individual coagulation factors

Pharmacokinetics of FVIII

In healthy persons, FVIII circulates in the plasma bound to the von Willebrand factor (VWF). The binding of FVIII to VWF protects FVIII from degradation. The very high molecular weight of the FVIII-VWF complex practically confines it to the plasma space. It can be calculated that only about 14% of the body load of FVIII is extravascular at steady state.

When FVIII is given to adult patients as short-term infusions (typically 5-15 min duration), plasma FVIII levels on average, rise by 0.020-0.025 U/mL or 2 to 2.5 U/dL for every U/kg administered.

FVIII activity time curves are described variably as monophasic or a biphasic two compartment model. An early phase may result more than one process: some (very limited) distribution of FVIII to intra- or extravascular sites and/or rapid clearance of high molecular weight forms and aggregates of FVIII by the reticulo-endothelial system. In addition, the peak plasma FVIII:C is often found 10-15 min after the end of the FVIII infusion. It is believed to complete within 4 hours (distribution half-life) and the remainder is the elimination half-life.

The presence of inhibitors may give a low IVR and/or a rapid clearance of FVIII:C. The differences between plasma-derived and the presently available types of recombinant FVIII are marginal, even though some of them were statistically significant in comparative cross-over studies.

There is a wide inter-individual variation in the pharmacokinetics FVIII:C. Weight-adjusted clearance (CL) of FVIII (i.e. in millilitres per hour per kilogram) has generally been found to decrease with age and/or body weight (BW) during growth from infancy to adulthood, with a corresponding increase in terminal half-life (t1/2).

An increased CL and shorter t1/2 of FVIII in patients with blood group O has also shown and similarly the clearance is shorter in patients with low levels of von Willebrand factor.

Crossover studies on different FVIII concentrates indicate that the pharmacokinetics of FVIII:C remains fairly constant within an individual, i.e., intra-individual variation in pharmacokinetics is lower than the inter-individual variation.

Pharmacokinetics of factor IX

Factor IX is produced by the liver and circulates in the plasma as a free molecule. Owing to it low molecular weight (55 kDa) it also readily diffuses into the interstitial fluid. FIX also binds rapidly and reversibly to the vascular endothelium, with a half maximal binding concentration similar to its normal concentration in plasma.

When plasma-derived FIX is given to adult patients as short-term infusions (typically 5-15 min duration) plasma FIX:C levels on average rise by 0.010-0.014 U/mL or 1.0 to 1.4 U/dL for every U/kg administered. The initial volume of distribution of 0.07-0.10 L/kg, exceeds the plasma volume.

Binding to the endothelium causes immediate disappearance of some of the infused FIX from the plasma. FIX:C then declines in a clearly biexponential fashion, in which the distribution phase of the curve represents diffusion of FIX into interstitial fluid. Thus, the Vdss of FIX is three to fourfold greater than the plasma volume.

The presently available recombinant FIX differs in both biochemistry and pharmacokinetics from plasma derived FIX, with a higher CL. Its IVR is approximately two thirds of plasma derived FIX.

FVIII and FIX half-life studies

Short half-life studies are influenced more by the distribution half-life than by the elimination half-life and so it is recommended that half-life studies are continued for at least 24-48 hours after infusion.

Model independent or dependent analysis may be used to analyze the data but will give different results.

Half-life's can be calculated either with dedicated software or from population PK models.

Vitamin K dependent factors

Coagulation factor	Beriplex®, Half-life of factors from SPC based on studies in 15 healthy volunteers		Octaplex® Range from SPC
	Median half life	Range	
Factor II	60 hrs	(25 – 135)	48 - 60 hours
Factor VII	4 hrs	(2 – 9)	1.5- 6 hours
Factor IX	17 hrs *	(10 – 127)	20 - 24 hours
Factor X	31 hrs	(17 – 44)	24 - 48 hours
Protein C	47 hrs *	(9 – 122)	
Protein S	49 hrs *	(33 – 83)	
* terminal half-life; two-compartment-model			

Continuous infusion of factors

Continuous infusion of coagulation factors has the obvious benefit of mimicking normal coagulation without peaks and troughs associated with bolus infusions.

It can be used to maintain a safe steady-state levels of coagulation factors without the risk of a levels falling below a minimum haemostatic level.

Several important issues related to continuous infusion that have been addressed in the 1990's are related to stability and microbiological safety of the reconstituted concentrates. Several

studies revealed most concentrates at that time were stable after reconstitution at room temperature for a few days or more, in various minipumps.

The addition of small amounts of heparin improved the stability of some and prevented local thrombophlebitis at the site of infusion caused by the concentrated proteins. The typical dose of UFH is 1-5 u/ml of the reconstituted solution. The addition of UFH to rVIIa leads to an immediate decrease in activity by 20 to 30%, and the addition of LMWH causes aggregate formation without decreasing the activity and addition of UFH is not recommended.

Another method is widely adopted to prevent local phlebitis is to run a parallel infusion of saline, 10 to 20 ml /hr through a three-way connector. This would be the preferred method in UHL.

Advantages of CI

More efficacious and cost effective when compared to the bolus infusion. This was demonstrated in a prospective controlled study

There is minimal risk of the levels following below a haemostatic level, which is not uncommon in bolus dosing, as the dosing is done based on the population half-lives, and is dependent on staff remembering to do the injections at the right time.

Adjusted continuous infusion

Continuous infusion of factor VIII or IX shows a progressive increase in the levels, which is related to gradual decrease in clearance after a steady haemostatic level has been achieved.

Trough factor levels may be maintained are dependent on the day post-surgery, and thus allowing for adjusting the rate of infusion to maintain a desired level.

The rate of continuous infusion is calculated based on the clearance obtained by a formal PK study or based on haemophilia population-based clearance.

- 3.5 mL/kg/h for factor VIII
- 4.5 mL/kg/h for pdFIX
- 6 to 7 mL/kg/h for rFIX

The rate of infusion (IU/kg/hr) = clearance (mL/kg/hr) x level (IU/ml)

Recommended dosages for Factor VIII and IX

The table below sets out recommended dosages of factor VIII or IX.

Limitations

It is difficult to be too prescriptive in defining the dose treatment for bleeding in haemophilia A and B, as individuals' levels and responses differ.

Studies in previously treated patients have shown that an adequate initial dose will result in resolution of a bleed with only one treatment, which is clearly cost-effective.

Furthermore, it is probable that the dose used should be individualized using pharmacokinetics. Often vial size is a constraint on the dose administered.

3. Education and Training

It is expected that staff working in the haemophilia centre will undertake the necessary professional development activities. Haematology specialty doctors will receive training in accordance with regional training program activities which are aligned to the national curriculum.

A training program is in place for the emergency department

Guidance for reconstitution and administration of factor concentrates are available on MedUsa (injectable medicines guide), the product SPC and the Trust transfusion guideline.

Any HCP assessed as competent in the delivery of IV medications can deliver factor concentrates to patients with specialist service input.

See also haemophilia clinical operations policy.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Outcome of bleed episodes	Success of treatment (case by case in real time)	Cons of week	Daily/weekly	Negative outcomes documented in MDT

5. Supporting References (maximum of 3)

References

1) Escobar MA Treatment on demand - in vivo dose finding studies Haemophilia 2003; 9: 360-367
2) Report of a Joint WHO/WFH/ISTH meeting (2002) - Delivery of Treatment for Haemophilia - WHO/WFH/ISTH/WG/02.6
3) Textbook of Hemophilia, second edition, 2010 by , Christine A. Lee (Editor), Erik E. Berntorp (Editor), W. Keith Hoots (Editor) : Chapter 6 - Continuous infusion of coagulation products in haemophilia, Angelika Batorova and Uri Martinowitz
4) Textbook of Hemophilia, second edition, 2010 by , Christine A. Lee (Editor), Erik E. Berntorp (Editor), W. Keith Hoots (Editor) : Chapter 16 - Pharmacokinetics, Sven Bjorkman and Erik Berntop
5) Protocols for the treatment of haemophilia and von willebrand disease, Third edition. April 2008, no.14.http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf
6) Management of Haemophilia, National Guidelines for New Zealand; http://www.haemophilia.org.nz/uploads/bloodline/TreatmentGUIDELINEFinalrevisedMarch05.pdf
7) Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Guideline. Approved by the British Committee for standards in Haematology, Haemophilia (2008), 14, 671-684
8) http://www.ukhcdo.org/UKHCDOguidelines.htm
9) Guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. British Journal of Haematology 2010: 149 (4); 498-507
10) http://www.bcshguidelines.com

6. Key Words

Haemophilia, bleeding disorders, factor concentrate, factor viii, factor ix, PCC, octaplex, von Willebrand disease

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Details of Changes made during review: **Updated Product list** **Addition of new section on storage and dispensing.**	