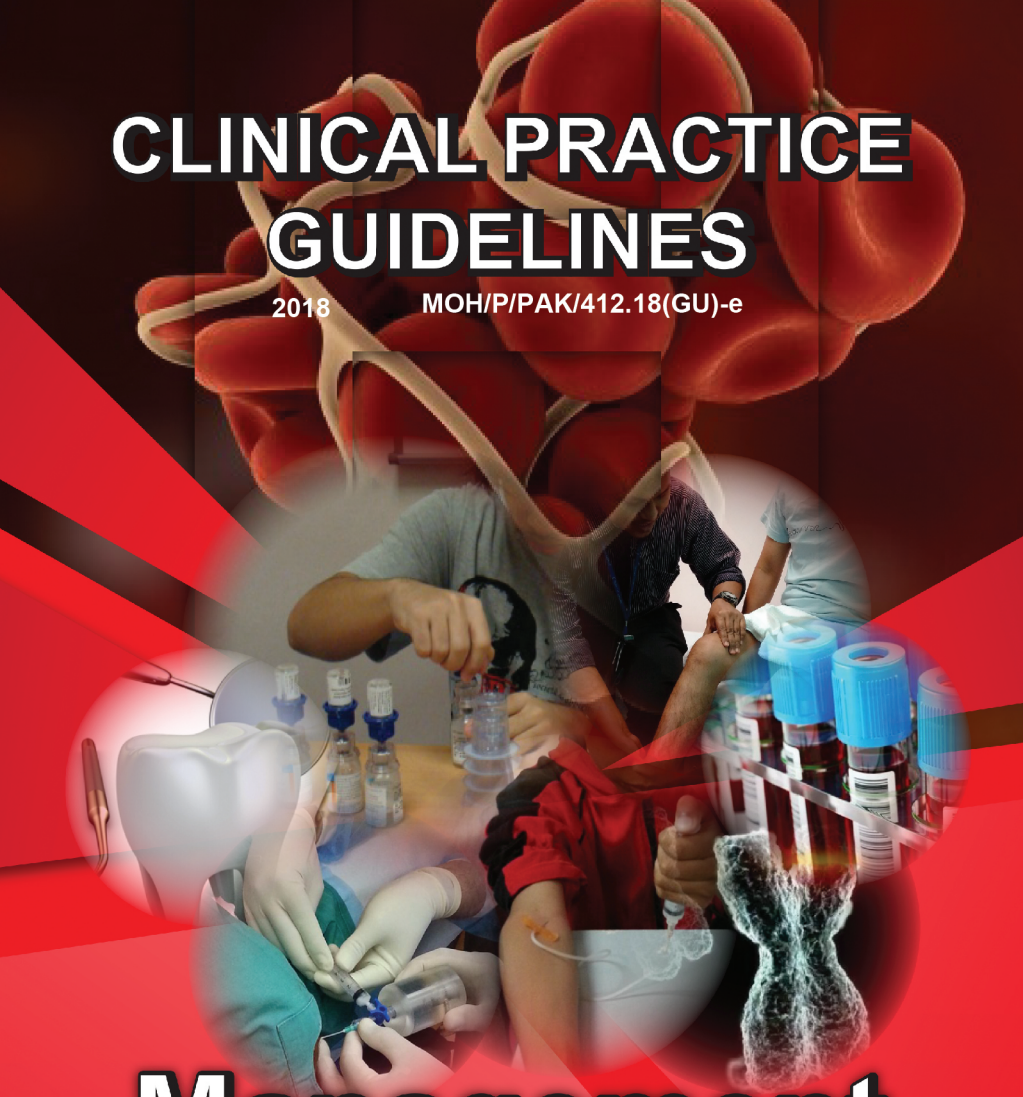
CLINICAL PRACTICE GUIDELINES

2018 MOH/P/PAK/412.18(GU)-e



Management of Haemophilia

Ministry of Health Malaysia
Malaysian Society of Haematology
Malaysian Society of Paediatric Haematology and Oncology
Academy of Medicine Malaysia

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Available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
http://maspho.org
http://haematology.org.my

Also available as an app for Android and IOS platform: MyMaHTAS

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2018 and will be reviewed in a minimum period of four years (2022) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group (DG) as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Investigations

- Factor VIII or factor IX assay should be performed in persons suspected of haemophilia with prolonged Activated Partial Thromboplastin Time and normal Prothrombin Time.
- Mixing test should be done to screen for factor inhibitor in haemophilia.
  - If it is not corrected, Bethesda or Nijmegen assay should be done to determine the factor inhibitor level.
- Mutation analysis for haemophilia should be performed on affected male and his mother.
- Cascade screening for haemophilia should be offered to at least first- and second-degree female relatives if the mother of persons with haemophilia is a confirmed carrier.

Pharmacological Treatment

- Prophylactic factor infusion should be given to **ALL** persons with severe haemophilia.
- Analgesia should be offered for pain relief according to its severity in haemophilia.

Non-pharmacological Treatment

- Rehabilitation should be offered in PWH during acute or sub-acute bleeds and those with chronic arthropathy.
- Protection, Rest, Ice therapy, Compression, Elevation (PRICE) should be commenced as a first aid measure in acute and sub-acute bleed in persons with haemophilia.

Inhibitors

- Bypassing agents should be used to treat acute bleeding in haemophilia with inhibitors.
- Immune tolerance induction should be considered in all persons with haemophilia with inhibitor.

Home therapy

- Home therapy should be advocated to all persons with haemophilia.

Special Situations

- All injectable vaccinations in haemophilia should be given subcutaneously.

Dental Care

- In persons with haemophilia,
  - comprehensive oral health care should be initiated early within six months after the first tooth erupts and no later than 12 months
  - routine dental examination with preventive care measures should be conducted regularly throughout life
  - good oral hygiene and dietary counselling should be advocated to prevent dental diseases
- Comprehensive oral health care in haemophilia should be performed by a multidisciplinary team which include a dental surgeon.

Monitoring

- Monitoring of care in persons with haemophilia should include:
  - Annual Bleeding Rate
  - inhibitor screening
  - Annual Haemophilia Joint Health Score
  - ultrasound of knee, ankle and elbow when feasible

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the DG for this CPG were from the Ministry of Health (MoH). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to humans and English. In addition, the reference lists of all retrieved literature and guidelines were searched further to look for relevant studies. Experts in the field were also contacted to identify relevant studies. All searches were conducted from 6 March 2016 to 15 August 2018. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2018 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were made to other CPGs on haemophilia e.g.

- Guidelines for the Management of Haemophilia (World Federation of Haemophilia, 2012)
- Guidelines for the Management of Haemophilia in Australia (Australian Haemophilia Centre Directors' Organisation, 2016)

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as references.

A total of 17 main clinical questions were developed under three different sections (screening, treatment and monitoring). Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 26 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in their meetings. All statements and recommendations formulated subsequently were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001),

while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

Upon completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of haemophilia in the following aspects:

a) diagnosis
b) treatment
c) monitoring

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- All patients with congenital haemophilia A and B

Exclusion Criteria

- Patients with:
  a. Acquired haemophilia
  b. Other congenital bleeding disorders

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of haemophilia including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policy makers
v. patients and their advocates
vi. professional societies

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings

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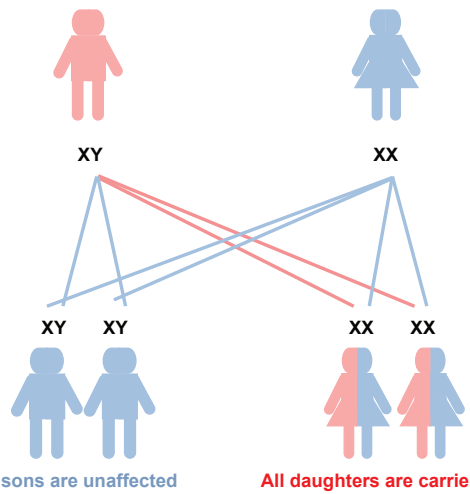
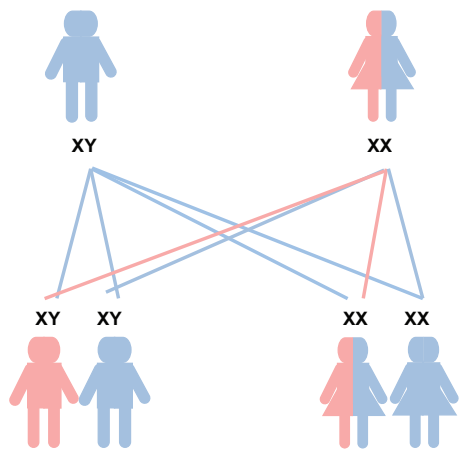
ALGORITHM 1. HAEMOPHILIA GENETIC INHERITANCE (X-LINKED)

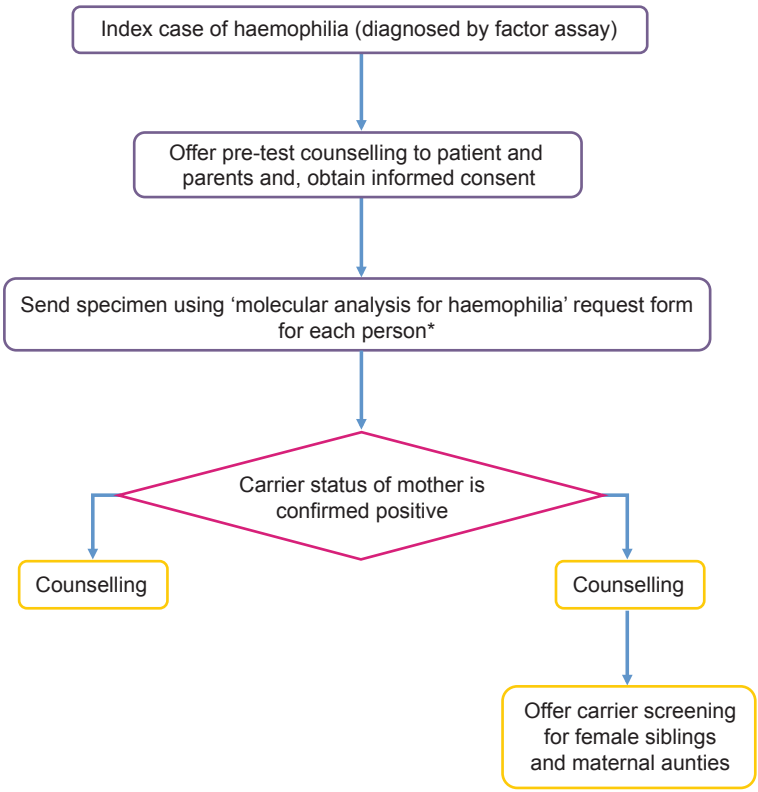
A. Father with haemophilia — Non-carrier mother (normal)



B. Non-haemophilia father (normal) — carrier mother

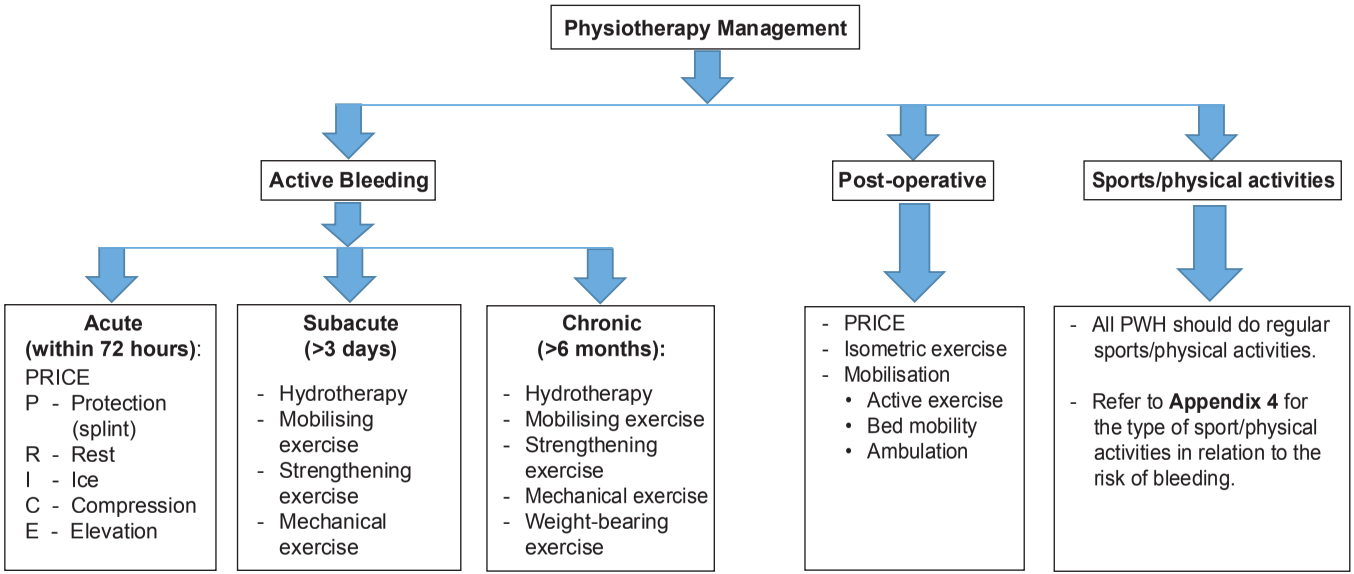


ALGORITHM 2. GENETIC TESTING FOR HAEMOPHILIA PATIENT AND CARRIER SCREENING



*Send samples in sodium citrate tubes of index case and both parents if testing is done in Pusat Darah Negara and in ethylenediaminetetraacetic acid tubes of index case and mother if testing is done in IMR. Refer to **Appendix 3** on **Guidelines on Sample Collection and Transportation**.

ALGORITHM 3. PHYSIOTHERAPY MANAGEMENT



- All these activities are preferably carried out within 24-hour of factor infusion.
- Sports and physical fitness are important to maintain good muscle tone to protect the joints from the haemophilic-induced injuries, and these activities contribute to improvement in quality of life.

1. INTRODUCTION

Haemophilia is a group of inherited blood disorders in which there is life-long defect in the clotting mechanism. The most common types of haemophilia are haemophilia A (factor VIII deficiency) and haemophilia B (factor FIX deficiency). They are inherited as X-linked recessive traits; therefore, males are affected and females are carriers. Females can be affected as well. In 30% of cases, no family history is obtainable because of spontaneous new mutation. The mean prevalence of haemophilia A in Malaysia has increased from 5.6 per 100,000 males in 1998 to 6.6 per 100,000 males in 2006, with a mean of 5.9 ± 0.4 per 100,000 males and for haemophilia B, 1.00 ± 0.11 per 100,000 males. The prevalence for the high income countries was 2.69 ± 1.61 per 100,000 males whereas the prevalence for the rest of the world was 1.20 ± 1.33 per 100,000 males.[1]

These rare disorders are complex to diagnose and manage. Persons with haemophilia (PWH) are at risk of life-threatening bleeding and musculoskeletal deformities if not treated properly. There are variations in practice among the clinicians in the management of haemophilia. The cost escalates when complications e.g. inhibitor development and/or chronic arthropathy develops. Standardising haemophilia management may help contain cost while optimising clinical outcomes.

The haemophilia services started in the blood bank in 1980s and hence for historical reasons, outpatient haemophilia care was provided by the blood bank and PWH referred to the haematology or paediatric wards when required. More recently, haemophilia care is being taken over by clinicians in line with haemophilia care internationally. In the past two decades, many advances have been made in the understanding of these bleeding disorders and their management. In the newly-developed National Haemophilia Programme, the need for a local evidence-based CPG on haemophilia is deemed important. Therefore, this document has been developed by a multidisciplinary team is intended to provide recommendations on the diagnosis, treatment and monitoring of haemophilia and its complications.

2. CLINICAL PRESENTATION

PWH can present with the following symptoms:[2]

- easy bruising in early childhood
- 'spontaneous' bleeding particularly into the soft tissues, muscles, joints and gums
- excessive bleeding following trauma or surgery

A newborn or infant with haemophilia can present with spontaneous intracranial bleed.

A child may also present with post-vaccination or vitamin K injection haematoma.

A positive family history is present in two-thirds of patients while another one-third may have spontaneous mutation.[2]

The most common site of bleeding in haemophilia is the joints (70 - 80%) especially hinged joints (e.g. ankles, knees and elbows).[2]

Bleeding is considered:[2]

- serious if it occurs in the
  - joints (hemarthrosis)
  - muscles, especially deep compartments (iliopsoas, calf and forearm)
  - mucous membranes in the mouth, gums, nose and genitourinary tract
- life-threatening if it occurs in the
  - neck or throat (including floor of the mouth)
  - intracranial
  - gastrointestinal

The severity of haemophilia is based on the clotting factor level as shown in **Table 1**.

Table 1. Relationship of bleeding severity to clotting factor level in haemophilia

Severity	Clotting factor level	Bleeding manifestations
Severe	<1 IU/dL (<0.01 IU/ml) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge
Moderate	1 - 5 IU/dL (0.01 - 0.05 IU/ml) or 1 - 5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5 - 40 IU/dL (0.05 - 0.40 IU/ml) or 5% to <40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding is rare

Source: World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012

3. INVESTIGATIONS

3.1 Laboratory Tests

Other bleeding disorders may have similar symptoms to haemophilia. Hence reliable laboratory services are crucial to ensure an accurate diagnosis so that management is given appropriately.

Screening tests for suspected hereditary bleeding disorders include:

- Prothrombin Time (PT)
- Activated Partial Thromboplastin Time (APTT)
- Platelet count

The interpretation of the screening tests is illustrated in **Table 2**.

Table 2. Interpretation of screening tests

PT	APTT	Platelet count	Possible diagnosis
Normal	Prolonged	Normal	Haemophilia A or B
Normal	Normal or prolonged	Normal or reduced	Von Willebrand Disease (VWD)
Normal	Normal	Normal or reduced	Platelet defects

*Normal value depends on individual laboratory reference range.

Adapted: World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012

If APTT is prolonged and there is positive family history of haemophilia, proceed to perform FVIII or FIX factor assay. Otherwise, mixing study should be done first. The interpretation of mixing test is illustrated in **Table 3**.

Table 3. Interpretation of mixing test

Mixing study results		Interpretation
Immediate	2-hour incubation	
Corrected	Corrected	Factor deficiency
Corrected	Not corrected	Time dependent inhibitor e.g. FVIII inhibitor
Not corrected	Not corrected	Immediately acting inhibitor e.g. Lupus anticoagulant antibody

Source: McKenzie SB & Wiliams L. Clinical Laboratory Haematology, Third Edition. San Antonio: Pearson Clinical Laboratory Science Series; 2015

Investigations of other causes of bleeding disorder must be performed if PT and APTT are normal.

With regards to factor VIII (FVIII) and factor IX(FIX) assays:

- FVIII or FIX assay is performed to confirm the deficiency of coagulation factor.

- The severity of haemophilia A and B is correlated with FVIII and FIX level respectively (refer to **Table 1** in **Chapter 2** on **Relationship of bleeding severity to clotting factor level in haemophilia**).
- To detect all mild Haemophila A, more than one type of FVIII assay is needed e.g. chromogenic assay.

With regards to inhibitor test in congenital haemophilia:[2]

- Refer to **Chapter 8** for indication on inhibitor screening.
- Mixing test can help to screen for factor inhibitor.
- Bethesda assay or Nijmegen assay can determine factor inhibitor level. Inhibitor level ≥0.6 Bethesda unit (BU) is considered positive.

Recommendation 1

- Factor VIII or factor IX assay should be performed in persons suspected of haemophilia with prolonged Activated Partial Thromboplastin Time and normal Prothrombin Time.
- Mixing test should be done to screen for factor inhibitor in haemophilia.
  - If it is not corrected, Bethesda or Nijmegen assay should be done to determine the factor inhibitor level.

3.2 Genetic Tests

Close collaboration between coagulation laboratory, genetics laboratory and a clinical genetic counselling service is fundamental for the provision of a successful genetic diagnostic service.[3, level III]

Haemophilia is an X-linked recessive disorder [refer to **Algorithm 1** on **Haemophilia Genetic Inheritance (X-Linked)**] which affects males, who will pass on the haemophilia gene to their daughters. Female carrying a FVIII or FIX gene mutation are carriers.[2]

The following are considered to be obligate carriers:[2]

- daughters of a PWH
- mothers of one son with haemophilia and who have at least one other family member with haemophilia
- mothers of one son with haemophilia and who have a family member as a known carrier of the haemophilia gene
- mothers of two or more sons with haemophilia

Genetic testing for carrier status should be offered to all at-risk female family members of PWH to facilitate genetic counselling. Mutation analysis is best performed on an affected male, while cascade carrier testing should be offered to first-degree female relatives. If the female is a carrier, then clotting studies including FVIII should be undertaken.

Ideally, management advice and genetic counselling should be offered to all PWH, carriers and their families to make informed choices, which should be provided through a centre with experience in managing haemophilia.[2; 4] In local setting, molecular testing is offered to the affected child and his mother. If the mother is a confirmed carrier, cascade screening will be done for the first- and second-degree female relatives (sisters and maternal aunties).

Genetic testing may also help in assessing risk of inhibitor development in PWH.[4]

The method selected for mutation detection will depend on resources and expertise available in a particular laboratory.[3, level III; 5, level III]

For Haemophilia A, it is recommended that severe haemophiliacs should be screened for the FVIII intron 22 inversion mutation followed by the FVIII intron 1 inversion mutation. This approach should identify the underlying mutation in 45 - 50% of severe haemophilia A patients. The remaining severe haemophilia A pedigrees should then be analysed further by full mutation analysis of FVIII.[3, level III]

For Haemophilia B, direct deoxyribonucleic acid (DNA) sequencing of the essential regions of FIX should be done without a pre-screening step.[5, level III]

Recommendation 2

- Mutation analysis for haemophilia should be performed on affected male and his mother.
- Cascade screening for haemophilia should be offered to at least first- and second-degree female relatives if the mother of persons with haemophilia is a confirmed carrier.*

*Refer to **Algorithm 2** on **Genetic Testing for Haemophilia Patient and Carrier Screening**.

Prenatal testing may be offered if couple is interested. However, it is not available in public hospitals.

4. GENERAL PRINCIPLES OF CARE

4.1 Stratification of Haemophilia Centre with regards to Haemophilia Services

Haemophilia is a complex disorder. The wide-ranging needs of PWH and their care givers are best met through a coordinated, comprehensive and multidisciplinary care by a team of healthcare professionals, in accordance with accepted protocols and national CPG.

Haemophilia treatment centres (HTCs) should be established to ensure that PWH have access to the full range of services necessary to manage their condition. The aim of care is to improve health and quality of life. This includes prevention of bleeding, long-term management of joint and muscle damage, and management of complications from treatment including inhibitor development and possible transfusion-transmitted.

HTC carries out the following functions and activities:[6, level III]

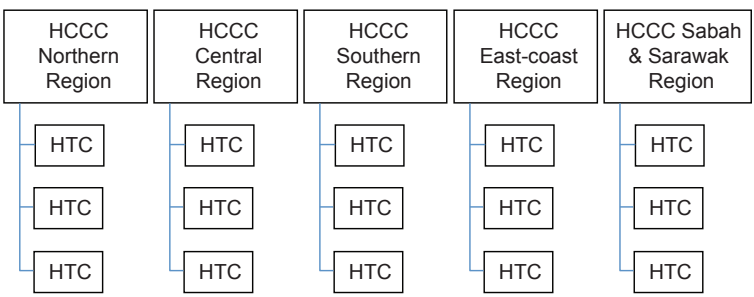
- provides care for PWH, including diagnosis, treatment, follow-up and rehabilitation
- provides PWH with safe and effective treatment products
- provides a 24-hour emergency treatment service
- provides basic diagnostic and monitoring laboratory support during normal working hours for the more common inherited bleeding disorders
- provides access to multidisciplinary support, locally or in conjunction with:
  - physiotherapy and orthopaedics
  - surgery
  - dental care
  - hepatology
  - infectious diseases
  - obstetrics and gynaecology
  - peadiatric if children are treated
  - genetics
  - nuclear medicine
  - clinical psychology
  - pharmacy
  - social work
- offers specific treatment for PWH with inhibitors and immune tolerance in collaboration with a Haemophilia Comprehensive Care Centre (HCCC)
- provides advisory service, including genetic counselling to PWH and healthcare professionals
- promotes information and training programmes on inherited bleeding disorders to PWH and healthcare professionals

HCCC, apart from performing above roles of HTC, also carries out the following additional functions and activities:[6, level III]

- co-ordinates the delivery of haemophilia services - both in the hospital and community including liaison with affiliated HTCs
- provides reference laboratory service with a full repertoire of tests for the diagnosis and monitoring of inherited bleeding disorders
- provides access to a genetic diagnosis service which include carrier detection and antenatal diagnosis
- collates data (e.g. product usage, PWH demographics)
- participates in research, including clinical trials

The pharmacist in HCCC should also provide Haemophilia Medication Therapy Adherence Clinic (HMTAC) and drug counselling.

In the local setting, the following stratification is proposed in the management of haemophilia (refer to **Figure 1**).



HTC = Other hospitals with specialist within a region and not assigned as HCCC

Figure 1. Proposed stratification of haemophilia centres in Malaysia

4.2 National Haemophilia Registry

- A national haemophilia registry is of utmost importance to ensure cost-effective treatment of PWH.

A national haemophilia registry is a database of information on PWH. The aims of the registry are:[7, level III]

- to increase awareness of the disease prevalence
- to identify the needs of PWH
- to recognise shortcomings in the healthcare delivery system
- to predict future needs and areas of concern
- to empower the national haemophilia organisation and clinicians to lobby effectively on behalf of PWH

- MoH registry on haemophilia:[7, level III]
  - contains demographic and clinical information obtained from all hospitals and clinics
  - reflects a true national picture of the condition
  - requires government support to motivate and sustain participation of all treating centres for data entry

Important data in a haemophilia registry should include:[8 - 9, level III]

- epidemiology and clinical care
- co-morbidity and mortality outcomes e.g. allergic reactions, transfusion-transmitted infections, thrombosis and deaths
- joint outcomes
- bleeding specifications and outcomes
- burden of disease and cost of treatment
- patient reported outcomes e.g. annual bleeding rate (ABR), quality of life (QoL) (refer to **Chapter 13** on **Monitoring**)

5. TREATMENT

Repeated joint bleeds is the major cause of morbidity in PWH. In patients with severe haemophilia, bleeding episodes may occur as frequently as 20 - 30 times per year. PWH are 20 - 50 times more likely to develop intracranial haemorrhage (ICH) compared with those without haemophilia, with a reported prevalence of 2.7 - 12% and an incidence rate of 290 - 748/10 000 patient-years.[10, level III] and a mortality rate of 19.6%.[11, level III] Factor replacement therapy, non-pharmacological and adjunctive treatments are essential in preventing joint damage and other potential serious and life-threatening events.

5.1 Pharmacological Treatment

5.1.1 Factor replacement therapy

There are two types of clotting factor concentrate (CFC) used for replacement therapy:

- Plasma-derived factor (pdF) Concentrates - manufactured via fractionation of human pooled plasma
- Recombinant factor concentrates - manufactured via DNA engineering technology

In a well-regulated environment, guided by regulatory agencies e.g. Food and Drug Administration (FDA)/European Medical Agency (EMA), products approved are of adequate efficacy and safety.[12, level III]

The World Federation of Haemophilia (WFH) publishes and regularly updates a Registry of CFC, listing all the currently available factor concentrates in the market approved by regulatory agencies. WFH does not express preference for recombinant over pdF. Choices of factor concentrates and their classes must be made according to local criteria.[2]

Efficacy of CFC can be assessed against the scale of response to infusion as shown in **Table 4**.

Table 4. CFC efficacy scale of response to bleeding episodes

Outcome	Treatment of bleeding episodes
Excellent	Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately eight hours of a single infusion
Good	Definite pain relief and/or improvement in signs of bleeding within approximately 8 - 12 hours of an infusion; requiring up to two infusions for complete resolution
Moderate	Probable or slight beneficial effect within approximately 12 hours of the first infusion; requiring >2 infusions for complete resolution
Poor	No improvement within 12 hours or worsening of symptoms requiring >2 infusions for complete resolution

Source: World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012

The currently manufactured products show a good safety record on lipid enveloped viruses e.g. human immunodeficiency virus (HIV) and hepatitis C virus. In the last 25 years, there has been no report on HIV, hepatitis B and hepatitis C transmission via plasma-derived products. However, the current viral inactivation/removal process does not eliminate a majority of the non-lipid viruses/prions e.g. hepatitis A virus, parvovirus B19, Creutzfeldt-Jakob. At the moment, the transmission is probably kept at a lower level by excluding at-risk blood donors.[2]

- Blood borne infectious diseases remain a concern in PWH using pdF especially the unknown/yet to be discovered viruses which may escape the current viral reduction process.

Factor concentrates vary widely in their purity. Those with low purity have a tendency to cause allergic reaction. The use of high purity FIX is preferred to PCC as a replacement therapy for haemophilia B as PCC may predispose to the risk of thromboembolism especially when used in high doses.[2]

Inhibitor development is the most serious complication of haemophilia treatment. Refer to **Chapter 8** on **Inhibitors**.

A multi-centred RCT demonstrated that PDF containing von Willebrand factor (vWF) had a lower incidence of inhibitor development than those treated with recombinant factor VIII (rFVIII).[13, level I] However the EMA's Committee for Medical Products for Human Use (CHMP) concluded that there was no clear and consistent evidence to indicate a difference in the incidence of inhibitor development between plasma-derived and recombinant factors.[12, level III]

PWH with HIV, hepatitis B and hepatitis C should be treated the same as patients without haemophilia. PWH who have and continue to receive pdF should be screened for these infections every 6 - 12 months or if clinically indicated.[2]

- In view of risk of blood-borne infection with plasma-derived products, recombinant factor concentrate is the preferred choice for factor replacement in haemophilia.

The optimal approach to haemophilia treatment is using CFC to prevent bleeds, chronic joint damage and reduce complications (short and long term). Factor replacement therapy can either be on-demand or prophylaxis.

On-demand therapy, also known as episodic therapy, is defined as therapy to stop an acute haemorrhage. Cessation of bleeding does not reverse the deleterious effects on synovial tissues by the blood which has accumulated in the affected joint.

Prophylactic factor replacement therapy is defined as regular infusion of CFC in an attempt to raise clotting factor levels and to keep them at 1% or higher at all times.[14, level I] It can be divided into primary, secondary or tertiary prophylaxis:[2]

- Primary - starts in the absence of joint disease before the second large joint bleed and before age three years old
- Secondary - starts after the second large joint bleed but before onset of joint disease
- Tertiary - starts after joint disease to prevent further damage

A systematic review advocated starting prophylaxis before the age of three in PWH for better joint outcome.[15, level I]

A Cochrane systematic review and a randomised controlled trial (RCT) reported that prophylactic factor replacement therapy was more effective than on-demand therapy in severe haemophilia in terms of:

- reduction in bleeding frequency (RR=0.30, 95% CI 0.12 to 0.76)[16, level I]
- protection from joint damage (RD=0.70, 95% CI 0.39 to 1.01)[16, level I]
- lower median number of total bleeding episodes per year which included joint bleeds (0 vs 27.9; $p<0.0001$)[17, level I]
- fewer annualised spontaneous (median of 0 vs 16.3) and trauma-related (median of 0 vs 6.4) bleeding events[17, level I]

Incidence of ICH is significantly reduced in the prophylactic group compared with the no prophylaxis group (0.00033 cases/patient year vs 0.017 cases/patient year; RR 50.06).[18, level II-2]

In a retrospective cohort study, regular prophylactic therapy reduced the risk of inhibitor development by 60% compared with on-demand therapy (RR=0.4, 95% CI 0.2 to 0.8) at 50 exposure days in severe haemophilia.[19, level II-2] In a more recent large prospective cohort study, the association was observed after 20 days with a HR ranged from 0.22 to 0.32. It was more pronounced in low risk FVIII genotypes.[20, level II-2]

However, the Cochrane systematic review showed no significant difference in the risk of inhibitor development and infection between prophylaxis and on-demand therapies.[16, level I]

There are many different prophylactic factor replacement therapy protocols used but optimal regimen remains to be defined. The commonly used protocols are as shown in **Table 5**.

Table 5. Prophylactic factor replacement therapy regimens in haemophilia

Protocol	Dosage
High dose prophylaxis; Malmo protocol	25 - 40 IU/kg three times/week for haemophilia A 30 - 50 IU/kg twice/week for haemophilia B
Intermediate dose prophylaxis; Utrecht protocol	15 - 25 IU/kg two to three times/week for haemophilia A 30 - 50 IU/kg once or twice/week for haemophilia B (after first/second joint bleed or two bleeds per month)
Low dose prophylaxis	10 IU/kg two times/week for haemophilia A 20 IU/kg once/week for haemophilia B (secondary prophylaxis)

Adapted:

1. World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012
2. Wu R, Luke KH, Poon MC, et al. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. Haemophilia. 2011;17(1):70-4

Prophylactic regimens should be individualised according to bleeding phenotype, activity and pharmacokinetics. Other issues e.g. age, venous access and availability of clotting factor must also be taken into consideration. Patients on high dose prophylaxis (Malmo protocol) showed improved HJHS and reduction in joint bleeds ($p<0.001$) but at a significant increase in cost.[21, level II-2] When high dose prophylaxis is not possible due to financial constraint, a low or intermediate dose could be used.

Prophylaxis should be initiated as soon as possible after a first major bleed (joint, muscle or intracranial bleed) and before the age of three if there is no major bleed. Prophylaxis before the age of three is being

advocated as evidence has shown better outcome compared with when it is started after that age.[15, level I]

There are two ways to start the prophylaxis:[15, level I]

i. Give full dose prophylaxis following one of the above regimes (refer to **Table 5**).
ii. Start once weekly first and escalate the frequency of infusions if significant spontaneous bleeding occurs until full dose prophylaxis is achieved. A detailed account of bleeding events should be maintained and frequency of infusions adjusted appropriately.

The on-going trials of new generation of coagulation factors with extended half-life show promising results which may improve the management of PWH once available locally.

Recommendation 3

- Prophylaxis should be given to **ALL** persons with severe haemophilia.
  - Primary prophylaxis should start following intracranial haemorrhage, first joint bleed, severe intramuscular bleed or by three years old, whichever comes first.
  - Malmo protocol is the preferred prophylactic therapy regimen in haemophilia.

5.1.2 Adjunct therapies

a. Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of vasopressin that boosts plasma level of FVIII and vWF in mild to moderate haemophilia A and certain subtypes of VWD. It may also be used in symptomatic carrier of haemophila A.

DDAVP is effective and safe in mild haemophilia A. It is also haemostatically effective in 96% of cases when used prophylactically in minor procedures.[22, level II-2]

The decision to use DDAVP must be based on baseline concentration of FVIII, increment achieved and duration of treatment required. This is applicable in minor form of bleeding. It should not be used in moderate to severe form of bleeding.[2] DDAVP can be given through various routes as shown in **Table 6**.

Table 6. Administration of DDAVP

Types	Dose	Time to peak	Side effects
IV	0.3 µg/kg diluted into 50 -100 ml of physiological saline and infused over 20 - 30 minutes	30 - 60 minutes	Rapid infusion can cause tachycardia, flushing, tremor and abdominal discomfort
Subcutaneous (SC)	0.3 µg/kg	90 - 120 minutes	
Intranasal	Adult: 1.5 mg/ml in each nostril Those <40 kg, a single dose in 1 nostril is sufficient		Due to anti-diuretic activity, observe for: • hyponatremia • water retention

Source: Mannucci PM, Desmopressin (DDAVP) in the Treatment of Bleeding Disorders (Revised edition). Montréal: WFH; 2012

A single dose of DDAVP either via IV or SC route can be expected to boost the level of FVIII to 3 - 6 folds higher than the baseline.[2] There is however some variability in response and a test dose is the only way to distinguish good responders from poor or non-responders. Plasma half-life is 5 - 8 hours for FVIII and 8 - 10 hours for vWF. PWH treated repeatedly with DDAVP may become less responsive because the stores are exhausted. The average FVIII responses if DDAVP is repeated at 24-hour interval are approximately 30% less than responses obtained after the first dose.[2; 23, level III] Due to its anti-diuretic side effect, plasma osmolality and sodium level should be measured when repeated doses are given.[2]

- DDAVP is relatively contraindicated in children less than two years old who may be at risk of seizure secondary to cerebral oedema due to hyponatremia.

b. Tranexamic Acid

Tranexamic acid (TXA) is an anfibrinolytic agent that promotes clot stability by inhibiting the activation of plasminogen to plasmin. It is particularly useful in controlling bleeding from skin and mucosal surfaces e.g. oral bleeding, epistaxis and menorrhagia.[2]

TXA is available in three preparations i.e. oral, IV and mouthwash. In centres where the mouthwash preparation is not available, the oral form (tablet/capsule) can be dissolved in water and subsequently used as a mouthwash (5% weight in volume or 500 mg in 10 ml). The dose is 15 - 25 mg/kg/dose every eight hours.

TXA can either be used alone or in combination with standard dose of CFC and can be a helpful adjunctive therapy in the prevention and treatment of all bleeds except those involving the renal tract. In patients with inhibitory antibodies, it can be used to treat bleeds or to manage surgery in combination with activated recombinant Factor VII (rVIIa) or activated Prothrombin Complex Concentrate (aPCC). However, combination use must be done with caution in any elderly PWH or those who have cerebral or cardiovascular risk factors.

TXA should not be used in the treatment of haematuria as it may prevent dissolution of clots in the ureters which may result in obstructive uropathy and potential damage to the kidney function.[2]

c. Others

There is no good evidence on the use of fibrin glue and floseal in haemophilia. However, these treatments have been used in local practice. These treatments had been used fairly commonly since 1990s in surgical procedures involving high risk patients which includes PWH. The procedures highlighted were circumcision, dental extraction/oral surgery and resection of pseudotumour. It had been observed that there was low risk of bleeding with significant reduction in the CFC usage when fibrin glue was added in the management of those surgical procedures.[24, level III]

5.1.3 Analgesia

Pain in PWH may be acute or chronic. This may include pain caused by venous access, joint or muscle bleed, post-operative pain, dental extraction and/or chronic haemophilic arthropathy.

Pain assessment can be done using the following pain scales as recommended by MoH (refer to **Table 7** and **Appendix 6**).

Table 7. Recommended pain scale by MoH

Age group	Scale
1 - 3 years and adult patient unable to communicate verbally	Face, Legs, Activity, Cry, Consolability (FLACC) Scale
>3 - 7 years	Visual Analogue Scale (VAS)
>7 years and adults	Numeric Rating Scale (NRS)

Source: Ministry of Health, Malaysia. Pain Medication Therapy Management Service: Guideline for Pharmacy (Second Edition) Petaling Jaya: MoH; 2018

Pain severity is categorised in **Table 8** and its management is described following it.

Table 8. Category of pain

Total pain score	Severity of pain
1 - 3	Mild
4 - 6	Moderate
7 - 10	Severe

Source: Ministry of Health, Malaysia. Pain Management Handbook. Putrajaya: MoH; 2013

Effectiveness of analgesics in PWH:

- Paracetamol is recommended for mild pain.[2]
- Cyclooxygenase-2 (COX-2) inhibitors are effective analgesics:
  - celecoxib in chronic synovitis and non-specific mild to moderate pain[25, level II-3]
  - etoricoxib in hemophilic arthropathy[26, level II-2]
- Mild opioid is recommended as an alternative in moderate pain.[2]
- If pain is moderate to severe in children, a strong opioid is necessary. Morphine is the opioid of choice.[27, level III] In haemophilia, morphine is recommended in severe pain.[2]

Safety of analgesics in PWH:

- The risk of upper gastrointestinal bleeding increases by two-folds in traditional nonsteroidal anti-inflammatory drugs (NSAIDs) compared with celecoxib or rofecoxib in haemophilic arthropathy although it is statistically not significant.[28, level II-2]
- Celecoxib was noted to have no serious adverse events including hypertension or other CV events in a non-comparative study.[25, level II-3]
- Etoricoxib was noted to have higher bleeding duodenal ulcer, upper respiratory tract infection and headache compared with placebo (p=0.043) in a cohort study.[26, level II-2]

Pain management strategies are as follows:

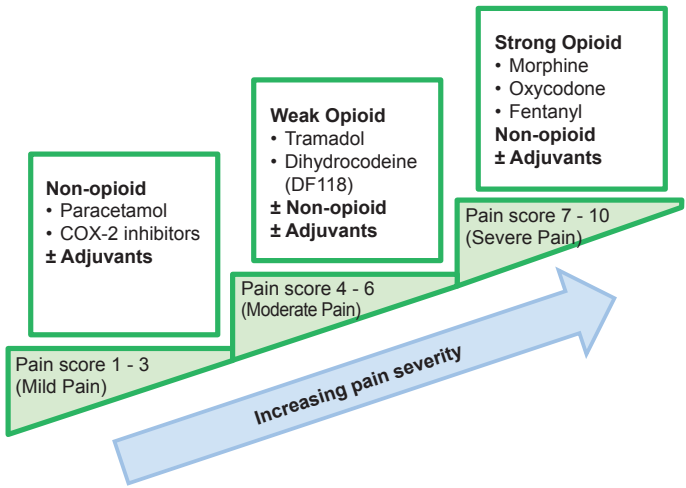


Figure 2. Pain relief ladder

Notes:
1. Celecoxib: effectiveness and safety are not established in children <2 years old
2. Etoricoxib: effectiveness and safety are not established n patients <16 years old
3. Tramadol: effectiveness and safety not established in children <12 years old; caution in children 12 - 18 years who have risk factors that may increase respiratory depression
4. Codeine: effectiveness and safety are not established in children <18 years old

Adapted:
1. Ministry of Health, Malaysia. Management of Cancer Pain. Putrajaya: MoH; 2010.
2. Micromedex® Solution (Available at http://www.micromedexsolutions.com/micromedex2/4.24.0/WebHelp/MICROMEDEX_2.htm)
3. Shann F. Drug Doses (Seventeenth Edition), Parkville: University of Melbourne; 2017
4. Etoricoxib package insert.

Recommendation 4
- Analgesia should be offered for pain relief according to pain severity in haemophilia*.

*Refer to **Table 8** and **Figure 2**.

5.2 Non-pharmacological Treatment

5.2.1 Rehabilitation of musculoskeletal system

Rehabilitation in PWH improves joint health status and muscle strength and, reduces pain. Physiotherapists play an important role in the

management of both acute and sub-acute bleeds, chronic synovitis, chronic arthropathy and other musculoskeletal pathology in PWH. Post-bleed rehabilitation include PRICE and exercise programmes for restoration of pre-morbid status, minimisation of re-bleed risk and prevention of secondary musculoskeletal complications.[2]

Rehabilitation must be stressed as an active part in the management of acute joint bleeding episodes in PWH:[2]

- PWH should be encouraged to change the position of the affected joint from a position of comfort to a position of function as soon as the pain and swelling begin to subside. The gentle passive movement will gradually decrease the flexion of the joint and strive for complete extension. Refer to **Appendix 5** on **Development of Abnormal Posture Following Bleeds**.
- Active movement should be done as much as possible with muscle contractions to minimise muscle atrophy and prevent chronic loss of joint motion.
- Active exercises and proprioceptive training should be continued until complete pre-bleed joint range of motion (ROM) and functioning are restored and, signs of acute synovitis resolve.
- If exercises progress cautiously, factor replacement is not necessarily required before the exercises.

Rehabilitation, e.g. hydrotherapy, mechanical exercises (static bicycle, treadmill or multigym) and strengthening exercises, significantly improve joint health status, ROM and pain score compared with no intervention in haemophilia.[29 - 30, level I] No adverse effects e.g. bleeding have been reported as a result of any of these exercises.[29, level I] Participation in physical activity, exercise and sports lead to physical and psychological benefits as well as supporting emotional and social well-being of PWH.[31, level II-2]

For PWH with significant musculoskeletal dysfunction, weight-bearing activities that promote development and maintenance of good bone density (e.g.weight training, walking and hiking) should be encouraged.[2]

Manual therapy treatment using ankle joint traction, passive stretching, proprioceptive training, isometric exercise and active counter-resistance exercise significantly improves gastrocnemius muscle circumference and reduces ankle pain compared with educational session and no intervention in haemophilia.[32, level III]

Prolonged immobilisation after fracture in PWH can lead to limited ROM. Physiotherapy should be started once the fracture is stabilised to restore:[4]

- ROM
- muscle strength
- function

Recommendation 5
- Rehabilitation should be offered in person with haemophilia during acute or sub-acute bleeds and those with chronic arthropathy for functional recovery.

5.2.2 Protection, Rest, Ice, Compression and Elevation

Protection, Rest, Ice, Compression and Elevation (PRICE) is important in pain management in haemophilia.[2; 33] It relieves acute pain and decreases risk of re-bleeding.[33; 34, level III] This is further explained in the following **Table 9**.

Table 9. Application of PRICE

Components	Application
Protection (P)	• Avoidance of weight bearing • Restriction of activities until swelling and temperature of the joint return to normal • Use of a sling, removable splint and compressive bandage for the affected joints
Rest (R)	• Immobilisation of the affected joint until pain resolves • Use of crutches when ambulating
Ice Therapy (I)	• Should not be applied directly to the skin Should not exceed 20 minutes at 2-hourly intervals • Always be guided by levels of pain and discomfort
Compression (C)	• Configuration follows the limb/joint shape • Provision of a graduated compressive force which is comfortable for the individual
Elevation (E)	• Elevation when sitting and lying in supine position

Adapted:

1. World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012
2. Hanley J, McKernan A, Creagh MD, et al. Musculoskeletal Working Party of the UKHCDO. Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline. Haemophilia. 2017;23(4):511-20
3. Rodríguez-Merchán EC. Articular Bleeding (Hemarthrosis) in Hemophilia: An Orthopedist's Point of View (Second edition). Montréal: WFH; 2008

Recommendation 6
- Protection, Rest, Ice therapy, Compression, Elevation (PRICE) should be commenced as a first aid measure in acute and sub-acute bleed in persons with haemophilia.

5.2.3 Joint protection

Target joints can be protected with braces or splints during physical activity. Adjunctive therapies for bleeding in muscles and joint are important, especially when clotting factor concentrates (CFC) are limited or not available. They include:[2]

- first aid measures e.g. PRICE
- removable splint or compressive bandage
- walking aid

It is advisable for PWH to use appropriate foot wear which provides good cushioning, arch support and wiggle room for toes to reduce risk of bleeding.[35, level III]

5.2.4 Sports/physical activity

PWH should be encouraged to perform physical/sport activities to promote:[2; 32, level III; 36, level III; 37, level I]

- physical fitness
- normal neuromuscular development
- psychological and social benefits
- quality of life (QoL)

Participation in non-contact sports, e.g. walking, swimming and cycling, are encouraged for PWH.[2] It does not increase the risk of bleeding nor development of target joints.[36, level III] PWH who want to cycle need proper and adequate protective gear and for children, should be under supervision.

High contact and collision sports (e.g. soccer, hockey, rugby, boxing and wrestling) and high-velocity sports (e.g. motocross racing and skiing) are best avoided because of the potential life-threatening injuries.[2]

5.2.5 Post-operative care

Physiotherapy plays an important role in management of PWH who has undergone surgical intervention e.g. total knee replacement (TKR) and total hip replacement (THR). An exercise plan is prescribed according to the mobility level of PWH on discharge. This includes:[38, level III]

- PRICE - immediately after operation
- isometric exercise - starts when the drains and bandages are removed; focused on quadriceps strengthening
- mobilisation - includes active exercise, bed mobility and ambulation after 7 - 10 days of post-operation

Post-operative rehabilitation should be carried out gradually by physiotherapist to improve strength, proprioception and normal function of the joint.[2]

The summary on non-pharmacological treatment is shown in **Algorithm 3** on **Physiotherapy Management in Haemophilia**.

5.2.6 Weight management

Body Mass Index (BMI) and body weight can increase due to lack of physical activity. In adults, normal BMI is 18 - 23 kg/m^2, overweight when BMI >23 - 29.9 kg/m^2 and obesity if BMI >30 kg/m^2. In children, overweight and obesity varies according to age.

A high BMI has been associated with:[2]

- significant limitation in ROM of the joints
- increased arthropathic pain and risk of developing target joints
- increased risk of cardiovascular diseases which may further damage arthropathic joints

Regular physical activity should be advised. The physiotherapist should advise PWH on modification in daily physical activities if there are restrictive functional limitations.[2] This should be accompanied by a proper calorie restricted diet by a dietitian.

6. TREATMENT FOR ACUTE BLEEDING IN SPECIFIC SITES

Acute bleed should be treated as soon as possible preferably within two hours. Amount of factors to be given is dependent on site and severity; usually it is given until bleeding resolves. Haemostatic agents e.g. TXA should be given concurrently except in genitourinary bleeding. For PWH on prophylaxis with good compliance, prophylactic regime should be reviewed if bleed is not due to trauma.[2]

- In PWH, bleeding in head, neck and gastrointestinal tract is a medical emergency. Factor replacement should precede investigation.

6.1 Central Nervous System

All post-traumatic head injuries and significant headache in PWH must be treated as ICH until proven otherwise.[2]

- The initial factor replacement therapy to raise factor levels to 100 IU/dL should precede all investigations.[2; 39, level III]

ICH must be confirmed by urgent imaging e.g. Computed Tomography (CT) scan/magnetic resonance imaging (MRI) before further administration of factors.[2]

Following ICH, prophylaxis is indicated.[2]

Refer to **Table 10** on recommended treatment.

6.2 Joints

Haemarthrosis is defined as bleeding into a joint space which may occur spontaneously or in response to trauma especially in moderate and severe haemophilia. The joints most commonly affected are the knees, elbows and ankles.[2]

Patients often describe a tingling sensation and tightness in the joint preceding the clinical signs of haemarthrosis. It is difficult to differentiate from flare ups of haemophilia arthropathy. However, for haemarthrosis, the joint rapidly loses ROM and becomes acutely painful, warm and swollen.

A re-bleed is defined as worsening of the condition while on treatment or within 72 hours of stopping treatment.

Recurrent haemarthroses are almost invariably associated with severe haemophilia. When it occurs in the same joint ≥3 times within a consecutive 6-month period, the joint will become a target joint and eventually lead to haemophilic arthropathy if not treated.[2]

A joint ceases to be a target joint when there is <2 bleeds into the joint within 12 consecutive months.[33]

The goal of treatment of acute haemarthrosis is to stop the bleeding as soon as possible. Subsequent treatment aims to prevent recurrent bleeding and progressive joint damage. The management for these conditions are:[2]

- Factor replacement therapy
  - Administer the appropriate dose of factor concentrate to raise the patient's factor level suitably (refer to **Table 10**).
  - If bleeding does not stop, a second infusion maybe required by repeating half the initial loading dose in 12 hours (haemophilia A) or 24 hours (haemophilia B) until satisfactory resolution (refer to **Table 5** and **Table 10**).
- Pain relief
  Refer to **Subchapter 5.2.3.**
- Radiological imaging
  Routine use of imaging is not indicated and should be reserved for patients presenting with atypical features, major swelling or trauma of a joint to exclude a concomitant traumatic lesion.
- Rehabilitation
  Rehabilitation should be emphasised in the active management of haemathrosis. Refer to **Subchapter 5.1.1.**
- Arthrocentesis (joint aspiration)
  Arthrocentesis may be considered for symptomatic relief of a tense haemarthrosis which shows no improvement 24 hours after conservative treatment.[2] It is safe when done by experienced physicians using established protocol.[40, level II-3]

Further evaluation for the presence of inhibitor, septic arthritis or fracture is necessary if the symptoms and signs continue longer than three days.

6.3 Musculoskeletal

Early identification and proper management of muscle bleeding are important to prevent complications e.g. re-bleeding, compartment syndrome, joint contractures and formation of pseudotumours.[2]
Clinical features of muscle bleeding are:[2]

- pain if the muscle is stretched or actively contracted
- affected limb is positioned in a comfortable posture to avoid pain
- tenderness upon palpation
- swelling (may not be visible)

The following groups of muscle bleeding are associated with neurovascular compromise and require immediate management to prevent permanent damage and loss of function:[2]

- iliopsoas muscle (risk of femorocutaneous, crural and femoral nerve palsy)
- superior-posterior and deep posterior compartments of the lower leg (risk of posterior tibial and deep peroneal nerve injury)
- flexor group of forearm muscles (risk of Volkmann's ischemic contracture)

The goals of treatment are to stop the bleeding, prevent re-bleeding and to restore muscle function. The management for this condition includes:[2]

- Factor replacement therapy
  Administer the appropriate dose of factor concentrate as soon as possible; ideally when the patient recognises the first symptoms of discomfort or after trauma (refer to **Table 10**).
- Pain relief
  Refer to **Subchapter 5.2.3.**
- Radiological imaging
  Ultrasonography (US) and MRI are important diagnostic tools to confirm diagnosis and monitor recovery especially at critical sites.
- Rehabilitation
  Refer to **Subchapter 5.1.1.**

In PWH, choice of sport and level of activity should be based on individual factor levels, bleeding history and physical health to prevent acute muscle bleeding. Routine musculoskeletal review helps to promote general muscle fitness and to individualise exercises for specific sports. Single dose prophylaxis is considered prior to engaging in physical activities that might precipitate bleed in severe haemophiliacs.[41, level III]

Iliopsoas haemorrhage

Iliopsoas haemorrhage has a unique presentation. It may mimic an acute abdomen. Symptoms may include pain in the lower abdomen, groin, lower back and pain on extension of the hip joint. There may be paraesthesia in the medial aspect of the thigh or other signs of femoral nerve compression e.g. loss of patellar reflex and quadriceps weakness.[2; 42, level III]

USG is a useful and fastest tool to diagnose iliopsoas haematoma.[42, level III]

Management of iliopsoas haemorrhage includes:[2]

- hospitalise the patient for control of pain and strict bed rest
- maintain the factor levels for 5 - 7 days or longer, as symptoms dictate (refer to **Table 10**)
- monitor recovery using an imaging study (USG or MRI)
- limit the patient's activity until pain resolves and hip extension improves; rehabilitation aimed at restoration of complete hip extension before returning to full activity

Fractures

The principle management of fracture in PWH is the same as those without haemophilia. It can be divided into:

- conservative management
- operative management

For conservative management, the factor replacement regimen is the same as treating intramuscular haemorrhage (refer to **Table 10**). On the other hand, in operative management, the factor replacement regimen is as per major surgery.

CFC should be given immediately to raise the level to at least 50% and maintained for 3 - 5 days. Low dose CFC may be continued for 10 - 14 days to prevent soft tissue bleeding.[2]

The management plan should follow the orthopaedic principle for fracture, including operative treatment under appropriate coverage of CFC.[2]

For fracture treated with conservative management:

- in the initial stage, it is safe to use backslab; do not use circumferential plaster
- full cast can be used once the bleeding is controlled with the factor replacement and swelling subsides
- the duration of immobilisation is as the fracture treatment in a normal patient

For fracture treated with surgery, avoid prolonged immobilisation and start physiotherapy as soon as the fracture is stabilised.[2]

For factor coverage, the following regimen is suggested:

- Day 1 - 2, raise the factor level to 80 - 100% and given 8-hourly for haemophilia A, 12-hourly for haemophilia B
- Day 3 - 5, raise the factor level to 30 - 60% and given 12-hourly for haemophilia A, daily for haemophilia B
- thereafter, raise the factor to 30%, given daily until soft callus is formed (total duration is approximately about two weeks)

Refer to **Subchapter 5.1.1** on **Rehabilitation of musculoskeletal system**.

6.4 Ear, Nose, Throat and Eye

For bleeding arising from the ear, nose, throat and eye in PWH, immediately raise patient's factor levels (refer to **Table 10**). Antifibrinolytic therapy e.g. TXA may be used as adjunctive therapy. They should be referred to the respective disciplines if necessary.[2]

6.5 Gastrointestinal Tract

For bleeding arising from the gastrointestinal tract in PWH, immediately raise patient's factor levels (refer to **Table 10**). Antifibrinolytic therapy e.g. TXA may be used as adjunctive therapy. Imaging may be necessary.[2]

6.6 Genitourinary Tract

For bleeding in the genitourinary tract in PWH, vigorous hydration should be started at 3 L/m^2 for a minimum of 48 hours. The factor level needs to be raised up to 50% if there is pain or persistent gross haematuria after 48 hours (refer to **Table 10**). Watch out for complications e.g. urinary tract obstruction that may require urological referral.[2]

- Avoid using anti-fibrinolytic agent as it may cause clots leading to urinary tract obstruction.

6.7 Oral Cavity

Refer to **Chapter 12**.

Table 10. Suggested plasma peak levels and duration of treatment for acute bleeding in specific sites and surgeries*

Type of Haemorrhage	Haemophilia A		Haemophilia B	
	Desired level (IU/dL)**	Duration (Days)	Desired level (IU/dL)**	Duration (Days)
Joint				
	40 - 60	1 - 2 , may be longer if response is inadequate	40 - 60	1 - 2 , may be longer if response is inadequate
Superficial muscle/ no neurovascular compromise (except iliopsoas)				
	40 - 60	2 - 3, sometimes longer if response is inadequate	40 - 60	2 - 3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss				
• Initial • maintenance	80 - 100 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy	60 - 80 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy
Central Nervous System/head				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 21	60 - 80 30	1 - 7 8 - 21
Throat and neck				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 14	60 - 80 30	1 - 7 8 - 14
Gastrointestinal				
• Initial • maintenance	80 - 100 50	7 - 14	60 - 80 30	7 - 14
Renal				
	50	3 - 5	40	3 - 5
Deep laceration				
	50	5 - 7	40	5 - 7
Surgery (major)				
• Pre-op • Post-op	80 - 100 60 - 80 40 - 60 30 - 50	 1 - 3 4 - 6 7 - 14	60 - 80 40 - 60 30 - 50 20 - 40	 1 - 3 4 - 6 7 - 14
Surgery (minor)				
• Pre-op • Post-op	50 - 80 30 - 80	 1 - 5, depending on type of procedure	50 - 80 30 - 80	 1 - 5, depending on type of procedure

*Table is based on country with no resource constraint.
** IU/dL=%

Source: World Federation of Haemophilia. Guidelines for the Management of Haemophilia (2nd edition). Montréal: Blackwell Publishing Ltd; 2012

In the absence of an inhibitor, each unit of FVIII/kg body weight infused via intravenous (IV) will raise the plasma FVIII level approximately 2 IU/dL. The half-life of FVIII is approximately 8 - 12 hours and FIX is 18 - 24 hours.[43, level III]

- A formula for dose of factor concentrate calculation is as follows:
  $$\text{Dose required} = \frac{(\text{desired \% rise - baseline level}) \times (\text{kg body weight})}{K}$$
- For severe haemophilia, the baseline level is assumed to be 0%.
  K = 2.0 for plasma-derived FVIII (Haemophilia A) or 1.5 for recombinant FVIII
  1.0 for plasma-derived FIX (Haemophilia B) or 0.6 for recombinant FIX

Source: Haemophilia and Bleeding Disorders Protocol. Ampang Hospital, 2012 (unpublished document)

Recommendation 7

- Acute bleed in persons with haemophilia (PWH) should be treated with factor replacement as soon as possible, preferably within two hours.
  - The desired factor level is dependent on site and severity*; usually it is given until bleeding resolves.
  - Factor replacement should precede investigation and aim to achieve factor level of 100% for life-threatening bleed.

*Refer to **Table 10**.

7. TREATMENT OF MUSCULOSKELETAL COMPLICATIONS

7.1 Synovitis

Synovitis is defined as hypertrophy and hypervascularity of the synovium characterised by painless chronic swelling of the affected joint, evidenced by clinical examination and imaging e.g. US and/or MRI.[33]

The goal of treatment is to deactivate the synovium as soon as possible and preserve joint function. The treatment modalities include:

- factor concentrate replacement (refer to **Table 10**)
- physiotherapy (refer to **Subchapter 5.1**)
- NSAIDs (COX-2 inhibitors) to reduce inflammations
- synovectomy including radiosynovectomy (RS)

RS is a local form of radiotherapy that involves intra-articular injection of small radioactive particles to treat synovitis. It offers a conservative alternative to surgical synovectomy in patients with synovitis and recurrent bleeding in the target joint, which has proven refractory to intensive treatment with clotting factor concentrates.[33]

RS is an effective, safe and minimally invasive procedure in haemophilic synovitis with:[44, level III]

- significant reduction in articular pain (69.4%), haemarthrosis (64.1%), and degree of synovitis (31.3%)
- improvement in WFH clinical score (19%)
- small number of patients (0.9%) develop complications e.g. knee septic arthritis, severe swelling or small cutaneous burn
- no patient develop cancer

There is no difference in outcomes between patients with prophylaxis and on-demand treatment.

In synovitis (haemophilia and VWD) treated with RS using rhenium-186, the mean time to progression (TTP) is:[45, level II-3]

- 72.0 + 4.8 months with a median follow-up of 36 months for ankle
- 67.5 + 6.5 months with a median follow-up of 35 months for elbow joint

There is significant inverse correlation between the number of joint bleeding in both ankle and elbow within six months after therapy and TTP ($p<0.05$). This is independent of patient's age, haemophilia type and severity, inhibitor status, radiological score, ROM status and pre-treatment bleeding frequency.

Recommendation 8

- Radiosynovectomy should be considered in haemophilic synovitis with recurrent bleeding in the target joint.

7.2 Joint Arthropathy and Contracture

Chronic haemophilic arthropathy may occur from the second decade of life or earlier, depending on the severity of bleeding and its treatment. The goals of treatment are to improve joint function, relieve pain and assist PWH to continue/resume normal ADL.

The treatment includes:
- pain management (refer to **Subchapter 5.2.3**)
- rehabilitation (refer to **Subchapter 5.1.1**)
- secondary prophylaxis should be optimised

Surgical intervention may be considered if these conservative measures fail. These may include prosthetic joint replacement for severe disease involving a major joint (knee, hip, shoulder and elbow). For surgical procedure, adequate resources, including sufficient factor concentrates, laboratory support and post-operative rehabilitation, must be available.

In PWH, joint contracture can be treated by:
- botulinum toxin injection[46, level II-3]
- muscle release surgery[47, level III]

7.3 Pseudotumour

Pseudotumour is a rare complication of haemophilia, occuring in 1 - 2% of the haemophilic population.

A pseudotumour is an encapsulated haematoma with a thick, fibrous capsule. Repeated cycles of bleeding and calcification will lead to progressive enlargement of the mass and subsequent erosion of the adjacent bone. The rich vascular supply of the capsule is the cause of excessive bleeding during and after surgery, and this vascular supply usually originates from more than a single artery.

There are two types of pseudotumour:
- proximal pseudotumour
- distal pseudotumour

Proximal pseudotumour frequently occurs in the proximal axial skeleton, especially around the femur and pelvis. This slow growing tumour occurs more frequently in adults and do not respond to conservative treatment.[48, level III]

Distal pseudotumour predominantly affects younger age group, develop rapidly and appear to be secondary to an intraosseous haemorrhage. The sites of the tumour includes tibia, metacarpal, phallanges, paranasal sinus,[48, level III] mandible and maxilla.[49, level III]

Pseudotumour generally presents with painless, firm, expanding masses that may appear to be multilocular and adherent to the deeper structures. It may remain asymptomatic until complications occur.[48, level III]

The typical radiological features are large soft-tissue masses and areas of adjacent bone destruction. Calcification within the mass is a frequent finding. Pseudotumour of the ilium may cause significant bony erosion with little new periosteal bone formation.[48, level III]

Untreated pseudotumour leads to complications e.g.:

- fistulisation to skin or intraabdominal organs
- infection
- pathological fracture
- septicaemia
- internal bleeding
- death

Treatment for pseudotumour

a. Proximal pseudotumour

- Surgical resection

Surgical resection is curative and should ideally be performed in a HCCC. This procedure is usually difficult and carries a high complication rate including vascular and neurological damage, haemorrhage and infection.

- Embolisation:[48, level III]
  - serves as a sole therapeutic modality to reduce the size and stabilise the pseudotumour where surgery poses a great risk of life-threatening haemorrhage
  - has a role to minimise the vascularisation of the pseudotumour and reduce its size prior to surgery

b. Distal pseudotumour

- Irradiation

Irradiation works by causing direct injury to the blood vessels feeding the pseudotumour and disruption to the endothelial proliferation of the wall of the pseudotumour. It is indicated when the pseudotumour occurs in multiple sites, inaccessible sites and sites where anatomy and function should be preserved. The treatment involves a total dose of 6 - 23.5 Gy (2 Gy per fraction) together with factor replacement. It is effective if the pseudotumour is <10 cm.[48, level III]

- Curettage and filling with:[50, level III; 51, level III; 52, level III]
  - fibrin seal and cancellous bone graft (involvement of soft tissue and bone)
  - cancellous bone graft alone (bone involvement)

8. INHIBITORS

Inhibitors are antibodies that neutralise clotting factors which develop following factor replacement therapy. Presence of inhibitors lead to ineffective factor replacement therapy. The cumulative incidence (i.e. lifetime risk) of inhibitor development is:[2]

- 20 - 30% in severe haemophilia A
- 5 - 10% in mild or moderate haemophilia A
- <5% in haemophilia B

Risk factors of inhibitor development are:

- high intensity treatment of clotting factor [FVIII concentrate >150 IU/kg/week within the first 8 - 12 weeks of therapy (HR=1.9, 95% CI 1.3 to 2.8)][53, level II-2]
- FVIII genotype - large deletions and nonsense mutations have higher risk compared with intron 22 inversions [pooled OR=3.6 (95% CI 2.3 to 5.7) and OR=1.4 (95% CI 1.1 to 1.8) respectively][20, level II-2]
- family history of inhibitors (RR=3.5, 95% CI 1.5 to 8.1)[19, level II-2]

Regular prophylaxis is associated with a lower risk of inhibitor development than on-demand treatment.[19 - 20, level II-2]

- Inhibitors can develop in all patients who have been exposed to factor concentrates.
- Presence of inhibitors should be suspected in the following situations:
  - poor response to replacement therapy
  - recovery assays are not as expected
  - increase bleeding episodes despite optimal prophylaxis
- Inhibitor should be screened:[2]
  - at regular intervals
    - for children - once every five exposure days until 20 exposure days, then every 10 exposure days between 21 and 50 exposure days, then at least twice a year until 150 exposure days
    - for adults with >150 exposure days, every 6 - 12 months
  - after intensive treatment for >5 days, within four weeks of the last infusion
  - prior to surgery

Recommendation 9

- Screening for inhibitor should be done in all persons with haemophilia exposed to factor replacement therapy.*

*Refer to the preceding yellow box.

8.1 Treatment of Acute Bleeding in PWH with Inhibitors

The main treatment option for bleeding episodes in PWH with inhibitors is bypassing agents e.g. rFVIIa or aPCC. These agents bypass the coagulation pathway that normally utilises FVIII. aPCC should be used with caution in patients planned for ITI as it may cause anamnestic response with the rise of inhibitor levels.

rFVIIa and aPCC are equally effective and well tolerated with no increase in thromboembolic risk in the treatment of acute bleeding episodes in haemophilia with inhibitors.[54, level I]

The dose of rFVIIa is 90 - 120 µg/kg rounded up to the nearest vial size, given every 2 - 3 hours until haemostasis achieved. Equivalent effectiveness and safety have been demonstrated with a single dose of 270 µg/kg vs three doses of 90 µg/kg[54, level I] aPCC can be used at doses of 50 - 100 IU/kg given every 8 - 12 hours, but should not exceed 200 IU/kg/day.[33; 54, level I]

Home treatment with bypassing products is effective in haemostasis and safe with no serious adverse events.[55, level II-3]

Recommendation 10
- Bypassing agents should be used to treat acute bleeding in haemophilia with inhibitors.

8.2 Prophylaxis Therapy in PWH with Inhibitors

There is a role for prophylaxis with bypassing agents in PWH with inhibitors. In a Cochrane systematic review:[56, level I]

- both bypassing agents as prophylaxis were significantly effective in reducing bleeding as compared with on-demand group
- there was lack of evidence on the superiority of one agent over the other
- there was no significant difference between high dose 270 ug/kg daily and low dose 90 ug/kg daily rFVIIa regimen in reducing overall bleeding and serious adverse events while the prophylaxis dose for aPCC is 85 ± 15 IU/kg three times a week or every other day

Prophylaxis can be considered after life-threatening bleed or in frequent bleeders. However, the high cost limits its use. Based on current local price, the estimated cost of prophylactic aPCC in a 50 kg patient is RM4.5 million/year (1 vial of 500 IU=RM2726).

Novel agents such as SC emicizumab, concizumab and fitusiran are being investigated as alternative prophylaxis for PWH with inhibitors. Emicizumab, a bispecific monoclonal antibody that bridges factor IXa and factor X, and given as a weekly SC injection has been approved by FDA and EMA.

8.3 Eradication of Inhibitors

The rationale for advocating immune tolerance induction (ITI) in PWH with inhibitor is because treatment with bypassing agents is suboptimal as compared with factor replacement therapy in PWH without inhibitor. Hence, eradication of inhibitor is important to put the patient back on prophylactic therapy with factor concentrate.

ITI is a therapy where repeated medium to large doses of factor concentrate are administered over a period of weeks to years to induce antigen specific tolerance and reduce inhibitory antibodies. It is carried out until the antibodies disappear. There are different regimens consisting of various factor dosages with or without immune suppression. The success rate in haemophilia A is about 50 - 80%[57, level III] and haemophilia B 13 - 31%.[58, level III]

Initiation of ITI should be postponed until the inhibitor titre has dropped to <10 BU. An inhibitor titre of <10 BU immediately before ITI initiation positively affects both the likelihood of success and the time required to achieve tolerance.[59, level III]

Consider starting ITI regardless of the inhibitor titre if:[59, level III]

- the inhibitor titre does not fall below 10 BU within a 1- to 2-year period of close observation or
- a severe life- or limb-threatening bleeding event occurs

- Prerequisite for starting ITI to ensure no interruption of treatment for best response:
  - commitment from PWH with inhibitor/care giver
  - good venous access
  - adequate budget

Refer to **Table 11** for dose recommendations on initial regimens and escalation of low-or intermediate-dose regimens based on response and breakthrough bleeds.

Table 11. Regimen for ITI

Historic peak inhibitor titre	Regimen
<5 BU	• Start ITI at a dose of 50 IU/kg every other day • To control clinically significant breakthrough bleeds, escalate to daily treatment, then only increase the dose by increments of 50 IU/kg/day up to 200 IU/kg/day • If the inhibitor titre on this ITI regimen increases above 40 BU, increase dose immediately to 100 IU/kg/day. If the inhibitor titre increases above 200 BU, increase the dose immediately to 200 IU/kg/day
>5 and <200 BU	• Start ITI at a dose of 100 IU/kg/day • To control clinically significant breakthrough bleeds, escalate the dose by increments of 50 IU/kg/day up to 200 IU/kg/day • If the inhibitor titre rises to >200 BU, increase dose immediately to 200 IU/kg/day
>200 BU	• Start ITI at a dose of 100 IU/kg/day

Source: Collins P, Chalmers E, Alamelu J, et al. First-Line Immune Tolerance Induction for Children with Severe Haemophilia A: A Protocol from The UK Haemophilia Centre Doctors' Organisation Inhibitor and Paediatric Working Parties. Haemophilia. 2017; 23:654-659

In a Cochrane systematic review, the time taken to eradicate inhibitor was shorter in the high dose regimen (200 IU/kg/day) as compared with low dose (50 IU/kg three times a week) resulting in less bleeding event (p=0.027). However, there was no difference in successful tolerance between the two regimens (RR=1.07, 95% CI 0.68 to 1.68).[60, level I]

The off-label use of rituximab had been shown in some studies to be effective in eradicating inhibitors in haemophilia. A durable remission was achieved in 53.1% with no serious adverse reactions reported. The response was better in mild/moderate haemophilia and with concomitant treatment with factor VIII concentrates and immunosuppressive agents.[61, level III]

Recommendation 11
- Immune tolerance induction should be considered in all persons with haemophilia with inhibitor.

9. HOME THERAPY

Home therapy is part of haemophilia comprehensive care, where the administration of replacement therapy is done outside hospitals, with its safety and effectiveness closely supervised.[62, level III]

Home therapy allows immediate access to clotting factor. The earlier the factor is initiated, ideally within two hours of bleeding onset, the faster the bleeding will resolve.[2] PWH who practice home therapy have better QoL compared with those who do not. They have a lower risk of hospitalisation for bleeding (RR=0.8, 95% CI 0.7 to 0.9).[63, II-2]

- **Requirements for home therapy**
  - Initiation of home therapy should only be done after adequate education and training. This is followed by close supervision of its safety and efficacy. Education should include:[2]
    - general knowledge of haemophilia
    - recognition of bleeds and common complications
    - first aid measures
    - dosage calculation, preparation, storage and administration of clotting factor concentrates
    - aseptic techniques and venepuncture techniques (or access of central venous catheter)
    - record keeping
    - proper storage and disposal of needles/sharps, and handling of blood spills

E-learning programme improves knowledge and skills of PWH on home treatment (p=0.002).[64, level I]

Recommendation 12
- Home therapy should be advocated to all persons with haemophilia.

Central venous access device

It is essential to have patent venous access for factor delivery in PWH. Peripheral venous is the route of choice; however, central venous access device (CVAD) facilitates easier factor administration in young children with small and difficult veins.[2]

CVAD is indicated in PWH with difficult venous access who require immune tolerance induction therapy or prophylaxis.[65, level III]

However, despite the benefits of CVAD, its usage in haemophilia should be approached cautiously because of its potential complications e.g. risk of surgery, infection, mechanical complication, thrombosis and should only be inserted and used in centres with expertise of CVAD.[2; 65, level III]

Risk factors for CVAD infections are:

- patient with inhibitors at insertion (p=0.0040)[65, level III]
- age under six years at the time of insertion[66, level III]
- external catheter devices compared to implanted ports[66, level III]

An arteriovenous fistula is a feasible option for venous access in haemophilia but formation of a fistula in a haemophiliac and its management should only be done in centres with this expertise and there are associated risks as well (inadequate maturation and hypertrophy of the fistula arm).[67, level II-2]

10. ADHERENCE IN HAEMOPHILIA TREATMENT

Adherence is defined as the extent to which a person's behaviour on taking medication, following diet, and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider.[68, level III] Life-long dedication and adherence to prophylactic therapy is crucial to prevent bleeding and maintain good health in PWH.

a. Factors influencing adherence

- Motivators for haemophilia treatment adherence:
  - experience of bleeding symptoms ($p<0.05$)[69, level III]
  - good relationship with healthcare providers ($p<0.001$)[69, level III]
  - positive belief in necessity of treatment ($p<0.01$)[69, level III]
  - haemophilia perceived as a highly chronic condition ($p=0.003$)[70, level III]
  - less negative emotions ($p=0.023$)[70, level III]

- Barriers for haemophilia treatment adherence:[69, level III]
  - absence or infrequent bleeding symptoms
  - increasing age (older patients) ($p=0.002$)

b. Measures to improve adherence

- Ensure adequate time and resources are allocated for family adherence education.[71, level II-2]
- Promote interventions aiming at PWHs' acceptance of their chronic condition.[70, level III]
- Target young adults as they are transitioning from adolescence and assuming primary responsibility for their haemophilia care.[71, level II-2]

c. Haemophilia Medication Therapy Adherence Clinic

- (HMTAC) is an adherence programme in Malaysia where trained pharmacists assist PWH and caregivers based on structured modules to:
  - understand haemophilia and its treatment
  - identify healthy lifestyle decisions which may impact bleeding tendencies and factor concentrate use
  - utilise HMTAC team members for queries or feedback on problems
  - maintain good attendance at work or school

- Objectives and benefits of HMTAC include:
  - to help PWH understand and treat haemophilia
  - to support PWH and their family through continuous supervision of all pharmacotherapy related to bleeding disorders

- to educate and empower PWH to be independent and be able to do home therapy
- to lower morbidity and to provide long-term cost-effective care

Recommendation 13

- Haemophilia Medication Therapy Adherence Clinic should be made available in all haemophilia treatment centres.

11. SPECIAL SITUATIONS

11.1 Surgeries and Invasive Procedures

Surgeries for PWH require proper planning, effective communication and multidisciplinary collaboration. It is best managed at or in consultation with a comprehensive HTC and the following requirements need to be considered:[2]

- surgery is scheduled early in the week and early in the day for optimal laboratory and factor support
- anaesthesiologist involved has experience in treating patients with bleeding disorders
- adequate laboratory support for monitoring factor level and inhibitor testing
- adequate quantities of factor concentrates must be available peri-operatively and during the duration of healing and/or rehabilitation

Pre-operatively, inhibitor screening and inhibitor assay must be carried out, particularly if the recovery of the replaced factor is less than expected.[2]

Surgical procedures can be either major or minor. A major procedure is defined as one that requires haemostatic support for a period exceeding five consecutive days.[2] It often refers to major abdominal, intracranial, cardiovascular, spinal, major orthopaedic (e.g. joint replacement) and any other surgery with risk of large volume blood loss or blood loss into a confined anatomical space. In children this may include adeno-tonsillectomy. Minor surgery refers to removal of skin lesions, arthroscopy, minor dental procedures and dental extractions.[73, level III]

Infusion of factor concentrates is also necessary before invasive procedures e.g. lumbar puncture, arterial blood gas or any endoscopy with biopsy.[2]

The dosage and duration of factor concentrate coverage depends on the type of surgery performed (refer to **Table 10**).

Recommendation 14

- Persons with haemophilia who need surgery or invasive procedure should have an optimal plan (which include adequate factor coverage peri-operatively) and managed by a multidisciplinary team.

11.2 Management of Pregnant Carrier

The care of known carriers of haemophilia should be undertaken by an obstetric unit in close liaison with a haemophilia care centre. A written management plan should include the haemostatic management of the mother and baby.[74, level III]

Gender identification should be made during antenatal period by US scan between 18 and 20 weeks. Foetal gender can also be determined by maternal blood sampling at around 10 weeks of gestation. If the foetus is found to be male, the diagnosis of haemophilia maybe confirmed by amniocentesis to decide the management at delivery.[74, level III] In our local setting, these tests are available in some private laboratories.

FVIII level should be measured in carriers during the third trimester of pregnancy and if it is <50 IU/dL, clotting factor replacement is necessary for surgical or invasive procedures during delivery.[2]

In a meta-analysis, delivery of infants with known or suspected haemophilia should be atraumatic, regardless of whether it is vaginal or caesarean, in order to decrease the risk of bleeding.[75, level II-2]

- Cranial bleeding occurred with a significantly higher frequency in newborns with haemophilia compared with the general population i.e.:
  - ICH (OR=44, 95% CI 34.7 to 57.1)
  - extracranial haemorrhage: (OR=8.2, 95% CI 5.38 to12.6)
- In newborns with haemophilia, delivery by caesarean section was associated with the lowest risk of ICH (OR=0.34, 95% CI 0.14 to 0.83).
- Assisted vaginal delivery (forceps and vacuum extraction) increased the risk of ICH (OR=4.39, 95% CI1.46 to 13.7).

- The care of known carriers of haemophilia in pregnancy should should involve a multidisciplinary team with expertise in haemophilia care.
- Route of delivery in haemophilia carriers should be as per obstetric indications.
- Assisted vaginal delivery and invasive procedures should be avoided in male foetus.

Intramuscular (IM) vitamin K and hepatitis B vaccination should be withheld until haemophilia is excluded. Oral vitamin K should be given if there is a delay in diagnosis or if haemophilia is confirmed.[74, level III]

- In view of limitation of laboratory services in the local setting, the management of a male newborn of a carrier mother are as follow:
  - the newborn is assumed to have haemophilia until proven otherwise
  - oral vitamin K should be given instead of IM vitamin K
  - hepatitis B vaccination should be given subcutaneously
  - APTT and factor assay should be done as soon as possible to confirm haemophilia; cord blood is preferable if feasible.

Recommendation 15
- All haemophilia carriers should have FVIII level done during third trimester of pregnancy.
  - If FVIII level is <50 IU/dL, clotting factor replacement is necessary for surgical or invasive procedures during delivery.
- Gender identification should be determined antenatally in haemophilia carriers.

11.3 Vaccination

Patients with bleeding disorders should receive the recommended vaccinations for their age group. However, these vaccinations should be given subcutaneously rather than intramuscularly to reduce the injection site complications.[2]

Hepatitis B vaccination by SC route is as effective as IM route.[76, level III]

Recommendation 16
- All injectable vaccinations in haemophilia should be given subcutaneously.

11.4 Circumcision

Circumcision is not absolutely contraindicated in PWH but should be performed cautiously by the surgeon in liaison with the haematologist in a haemophilia care centre. However, it should be taken into consideration that bleeding and other complications maybe more serious in those with inhibitors.

Fibrin glue is a topical, biological sealant which stimulates the final stages of coagulation. It diminishes the risk of post-operative bleeding and reduces the need of factor replacement therapy.[77, level III; 78, level II-2]

- Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia Kali Ke-77 has decided that circumcision in PWH is considered life-threatening and hence it is not obligatory.[79]

12. DENTAL CARE

12.1 Preventive Dental Measures

Routine dental examination with preventive care should be conducted regularly.[80, level III] In PWH, it should be initiated at the time the baby teeth start to erupt.[2; 81, level III] It is advisable to refer all PWH for oral assessment within six months of eruption of the first tooth and no later than 12 months of age.[82]

Good oral hygiene practice helps to prevent periodontal disease (gum disease), dental caries, gum bleeding and the need for dental extraction. Brushing teeth twice a day (using soft bristle toothbrush) with toothpaste containing fluoride will remove plaque deposits.[2; 81, level III] Dental floss or interdental brush should be used wherever possible.[2]

Early childhood caries (ECC) is a significant oral health related disease in the baby teeth of young children. Dietary counselling including reduced sugar intake should be part of the oral health advice for PWH[83, level III] and those with high risk of ECC.[82]

Properly designed and implemented oral health educational programmes are helpful to make positive changes in oral health of PWH.[84, level III; 85, level II-3; 86, level II-1; 87, level III]

Recommendation 17

- In person with haemophilia,
  - comprehensive oral health care should be initiated early within six months after the first tooth erupts and no later than 12 months
  - routine dental examination with preventive care measures should be conducted regularly throughout life
  - good oral hygiene practice and dietary counselling should be advocated to prevent dental diseases

12.2 Dental Procedures

Effective and safe dental procedures should be a priority in PWH. A multidisciplinary approach involving dental surgeon and the haemophilia team is important for comprehensive oral health care.[2; 80, level III] Before performing any invasive dental or surgical procedures, the dental surgeon must liase with the haematologist in order to prevent or minimise potential bleeding or infection risks. Careful planning for haemostatic cover is crucial for PWH with inhibitors.[2] With respect to local anaesthetic (LA) and factor replacement therapy, the recommendations is as stipulated in **Table 12**.

Table 12. Dental anaesthetic procedures and factor replacement therapy

Procedures that do not require factor cover (applies to adult patients only). Paediatric patients may receive factor replacement therapy before local anaesthetic infiltration as advised by haematologist	Procedures that require factor cover (applies to both adult and paediatric patients)
• Labial/buccal infiltration • Intra-papillary injections • Intra-ligamentary injections	• Inferior dental block/ mandibular block* • Lingual infiltration*

Source: Anderson JA, Brewer A, Creagh D, et al. Guidance on The Dental Management of Patients with Haemophilia and Congenital Bleeding Disorders. Br Dent J. 2013;215(10):497-504

***In local practice, these procedures are best avoided for paediatric patient.**

Locally, different types of dental local anaesthetic are used e.g. mepivacaine hydrochloride (HCL) 2%, lignocaine HCL 2% and articaine HCL 4%. The articaine HCL 4% with 1:100,000 epinephrine has been described for infiltration as an alternative to inferior dental block in the restoration of mandibular molars and may remove the need for pre-operative factor cover.[80, level III]

PWH must seek immediate care from the haematologist/dental surgeon post-operatively if one of these events occur:[2]

- prolonged bleeding
- difficulty in speaking
- difficulty in swallowing
- difficulty in breathing

Refer to **Subchapter 5.2.3** on **Analgesia**.

Malocclusion e.g. overcrowding teeth may lead to periodontal (gum) disease if left untreated.[88, level III] Therefore, an orthodontic assessment for PWH should be considered between the ages of 10 - 14 which is during the late mixed to early permanent dentition stages.[2]

Recommendation 18

- Comprehensive oral health care in haemophilia should be performed by a multidisciplinary team which include a dental surgeon.

12.3 Management of Oral Bleeding

Causes of oral bleeding in PWH include:

- eruption of permanent teeth with exfoliation of baby teeth[83, level III]
- gingival/gum bleeding associated with poor oral hygiene[2]
- trauma[2]
- invasive dental procedures e.g. dental extractions, surgical procedures, etc.[2]

In children with haemophilia, the surrounding gum may appear bluish and swollen when the baby teeth are erupting or teething. Normally, these conditions do not bleed. Therefore, it is suggested to allow the baby teeth to self-exfoliate in order to minimise risk of bleeding.[83, level III] In local setting, extraction is indicated when the baby tooth is mobile and causes gum bleeding. The need for factor coverage should be discussed with the haematologist.

The type of dental procedures significantly affects the bleeding outcome and can be categorised according to risk of bleeding. High-risk procedures have higher bleeding outcome compared with low-risk procedures (OR=8.97, 95% CI 3.5 to 23).[89, level III] The risk of bleeding in dental procedures is shown in **Table 13**.

Table 13. Dental procedures and risk of bleeding

Level of risk	Type of dental procedure
High-risk	• Flap elevation • Teeth extractions • Crown lengthening procedure • Soft tissue biopsy • Scaling and/or root planning • Inferior alveolar nerve block
Low-risk	• Restorative treatment e.g. filling, crown, bridge, etc. • Prosthodontics treatment e.g. denture fabrication, root canal treatment, etc. • Orthodontic treatment

Source: Givol N, Hirschhorn A, Lubetsky A, et al. Oral Surgery-Associated Postoperative Bleeding in Haemophilia Patients - A Tertiary Centre's Two Decade Experience. Haemophilia. 2015; 21(2):234-40

Antifibrinolytic agents e.g. TXA and epsilon aminocaproic acid therapy administered systemically in PWH undergoing minor oral surgery or dental extraction are beneficial in preventing post-operative bleeding (RD= -0.57, 95% CI -0.76 to -0.37). The antifibrinolytic agents reduce the need for clotting factor concentrates and post-operative bleeding. No significant adverse events have been reported.[90, level I]

Antifibrinolytic therapy in the form of TXA 5% weight/volume mouthwash (four times a day) should be kept in the mouth for two minutes before discarding.[91, level III] Oral TXA and/or 5% TXA mouthwash should be prescribed alone or in combination pre- and post-dental extraction for up to seven days. The mouthwash should not be given to younger children as they may inadvertently swallowed it, leading to overdosage.[80, level III]

In local setting, compression of the bleeding area using gauze soaked with diluted TXA (TXA 500 mg diluted in 10 ml of distilled water) is used until bleeding stops.

In PWH undergoing dental extractions, bleeding may be minimised by using either resorbable or non-resorbable sutures, surgical splints and other additional local haemostatic measures.[80, level III] Factor replacement may be required for PWH according to the haematologist's care plan.[2]

- The relative risk of bleeding in person with haemophilia depends on the types of dental procedures.
- Antifibrinolytic therapy reduces the need for clotting factor concentrate and post-operative oral bleeding.

13. MONITORING

Haemophilia care involves managing PWH from birth until adulthood. Clinical follow-up of PWH has become more complex with the introduction of new treatment strategies and the emergence of new tools to evaluate the medical and social consequences.

Regular and standardised evaluation should be done at least 12-monthly so that problems are identified early and treatment modified accordingly.[2] The parameters to monitor are:

- inhibitors
- bleed frequency
- joint health
- radiological measures

13.1 Inhibitors

Refer to **Chapter 8** on **Inhibitors**.

13.2 Bleeding Frequency

Bleeding pattern is the key parameter to evaluate the efficacy of treatment strategy and thus, information on bleeding episodes should be thoroughly documented. Issues related to haemostasis (bleed record) should be evaluated.[2]

Standard assessment of bleed frequency includes ABR, which is the number of bleeds collected over 12 consecutive months. In addition to ABR, annual joint bleeding rate (AJBR) should be specified.[92, level III]

ABR is calculated based on the following formula:[93, level I]

$$\textbf{ABR} = \frac{\text{Number of bleeding events}}{\text{(Number of days receiving treatment/365.25 days)}}$$

Information to be recorded on haemarthrosis and other types of bleeding are:[92, level III; 94, level III]

- number of episodes
- time and site of each bleed
- provoked (i.e. traumatic) or spontaneous bleed
- target joint or non-target joint bleed
- dose, number, interval and response to factor administration

In PWH treated with early prophylaxis, self-reported bleeding does not significantly correlate with any other outcome parameters (ABR with HJHS: r=0.107; Functional Independence Score in Haemophilia (FISH): r=0.300; Pettersson scores: r=0.016; Arnold-Hilgartner (AH)

scores: r=0.081; and additive and progressive scores: r=0.073 and 0.066 respectively).[95, level III]

In addition to self-reported bleeding, outcome assessment in PWH on long-term prophylaxis should include objective joint assessment, assessment of activities and health-related QoL.[15, level III]

13.3 Joint Health

Preservation of good joint status is an important component of haemophilia care. The HJHS is a clinical measure of joint structure and function. It is more efficient than WFH score at differentiating:[96, level III]

- severe from mild and moderate haemophilia (97%, p=0.003)
- subjects treated with prophylaxis from those treated on-demand (74%, p=0.003)

Inter-physiotherapist discrepancies in routine HJHS have been shown to hamper comparison of scores between treatment regimens.[97, level III] Thus, training of physiotherapist on HJHS assessment is essential.

HJHS may be used safely as a first-line tool for monitoring of joint health as it has significantly strong correlation with radiological scores (r=0.67), moderate correlation with physical domains of the quality of life questionaire (SF-36) (r= -0.50), utility (r= -0.41),[15, level III] and MRI scores (r=0.444 with additive score and r=0.440 with progressive score).[95, level III]

It is recommended to do HJHS at least once a year.[94, level III] Refer to **Appendix 8** on **HJHS Score**.

13.4 Radiological Measures

Diagnostic imaging provides objective information on the joint status in PWH.

In PWH on prophylaxis, imaging of the six major joints (knees, ankles and elbows) should be considered at the age of eight years or before if clinically indicated. Usual interval is at 4- to 5-year intervals.[94, level III]

When using conventional radiography for assessment, WFH recommends the use of Pettersson score.[2] The Pettersson scoring system has excellent reliability when used by radiologists experienced in reading musculoskeletal images. It can be used for assessment of advanced osteochondral changes.[92, level III] Refer to **Appendix 9** on **Pettersson Score**.

MRI and USG can detect early soft-tissue and osteochondral changes in a joint before they become apparent on physical examination or plain radiographs.[92, level III]

A systematic review showed that USG had the ability to detect pathological changes e.g. synovial thickening and osteochondral abnormalities in haemophilic joints. There was association between USG findings and functional status of the joint. However, its ability to detect a change in arthropathy with therapy has yet to be determined.[98, level III]

The current practice of prescribing clotting factor or conservative measures based on pain perception seems inadequate. There are discrepancies between musculoskeletal USG findings and patient/ physician-perceived pain aetiology. Only approximately one-third of the painful musculoskeletal episodes are judged correctly either by the patient or physician. Thus, USG should be part of the assessment when PWH presents with musculoskeletal pain.[99, level III]

In a systematic review on MRI as a tool for evaluating haemophilic arthropathy in children, MRI had good diagnostic accuracy for discriminating the presence of arthropathy. The association between early MRI findings and long-term functional joint outcomes has yet to be determined.[100, level II- 2]

Recommendation 19

- Monitoring of care in person with haemophilia should include:
  - Annual Bleeding Rate
  - inhibitor screening*
  - Annual Haemophilia Joint Health Score
  - ultrasound of knee, ankle and elbow when feasible

*Refer to **Chapter 8** on **Inhibitor**.

14. IMPLEMENTING THE GUIDELINES

The management of haemophilia should be guided by evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

14.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

a. wide dissemination of the CPG to healthcare providers (hard- and soft-copies)
b. regular topic update for healthcare providers via continuous medical education (seminar/conference/course)
c. National Haemophilia Programme
d. involvement of governmental/NGOs e.g. World Haemophilia Day, Haemophilia Camp, etc.
e. accessibility to relevant multidisciplinary teams

Existing barriers for application are:

a. poor understanding/limited knowledge on the topic
b. insufficient resources in terms of budget, expertise, diagnostic tools, medications
c. no national registry
d. variation in clinical management and preferences
e. low priority on the issue by the stakeholders

14.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:

a. ensure widespread distribution of the CPG to health care personnel via printed copies, electronic websites, etc.
b. reinforce training of health care personnel by regular seminars or workshops to ensure information is made available
c. develop multidisciplinary teams at hospital and community level to include involvement of specialists, medical/dental officers, pharmacists, allied health professional and nurses
d. ensure screening and monitoring facilities, and medications are available at HTC
e. ensure widespread distribution of patient education materials

The following is proposed as clinical audit indicator for quality management of haemophilia:

$$\text{Percentage of prophylactic factor infusion given to person with severe haemophilia} = \frac{\text{Total number of persons with severe haemophilia receiving prophylaxis factor infusion in a year}}{\text{Total number of persons with severe haemophilia in the same year}} \times 100\%$$

$$\text{Percentage of monitoring* done in PWH} = \frac{\text{Total number of PWH being monitored* in a year}}{\text{Total number of PWH in a year}} \times 100\%$$

*Monitoring by ABR, inhibitor screening and HJHS

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effective and safe treatments for/in haemophilia?

1. HEMOPHILIA A/
2. congenital hemophilia a.tw.
3. hemophilia a.tw.
4. hemophilia.tw.
5. haemophilia.tw.
6. HEMOPHILIA B/
7. christmas disease.tw.
8. ((f9 or factor ix) adj deficienc*).tw.
9. ((haemophilia or hemophilia) adj b).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. FACTOR VIIA/
12. (activated adj1 factor vii).tw.
13. (coagulation adj1 factor viia).tw.
14. factor viia.tw.
15. Novoseven.tw.
16. activated blood coagulation factor vii.tw.
17. Factor Eight Inhibitor Bypassing Agent.tw.
18. Activated Prothrombin Complex Concentrate.tw.
19. Activated PCC.tw.
20. aPCC.tw.
21. Immune Tolerance/
22. Immune Tolerance.tw.
23. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 10 and 23
25. limit 24 to English language and humans

Appendix 2

CLINICAL QUESTIONS

1. What are the clinical presentations of haemophilia?
2. What are the accurate laboratory tests for haemophilia?
3. What are the accurate laboratory tests for inhibitor detection in haemophilia?
4. Who and what tests should be done for haemophilia screening?
5. What are the general principles of care in haemophilia?
6. Are the following non-pharmacological treatments effective and safe in haemophilia?
   - Rehabilitation for musculoskeletal
   - PRICE
   - Joint protection
   - Sports/physical activity
   - Post-operative care
7. Are the following pharmacological treatments effective and safe in haemophilia?
   - Factors - plasma-derived factors, recombinant
   - Adjuvant - desmopressin, tranexamic acid, others
8. What are the effective and safe treatments for pain in haemophilia?
9. What are the effective and safe treatments for acute bleeding in various body systems in haemophilia?
   - Central Nervous System
   - Joint
   - Muscles
   - Nose, throat and eye
   - Gastrointestinal tract
   - Genitourinary tract
10. What are the effective and safe treatments for complications in haemophilia?
    - Synovitis
    - Pseudotumour
    - Inhibitors
11. What are the benefits and requirements for home therapy in haemophilia?
12. What are the factors to improve adherence/compliance in haemophilia treatment?
13. What are the management in the following special situations of haemophilia?
    - Surgeries and Invasive Procedures
    - Delivery of Infant with Known/Suspected Haemophilia
    - Vaccination
    - Circumcision

14. What are the effective and safe preventive measures for oral diseases in haemophilia?
15. What are the effective and safe dental procedures in haemophilia?
16. What are the effective and safe methods for the management of oral bleeding in haemophilia?
17. How to monitor effectively and safely the following parameters in haemophilia on treatment?
    - Inhibitors
    - Bleeding frequency
    - Joint health
    - Radiological measures

Appendix 3

GUIDELINES ON SAMPLE COLLECTION AND TRANSPORTATION FOR COAGULATION TEST

Variables	Recommendations
Patient identification	• Ensure correct patient identification
Venepuncture	• Non-traumatic venepuncture • Avoid drawing blood from indwelling IV line • Avoid inappropriately narrow gauge needle • Avoid capillary blood
Condition	• Relaxed and in warm surroundings
Pressure cuff	• Withdraw blood without pressure cuff, if possible. If need to use pressure cuff, do not apply more than one minute.
Tube and anticoagulant	• 3.2 % sodium citrate anticoagulant tube. Citrate tubes must be properly filled. • Once drawn, the tube should be gently inverted five times.
Ratio	• Anticoagulant/blood ratio is 1:9.
Time	• The sample must reach the laboratory within three hours of collection.
If test is outsourced to referral laboratory	• Freeze platelet-free plasma. Specimens can be stored at -20°C for up to two weeks or at -70°C for up to six months. • Transport the frozen specimen with ice-pack or dried-iced immediately to referral laboratory.

Adapted:

1. Kitchen S, McCraw A, Echenagucia M. Diagnosis of Hemophilia and Other Bleeding Disorders, A Laboratory Manual (Second Edition). Montréal: WFH World Federation of Hemophilia; 2010
2. Mackie I, Cooper P, Lawrie A, et al. Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. Int J Lab Hematol. 2013;35(1):1-13

Appendix 4

RECOMMENDED SPORTS/PHYSICAL ACTIVITIES IN HAEMOPHILIA

Different sports/physical activities carry different risks in PWH. It is important to understand these risks in order to choose the appropriate sports/physical activities as shown in the table below. Levels 1 - 2 indicate that the benefits of these sports/physical activities outweigh the associated risks. All sports rated 3 are not recommended for PWH.

Activity Category

1	1.5	2	2.5	3
Safe	Safe to moderate risk	Moderate risk	Moderate to dangerous risk	Dangerous

The following is the list of sports/physical activities with the related coding:

Activity	Category				
	1	1.5	2	2.5	3
Aerobics			2		
Archery	1				
Aquatics	1				
Badminton		1.5			
Baseball				2.5	
Basketball				2.5	
Bicycling		1.5			
Bicycle Motorcross (BMX)					3
Bowling			2		
Boxing					3
Canoeing				2.5	
CV Training Equipment					
• Elliptical Machine	1				
• Rowing Machine		1.5			
• Ski Machine		1.5			
• Stationary Bike	1				
• Stepper			2		
• Treadmill		1.5			
Cheerleading				2.5	
Circuit Training		1.5			
Dance			2		
Diving/Competitive					3
Diving/Recreational			2		
Exercise Classes					
• Body Sculpting		1.5			
• Cardio Kick-Boxing			2		
• Physioball		1.5			
• Spinning		1.5			
Fishing	1				
Football					3
Frisbee	1				
Frisbee Golf		1.5			
Ultimate Frisbee			2		
Golf	1				
Gymnastics				2.5	
Hiking	1				
Hockey (Field, Ice, Street)					3
Horseback Riding				2.5	
Ice-Skating				2.5	

Activity	Category				
	1	1.5	2	2.5	3
Inline Skating				2.5	
Jet Skiing				2.5	
Jumping Rope			2		
Kayaking				2.5	
Lacrosse					3
Martial Arts - Karate/Kung Fu/Tae Kwon Do				2.5	
Martial Arts/Tai Chi	1				
Motorcycling/Motor Cross Racing					3
Mountain Biking				2.5	
Pilates		1.5			
Power Lifting					3
Racquetball				2.5	
River Rafting				2.5	
Rock Climbing					
• (Indoor/Challenge Course)			2		
• Rock Climbing (Natural Setting)					3
Rodeo					3
Roller-skating			2		
Rowing/Crew			2		
Rugby					3
Running and Jogging			2		
Scooter (Motorised)					3
Scooter (Non-motorised)				2.5	
Scuba Diving				2.5	
Skateboarding				2.5	
Skiing/Cross Country			2		
Skiing/Downhill				2.5	
Skiing/Telemark				2.5	
Snorkelling	1				
Snowboarding				2.5	
Snowmobiling					3
Soccer				2.5	
Softball				2.5	
Surfing				2.5	
Swimming	1				
T-Ball			2		
Tennis			2		
Track and Field				2.5	
Trampoline					3
Volleyball				2.5	
Walking	1				
Water-skiing				2.5	
Weight Lifting/Resistance Training		1.5			
Weight Lifting/Power Lifting					3
Wrestling					3
Yoga			2		

Source: National Hemophilia Foundation, for all bleeding and clotting disorders, Playing it Safe, Bleeding Disorders, Sports and exercise. 2005 (Available at: https://www.hemophilia.org/sites/default/files/document/files/Playing-It-Safe.pdf)

Appendix 5

DEVELOPMENT OF ABNORMAL POSTURE FOLLOWING BLEEDS

Joint bleeds	Position of comfort	Habitual posture	Potential problems
Knee	Flexion	Walking on flexed knee, with hip flexed and/or ankle plantarflexed to compensate	Pain in patellofemoral joint; stress on ankle; overuse of hamstrings; weak quadriceps
Elbow	Flexion	Loss of elbow extension, arm may be carried with shoulder extended	Eventual difficulty with forward elevation of the arm
Ankle	Plantarflexion	Walking on toes, with knee and/or hip flexed to compensate	Ankle in unstable position, with small area of weight-bearing on talus and sole of foot; overuse of calf muscles; pressure on knee
Hip (unusual site)	Flexion, external rotation	Hip flexed, increased lumbar lordosis, compensatory knee flexion	Incomplete hip extension during gait; compensation with increased rotation of pelvis or spine
Shoulder	Adduction, internal rotation	Arm held close to body	Difficulty with ADL and self-care
Wrist and fingers	Flexion	Wrist flexed, hand closed	Difficulty extending wrist and fingers; inefficient grip
Toes	Extension (dorsiflexion)	Extension (dorsiflexion)	Difficulty wearing shoes
Muscle bleeds	**Position of comfort**	**Habitual posture**	**Potential problems**
Hamstrings	Knee, flexion, hip extension	Knee flexed	Altered gait; knee flexed, walking on toes
Biceps brachii	Elbow flexion, shoulder internal rotation	Elbow flexed	Incomplete elbow extension; decreased protective balance reactions
Calf (gastrocnemius)	Ankle plantarflexion, knee flexion	Ankle plantar-flexed, knee flexed	Walking on toes, knee flexed; stress on knee and ankle joints
Hip flexor (iliopsoas)	Hip flexion, some external rotation and increased lumbar lordosis	Hip flexed, extreme lordosis, walking on toes	Back pain; incomplete hip extension; stress on knee and ankle
Wrist and finger flexors	Wrist and finger flexion, elbow flexion	Wrist and finger flexion, elbow flexion	Inability to open hand; weak grip due to incomplete wrist extension
Thigh (quadriceps)	Knee extension	Knee remains extended	Incomplete knee flexion; risk of re-injury with sudden knee flexion; functional difficulties on stairs, squatting, etc.
Hip extensors	Hip extensors	Hip extensors	Unable to sit
Wrist and finger extensors	Wrist and finger extension, elbow flexion	Wrist and finger extension, elbow flexion	Walking on toes, knee flexed; stress on knee and ankle joints

Source: Mulder, Kathy. Exercises for People with Hemophilia. World Federation of Haemophilia. 2006,
(Available at https://www.researchgate.net/publication/228383305_Exercises_for_People_with_Hemophilia)

Appendix 6

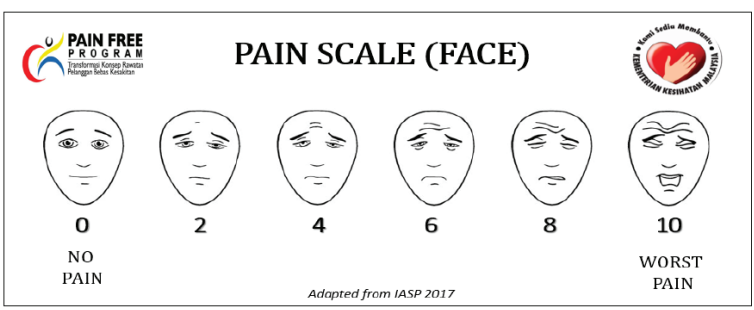
PAIN ASSESSMENT TOOLS

FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY (FLACC) SCALE

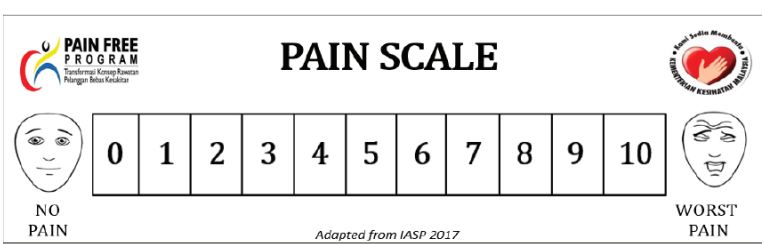
CATEGORIES	SCORING		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squiring, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talk to, distractable	Difficult to console

Each of the five categories (F) face, (L) leg, (A) activity, (C) cry and (C) consolability is scored from 0 – 2 resulting in total range of 0 – 10

VISUAL ANALOG SCALE



NUMERIC RATING SCALE



Source: Ministry of Health, Malaysia. Pain Medication Therapy Management Service: Guideline for Pharmacy (Second Edition). Petaling Jaya: MoH; 2018

ANALGESIC MEDICATION TABLE

Drug class	Drug	Recommended dosages	Side effects	Cautions and contraindications
Simple analgesic	Paracetamol	Adults (oral or IV): 0.5 - 1 gm, 6 - 8-hourly Max: 4 gm/day Child >1 month old (oral or IV): 20 mg/kg stat, then15 mg/kg every 4 - 6-hourly Max: 60 mg/kg (up to 90 mg/kg for 48 hours)	Rare	Hepatic impairment, alcohol dependence Preferred drug particularly in elderly patients Liver damage following over-dosage
Selective Cox-2 Inhibitors	Celecoxib	Adults (oral): 100 - 400 mg, 12 - 24-hourly Max: 800 mg/day *Child 2 years or older (oral): (10 - 25 kg): 50 mg 12-hourly (>25 kg): 100 mg 12-hourly or 4 mg/kg daily	Renal impairment Allergic reaction in susceptible individuals Increase in CVS events	Not recommended in severe renal and/or hepatic impairment Initiate therapy at lowest recommended dose in elderly Ischaemic heart disease Cerebrovascular disease Contraindicated in hypersensitivity to sulfonamides Associated with a lower risk of serious upper gastrointestinal side effects compared to NSAIDs
	Etoricoxib	Children and adults >16 years old (oral): 60 - 90 mg daily 120 mg daily in acute pain Max: 90/day; long-term use should be limited to a maximum of 90 mg daily 120 mg daily may be used for acute pain relief but for short-term only	Hypertension Renal impairment Increase in CVS events	Uncontrolled hypertension Ischaemic heart disease Cerebrovascular disease Associated with a lower risk of serious upper gastrointestinal side effects compared to NSAIDs

Drug class	Drug	Recommended dosages	Side effects	Cautions and contraindications
Weak opioids	Tramadol	Adults (oral or IV): 50 - 100 mg, 6 - 8-hourly Max: 400 mg/day	Dizziness Nausea Vomiting Constipation	Risk of seizures in patients with history of seizures with high doses In elderly, start at lowest dose (50 mg) and maximum of 300 mg daily
		Child (oral or IV): 2 - 3 mg/kg stat, then 1 - 2 mg/kg every 4 - 6-hourly	Drowsiness	Interaction with tricyclic antidepressant, selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor. Safety and effectiveness not established in children <12 years old; caution in children 12 - 18 years old who have risk factors that may increase respiratory depression
	Dihydrocodeine tartrate (DF118)	Adults (oral): 30 - 60 mg, 6 - 8-hourly Max: 240 mg/day	Nausea Vomiting Constipation Drowsiness	Respiratory depression Acute alcoholism Paralytic ileus Raised intracranial pressure
		Child (oral): 0.5 - 1 mg/kg every 4 - 6-hourly		
	Combinations of paracetamol 500 mg + codeine 8 mg (Panadeine®)	Children and adults (oral): 1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day	Constipation	Reduce dose in elderly Safety and effectiveness not established in children <18 years old
	Combinations of paracetamol 325 mg + tramadol 37.5 mg (Ultracet®)	Adults (oral): 1 - 2 tablets, 6 - 8-hourly Max: 8 tablets/day	Nausea Vomiting Drowsiness	Hepatic impairment Renal impairment Alcohol dependence Epilepsy Safety and efficacy is not established in children <12 years old; caution in children 12 – 18 years old who have risk factors that may increase respiratory depression

Drug class	Drug	Recommended dosages	Side effects	Cautions and contraindications
Strong opioids	Morphine	Adults: (oral immediate-release): 5 - 10 mg every 4-hourly (elderly: 2.5 - 5 mg every 4 - 6-hourly) (oral sustained-release): To be given in 12-hourly dosing (SC/IM): 5 - 20 mg every 4-hourly as needed (IV): 2 - 10 mg every 4-hourly as needed	Common: Nausea Vomiting Constipation Drowsiness Sedation Not common in cancer pain: Sweating Euphoria Respiratory depression	Acute bronchial asthma Respiratory depression Dose adjustment for renal impairment and head injuries Transdermal fentanyl - • Not to be used unless opioid dose is stable • Minimum dose: 12 µg/hr = 30 mg oral morphine in 24 hours
		Child: (oral immediate-release): 1 - 12 months old: 0.08 - 0.2 mg/kg every 4-hourly 1 - 2 years old: 0.2 - 0.4 mg/kg every 4-hourly 2 - 12 years old: 0.2 - 0.5 mg/kg every 4-hourly (max: 5 mg per dose) (oral sustained-release): 1 - 12 years old: 0.2 - 0.8 mg/kg every 12-hourly (SC/IV): Neonates: 25 - 50 µg/kg every 6-hourly 1 - 6 months old: 100 µg/kg every 6-hourly (max: 2.5 mg per dose) 6 months - 2 years old: 100 µg/kg every 4-hourly (max: 2.5 mg per dose) 2 -12 years old: 100 - 200 µg/kg every 4-hourly (max: 2.5 mg per dose)	Pruritus Myoclonus	• Not to be used in opioid naive patients

Drug class	Drug	Recommended dosages	Side effects	Cautions and contraindications
	Oxycodone	Adults (oral): Immediate-release: 5 - 10 mg every 4 - 6-hourly Controlled-release: To be given in 12-hourly dosing		
		Children (oral): 0.2 mg/kg every 4 - 6-hourly Controlled-release: 0.6 - 0.9 mg/kg every 12-hourly		
	Oxycodone + Naloxone	Children >12 years old and adults (oral): Oxycodone 10 mg/ naloxone 5 mg every 12-hourly titrated every 1 - 2 days (max: oxycodone 80 mg /naloxone 40 mg/ day)		
	Transdermal fentanyl	Equianalgesic dose of total 24 hours opioid requirement (refer to Conversion Table)		

*Celecoxib capsules can be opened and the contents emptied onto a teaspoon of applesauce or dispersed in water. One 200 mg of celebrex capsule is to be dispersed in 20 ml of water to yield a 10 mg/ml dispersion. Suspension should be freshly prepared, required volume immediately administered and balance discarded (internet communication, 9 September 2018 at https://www.rch.org.au/uploadedFiles/Main/Content/pharmacy/Celecoxib.pdf)

SUGGESTED DOSE CONVERSION RATIO

From \ To	Codeine (mg/day)	Oral Morphine (mg/day)	SC Morphine (mg/day)	Oxycodone (mg/day)	Fentanyl transdermal patch (µg/hr)
Codeine (mg/day)		8	20	12	24
Oral Morphine (mg/day)	8		2.5	1.5	3
SC Morphine (mg/day)	20	2.5		0.6	1.2
Oxycodone (mg/day)	12	1.5	0.6		2
Fentanyl transdermal patch (µg/hr)	24	3	1.2	2	

Adapted:

1. Ministry of Health Malaysia, Management of Cancer Pain. Putrajaya: MoH; 2010
2. Micromedex® Solution (Available at http://www.micromedexsolutions.com/micromedex2/4.24.0/WebHelp/MICROMEDEX_2.htm)
3. Shann F, Drug Doses, 17th Edition. Victoria, Australia. 2017; 24-104
4. Etoricoxib package insert

HAEMOPHILIA JOINT HEALTH SCORE

Assessment #:

Haemophilia Joint Health Score Worksheet 2.1

Evaluator Name: _____

Subject ID #: _____

Date of Evaluation: _____
yyyy / mm / dd

SWELLING None (N), Puffy (P), Spongy (S), Tense (T) **Landmarks:** Visible (V); Partially Visible (PV); Not Visible (NV) Palpable (P); Not Palpable (NP)	**Left Elbow** ☐N ☐P ☐S ☐T ☐V ☐PV ☐NV ☐P ☐NP	**Right Elbow** ☐N ☐P ☐S ☐T ☐V ☐PV ☐NV ☐P ☐NP	**Left Knee** ☐N ☐P ☐ ☐ ☐V ☐PV ☐NV ☐P ☐NP	**Right Knee** ☐N ☐P ☐S ☐T ☐V ☐PV ☐NV ☐P ☐NP	**Left Ankle** ☐N ☐P ☐S ☐T ☐V ☐PV ☐NV ☐P ☐NP	**Right Ankle** ☐N ☐P ☐S ☐T ☐V ☐PV ☐NV ☐P ☐NP
SCORE	☐	☐	☐	☐	☐	☐
	0 = No swelling 1 = Mild – appears, feels slightly swollen: landmarks visible 2 = Moderate – looks swollen, feels spongy: some landmarks partly obscured 3 = Severe – looks very swollen; is tense: bony landmarks fully obscured					
Comments: Please provide any comments in the space provided (If necessary may note circumference in cm)						
DURATION OF SWELLING Note number of months Please checkmark one ☐ Patient Report ☐ Parent Report ☐ Reported from chart ☐ Other: _____						
	☐	☐	☐	☐	☐	☐
	0 = No swelling or <6 months 1 = ≥6 months					

Assessment #:

Subject ID #: _____

Haemophilia Joint Health Score Worksheet 2.1

Evaluator Name: _____

Date of Evaluation: _____
yyyy / mm / dd

	Left Elbow	Right Elbow	Left Knee	Right Knee	Left Ankle	Right Ankle
MUSCLE ATROPHY						
SCORE	☐	☐	☐	☐	☐	☐
	0 = None – no atrophy 1 = Mild – muscle has slightly less contour, or mild flattening of the muscle belly is noted 2 = Severe – moderate/severe muscle wasting and depression or flattening of the muscle belly is noted					
Comments: Please note decreased contour, muscle flattening, marked wasting.						
CREPITUS ON MOTION Note: Audible (A) Mild (M) Palpable (P) Severe (S) If none apply: None (N)	**Left Elbow** ☐ A ☐ P	**Right Elbow** ☐ A ☐ P	**Left Knee** ☐ A ☐ P	**Right Knee** ☐ A ☐ P	**Left Ankle** ☐ A ☐ P	**Right Ankle** ☐ A ☐ P
	☐ M ☐ S ☐ N	☐ M ☐ S ☐ N	☐ M ☐ S ☐ N	☐ M ☐ S ☐ N	☐ M ☐ S ☐ N	☐ M ☐ S ☐ N
SCORE	☐	☐	☐	☐	☐	☐
	0 = No crepitus 1 = Mild – slightly audible and/or palpable 2 = Severe – Consistently moderately or very pronounced audible and/or palpable grinding and crunching					

Assessment #:

Haemophilia Joint Health Score Worksheet 2.1

Evaluator Name: _____

Subject ID #: _____

Date of Evaluation: _____
yyyy / mm / dd

FLEXION LOSS Note Range of Motion (ankle record from 90˚ starting point)	**Left Elbow** Flex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Elbow** Flex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Left Knee** Flex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Knee** Flex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Left Ankle** PlantarFlex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Ankle** PlantarFlex: Measured in: 1) Supine ☐ 2) Sitting ☐
	The recommendation is to score using both methods (normal contralateral side and normative tables) and then record the worse score.					
SCORE	☐	☐	☐	☐	☐	☐
	Contralateral Side:	0 = <5˚ 1 = Loss of 5˚ - 10 ˚	2 = Loss of 11˚ - 20˚ 3 = Loss of >20˚	Normative Tables :	0 = Within Range 1 = Loss of 1 to 4˚	2 = Loss of 5˚ - 10˚ 3 = Loss of >10˚

EXTENSION LOSS Note Range of Motion (ankle record from 90˚ starting point) **Hyperextension**: record as "plus" (+) _____degrees **Loss of extension** record as "minus" (-) _____degrees	**Left Elbow** Ext: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Elbow** Ext: Measured in: 1) Supine ☐ 2) Sitting ☐	**Left Knee** Ext: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Knee** Ext: Measured in: 1) Supine ☐ 2) Sitting ☐	**Left Ankle** DorsiFlex: Measured in: 1) Supine ☐ 2) Sitting ☐	**Right Ankle** DorsiFlex: Measured in: 1) Supine ☐ 2) Sitting ☐
	The recommendation is to score using both methods (normal contralateral side and normative tables) and then record the worse score.					
SCORE	☐	☐	☐	☐	☐	☐
	Contralateral Side:	0 = <5˚ 1 = Loss of 5˚ - 10 ˚	2 = Loss of 11˚ - 20˚ 3 = Loss of >20˚	Normative Tables :	0 = Within Range 1 = Loss of 1 to 4˚	2 = Loss of 5˚ - 10˚ 3 = Loss of >10˚

Assessment #:

Evaluator Name: _____

Haemophilia Joint Health Score Worksheet 2.1

Subject ID #: _____

Date of Evaluation: _____

yyyy / mm / dd

JOINT PAIN Active joint mov't through range with gentle pressure (at end range)	**Left Elbow** Comments:	**Right Elbow** Comments:	**Left Knee** Comments:	**Right Knee** Comments:	**Left Ankle** Comments:	**Right Ankle** Comments:
SCORE	☐	☐	☐	☐	☐	☐
	0 = No pain through active range of motion 1 = No pain through active range; only pain on gentle overpressure or palpation 2 = Pain through active range					
STRENGTH Using the Daniels & Worthingham's scale. Within available ROM, note grade	**Left Elbow** Flexion Extension	**Right Elbow** Flexion Extension	**Left Knee** Flexion Extension	**Right Knee** Flexion Extension	**Left Ankle** # of heel raises____ PlantarFlex. DorsiFlex	**Right Ankle** # of heel raises____ PlantarFlex. DorsiFlex
SCORE	☐	☐	☐	☐	☐	☐
	0 = Holds test position against gravity with maximum resistance (gr.5) 1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4) 2 = Holds test position against gravity with minimal resistance (gr.3+), or holds test position against gravity (gr.3) 3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-) 4 = Trace (gr.1) or no muscle contraction (gr.0) NE = Non-evaluable				**# of Heel Raises:** (to be used only for plantarflexion scoring) Score 0 = 4 to 5 heel raises Score 1 = 2 to 3 heel raises Score 2 = Sufficiently plantar flexes to clear heel Score 3 = Plantar flexes ankle through range (gravity eliminated) Score 4 = trace or no muscle contraction	

Assessment #:

Haemophilia Joint Health Score Worksheet 2.1

Evaluator Name: _____

Subject ID #: _____

Date of Evaluation: _____
yyyy / mm / dd

GAIT (Skills)	Left Knee	Right Knee	Left Ankle	Right Ankle
Walking Stairs Running Hopping on 1 leg				
	Individual joints to be observed but not scored			
	Note: N (Normal), L (limp), TW (toe walking), WSF (walking on side of foot), US (uneven strides), NPO (no push off), AWS (abnormal weight shift), FTO (foot turned out), NHS (No heel strike), EHO (early heel off) OR DSP (decreased stance phase), LKE (limited knee extension), KH (knee hyperextension)			
	0 = All skills are within normal limits 1 = One skill is not within normal limits 2 = Two skills are not within normal limits 3 = Three skills are not within normal limits 4 = No skills are within normal limits NE = Non-evaluable		**Global Score** ☐	

Axial alignment to be observed and not scored

AXIAL ALIGNMENT	Left Knee	Right Knee	Left Ankle	Right Ankle
To be measured in weight-bearing position	_____ degrees Please checkmark one: ☐ valgus or ☐ varus	_____ degrees Please checkmark one: ☐ valgus or ☐ varus	_____ degrees Please checkmark one: ☐ valgus or ☐ varus	_____ degrees Please checkmark one: ☐ valgus or ☐ varus

Subject ID #: _____ **Name of Physiotherapist:**_____

Assessment #: _____ **Date:** _____
yyyy / mm / dd

Hemophilia Joint Health Score 2.1 – Summary Score Sheet

Hemophilia Joint Health Score 2.1 – Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE

Sum of Joint Totals ☐

+

Global Gait Score ☐

(☐ NE included in Gait Items)

HJHS Total Score **=** ☐

NE = Non-evaluable

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or <6 months
1 = ≥6 months

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss

Contralateral:	Normative Tables:
0 = <5˚	0 = within range
1 = 5˚ - 10˚	1 = 1˚ - 4˚
2 = 11˚ - 20˚	2 = 5˚ - 10˚
3 = 20˚	3 = >10˚

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Extention loss (from hyperextension)

Contralateral:	Normative Tables:
0 = <5˚	0 = within range
1 = 5˚ - 10˚	1 = 1˚ - 4˚
2 = 11˚ - 20˚	2 = 5˚ - 10˚
3 = 20˚	3 = >10˚

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Strength (Using the Danials & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr.3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)

NE = Non-evaluate

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____
_____
_____
_____

Source: Feldman BM, Funk S, Hilliard P, et al. Haemophilia Joint Health Score 2.1, World Federation of Haemophilia; 2011 (Available at http://wfh.org/2/7/7_0_Assessment_Tools_HJHS.htm)

Appendix 9

Pettersson Score

Radiologic Change	Finding	Score (Points)
Osteoporosis	Absent Present	0 1
Enlargement of epiphysis	Absent Present	0 1
Irregularity of subchondral surface	Absent Present Pronounced	0 1 2
Narrowing of joint space	Absent <50% >50%	0 1 2
Subchondral cyst formation	Absent 1 cyst >1 cyst	0 1 2
Erosions at joint margins	Absent Present	0 1
Incongruence between joint surfaces	Absent Slight Pronounced	0 1 2
Deformity (angulation and/or displacement of articulating bones)	Absent Slight Pronounced	0 1 2

Possible joint score: 0 - 13 points

Add up the score for each radiologic change to get the total score. The higher the total score, the worst is the arthropathy. There's no specified degree of score to say it's mild/moderate or severe.

Source: Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophili arthropathy. Clin Orthop Relat Res. 1980;(149):153-159

LIST OF ABBREVIATIONS

µg	microgramme
ABR	Annual Bleeding Rate
AGREE	Appraisal of Guidelines for Research and Evaluation
AH	Arnold-Hilgartner
AJBR	annual joint bleed rates
aPCC	activated prothrombin complex concentrate
APTT	Activated Partial Thromboplastin Time
BMI	body mass index
BU	Bethesda unit
CCC	Comprehensive Care Centre
CFC	clotting factor concentrate
CHMP	Committee for Medical Products for Human Use
COX-2	Cyclooxygenase-2
CPG(s)	clinical practice guidelines
CT	computer tomography
CV	cardiovascular
CVAD	central venous access device
DG	Development Group
DNA	deoxyribonucleic acid
DDAVP	desmopressin
dL	decilitre
EDTA	ethylenediaminetetraacetic acid
EMA	European Medical Agency
FDA	Food Drug Agency
FISH	Functional Independence Score in Haemophilia
FIX	factor IX assay
FLACC	Face, Legs, Activity, Cry, Consolability
FVIII	factor VIII assay
g	gramme
GRADE	Grading Recommendations, Assessment, Development and Evaluation
Gy	Gray
HAV	hepatitis A virus
HCCC	Haemophilia Comprehensive Care Centre
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HMTAC	Haemophilia Medication Therapy Adherence Clinic
HR	hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
HTC	Haemophilia Treatment Centre
ICH	intracranial haemorrhage
IM	intramuscular
ITI	immune tolerance induction
IU	international unit
IU/kg	international unit/kilogram
IV	intravenous
kg	kilogramme

LA	local anaesthesia
MaHTAS	Malaysian Health Technology Assessment Section
mg	milligramme
ml	millilitre
MoH	Ministry of Health
MRI	magnetic resonance imaging
NSAID(s)	non-steroidal anti imflammatory drug(s)
OR	odds ratio
p	p value
PCC	prothrombin complex concentrate
pdF	plasma-derived factor
PRICE	protection, rest, ice therapy, compression, elevation
PT	prothrombin time
PWH	person with haemophilia
QoL	quality of life
RC	Review Committee
RCT(s)	randomised controlled trial(s)
RD	risk difference
rFVIIa	recombinant FVIIa
ROM	range of motion/movement
RR	risk ratio
RS	radiosynovectomy
SC	subcutaneous
THR	total hip replacement
TKR	total knee replacement
TTP	time to progression
TXA	tranexamic acid
USG	ultrasonography
VAS	Visual Analogue Score
VWD	von Willebrand Disease
vWF	von Willebrand Factor
vs	versus
WFH	World Federation of Haemophilia

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