Haemophilia Protocols
(version 3.1: June 2017)

Oxford Haemophilia & Thrombosis Centre
Churchill Hospital
Oxford
OX3 7LE
Contents
Introduction
Haemophilia team 3
Patient access 5
Shared care 6

Emergencies
Medical emergencies and transfer of patients 9
Head injury 9
Management of allergic reactions 10

Prophylaxis and dosage 12

Surgery and dental treatment
Surgical protocols 17
Dental treatment 17

Miscellaneous issues
Haematuria 21
Analgesia 22

Viral issues and vaccinations
Vaccination protocols 23
HIV and hepatitis C 24

Travel 25

Inhibitors 26

Genetic Testing 29

Von Willebrand Disease 30

Rare Inherited bleeding & platelet disorders 34

Acquired coagulation inhibitors 35

Carriers and genetic counselling
Carrier testing 36
Prenatal diagnosis 38
Management of delivery 40
Genetic counselling 42

Appendices 46

Version 3.1 June 2017
Members of Haemophilia Team

Medical Staff

Consultant haematologists
David Keeling
Nicola Curry
Susie Shapiro

Consultant paediatric haematologists
Georgina Hall
Neha Bhatnagar

Haematology SpR and FY2 doctor
Rotate on 4 monthly basis

Paediatric haemophilia Trust doctor
Catriona Buchanan

Haemophilia Nurses
Joanne Burke
Kayleene Coutts
Marie Eales
Sarah Pool
Alice Wilkinson
Simon Fletcher (clinical trials)
Sayma Raza-Burton
Chris Deane (clinical trials)

Nursing assistant
Karena Carter

Physiotherapists
Stephanie Taylor
Claire Rogers
Lisa Guerin

Consultant orthopaedic surgeons
Chris Dodd (knee)
Mark Rogers (ankle)
Chris Little (elbow)
Peter McLardy-Smith (hip)

Consultant hepatologist
Jane Collier

Infectious diseases consultant
Chris Conlon/John Fratt

Dental surgeon
Mark Taylor

Administrative team

Unit Manager
Kevin Clarke

Data manager
Karen Cairns
Maeve Henry Aine

A and C manager
Sharon Osborne

Version 3.1 June 2017
<table>
<thead>
<tr>
<th><strong>Secretaries</strong></th>
<th>Julia Rainford</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Davina Earl</td>
</tr>
<tr>
<td></td>
<td>Lauren Marlow</td>
</tr>
<tr>
<td><strong>Receptionists</strong></td>
<td>Jenny Ing</td>
</tr>
<tr>
<td></td>
<td>Karen Ashfield</td>
</tr>
<tr>
<td></td>
<td>Susan Luland</td>
</tr>
</tbody>
</table>

**Laboratory Staff**

<table>
<thead>
<tr>
<th><strong>Laboratory manager</strong></th>
<th>Peter Baker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomedical Scientists</strong></td>
<td>James Beavis</td>
</tr>
<tr>
<td></td>
<td>Peter Burt</td>
</tr>
<tr>
<td></td>
<td>Sarah Harper</td>
</tr>
<tr>
<td></td>
<td>Jo Sewell</td>
</tr>
<tr>
<td></td>
<td>Patricia Bignall (Genetics)</td>
</tr>
<tr>
<td></td>
<td>Pam Wright (Genetics)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Medical Laboratory Assistant</strong></th>
<th>Steve Howgate</th>
</tr>
</thead>
</table>
UKHCDO guidelines:

Treatment should be in line with current UKHCDO guidelines. These are available on line at http://www.ukhcdo.org/guidelines/.

Patient access for treatment/advice.

During normal working hours all patients have open access to either OHTC (Oxford haemophilia & thrombosis centre) or CHOX (Children’s Hospital Oxford). They can contact the centre by telephone or in case of emergency come to the centre for treatment.

Out-of-hours (evening from 1700 to 0900; weekends; public holidays) cover is provided by the haematology SpR. The patients should ring OUH hospital switchboard (01865- 741166) and ask for the haematology SpR in the first instance. The SpR will give appropriate advice or make arrangements to administer treatment, and always has recourse to the on call consultant. There are separate on call rotas for the adult and paediatric haemophilia consultants. All clinic letters for OHTC/CHOX patients are available from the network drive – ‘haem data’ or via Alden. Haematology registrars must have access to the haem data network drive prior to commencement of on-call duties.

Out of hours review:
Haemodynamically unstable patients should be sent to ED. For all other situations:
If children need to be reviewed, they will be asked to go to Kamran ward at CHOX, John Radcliffe site. If adults need to be reviewed, this can take place on the haematology ward at the Churchill Hospital. The process for out of hours adult review is outlined below and should be followed by the Haem SpR at OHTC in the working week, or the Haem SpR on call:

The Haem SpR should provide Triage (or the haematology ward) with: Patient name, DOB, MRN/NHS number and a contact telephone number for the patient. The SpR and Triage (or the ward) will agree on an appropriate time for assessment and this discussion must take place prior to asking the patient to attend the unit. Patient review and treatment is undertaken by the Haem SpR.
Shared patient care with haemophilia centres.

Adults:
All adult patients with inherited bleeding disorders across the region (Oxfordshire, Buckinghamshire, Berkshire, Northamptonshire, Gloucestershire) are under the care of OHTC. The exception is that OHTC has shared care clinic arrangements for patients with inherited moderate and mild bleeding diseases in Northampton.

In the event of an emergency or when minor surgery is planned locally, and when patients with inherited bleeding disorders attend a District General Hospital the local haematology teams should be contacted, in addition to the haemophilia team at OHTC:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Lead Consultant</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheltenham &amp; Gloucester Hospitals</td>
<td>Dr. Phil Robson</td>
<td><a href="mailto:philip.robson@nhs.net">philip.robson@nhs.net</a> 0300-422-5249 0300-422-5253 (secs)</td>
</tr>
<tr>
<td>Great Western Hospital, Swindon</td>
<td>Dr. Claire Davies</td>
<td><a href="mailto:claire.davies@gwh.nhs.uk">claire.davies@gwh.nhs.uk</a> 01793 605007</td>
</tr>
<tr>
<td>Milton Keynes Hospital</td>
<td>Dr. Sarah Davies and Dr. Magbor Akanni</td>
<td><a href="mailto:sarah.davis@mkuh.nhs.uk">sarah.davis@mkuh.nhs.uk</a> 01908 660033 bleep 1854 (Wed – Fri) <a href="mailto:magbor.akanni@mkuh.nhs.uk">magbor.akanni@mkuh.nhs.uk</a> 01908 660033 bleep 1506 (Mon – Wed)</td>
</tr>
<tr>
<td>Royal Berkshire Hospital, Reading</td>
<td>Dr. Rebecca Sampson</td>
<td><a href="mailto:rebecca.sampson@royalberkshire.nhs.uk">rebecca.sampson@royalberkshire.nhs.uk</a> 0118 3225111 bleep 922</td>
</tr>
<tr>
<td>Stoke Mandeville Hospital, Bucks</td>
<td>Dr. Renu Riat</td>
<td><a href="mailto:renu.riat@buckshealthcare.nhs.uk">renu.riat@buckshealthcare.nhs.uk</a> 09782 226690</td>
</tr>
<tr>
<td>High Wycombe Hospital</td>
<td>Dr. Jonathan Pattinson</td>
<td><a href="mailto:jonathan.pattinson@buckshealthcare.nhs.uk">jonathan.pattinson@buckshealthcare.nhs.uk</a> 01494 425224</td>
</tr>
<tr>
<td>Northampton Hospital</td>
<td>Dr. Suchi Krishnamurthy</td>
<td><a href="mailto:suchitra.krishnamurthy@ngh.nhs.uk">suchitra.krishnamurthy@ngh.nhs.uk</a> 01604 634700 (ask for haemophilia)</td>
</tr>
</tbody>
</table>

Children:
CHOX have shared care arrangements with local DGH hospitals, as agreed between CHOX and each paediatric team (DGH haemostasis lead details, see below). The role of the lead is to ensure that notes and Open Door Access are in place should patients require emergency admission to a local hospital. The local hospital will have copies of all the letters from the CCC in Oxford and know who to contact for management advice. The local lead consultant is not required to see the child for regular clinic review. If the child has other paediatric issues managed locally then the local lead will inform Oxford.
**Hospital** | **Lead Consultant** | **Contact Details**
---|---|---
Great Western Hospital, Swindon | Dr Francine Toussiant | Francine.Toussaint@gwh.nhs.uk
 |  | Sec: 01793 604925
Milton Keynes Hospital | Dr Mya Aye | Mya.Aye@mkuh.nhs.uk
 |  | Sec: 01908 996501
Royal Berkshire Hospital, Reading | Dr Cathy Golding (P/T) | Catherine.Golding@royalberkshire.nhs.uk
 |  | Sec: 01183 227531
Stoke Mandeville Hospital, & Wycombe, Bucks | Dr Beth Cheeseborough | Beth.Cheesebrough@buckshealthcare.nhs.uk
 |  | Sec: 0296 316369
Wexham Park, Slough | Dr Johanna Aspel | Johanna.Aspel@fhft.nhs.uk
 |  | Sec: 01753 634605
Northampton General Hospital | Dr Bindu Koodiyedath | Bindu.Koodiyedath@ngh.nhs.uk
 |  | Sec: 01604 545521
Cheltenham & Gloucester Hospitals | Dr Thomas Kus | Thomas.Kus@glos.nhs.uk
 |  | Sec: 03004 228491

**Northampton (Haemophilia Centre) care arrangements:**

1) Patients with severe bleeding disorders who live in Northampton and its environs will receive care from Oxford. Patients with mild and moderate disease will receive care from Northampton.

**Non-haemophilia centre shared care arrangements:**

2) These patients should be seen in Oxford for diagnosis/confirmation of diagnosis and registration. Thereafter follow up arrangements should be agreed for each individual patient and recorded in the notes. Many patients will remain under the sole care of Oxford. If patients are seen locally at DGHs they should also be seen at OHTC or CHOX at a minimum annually (severe and moderate disease) or 5 yearly (mild disease). Patients with severe and moderate disease should be routinely seen/followed up in clinic (which may include a telephone clinic for mild patients) every 6 months for severe and moderate disease or annually if they have mild disease.

**All patients:**

3) Effective communication should be maintained between the two centres. All correspondence should be copied to each other.
4) OHTC/CHOX treatment protocols will be shared with neighbouring haemophilia centres.
5) Children with severe haemophilia on prophylaxis should be reviewed at least every three months until the age of 2 years after which they are seen every 4 months until the age of 5 years. This will ensure maintenance of correct prophylactic dose (which may need changing frequently because of rapid growth rate), and addressing any other haemophilia related problems. Children with moderate to mild haemophilia may be reviewed bi-annually or annually.
6) All patients with severe or moderate haemophilia should be reviewed at least every six months. Those with a mild condition should be offered annual review. However patients exposed to HIV or hepatitis may need more frequent visits for their infective conditions as demanded by their co-existing viral infections.
7) Supply of concentrates. OHTC will supply concentrates for satellite haemophilia centres and DGHs who must in return submit accurate treatment records (within 7 days of treatment occurring) and in addition must submit stock control records, monthly (see appendix a).
Medical emergencies and transfer of patients from OHTC to JR

In the event of a medical emergency, dial 2222 to call the Resuscitation Team.

If a patient needs emergency transfer to the John Radcliffe, follow the South Central Ambulance Service Emergency Inter - hospital transfer Flow chart for Acute Trusts which is situated in the haemophilia nurses’ office. Dial (9) 0300 123 9826 for an ambulance then speak to the team or unit who will receive the patient.

Head injury

Head injury can have potentially dangerous consequences in PWH.

1. For any significant head injury, replacement therapy with factor concentrate should be given without delay. The dose should be calculated to raise the level to 1.00 IU/mL.
2. Have a low threshold for requesting a CT head.
3. A neurological examination should be performed. Criteria for admission include the following.

- Loss of consciousness
- Focal neurological deficit
- Nausea or vomiting
- Extensive external signs of injury
- History of significant injury

If admission is felt necessary, neurological observations for signs of raised intracranial pressure should be started. If there is any suspicion of an intracranial bleed, urgent CT brain scan should be arranged. Trough levels should be kept ≥ 0.50 IU/mL at least and maybe higher in the early acute stage.

If the patient is considered to be well enough to go home after adequate initial replacement therapy they should be instructed to contact the centre immediately if they develop any of the following, and admission organised.

- Headache
- Dizziness
- Nausea or vomiting
- Confusion/ changes in behaviour
- Drowsiness or disorientation
- Diplopia or blurred vision
- Fits/convulsions

The patient must receive a head injury information sheet on discharge.
(Found in the red folders in the clinic rooms at OHTC and on haemdata).
Management of allergic reactions

Anaphylactic reactions can be of particular concern in patients with haemophilia B and inhibitory antibodies. All nursing and medical staff must undergo annual resuscitation training, in line with current trust requirements. In the case of staff dealing with children, this should also include the paediatric training component.

OHTC: IM Adrenaline 1:1000 is kept adjacent to the resuscitation trolley, next to the ‘hypo’ box, in room 6 clinic room.

CHOX: IM adrenaline is kept in the clean utility of the paediatric out patients department, next to Lion room. On Kamran ward it is kept in the drug room.

Mild Reactions:

Mild reactions are manifested by pruritus and an urticarial rash.

Treatment:
Stop the infusion
Check BP, PR and oxygen saturation
Consider chlorphenamine.

Severe Reactions:

Clinical features may include:

- Hypotension
- Skin and mucosal urticaria
- Angioedema
- Wheeze
- Abdominal cramps

Treatment:


Full protocols and training information are available on the “anaphylaxis” page on the OUHFT intranet: http://orh.oxnet.nhs.uk/Anaphylaxis/Pages/Default.aspx

and at: www.resus.org.uk
Figure 3. Anaphylaxis algorithm
**Prophylaxis and dosage of factor VIII/IX**

Boys with severe haemophilia (<0.01 IU/mL factor VIII or IX) should be considered for prophylaxis. A decision on exactly when to start treatment will usually be taken in the paediatric clinic, but is likely to be after the child has suffered at least one spontaneous joint bleed.

**Standard half-life products:**

The principal recommendations regarding prophylaxis, using standard half-life (SHL) factor concentrates, in the current UKHCDO guidelines (BJH 2010; 14: 498-507) are as follows:

1. Prophylaxis should be commenced by the second joint bleed or significant soft tissue bleed or, at CHOX, in any patient (PUP) who has received more than one dose of factor for acute mucosal or any other bleeding.
2. Prophylaxis may be introduced by initially administering factor concentrate once weekly but escalating to more frequent administration as venous access permits in order to prevent the occurrence of any joint or soft tissue bleeds.
3. Prophylaxis should consist of a SHL factor VIII concentrate dose (25 – 40 iu/kg) administered ideally every 48 h, or a SHL factor IX concentrate dose (25 – 40 iu/kg) every 72 h unless circumstances dictate otherwise, such as the need for attendance at the haemophilia centre for prophylaxis administration.
4. The minimum dosage of factor concentrate that prevents breakthrough bleeds should be used. Daily injections of FVIII SHL factor concentrate can significantly reduce the amount of concentrate required to prevent bleeds and maintain trough factor levels >0.01 IU/mL and should be considered in very active older boys or where breakthrough bleeds are occurring on a less frequent prophylactic regimen.
5. Prophylactic doses should be tailored to provide maximum cover for particular physical activities, e.g. school, physical education lessons, sport training sessions. Prophylaxis should be administered ideally in the morning to optimize factor VIII and IX levels.
6. Children and neonates with severe haemophilia who have had a spontaneous central nervous system bleed should continue long term prophylaxis following initial treatment of the bleeding episode.
7. Insertion of an indwelling venous access device should be considered if venous access and/or adherence to treatment are difficult.
8. The prophylaxis dose should be rounded up to the nearest whole vial size.

The usual starting dose is: factor VIII 25 iu/kg (range: 25 iu/kg - 40 iu/kg) on alternate days and for factor IX 25 iu/kg every three days. Prophylaxis should be given in the morning so that levels are lowest when the boy is sleeping. Doses can then be adjusted to give trough levels ≥0.01 IU/mL. If breakthrough spontaneous bleeding occurs despite a trough level of 0.01 IU/mL, a higher trough level may be indicated. If trough levels are not satisfactory then the dose may be increased. If more than 40 iu/kg are required then consideration should be given to making injections more frequent.

Patients with haemophilia B associated with deletions are at particular risk of developing inhibitors and these can trigger severe allergic reactions. For this reason, such patients...
should have the first 20-25 doses in a hospital setting to monitor for signs of hypersensitivity/anaphylaxis where adrenaline and resuscitation facilities are on hand.

Adults benefit from continued prophylaxis once they reach adulthood. The UKHCDO guidelines make the following recommendations in the case of adults:

1. Adolescent and adult patients with severe haemophilia should be encouraged to continue regular prophylaxis at least until they have reached physical maturity.
2. In some individuals who have demonstrated a much milder phenotype, adapting formal prophylaxis to a more targeted policy may be considered but in such cases, there must be an agreed plan for monitoring and reintroduction of prophylaxis if necessary.
3. If significant haemarthroses occur after discontinuing prophylaxis, prophylaxis should be reinstated to prevent joint damage and to maintain quality of life, especially if bleeding interferes with education or employment.
4. The dose and frequency of infusions should be adjusted, based on bleeding phenotype and ideally individual pharmacokinetics. The minimum amount of concentrate should be used to prevent haemarthroses irrespective of trough levels.
5. Pharmacokinetic studies may help dose adjustment and improve cost effectiveness. At a minimum, trough levels should be monitored but more information can be obtained from half-life studies.
6. Patients on long term prophylaxis should have their regimens critically reviewed at least every 6 months. If no breakthrough bleeds have occurred a trial of dose reduction is appropriate, especially if the trough level >0.01 IU/mL.
7. Short or long term secondary prophylaxis should be considered in patients with advanced arthropathy if recurrent bleeding episodes significantly interfere with work or mobility.
8. Long term secondary prophylaxis is indicated following intracranial haemorrhage if no underlying cause can be corrected.

### Dosage of Factor VIII/IX in haemophilia patients without inhibitors

<table>
<thead>
<tr>
<th>Desired Factor Level IU/mL</th>
<th>Dose of factor VIII (K=2) iu/kg</th>
<th>Dose of factor IX BeneFIX (K= 0.8) iu/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>haemarthrosis, muscle haematoma, minor surgery, simple dental extractions</td>
<td>0.50</td>
<td>25</td>
</tr>
<tr>
<td>life-threatening haemorrhage, major surgery</td>
<td>1.00</td>
<td>50</td>
</tr>
</tbody>
</table>

**Extended half-life (EHL) products**

There are several FVIII and FIX extended half-life factor concentrates that are currently either in clinical trial or have recently come into clinical use. These products use a variety of techniques (i.e. pegylation, fusion to Fc fragments or fusion to albumin) to extend the half-life of either clotting factor. In general, EHL factor VIII concentrates extend the plasma half-life of FVIII by 1.5 times (i.e. approx. 18 hours in adults). The half-life for factor IX is extended, on average, four – to fivefold (i.e. approx. 72-96 hours in adults). The potential benefits of EHL are: the ability to
reduce injection frequency for patients as well as giving the option for maintaining a higher trough level.

**Factor VIII EHL:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Cell line</th>
<th>Biochemical strategy</th>
<th>Age (years)</th>
<th>Subjects</th>
<th>Incremental recovery (IU dl⁻¹)(IU kg⁻¹)</th>
<th>Half-life (h)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bax 855</td>
<td>Baxalta</td>
<td>CHO</td>
<td>Full-length rFVIII with lysine PEGylation (20 kDa PEG)</td>
<td>12–65</td>
<td>26</td>
<td>Mean (SD) 2.49 (0.69)</td>
<td>Mean (SD) 14.3 (3.8)</td>
<td>[15]</td>
</tr>
<tr>
<td>Bevy 94-9027</td>
<td>Bayer Healthcare</td>
<td>BHK</td>
<td>B-domain-deleted rFVIII with site-specific PEGylation (single 60 kDa PEG)</td>
<td>≥18</td>
<td>14</td>
<td>Mean (range) 2.9 (2.1–4.1)</td>
<td>Mean (range) 18.2 (13.7–28.1)</td>
<td>[14]</td>
</tr>
<tr>
<td>Nk-GP</td>
<td>Novo-Nordisk</td>
<td>CHO</td>
<td>B-domain-truncated rFVIII with site-specific PEGylation (single 40 kDa PEG)</td>
<td>≥18</td>
<td>26</td>
<td>Mean (SD) 2.4 (0.6)</td>
<td>Mean (SD) 19 (5.53)</td>
<td>[18]</td>
</tr>
</tbody>
</table>

Bax 855 = Adynovate
rFVIII-Fc = Eloctate

**Factor IX EHL:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Cell line</th>
<th>Biochemical strategy</th>
<th>Age</th>
<th>Subjects</th>
<th>Incremental recovery (IU dl⁻¹)(IU kg⁻¹)</th>
<th>Half-life (h)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9-GP</td>
<td>Novo-Nordisk</td>
<td>CHO</td>
<td>Factor IX with site-specific PEGylation (single 40 kDa PEG)</td>
<td>12–65</td>
<td>15</td>
<td>Mean (SD) 1.4 (0.4)</td>
<td>Mean (SD) 96 (42)</td>
<td>[21]</td>
</tr>
<tr>
<td>rFIX-Fc</td>
<td>Sobi</td>
<td>HEK293H</td>
<td>Factor IX fused with IgG₁Fc</td>
<td>≥18</td>
<td>11</td>
<td>Mean (range) 0.87 (0.63–1.2)</td>
<td>Mean (range) 57.6 (47.9–67.2)</td>
<td>[24]</td>
</tr>
<tr>
<td>rFIX-FP</td>
<td>CSL Behring</td>
<td>CHO</td>
<td>Factor IX fused with recombinant human albumin</td>
<td>12–65</td>
<td>28</td>
<td>Mean (SD) 1.4 (0.28)</td>
<td>Mean (SD) 91.6 (20.7)</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥6–12</td>
<td>15</td>
<td>Mean (SD) 1.5</td>
<td>Mean (SD) 94.8</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;6</td>
<td>12</td>
<td>Mean (SD) 0.93 (0.20)</td>
<td>Mean (SD) 89.6 (11.2)</td>
<td>[24]</td>
</tr>
</tbody>
</table>

rFIX-Fc = Alprolix


The recent guidelines from the UKHCDO (*Haemophilia* 2016; 22: 487-98) recommend the following for EHL products:

1. Previously untreated patients (PUPs) should be offered entry into a PUP study, if available or, until further data are available, to commence treatment with product licensed for PUPs.
2. In minimally treated severely affected patients, switching to an EHL-CFC can be considered after 50 EDs. A limited half-life study should be performed (defined at OUH as at least 3 time points). These patients should be tested for an inhibitor before and at approx. 10 EDs after switching product.

3. Patients with a past history of an inhibitor that has been tolerised within the last year should not switch CFC.

4. An initial consultation should cover options for regimens and it should be made clear to patients that EHL-CFC may not reduce infusion frequency for all individuals.

5. A test dose of EHL-CFC should be given and IR and half-life data should be derived so that treatment can be optimised.

6. After switching to an EHL-CFC, individuals should be followed up 4 weekly for 3 months to assess the pattern of bleeding (in person or via telephone). Trough levels should be taken at about 10 EDs and 3 months after switching, or at other times – if indicated.

7. All patients should be assessed for regimen efficacy based on ABR, adherence, convenience, joint score and annualised treatment cost after 1 year on an EHL-CFC.

8. Treatment of bleeding episodes should be based on the severity of the bleed, the individual’s incremental recovery and the time of the previous dose. If bleeds do not resolve after 2 doses, patients should discuss further treatment with their treating centre.

In addition, NHS England has set out the following criteria, and these must be followed in order that patients with haemophilia may be switched to an EHL-CFC:

**NHS England Criteria (Sept 2016) for the Prescribing of Enhanced Half-Life Blood Factors:**

1. The initiation and on-going prescription of EHL-CFCs is conditional on compliant use of the Haemtrack™ secure therapy recording system for haemophilia patients.

2. A change in regimen to an EHL-CFC will be accompanied by education and training with specific reference to the difference in pharmacokinetics between standard and EHL-CFCs, and how EHL use will differ from the patient’s standard product.

3. Patients must be prepared to use multiple vials, including small dose vials, to enable specific doses at the most clinically appropriate dose and to minimise waste. Patients must ensure that any remaining standard blood factor product has been used up prior to commencing treatment with an EHL regimen.

4. Any patient who, after undergoing specific education and training, is considered to be at significant risk of non-adherence with an EHL regimen or other criteria associated with these criteria must not be initiated on treatment with an EHL-CFC.

5. Patients will have the pharmacokinetic half-life of their existing regimen established in order to evaluate their capacity to benefit from using an EHL-CFC and to assist in the determination of their initial EHL regimen. Patients determined as unlikely to benefit will not proceed to initiation with an EHL-CFC. Any patient who does not achieve the anticipated benefits of an EHL-CFC will change back to their original product and regimen in accordance with the current UKHCDO Guideline (Collins et al 2016).

6. A trough blood factor activity level will be obtained and recorded after 5 to 10 treatments with an EHL product. Doses may need to be adjusted accordingly to ensure a minimum therapeutic effect:
a. EHL rVIII (currently the only product available is Elocta®) may be prescribed if it is felt it will confer a clinical benefit and reduce the weekly number of doses by at least 1 dose per week. For an initial PK measurement use 25 iu/kg. The prescribed prophylaxis dose should be the same as the current regimen but with an extended dose interval as described. For example, alternate day treatment can be switched to every 3 days at the same dose. The target trough level should be the same as with previous standard blood factor. If this cannot be achieved with the same dose at extended intervals then the patient should be changed back to their previous regimen.

b. EHL rFIX may be prescribed if it is felt it will confer a clinical benefit compared with standard rFIX. For an initial PK measurement use:
   i. 30 iu/kg for Fc-rFIX (eftrenonacog alfa; Alprolix®)
   ii. 15 IU/kg for albumin-fusion rFIX (albutrepenonacog alfa; Idelvion®)

To ensure optimal value the following maximum conversion ratios must be adhered to:
- Benefix® to Alprolix® 100:54 (i.e. 0.54)
- Benefix® to Idelvion® 100:27 (i.e. 0.27)

Data indicate that mean prophylaxis doses should be about 30 IU/kg/week with Alprolix® in one or two divided doses, and about 15 IU/kg/week with Idelvion® in one or two divided doses. Trial data indicates that these doses are sufficient to deliver trough activity levels >1% in most adult patients. Higher doses per Kg body weight may be required to achieve the same minimum trough level in children but if the maximum conversion ratios are adhered to then best value will still be assured.

7. Based on an individual’s pharmacokinetic results, the patient will be provided with written guidance on doses for the management of specific types of bleeding episodes and guidance on when to administer a second dose. If a bleeding episode does not respond to two doses of blood factor the patient must attend their nominated centre for care. An escalation in the rate, frequency or severity of bleeding episodes compared with recent observations whilst using a SHL-CFC will require the patient to change back to the previous standard product.

8. Patients should be switched back to their previous SHL-CFC regimen if any of the following occur relative to the recent use of that regimen:
   a. The anticipated clinical benefits do not materialise after 3 months of using an EHL regimen
   b. There is an increase in the rate, frequency or severity of bleeding episodes
   c. The blood factor activity trough level is reduced
   d. There is evidence, including strong circumstantial evidence, that the patient is not adherent to the prescribed regimen
   e. The patient, or their responsible carer, is not compliant with Haemtrack™

9. Patients or their responsible carer must provide written consent of the acceptance of these conditions and clinical criteria for the use of EHL-CFCs.
Surgical Protocols

All surgical interventions should be performed in collaboration with OHTC or CHOX.

**Surgery should be planned ideally for late morning or early afternoon.** This will allow sufficient time for transport of blood samples and performing factor assays.

**Prior to any invasive procedure, the infection control team must be informed if the patient falls into the ‘at risk’ category with regards potential exposure to vCJD. Infection control will then make a risk assessment for each individual case.**

**Elective Surgery**

An inhibitor screen should be performed prior to surgery. In most cases, a negative result from the last couple of months is satisfactory. Weight should also be recorded. A proforma detailing the haemostatic therapy required will be written for adult patients by the OHTC team and placed in the notes of the patient and saved into the EPR notes. (Form found on haemdata: ‘surgical proforma’).

**Factor concentrate replacement.**

1. Just prior to the procedure, give factor to the patient aiming to raise the level to 1.00 IU/mL and take a post-infusion sample.
2. A second post-operative factor level may be taken for individual patients, but commonly for those with short half-lives.
3. For factor VIII: further doses are usually given twice a day (SHL), and for factor IX (SHL) once a day or twice a day with pre- and post-dose factor assays as required.
4. In general, patients should have a minimum of 5 days of treatment. However, the duration will depend on the nature of surgery and up to 14 days of treatment may be required.

**Thromboprophylaxis (adults and high risk children)**

Patients with von Willebrand disease should have routine thromboprophylaxis during surgery. Haemophilia A patients do not routinely require thromboprophylaxis, haemophilia B patients should receive thromboprophylaxis whilst their factor IX level is within the normal range. For other patients this should be considered for each individual case.

**Analgesia**

NSAIDs are generally contraindicated but COX 2 inhibitors can be used. Intramuscular injections should not be given routinely.

**Anti-fibrinolytic Therapy**

Tranexamic acid is commonly used as an adjunct to reduce blood loss depending on the type of surgery. It can be administered with all forms of factor concentrate.
Liver Biopsy

1-2 weeks before the biopsy make sure that a platelet count, PT and inhibitor screen have been performed. Liver biopsy must not be done in patients with inhibitors.

Biopsy should be planned for late morning or early afternoon.

If there are no complications a total of 3 days of treatment is sufficient.

Endoscopy

A simple endoscopic procedure should not cause any bleeding and it is safe to raise the factor level to 0.50 IU/mL. It is not necessary to repeat the dose if the procedure was atraumatic and non-invasive. If any intervention i.e. biopsy is planned then the levels should be raised to 1.00 IU/mL and maintained at or > 0.50 IU/mL. In such an event the duration of treatment will depend on the actual procedure performed but in general a total of 3-4 day treatment is sufficient.

Lumbar Puncture

Factor levels should be raised to close to 1.00 IU/mL and this must be confirmed before the procedure – DO NOT proceed to LP if level is < 0.80 IU/mL. Thereafter the level should be maintained above 0.50 IU/mL for 24 hours. (see VWD section for treatment of VWD).
Protocol for patients with bleeding disorders having dental treatment


Please note: The details given below for management of dental treatment do NOT apply to patients with inhibitors. A separate individualised care plan should be discussed for these patients.

In all cases consider the aspect of the dental treatment that is most likely to result in bleeding (e.g. most dental injections do not require cover but if an injection is being administered for a dental extraction FVIII levels will need to be ≥ 0.50 IU/mL)

Procedures NOT requiring cover:
- Patient homecare such as flossing or tooth-brushing
- Routine peri-odontal probing
- Minor/supra-gingival scaling including polishing and ultra-sonic scaling
- Direct or indirect restoration (filling) with supra-gingival margins
- Any orthodontic procedure (fitting or adjustment of braces)
- Maxillary buccal or palatal infiltrations
- Periodontal/inter-ligamentary anaesthesia
- Intra-papillary injections

Procedures requiring cover:
- Extensive/sub-gingival scaling or root planning and detailed 6-point periodontal examination
- Root canal treatments including extirpation of pulp
  Aim for one visit
  Avoid molars if possible
- Any dental extraction irrespective of complexity
- Regional block anaesthesia including inferior alveolar and posterior superior alveolar nerve block and true mental blocks (risk of muscle haematoma)
- Lingual infiltration and floor-of-mouth injections (risk to vessels in floor of mouth)
- Biopsy
- Any implant surgery
- Direct or indirect restoration (filling) with sub-gingival margins

Treatment Guide
For patients with Haemophilia A and B, severe and moderate:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Level of factor required (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root planning/ “deep” scaling</td>
<td>0.30</td>
</tr>
<tr>
<td>Inferior alveolar nerve block</td>
<td>0.50</td>
</tr>
<tr>
<td>Extraction of tooth/teeth</td>
<td>0.50 – 1.00</td>
</tr>
</tbody>
</table>

Version 3.1 June 2017
Mild Haemophilia A:
- Consider the need for desmopressin or factor concentrate (check to see if there is a high risk of inhibitor formation from the patient’s genetic mutation)
- Follow desmopressin guidance, as required

Von Willebrand Disease:
- Patients requiring cover should have desmopressin or Voncento to achieve FVIII and VWF activity of at least 0.50 IU/mL

ALL PATIENTS
All patients undergoing dental procedures should be considered for tranexamic acid
Patients can be given:
- 5% tranexamic acid mouthwash 10ml qds for 5 days
Or
- Oral tranexamic acid 15-25mg/kg tds for 5 days

The OHTC preferred therapy for adults is:
- 1g tranexamic acid tablets crushed and dissolved in water/juice and swilled around the mouth and gums for 2 minutes, then swallowed
- First dose, pre-dental surgery
- Subsequent doses t.d.s. for 5 days

If tranexamic acid mouthwash is used, a special order to pharmacy is required and the mouthwash is made up from the IV ampoule.
Haematuria

Spontaneous haematuria is not an infrequent occurrence in severe haemophilia. Apart from oral hydration it usually does not require any other treatment and stops in a few days. Replacement therapy may become necessary if haematuria persists or is profuse.

1. Encourage increased oral fluid intake (of at least 2 litres per day in an adult).
2. If haematuria persists and/or is severe, consider admitting for intravenous hydration followed by factor concentrate administration to raise levels to 0.50 IU/mL. A second dose may be required 8-12 hours later.
3. Antifibrinolytic therapy with tranexamic acid is specifically contraindicated as this can lead to clot colic.

Consider investigating haematuria in the following cases

- Elderly patients
- Mild haemophilia
- Recurrent haematuria
**Analgesia guidelines**

Any patient with a bleeding tendency **should not routinely have:**

- Intramuscular Injections
- Aspirin and conventional non-steroidal anti-inflammatory drugs. These drugs cause a non-selective inhibition of cyclo-oxygenase enzymes (inhibit COX 1 and COX 2) and therefore lead to platelet dysfunction. However, clinical judgement for individual cases must be used to balance the risks versus the benefits for certain clinical conditions. COX-2 inhibitors such as etoricoxib are useful agents in the management of painful arthritis, particularly when several joints are affected. For those patients at an increased risk of gastric ulceration or those with a known history of previous GI bleeding, prescription of a concomitant PPI should be considered. The evidence for routine dual prescribing of a PPI with etoricoxib is weak and patients should be treated on an individual basis.
- Please refer to the BNF for details of the ‘analgesia ladder’ which guides incremental treatment for pain. Paracetamol and codeine are the usual first line oral therapeutic agents. The potential for tolerance and addiction should not be overlooked when stronger opiate analgesics are prescribed for prolonged periods.
**Vaccination protocols.**


Patients with haemophilia A and B as well as those with factor VII deficiency who will be treated with recombinant products no longer need to be vaccinated against hepatitis A and B as there is no risk of transmission of hepatitis though treatment with these products. Patients with pre-existing chronic hepatitis C (HCV) who develop community-acquired acute hepatitis A or B can develop acute liver failure. Patients who travel abroad are particularly vulnerable to develop hepatitis. For these reasons, vaccination against both hepatitis A and B would still be prudent in this particular subgroup of patients.

Patients with von Willebrand disease and other rare disorders of coagulation who will be treated with plasma-derived products should still be offered vaccination against hepatitis A and B. Hepatitis A and B vaccines can be given separately or in combination. Please refer to the BNF for up to date vaccine formulations. If a child is going to receive recombinant products, it is worth waiting until they are one year of age to give the combined “Twinrix” formulation. In the case of children receiving plasma preparations, vaccination against hepatitis B should be commenced shortly after birth and then separate vaccination against receive hepatitis A may be given once they are a year old.

An adequate response towards hepatitis B should be documented in the clinical records and correspondence with the GP after completion of vaccination. It usually takes three months to achieve an adequate protective level of protective antibodies. It is now generally accepted that revaccination is not required in recipients of recombinant products as cellular immunity is just as important as humoral immunity (reflected by antibody levels).

**All vaccines should be given subcutaneously, in line with UKHCDO recommendations**
**Viral Issues**

**Hepatitis C.**

Patients who have contracted hepatitis C from exposure to blood products should be followed up by Dr. Jane Collier. Any patients needing admission under her care are usually admitted to ward 5F at the John Radcliffe hospital.

Patients should have (had) HCV PCR analysis to confirm active hepatitis infection. If a patient is found to be positive by PCR, genotype testing, HCV viral load, hepatitis B and HIV serology should be checked. A liver biopsy may be required to determine the extent of hepatic fibrosis, especially for genotype 1, although fibroscans are replacing biopsies in many cases.

Many of the patients exposed to hepatitis C are undergoing eradication therapy with new agents such as protease inhibitors (e.g. boceprevir). For those patients who have successfully eradicated hepatitis C and have no evidence of cirrhosis on fibroscan (i.e. < 14), with normal LFT’s and are not diabetic – they should have annual hepatitis C PCR tests performed at their haemophilia appointments. For those patients who remain cirrhotic, whether or not their hepatitis C has been eradicated, they will remain under the care of Dr Collier and will have regular hepatology follow-up.

**HIV.**

Patients who have contracted HIV are followed up by Professor Chris Conlon/Professor. John Fratt and their team at the infectious disease outpatient clinic. The medical team at the OHTC are often involved in taking blood tests for these patients but all other issues related to HIV are managed by the infectious diseases team.
Travel

Documentation required for all patients

The patient should contact the Centre well in advance of their planned trip so that travel letters can be issued and often emailed directly to the patient.

Two letters are usually sent:

1. Letter stating patient’s basic diagnosis and OHTC’s contact phone number.
2. Customs declaration form for those carrying medical supplies.

A pro-forma of these letters can be found on haemdata under Travel Letters.

Patients also require the following:

The contact name/address/phone number of the haemophilia centre in the relevant country can be provided to the patient, as needed. The source which should be consulted for the most up-to-date information is the “Passport” section of the website of the World Federation of Haemophilia (www.wfh.org), or for European centres only, the following webpage can be used: http://www.euhanet.org/MappedCentres.aspx

Personal UKHCDO Bleeding Disorders card (or International Haemophilia Card) which patients should carry at all times.

It is also strongly recommended that patients purchase travel insurance before going abroad.

Duration of travel abroad:

Haemophilia factor concentrate may be issued for a patient travelling abroad for up to 3 months only. The NHS/commissioners will not sanction extending the duration beyond 3 months.
Inhibitors

When to screen for inhibitors:

- After every 3rd exposure-day or every 3 months until the 20th exposure-day
- After every 3 – 6 months up to 150 EDs
- Every six to 12 months thereafter for haemophilia A, and when clinically indicated for haemophilia B
- Prior to any surgical procedure
- If the frequency of bleeding increases or if the clinical or laboratory response to replacement therapy is poor
- If the patient is changed to a new type of factor VIII concentrate screen for inhibitors prior to the change and at least twice in the first 6 months following the change or if there is a change in frequency of bleeding
- Previously untreated and minimally treated patients with severe haemophilia A who have received an intensive FVIII exposure (≥ 5 EDs) should be closely monitored
- Mild and moderate haemophilia A - annual testing (if exposed to FVIII concentrate); or after intensive exposure (≥ 5 EDs); or after surgery
- Mild and moderate haemophilia A – patients with a mutation conferring a high inhibitor risk and/or family history of inhibitors should undergo testing after all exposures
- Haemophilia B – patients must be tested after an allergic reaction to replacement therapy prior to any further FIX exposure occurs

Any positive inhibitor test must be confirmed on a repeat sample, as soon as possible. The NHD must be notified of all patients with a persistent positive inhibitor.

Immune tolerance induction
Immune tolerance induction (ITI) is recommended for patients with congenital haemophilia A or B and a confirmed factor VIII or IX inhibitor. It is recommended that prior to the initiation of ITI, bleeding should be managed on-demand using bypass therapy, preferably using recombinant factor VIIa (NovoSeven) to avoid an anamnestic rise in inhibitor titre.

Severe haemophilia A
Patients can be stratified as good risk (starting inhibitor titre < 5 BU/mL and a peak titre < 200 BU/mL); and poor risk (starting inhibitor titre > 5 BU/mL and a peak titre > 200 BU/mL).

ITI should be started as soon as an inhibitor has been confirmed and it is practically possible to do so.

Once ITI has started it is important to avoid interruption. First line ITI should be conducted using
rFVIII concentrate, usually with the product the patient was receiving at the time of inhibitor development. At CHOX, the inhibitor titre is monitored weekly after initiation of ITI to define the peak inhibitor titre. Once peak titre has been defined, the inhibitor titre is monitored monthly thereafter until it is no longer detectable. ITI is continued as long as there is a sustained downward trend in inhibitor titre.

Recovery should then be determined monthly until normal and then half-life determined three-monthly until tolerance is confirmed. Tolerance is defined as the restoration of normal factor VIII recovery and half-life (pragmatically, this means a 48 hr trough of ≥ 0.01 iu/mL and/or the FVIII half-life after a washout of > 7 hr). Dose tapering may be instituted for good risk patients only once the Bethesda titre is reproducibly negative. For poor risk patients ITI should be continued at full dose until full tolerance is achieved.

If there is an upward trend in titre, or inadequate reduction in titre over a 6 month period, the ITI regimen may need modification

If ITI fails, other treatment strategies should be considered: novel agents such as ACE910 are currently in trial for patients with long-standing inhibitor, change to a pdFVIII with a high VWF content; add immunosuppression or a combination of these strategies.

Mild/moderate haemophilia A:
These patients tend to respond less well to ITI. ITI should be reserved for those patients that develop recurrent bleeding. In patients with an acquired haemophilia bleeding pattern, immunosuppression therapy may be considered.

Haemophilia B:
Children with major factor IX deletions (or other genetic abnormalities known to be associated with a risk of inhibitor development) should receive their first 20-25 exposures to factor IX in hospital.

The success rate for inhibitors in patients with haemophilia B is low (25%) and there are additional risks of anaphylaxis and irreversible nephrotic syndrome. Successful reports have used immunosuppression therapy in addition to the Malmo regime.

**Recovery and half-life estimation**

In routine clinical practice, a pre- and a single measurement taken 5-10 minutes post-infusion, is usually used to estimate recovery. Factor recovery % should be calculated with reference to the recovery constant (K) for that product. K is commonly taken as 2.0 for factor VIII and 1.0 for plasma derived factor IX but different values apply to recombinant factor IX in children and adults.

\[
\text{Recovery} \% = \frac{\text{measured factor increment}}{\text{expected factor increment}} \times 100
\]

\[
\text{Expected factor increment (IU/mL)} = \frac{IU/kg \text{ infused} \times K}{100}
\]
Half-life studies should be conducted after a wash out period or when the factor VIII or IX level has reached baseline. A dose of 50 iu/kg should be given and samples taken at 1, 4, 8, and 24 hours or until activity has fallen to baseline.

Normal recovery values range from 0.75 IU/mL to 1.00 IU/mL. Recovery and half-life are commonly lower in children. A consensus statement recently accepted that recovery as low as 0.66 IU/mL and half-life as short as 6 hours may be observed in children.

**Management of Bleeding in Patients with Inhibitors**

The management of an acute bleed depends on a clinical assessment of severity, knowledge of the inhibitor level to human factor VIII and if titres are low whether the patient is a high or low responder. Tranexamic acid should be considered for all bleeds.

*Minor haemorrhage:* These may be managed with larger than normal doses of FVIII in low responders. Otherwise FEIBA or rVIIa should be used.

*Major haemorrhage* may be treated with factor VIII if inhibitor titres are low enough to allow satisfactory plasma levels to be achieved. Otherwise rVIIa is recommended. If this fails FEIBA should be given.

*Surgery:* Either NovoSeven or FEIBA may be used: a final decision in an individual case will be taken by the consultant in charge. In view of the potentially high cost, prior authorisation will need to be sought from the commissioners in the case of elective surgery.

*Haemophilia B:* Recombinant factor VIIa is the treatment of choice for bleeding in patients with high-responding factor IX inhibitors or reactions as FEIBA contains factor IX which could trigger further reactions.
Genetic testing

Haemophilia.

FVIII/FIX mutation analysis should be undertaken in all patients with haemophilia A and B. This information is important as several F8 or F9 mutations confer a high risk of inhibitor formation. Severe haemophilia A patients have a 30% risk of inhibitor development with the risk of developing an inhibitor at its highest during the first 20-50 exposure days. Mild haemophilia A patients have a lower risk of inhibitor development but, unlike severe haemophilia A, the risk persists with every exposure. It is important to use mutation information to guide therapy decisions for mild haemophilia A patients (i.e. whether to use DDAVP or rFVIII products) to minimise inhibitor development for at risk patients.

VWD.

Not all VWD patients require mutation testing. At OHTC we test all type 2 and type 3 patients and will offer testing to type 1 patients with VWD levels less than 0.30 IU/mL.

Rare bleeding disorders.

OHTC can provide genetic testing for all single factor rare bleeding disorders. Extended coagulation testing can be sent to Thrombogenomics (see folders in clinic rooms for referral forms and genes tested).

Platelet defects.

OHTC can provide genetic testing for MYH-9, GP1B, GP2B3A mutations. Extended platelet testing can be sent to Thrombogenomics.

Whole Genome Sequencing.

The rare disease programme is currently offering WGS testing for patients with rare bleeding disorders via the 100,000 genome project. Ideally samples should be sent from multiple members of a family if a genetic cause for a bleeding disorder is being considered. To enter a patient/family into the 100,000 genome project a ‘Clinical Genomic Sequencing Application Form’ should be completed, found here:

http://ouh.oxnet.nhs.uk/MolecularGenetics/Document%20Library/GM_MDT_Clinical%20Sequencing_Application%20Form_V2.docx

The form will be reviewed by the Genomic Medicine MDT and if agreed the genomic consenting process can be done by the genetics clinics (or if a clinician wishes to consent a patient themselves, an online module found at the www.genomicsengland.co.uk website must be completed). Consenting clinics are found at all DGH hospitals across Oxfordshire and in Oxford.

Version 3.1 June 2017
Von Willebrand Disease

Diagnosis of VWD requires multiple tests. The diagram below outlines the diagnostic path:
Treatment and Management of VWD

Full details are provided in the UKHCDO guidelines:
Laffan et al. The diagnosis and management of von Willebrand disease: a UKHCDO guideline approved by the
BCSH. BJH 2014 doi:10.1111/bjh.13064

In deciding upon treatment the following information is important:
- The nature of the bleeding episode
- The factor VIII and VWF levels and the VWD subtype
- The patient’s previous bleeding history and response to treatment
- The factor VIII and VWF response to Desmopressin

Due to the potential risks of infection blood products should be avoided if possible.

Tranexamic acid:

This can be used alone in the management of epistaxis, mouth bleeds and menorrhagia and it is used in combination with Desmopressin or VWF containing concentrates to cover dental extractions and surgery.

Desmopressin:

This is a very valuable drug as it can often be used instead of blood products. The patient information leaflet may be found on haemdata. All patients who may respond to desmopressin (DDAVP) should be have a trial to see if it effective in their individual case. It is often effective in type 1 disease where increasing levels 2 - 5 fold is sufficient for haemostasis. Desmopressin will not be effective in type 3 disease.

Its use in type 2B disease is controversial. It has been said to be contraindicated as the release of the abnormal VWF may induce platelet agglutination and thrombocytopenia.

In type 2N disease, there is often good response, but this is short-lived. A desmopressin trial is advisable.

Patients who are unresponsive to desmopressin, or in whom it is contraindicated, should be treated with a virus-inactivated concentrate that contains either FVIII/vWF or VHP-vWF, i.e. Voncento.

The bleeding time in patients with vWD may be shortened by infusion of normal platelets even if there has been a poor response to replacement of vWF. If mucosal bleeding persists and the bleeding time remains prolonged after adequate replacement therapy with a vWF containing concentrate platelet infusions should be considered.

Factor replacement:
For those patients who are unresponsive, or insufficiently responsive to the measures outlines above, a VWF concentrate should be used. The formulation currently used in our centre is Voncento. Dosage regimes for concentrate can be found in the UKHCDO guidelines
on treatment of VWD (see below for a summary). Recombinant VWF concentrate is currently in clinical trial.

**Treatment of specific problems in VWD**

**Dental Treatment**
In responsive patients a single dose of desmopressin given with tranexamic acid is usually sufficient to cover dental extractions. If desmopressin cannot be used a single dose a VWF containing concentrate can be used aiming for levels of 0.50iu/mL.

Give tranexamic acid, one dose before treatment (orally or iv), and continue orally for 5 days.

**Menorrhagia**
Menorrhagia is very common in women with VWD and conversely VWD is common in women presenting with menorrhagia. The options for treatment include tranexamic acid, the combined oral contraceptive pill (COC), the Mirena coil and desmopressin (commonly via intranasal form). For patients with resistant menorrhagia, a multidisciplinary approach with close liaison with gynaecology is recommended. Options may include: GnRH analogue therapy; prophylaxis with VWF concentrate; uterine artery embolization; thermal ablation of the endometrium and finally hysterectomy.

**Pregnancy**
During pregnancy, VWF starts to rise as early as the sixth week and by the third trimester may have increased so that many patients with type 1 disease have results in the normal (non-pregnant) range. Levels can fall quickly after delivery, often within 2-3 days. These rises may not be seen with type 2 disease. In type 2B disease the increase in the abnormal VWF can cause thrombocytopenia.

All women with type 2 and 3 VWD, and women with type 1 VWD in whom levels are unlikely to rise should be delivered at OHTC/JR. The delivery of type 1 VWD can be managed as normal if the VWF:GPIbM level is > 0.50 iu/mL by 34-36 weeks gestation. In type 3 disease factor VIII and VWF levels do not rise and VWF concentrates are required to cover delivery or caesarean section. VWF activity should be > 0.50 IU/ml for caesarean section and > 0.40 IU/mL for vaginal delivery. Neuraxial anaesthesia is not recommended in women with type 2 or 3 VWD or in women with type 1 VWD in whom the plasma VWF levels have failed to normalise.

Treatment after delivery will be individualised, and will depend on mode of delivery. VWF activity levels should be maintained above 0.50 iu/mL for 3 days for vaginal delivery and 5 days for Caesarean section. Tranexamic acid is a useful adjunctive therapy and we recommend 1g to be given during active labour (orally or i.v.) and then 1g orally t.d.s. until the lochia runs clear. (A spreadsheet outlining management for all pregnant patients can be found on haemdata under: ‘Pregnancy H&T Patients’).

Cord blood screening for VWD is unlikely to give reliable results in type 1 disease though type 2 and type 3 can be tested for.
**Angiodysplasia and VWD**

Angiodysplasia is reported in up to 6% of patients with VWD and may cause gastrointestinal haemorrhage. The diagnosis can be made by endoscopy, isotope scanning or angiography. If angiodysplasia occurs in the stomach or duodenum then proton pump inhibitors may reduce bleeding. Surgical resection should be avoided if at all possible. In patients with recurrent bleeding prophylaxis with VWF containing concentrates may be effective. Thalidomide, oestrogen and statin therapies have been used with some success. Dr Adam Bailey, Consultant Gastroenterologist (bleep 1585) takes a special interest in these patients.

**Surgery in VWD**

Operative procedures should be covered with desmopressin in responsive patients unless contraindicated. Operative procedures should also be covered with tranexamic acid unless this is contraindicated.

The factor VIII plasma concentration should be about 1.00 IU/mL to cover major surgery and sustained above 0.50 IU/mL in the post-operative period.

If mucosal bleeding persists after adequate replacement therapy with a VWF containing concentrate platelet infusions may be considered.

Neuraxial anaesthesia is contraindicated in patients with type 2 and type 3 VWD.

**Endoscopy**

A simple endoscopic procedure should not cause any bleeding and it is safe to raise the factor level to 0.50 IU/mL. It is not necessary to repeat the dose if the procedure was atraumatic and non-invasive.

If any intervention i.e. biopsy is planned then the levels should be raised to 1.00 IU/mL and maintained at or > 0.50 IU/mL.
Rare inherited coagulation disorders and inherited platelet disorders.


Management
For information about the management of bleeding, surgery, pregnancy and delivery and the management of neonates, please refer to the UKHCDO guidelines above.
Acquired coagulation inhibitors.
Collins et al. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO, approved by the BCSH. *BJ H*, 2013; 162: 758–73

Acquired haemophilia A (AHA) has an incidence of about 1.5/million/year and presents most commonly in the elderly at a median age of 75–80 years. Other inhibitors are much less common. The mortality associated with AHA has been reported to be between 8% and 42%. 3–12% of deaths have been attributed to the effects of immunosuppression and infection whilst 3–8% were attributed to bleeding. The diagnosis of AHA should be considered if acute or recent onset of bleeding is accompanied by an unexplained prolonged APTT. Acquired inhibitors for other clotting factors may be considered if acute or recent onset of bleeding is accompanied by unexplained prolonged screening tests - PT, APTT or TT that fail to correct with normal plasma.

**Acquired haemophilia A**
The management of acquired coagulation inhibitors can be considered as a two pronged approach:
- Treatment of bleeding (if indicated)
- Treatment to eradicate the inhibitor

**Bleeding:**
Bleeding should be treated without delay using rFVIIa or FEIBA. Tranexamic acid should be used for all bleeding episodes, especially mucosal surface bleeding. Not all bleeds need haemostatic treatment and many subcutaneous bleeds can be managed conservatively. If the initial bypassing agent is ineffective the other should be tried at an early stage.
rFVIIa at doses higher than 90 microg/kg is not recommended except as rescue therapy because of the increased risk of thrombosis. FVIII replacement combined with plasmapheresis and immunoadsorption can be considered for severe bleeding or if first-line therapy is unsuccessful.

**Immunosuppression:**
Patients with AHA should start immunosuppression as soon as the diagnosis is made: prednisolone 1 mg/kg/d either alone or combined with cyclophosphamide 1–2 mg/d orally. Rituximab can be considered as first-line therapy if standard immunosuppression is contraindicated.
If there is no response within 3–5 weeks, second-line therapies should be considered. The most common second-line treatment is with rituximab combined with other agents. Alternative options are calcineurin inhibitors, multiple immunosuppressive agents and immune tolerance protocols.

Patients should be followed up at least monthly for the first 6 months because relapse is common.
Patients with a past history of acquired haemophilia should have a coagulation screen, or preferably a FVIII level measured before any invasive procedure.

**Other coagulation inhibitors.**
Please refer to the guideline above for details.
Carrier testing & Antenatal Diagnosis for haemophilia

Carrier Testing

The genes for both factor VIII and IX are located on the X chromosome meaning inheritance is sex-linked and recessive. The daughters of men with haemophilia are obligate carriers of the condition, with a 50:50 chance of passing on the condition to a son.

The severity of haemophilia within a given family remains constant. One third of cases arise in families with no previous family history, reflecting new mutations. Genotypic analysis should be offered to all women at risk; both for those at risk of being a carrier and for those who are known obligate carriers, as this will facilitate antenatal testing, if required. Carrier testing can take time to perform and it may seem logical to initiate testing as soon as possible in young women with a family history of haemophilia. However, testing of children ignores the ethical and/or legal rights of those children as testing cannot be considered to have been obtained with the informed consent of the individual child concerned. These issues must be discussed openly with the family.

Most female carriers of haemophilia have levels of factor VIII (or IX) within the normal range but a significant proportion will have a modest reduction in the baseline level. The baseline level is seldom lower than 0.20 IU/mL and women may be at risk of bleeding in the setting of surgery or other invasive procedures.

General approach for carrier testing:

1. Family trees for all our registered patients with haemophilia should be constructed and obligate and potential carriers identified.
2. All obligate or confirmed potential carriers should be registered with HCIS and the NHD. All potential carriers should be registered locally with HCIS until testing is completed. (See appendix B for flowsheet).
3. All obligate and potential carriers should be offered factor level testing in childhood, and certainly before any invasive procedure, but this should not be relied upon as giving an indication of carrier status. This enables those females with low factor levels to be picked up, as therapy may be required at the menarche/for surgery.

4. Carriers with normal clotting factor levels do not need a bleeding card but those with levels below the normal range should be provided with a card. (A DDAVP trial should be offered to those patients with low factor VIII levels). All potential and obligate carriers should be offered an appointment in clinic.

5. The genetic mutation in index cases should be identified and recorded in the relevant notes.

6. Genetic testing of carriers should only be carried out at an age when the girl can be regarded as be able to give written informed consent. It is not acceptable to screen, for example, young infants but as a rough guideline testing at or beyond the age of 16 years of age is reasonable.

7. Counselling should be offered both before and after results become available. Counselling can be offered either at OHTC/CHOX or under the Clinical Genetics team.

8. The general practitioner should be informed of any results.
**Prenatal Diagnosis of Haemophilia**

Prenatal diagnosis of haemophilia should be offered to all carrier women. Prenatal diagnosis that is undertaken in the early stages of pregnancy (i.e. between 9 – 13 weeks) is usually only performed where a termination of the pregnancy is being contemplated. For those women carrying a male fetus to term there is an increasing move towards the use of amniocentesis in the third trimester to inform delivery plans.

Women will require counselling about haemophilia before they make any decisions regarding prenatal diagnosis. Those women who do not wish to have any invasive prenatal diagnosis performed are encouraged to have the sex of their fetus determined at the 20 week scan.

**Maternal blood sampling** is used as a non-invasive test to determine the sex of the fetus for women contemplating termination of an affected fetus. This test looks for the presence of free fetal DNA (ffDNA) using a PCR technique which detects the fetal SRY locus. This locus is only present in male fetuses. This test has a reported accuracy of between 97% - 100%. A maternal blood sample can be taken as early as 7 weeks gestation however the reliability of results is much improved if samples are taken at 9 weeks. A dating US scan is used to confirm gestational age prior to blood sample draw and the fetal sexing result is provided within 7 days. This non-invasive technique can eliminate the need for CVS for any fetus found to be female. In the future it may be possible to determine the presence of the affected gene by this method.

Request forms are found in each clinic room. Please hand-write the EDTA tubes. Further information about the fetal sexing tests run by NHSBT may be found here: [http://ibgrl.blood.co.uk](http://ibgrl.blood.co.uk)

**Chorion villus sampling (CVS)** is the principal invasive method used for antenatal diagnosis of haemophilia if a termination is contemplated. It permits diagnosis during the first trimester, although it should not be carried out before 11 weeks of gestation (earlier biopsy may be associated with a risk of subsequent fetal limb abnormalities). The CVS sample is obtained under ultrasound guidance by either the trans-abdominal or trans-vaginal route (according to the location of the placenta) and is then subjected to DNA analysis. The mother’s factor level should be checked prior to CVS, as haemostatic cover may be required. All invasive methods used for antenatal diagnosis may cause feto-maternal haemorrhage, and anti-D immunoglobulin should be given according to BCSH guidelines if the mother is Rh D negative.

**Third trimester amniocentesis** is being offered at OUH at approximately 34 - 36 weeks gestation. The purpose is to determine whether a male fetus is affected by haemophilia, and therefore helps to guide decisions about place and mode of delivery. If a male fetus is not affected by haemophilia, a carrier mother may be able to deliver at her local obstetric unit. Additionally, this information may facilitate decisions about the safest mode of delivery of the child and can be used in discussions weighing up the risks and benefits of Caesarean Section versus vaginal delivery. The risks of third trimester amniocentesis include a 1 in 200 risk of premature rupture of membranes and a small risk of introducing infection.
General principles:

1. The carrier status of young women should ideally be established before they become pregnant, and accompanied by preconception counselling. PND cannot be offered to women where the causative mutation is not known.
2. For those women seeking PND: gestational age should be confirmed prior to fetal DNA testing. Clotting factor levels and Rhesus status should be checked when the maternal blood sample is taken at ~9 weeks.
3. If the blood sample confirms a male fetus, and the mother wishes to proceed to CVS, the prenatal diagnosis unit at the John Radcliffe Hospital (X. 21716) should be contacted as soon as possible and a date for CVS arranged. Please also inform the molecular genetics lab (X. 72770) at the earliest opportunity of the time/date of the CVS.
4. There should be a clear agreement, recorded in the notes, as to who will take on the responsibility of conveying any PND results to the woman. The way in which the result is to be imparted should also be recorded; e.g. by phone.
5. A termination date should be scheduled at the earliest opportunity. This can be ‘pre-booked’ pending the genetic results from the CVS, in order to facilitate early termination. There are two obstetric doctors (Dr Shelley Hayles and Dr Jane Moore) who can be contacted to arrange a termination of pregnancy. A surgical termination of pregnancy can be conducted up to 13 weeks gestation at OUH but after this time a late medical termination will need to be arranged. Dr Hayles & Dr Moore can be contacted on Wednesdays via extension: 22007 (at the Women’s centre) or via e-mail: shelley.hayles@nhs.net or jane.moore@obs-gyn.ox.ac.uk.
6. Silver Star will often book late amniocentesis procedures. Please ensure that the molecular genetics laboratory (X. 72770) is informed of the time/date of the procedure.
7. PND genetic results take 5 working days. Good communication is key to ensuring the most efficient turnaround times.
Management of Delivery in Carriers of Haemophilia

The levels of factor VIII and von Willebrand factor rise during normal pregnancy. By contrast, factor IX levels do not rise significantly in pregnancy and carriers of haemophilia B with a low baseline factor IX level are more likely to require haemostatic support to cover delivery.

Caesarean section is not needed as a routine just because a fetus may have, or is known to have, haemophilia. Nevertheless, NICE guidelines recommend that all women have the opportunity to request Caesarean section as their preferred mode of delivery, and at OUH there is a Mode of Birth Clinic where women are counselled between Caesarean Section and NVD. It is possible that a third trimester amniocentesis procedure will help in decision making for women considering a Caesarean section on the basis that it may reduce the risk of intra-cranial haemorrhage for an affected haemophilia male fetus. This service is offered on an individual patient basis.

Ultrasound examination to determine the fetal sex during pregnancy is strongly recommended. Even if the mother does not wish to know the result, it is important that this information is available to the obstetrician at the time of delivery. This may influence decisions in the management of the delivery: if the fetus is female she is unlikely to have a very low factor level.

The risk of intracranial bleeding after a vaginal delivery is small but is nevertheless a recognised complication (2.5-4%) (Kulkarni and Lusher 1999). It is not generally necessary as a routine to administer a prophylactic dose of coagulation factor concentrate to a haemophilic neonate after a normal vaginal delivery. However, recent UKHCDO guidelines do recommend infusion of concentrate in certain circumstances such as instrumental or traumatic delivery as well as after a prolonged second stage. Ventouse extraction should be avoided as the use is associated with a high risk of cephalhaematoma or intracranial bleeding. Application of fetal scalp electrodes to monitor fetal heart rate is also best avoided. Recent UKHCDO guidelines recommend that cranial ultrasonography should be undertaken prior to discharge in all neonates with severe or moderate haemophilia. Due to the low sensitivity of ultrasound for the detection of subdural bleeding, cranial MRI should be undertaken in symptomatic neonates even if an ultrasound is normal.

After delivery, a cord blood sample should be obtained for coagulation factor assay and a genetics sample, if sufficient blood can be drawn.

Vitamin K should be given orally NOT i.m.

At the time of delivery the treating midwife or obstetrician should liaise with the neonatal doctor – alerting them to the birth of a baby boy with suspected haemophilia.

Be aware of the risk of delayed post-partum haemorrhage in mothers who are carriers.

Points to remember

1. Good liaison is essential between the haemophilia centre and obstetricians.
2. Baseline factor VIII (or IX level) should be checked at booking, and in the third trimester (ideally at around 34 weeks).

3. An indication of fetal sex can be obtained by assay for free Fetal DNA at 8-10 weeks gestation and this can be confirmed by ultrasound at 16-20 weeks.

4. Haemophilia status in suspected male fetuses can be confirmed by CVS at 11½ -14 weeks gestation or after 16 weeks by amniocentesis. Late amniocentesis, at 34 - 36 weeks gestation, can be performed on an individual patient basis.

5. Caesarean section is not routinely indicated merely because of possible haemophilia but long labour should be avoided so threshold for CS is likely to be lower.

6. Neuraxial (epidural or spinal) anaesthesia in a carrier is permitted from a haemostatic point of view if the factor level is more than 0.50 IU/mL but may be best avoided in labour if the fetus is known to be or may be affected as it increases the risk of an instrumental delivery.

7. If neuraxial analgesia or anaesthesia has been used, remove catheter immediately after delivery or if delayed removal, check factor levels prior to removal. The factor level should be > 0.50 IU/mL for removal. The decision to remove the catheter should be discussed with the duty anaesthetic consultant.

8. Avoid the use of:
   a. fetal scalp electrodes for monitoring during delivery
   b. Ventouse delivery
   c. high and mid-rotational forceps during delivery

9. Take cord blood for factor level (and if possible a genetics sample) and inform neonatal team of the birth of a baby boy with suspected haemophilia.

10. Perform ultrasound of the brain in the affected newborn if born by vaginal delivery and in all infants with moderate and severe haemophilia. In symptomatic infants, an MRI is warranted.


12. Give recombinant products to baby if the delivery is traumatic or has required instrumental delivery and consider treatment after a prolonged second stage of labour.

13. Thromboprophylaxis should be considered for women carriers of haemophilia with conventional risk factors for VTE if factors VIII, IX and VWF are within the normal range.

14. Factor levels for the mothers should remain above 0.50 iu/mL for the first 3 days after vaginal delivery and the first 5 days after Caesarean section. Factor replacement will be given on an individual basis.
Genetic Counselling for Haemophilia

Pasi et al. Clinical Genetics Services for Haemophilia, compiled by the Genetics Working Party on behalf of the UKHCDO.
http://www.ukhcdo.org/guidelines/

Genetic counselling is an important part of comprehensive haemophilia care. The current UK guidelines are summarized below, but further information can be sought using the reference above.

Record keeping:

It is recommended that Haemophilia Centres develop family genetic records of patients with haemophilia and other inherited bleeding disorders.

It is recommended that these notes should:
1. be a separate ‘genetic’ file
2. be kept within the Haemophilia Centre
3. contain the family pedigree which should be compiled using standard conventions
4. contain the results of all relevant genetic tests
5. contain informed written consent for genetic studies, sharing of appropriate family information and inclusion on a register
6. contain copies of all pedigree-related correspondence
7. be kept confidential and only accessed by authorized staff of the OHTC

In conjunction with the development of the family genetic records, it is recommended that a haemophilia genetic register system is also established in each centre.

The pedigree should be updated at least annually, taking advantage of one of the regular clinic visits of the index patient where possible. At these updates it is important to try and confirm the family relationships that have previously been documented and to add new family members that have been born in the intervening period. Reminders should be put in place to ensure this happens.

It is recommended that a post-consultation letter is sent to all families indicating the genetic risks, options available and the offer of genetic counselling to other at-risk relatives. The letter should include a recommendation to contact the haemophilia centre preferably prior to any pregnancy but in the event of a pregnancy, as soon as a pregnancy is confirmed.

Consent:

If the person is alive it is recommended that consent is obtained from them or a person with parental responsibility to access the required information. Disclosure without consent should be carefully considered and documented including the reasons for disclosure and the absence of consent.

In order to avoid these difficulties the working party recommends the use of an information sheet with written consent for genetic testing.
Antenatal diagnosis:

Counselling for antenatal diagnosis should be performed by a combination of Haemophilia Centre and fetal medicine staff.

For all invasive procedures that may be used for antenatal diagnosis it is important that the following issues are always addressed:

1. Obtaining written informed consent for the procedure.
2. Assessment of the individual woman’s need for haemostatic cover [e.g. desmopressin (DDAVP) or recombinant coagulation factor concentrates] for the procedure dependant upon their diagnosis and level of coagulation factor.
3. Agreeing in advance and before leaving the hospital the arrangements regarding the method of communication of the result.
4. Ensuring post-procedure check of the fetal heart.
5. Ensuring administration of anti-D when appropriate.

For antenatal diagnosis, procedures and communication between Haemophilia Centre, fetal medicine department, laboratories and GP should be formalized in a written protocol.

Genetic testing in children:

The following are recommended:

1. Genetic tests can only be performed after written informed consent has been obtained.
2. Boys with haemophilia should have their genotype established, as this has potential clinical benefit to the patient and his family.
3. Phenotypic testing of females who are potential carriers should be performed when easy peripheral venepuncture is possible. Testing should be performed when the child is more than 1 year of age (unless required earlier for a specific clinical reason) with results confirmed on at least two occasions.
4. Genotypic testing for females who are potential carriers of haemophilia should be offered when the individual is able to understand the issues concerned and give informed consent.
5. In other inherited bleeding disorders all potentially affected children should be tested phenotypically.
6. Individuals or families should be sent written information regarding the result and interpretation of any tests (genetic or phenotypic). This letter should indicate whether further genetic tests should be considered in the future.
7. All individuals tested should have their own set of case notes.

Within Haemophilia Centres regular meetings of clinical and laboratory staff from the genetics and coagulation laboratories are essential to review the genetics service, to identify any problems and to ensure the quality of the service.

There should be specific laboratory request forms for genetic studies in inherited bleeding disorders.
It is the responsibility of the clinician dealing with the particular case, and not the laboratory, to ensure that informed consent is obtained. Samples and request forms must be clearly and accurately labelled with:

1. patient’s first name and surname;
2. patient’s date of birth.

This is the minimum patient identification data set required for samples to be accepted for investigation.

All putative mutations must be assessed for likely pathogenic effect, and validated so far as possible in other affected family members. Their absence in appropriate non-affected family members should be confirmed where possible.

Accurate and readily accessible records of all stored samples and patient/family studies must be kept for all families with inherited bleeding disorders. Such records should include the results of genetic and phenotypic studies. Mutation information should be maintained on a controlled and confidential database, and appropriately transferred to the patient’s notes.

Laboratory reports should be timely, accurate and concise. The clinical question being asked should always be restated in the text. Reports should include the following:

1. a brief summary section;
2. the family pedigree including name and date of birth of each individual together with the determined genotype
3. an interpretative section.
Appendix A:

1. **Record of treatment with factor concentrates.**

   Each time factor is sent to a DGH this sheet must be included in the delivery box, and must be completed for every patient.

   Printouts of this form can be found on haemdata or at OHTC.

<table>
<thead>
<tr>
<th>Factor Dispensed</th>
<th>Name of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Name of Product</td>
</tr>
<tr>
<td></td>
<td>Concentration</td>
</tr>
<tr>
<td></td>
<td>No. of boxes</td>
</tr>
</tbody>
</table>

**Factor Given** (to be completed by receiving hospital and returned when further supplies of factor are requested or patient is discharged)

<table>
<thead>
<tr>
<th>Patients Name</th>
<th>Diagnosis</th>
<th>Product</th>
<th>Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS No.</td>
<td>Date</td>
<td>Time</td>
<td>No. Units</td>
</tr>
<tr>
<td></td>
<td>Batch Number</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Printouts of this form can be found on haemdata or at OHTC.
2. **Request form for factor concentrate.**

---

**Request Form for Factor concentrate to be delivered to a Patients Home or Hospital Outside of OUH**

<table>
<thead>
<tr>
<th>Name of person making the request:</th>
<th>Name &amp; Contact details of Dr treating patient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Patient Name:</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>D of B:</td>
<td></td>
</tr>
<tr>
<td>NHS Number</td>
<td></td>
</tr>
<tr>
<td>Product Requested</td>
<td>When is product needed by</td>
</tr>
<tr>
<td>Amount to be dispensed</td>
<td></td>
</tr>
<tr>
<td>Address for Delivery</td>
<td></td>
</tr>
<tr>
<td>Signed:</td>
<td>Print Name:</td>
</tr>
<tr>
<td>Dispensed By: (Print Name)</td>
<td>Signed:</td>
</tr>
<tr>
<td>Courier Reference No:</td>
<td>Signed:</td>
</tr>
</tbody>
</table>

This form is completed by the clinical team at a DGH requesting factor concentrate from OHTC. This must be completed prior to stock release.
3. DGH stock control forms. (See haemdata also).
Appendix B:
Carrier diagnosis

Haemophilia Carrier Procedure.

Procedure: If patient 18 years or younger:

Obligate carrier/ ?carrier

Formal referral to CHOX team
PIS given pre-clinic

Factor VIII or IX level taken by CHOX team

Discussion in clinic re.
inheritance and need
for definitive genetic
testing when older

OBLIGATE CARRIERS:

If factor level > 50% - register as carrier, no haemostasis card, no regular follow-up – genetics tested once 16+ years.

If factor level < 50% - register as carrier, issue haemostasis card, follow-up as appropriate. Genetics tested once 16+ years

?CARRIERS:

If factor level > 50% - register as carrier locally, no haemostasis card, no regular follow-up – genetics tested once 16+ years.

If factor level < 50% - register as carrier or if history unclear register as 'low factor level', issue haemostasis card, follow-up as appropriate. Genetics tested once 16+ years.

Annually:

Data manager will review all obligate carriers/ ?Carriers/ girls with low factor levels who have reached 16 and discuss with clinical teams.

Genetic testing: at CHOX if a sibling, at OHTC if family not seen regularly at CHOX

Version 3.1 June 2017
Haemophilia Carrier Procedure.

Procedure if patient 19 years or older:

Obligate carrier/ ?carrier

Referral/asked to attend by Adult team

Factor VIII or IX level and genetics taken by team

If confirmed as a carrier with testing

If factor level > 50% - register as carrier, no haemostasis card, no regular follow-up. Full discussion about inheritance of haemophilia, advise re: pre-pregnancy counselling, if appropriate & implications for future children.

If factor level < 50% - register as carrier, issue haemostasis card, follow-up as appropriate. Full discussion about inheritance of haemophilia, advise re: pre-pregnancy counselling, if appropriate & implications for future children.