Hemophilia is a rare disorder whose clinical management poses substantial complexity. Evidence-based guidelines offer practical recommendations on the general approach to the disorder, as well as the management of complications such as musculoskeletal disease. Administration of coagulation factor replacement therapy, either prophylactically as the mainstay of disease management or to provide for optimization of hemostasis during surgery or invasive procedures requires insight into the disorder and a clear therapeutic goal. The available guidelines regarding use of prophylaxis are summarized as follows.

**Prophylactic factor replacement therapy**

Prophylaxis is defined as the treatment by intravenous injection of factor concentrate in order to prevent anticipated bleeding.

**Key Points (from WFH Guidelines)**¹:

- Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.²⁻⁷ (Level 2 evidence)
- In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for four to eight weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis.⁸⁻⁹ (Level 3 evidence)
- Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury.⁹⁻¹¹ (Level 4 evidence)

*Note: See appendix for explanation of level of evidence*

Prophylaxis may be administered continuously or episodically (Table 1)¹.

**Table 1: Definitions of factor replacement therapy protocols**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic (&quot;on demand&quot;) treatment</td>
<td>Treatment given at the time of clinically evident bleeding</td>
</tr>
<tr>
<td>Continuous prophylaxis Primary prophylaxis</td>
<td>Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years**</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies</td>
</tr>
<tr>
<td>Tertiary prophylaxis</td>
<td>Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints</td>
</tr>
<tr>
<td>Intermittent (&quot;periodic&quot;) prophylaxis</td>
<td>Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year</td>
</tr>
</tbody>
</table>

* continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.
**large joints = ankles, knees, hips, elbows and shoulders
Medical and Scientific Advisory Council (MASAC) 2007 recommendation, adopted by the National Hemophilia Foundation (NHF)²:

- Consider prophylaxis optimal therapy for severe hemophilia A or B (factor VIII or factor IX <1%)
- Initiate early (prior to the onset of frequent bleeding), with the aim of keeping the trough FVIII or FIX level above 1% between doses
- Keep trough FVIII or FIX level above 1% between doses, can be accomplished with 25-50 FVIII units/kg three times per week or every other day, or 40-100 FIX units/kg two to three times weekly
- Regular patient follow-up to evaluate joint status, document complications, and record bleeding episodes

Treatment of Acute Bleeding Episodes

Key Points (from WFH Guidelines)¹:
If prophylaxis is not available, and treatment is primarily in response to recognition of a bleeding episode, acute bleeds should be treated as quickly as possible, preferably within two hours. If in doubt, treat.¹³ (Level 4 evidence)

WFH Guidelines for Management of Acute Bleeding Episodes:
Suggested plasma factor peak level and duration of administration.* (Table 2)¹.

Table 2: Suggested Plasma Factor Peak Level and Duration of Administration

* Assumes no significant resource constraint
Surgery and invasive procedures

Key Points (from WFH Guidelines)¹:

- A hemophilia patient requiring surgery is best managed at or in consultation with a comprehensive hemophilia treatment centre.¹⁴,¹⁵ (Level 3 evidence)
- Pre-operative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected.¹⁶,¹⁷ (Level 4 evidence)
- Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks post-operatively.¹⁸ (Level 4 evidence)

The dosage and duration of clotting factor concentrate coverage depends on the type of invasive procedure performed (see Table3)*

Table 3. Suggested plasma factor peak level and duration of administration.*

*Assumes no significant resource constraint

References:

12. MASAC Recommendation Concerning Prophylaxis http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=57&contentid=1007
### Appendix: Levels of Evidence

**Oxford Centre for Evidence-Based Medicine, 2011 Levels of Evidence**

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>STEP 1 (LEVEL 1)*</th>
<th>STEP 2 (LEVEL 2)</th>
<th>STEP 3 (LEVEL 3)*</th>
<th>STEP 4 (LEVEL 4)**</th>
<th>STEP 5 (LEVEL 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Systematic review of current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>V/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or “poor or non-independent reference standard”**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case control studies, or poor quality prognostic cohort study**</td>
<td>V/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort follow-up study**</td>
<td>Case-series, case-series, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Randomized trial</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort follow-up study**</td>
<td>Case-series, case-series, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.