Bleeding Disorder Management in Malaysia

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GANSID HCP Training

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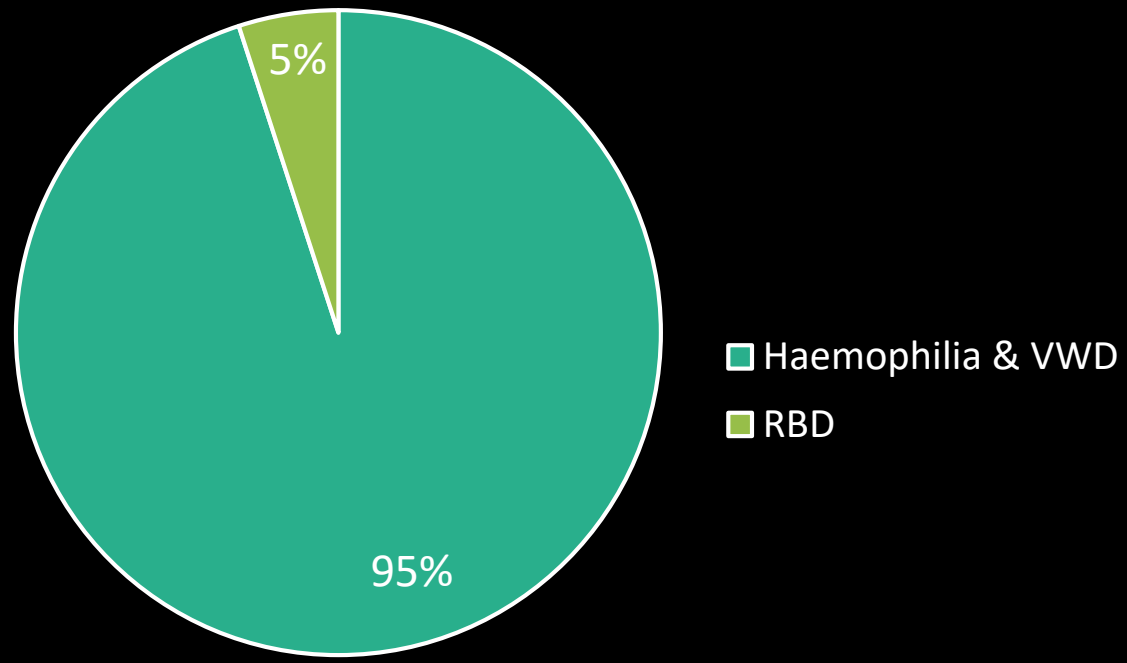
Inherited Bleeding Disorders

- Prevalence of haemophilila and symptomatic VWD → 1 in 10,000
- Prevalence of RBD → 1 in 500,000 to 1 in 2,000,000

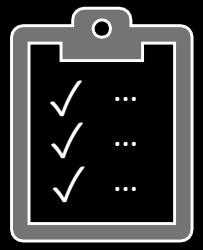


Naderi M, et al. J Pediatr Rev. 2014;2(2):31-46

WFH Annual Global Survey 2023

119

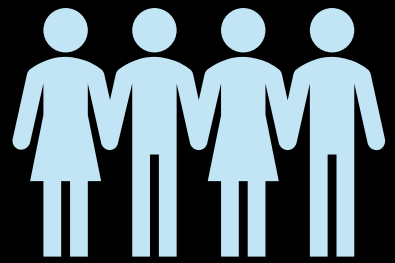
Number of countries



78%

Response rate

(119/152)



390,630

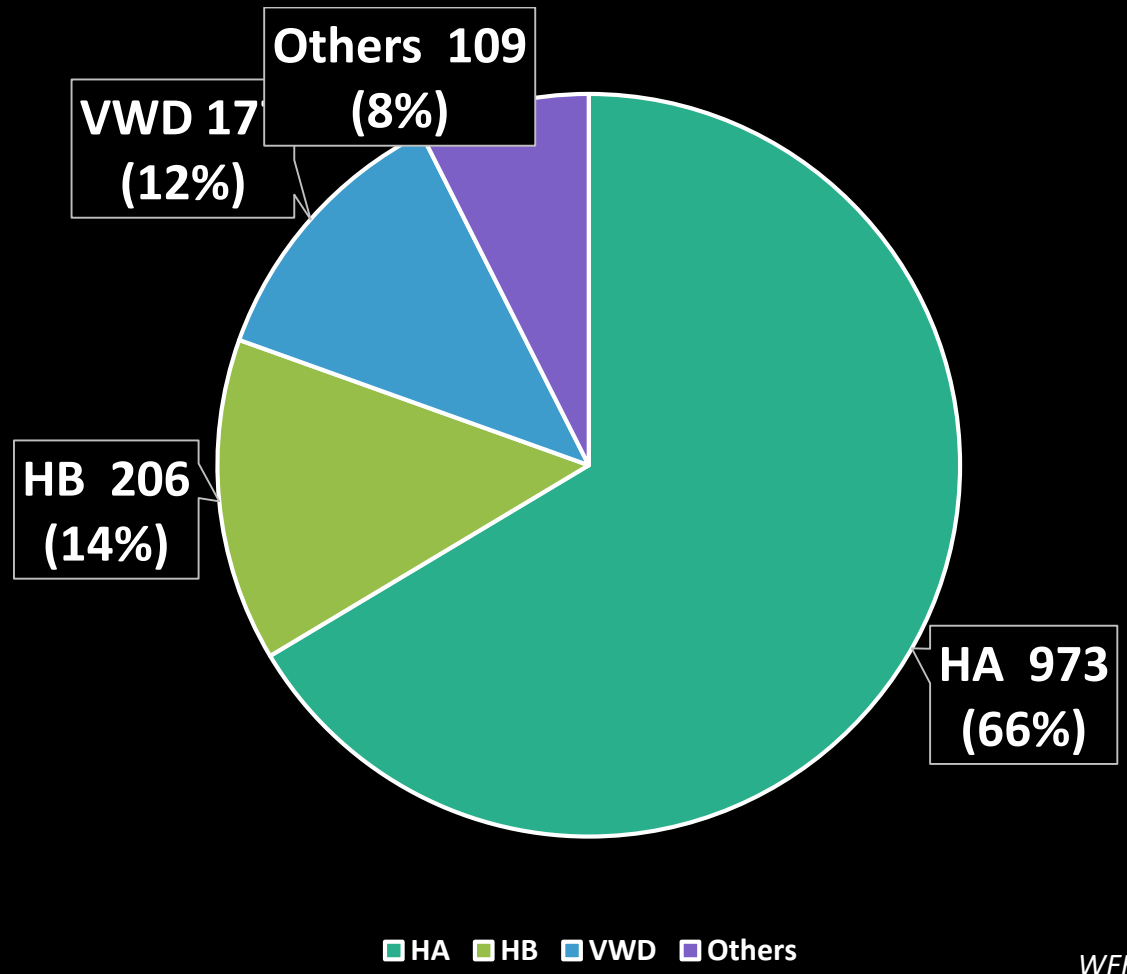
Number of identified patients

(2023 World population 8.0 billion)

218,804	People with Hemophilia
179,703	Hemophilia A
37,385	Hemophilia B
1,716	Hemophilia type unknown
101,128	von Willebrand disease
70,698	Other bleeding disorders

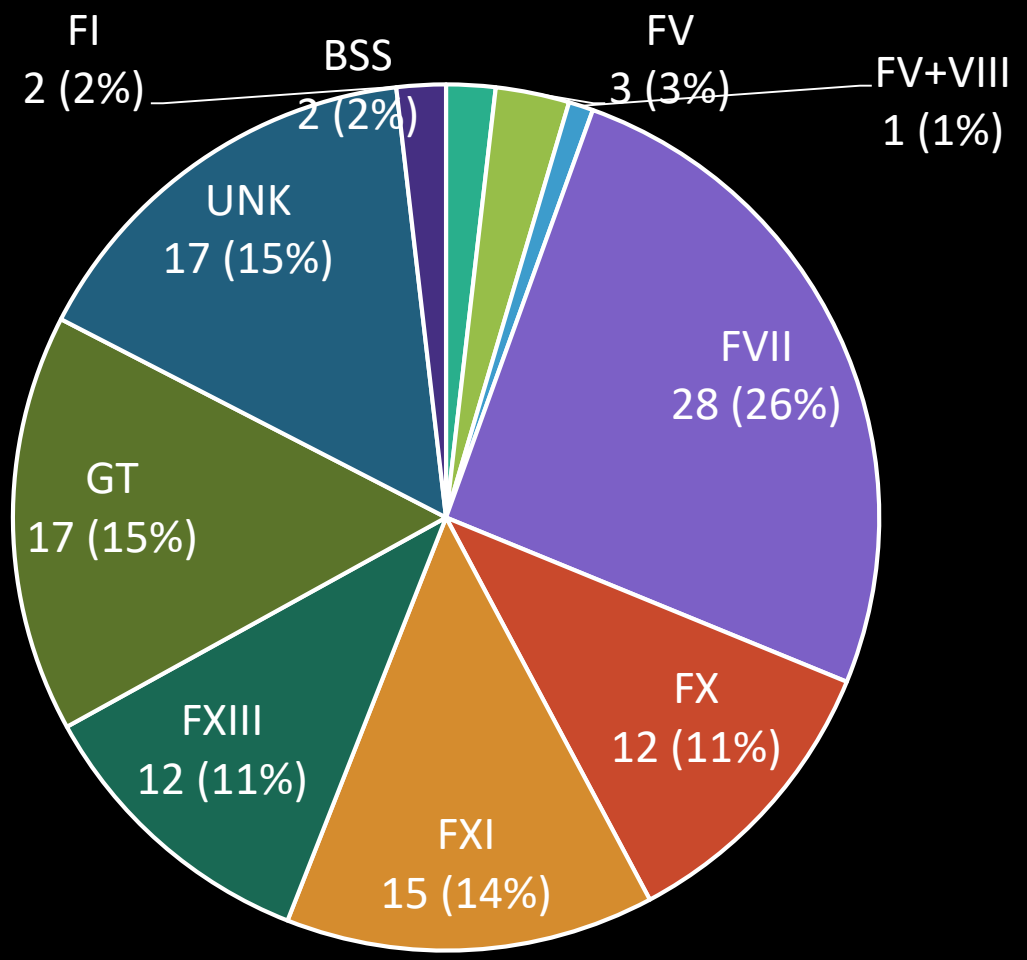
Malaysia 2023

- Population 34,308,525
- Total haemophilia 1,179



Other Rare Bleeding Disorders

n = 109



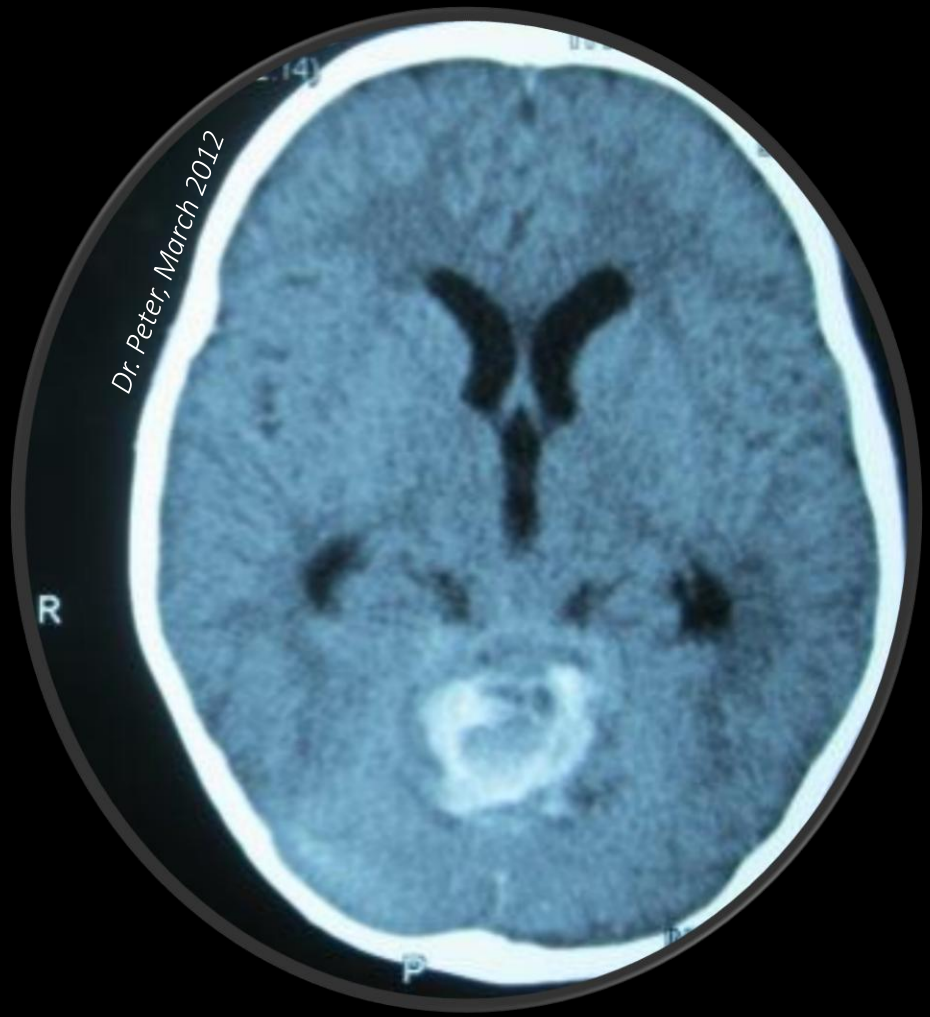
Haemophilia in Malaysia

- Number of patients diagnosed with haemophilia = 1,179
- Global prevalence of haemophilia = 1 in 10,000 population
- Population of Malaysia in 2023 = 34,308,525
- Actual number of haemophilia = 3,430
- > 60% go undiagnosed

Challenges

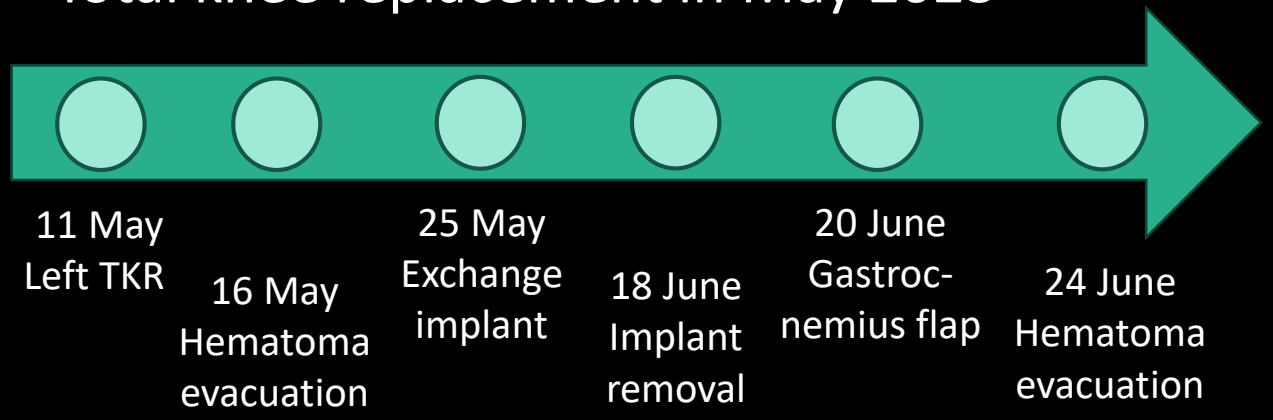
Laboratory (diagnostic) factor

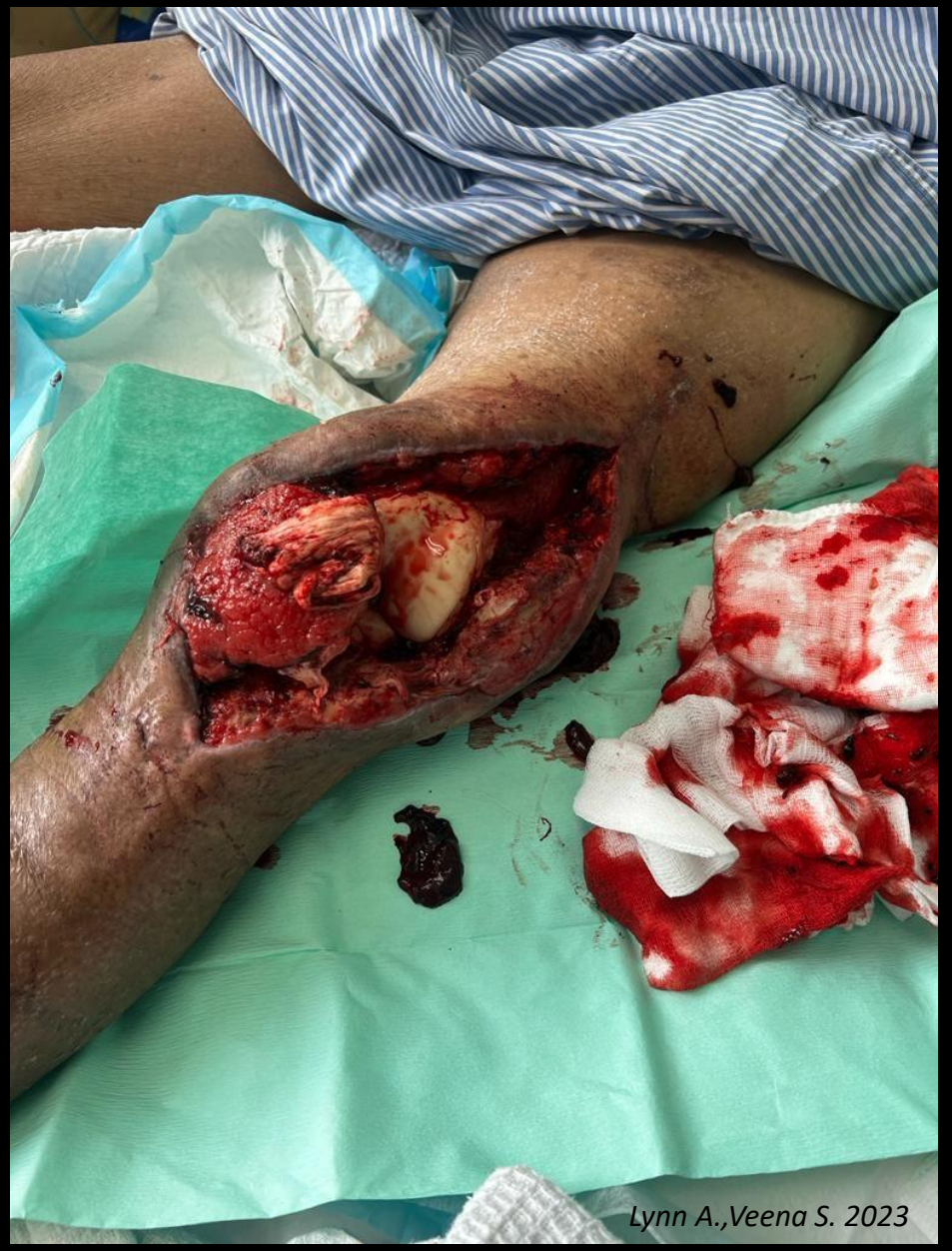
- 2-year-old boy
- c/o sudden onset of headache
- Vomiting >10x
- GCS 9/15
- CT Brain → ?Posterior fossa tumour
- APTT 127 sec



Clinician factor

- 67-year-old man
- Coronary angiogram in Oct 2020
  - APTT 56.9 in Sept 2020 – not investigated
  - Developed hematoma and pseudoaneurysm post-femoral puncture
- Total knee replacement in May 2023

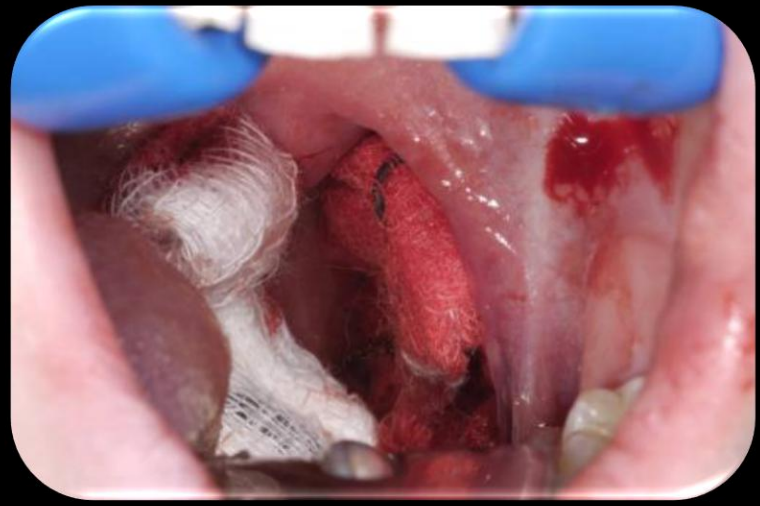




Clinician factor (2)

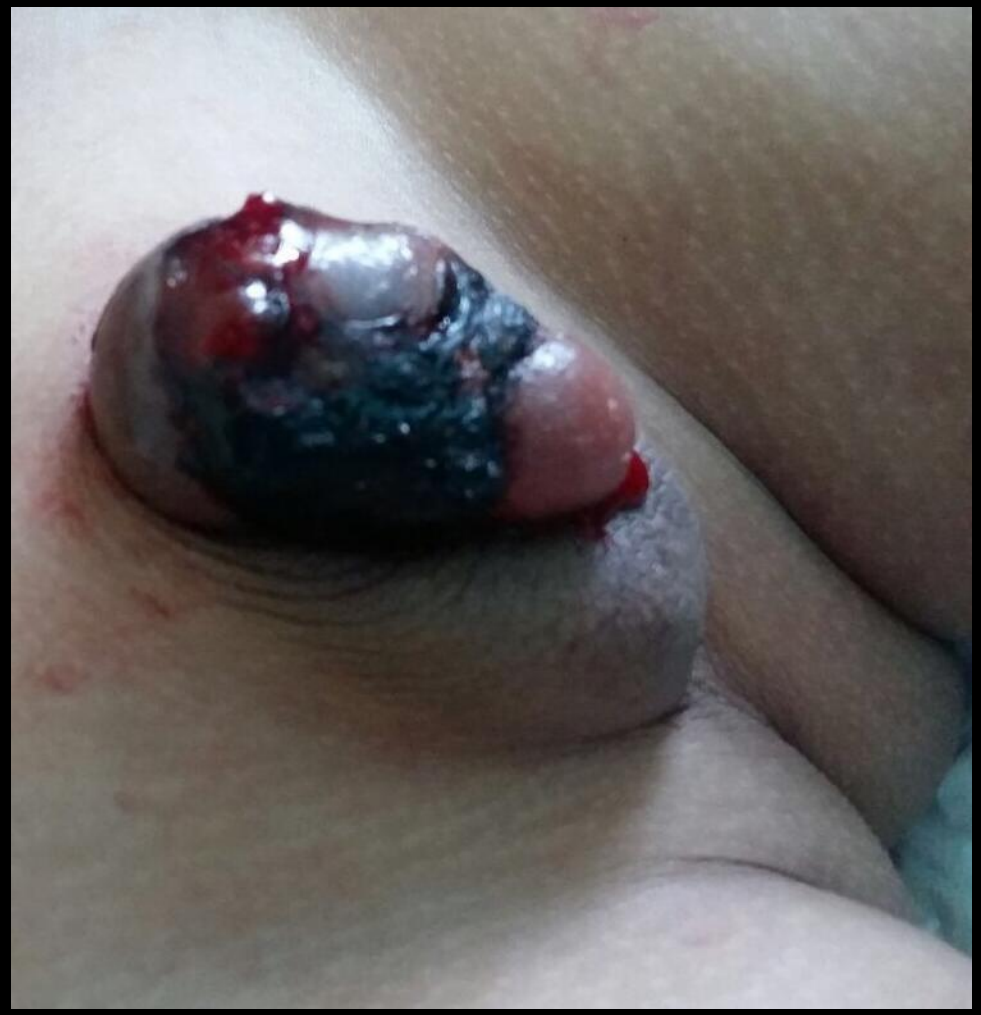
- 26-year-old medical officer
- Planned for tonsillectomy
- APTT 36 (27-38)s
- Tonsillectomy done – op went well
- Discharged home on same day

- Bled that night → cauterize
- Rebled - cauterize x3 → Hb fell to 8.0 → transfuse 2 PRBC
- Referred to haematologist



Patient / Parental factor

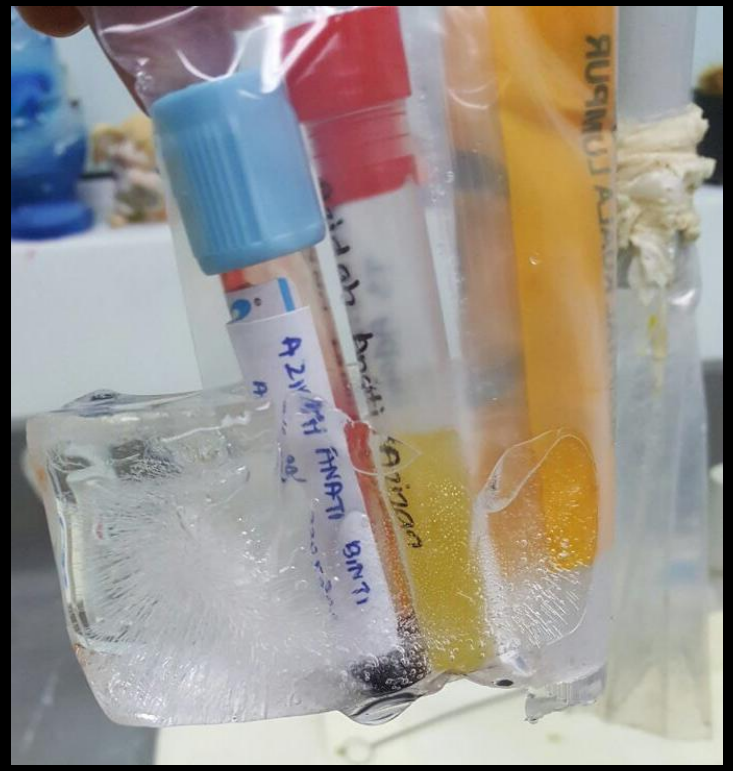
- Family h/o haemophilia
- Mom did not reveal
- Did not come for carrier screening
- Brought son for circumcision

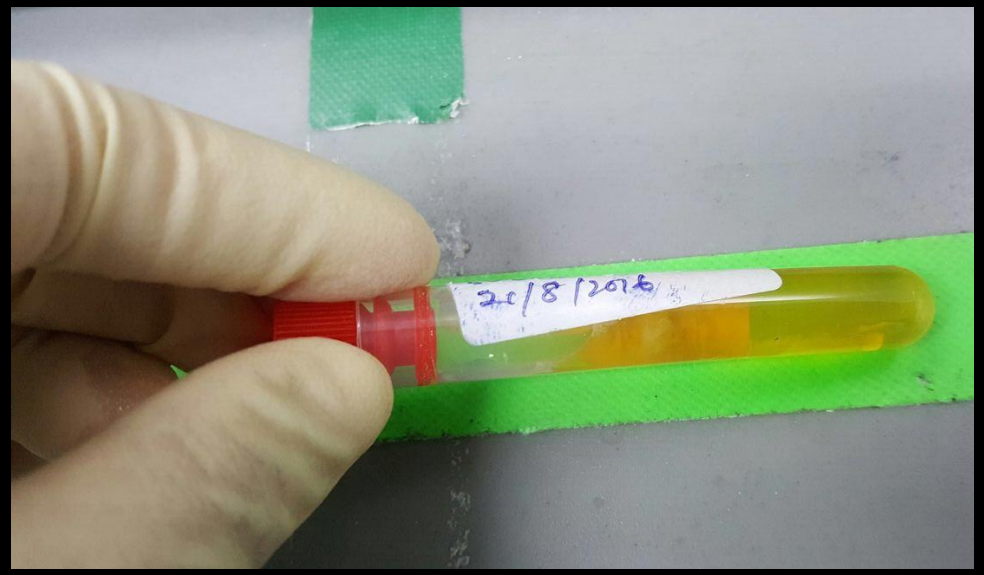


Overcoming challenges

Before 2010

- Laboratory diagnosis in one centre
  - Pre-analytical variables
  - Delay in getting results / wrong results



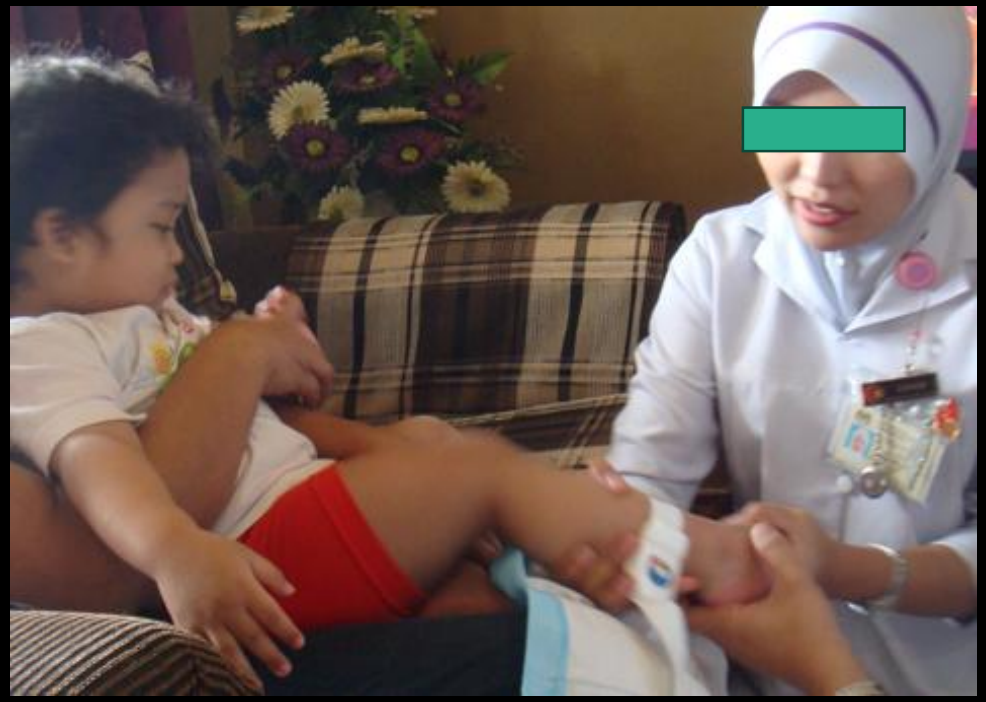


Laboratory training 2011 -

- Since 2020, all state hospitals are able to do factor and inhibitor assays

Clinical training

- Clinicians / nurses



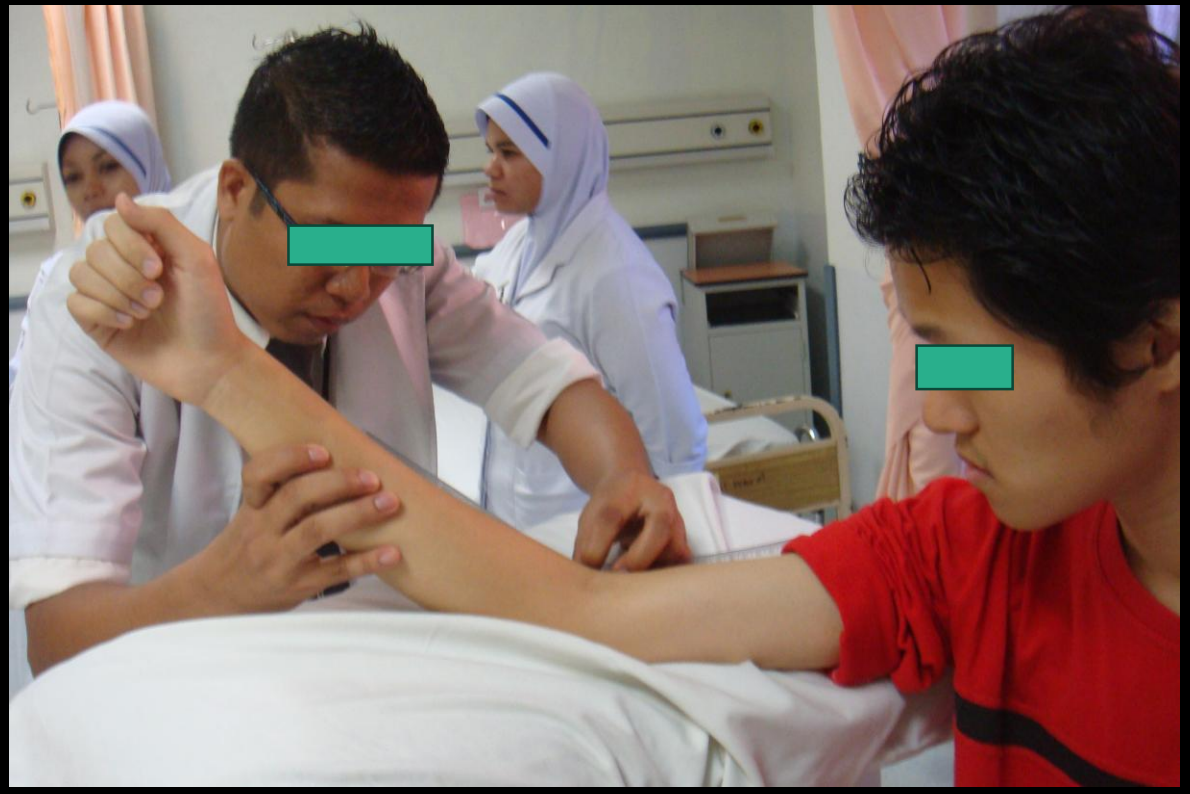
HMTAC Training

- Pharmacist-led Haemophilia Medication Therapy Adherence Clinic
- Patient education modules
- Empowering patients

→ An educated patient & family

Physiotherapy training

Haemophilia Joint Health Score (HJHS)



Patient workshops

- Improve outreach and diagnosis
- Increase access to sustainable care

Management of Haemophilia

Case 1

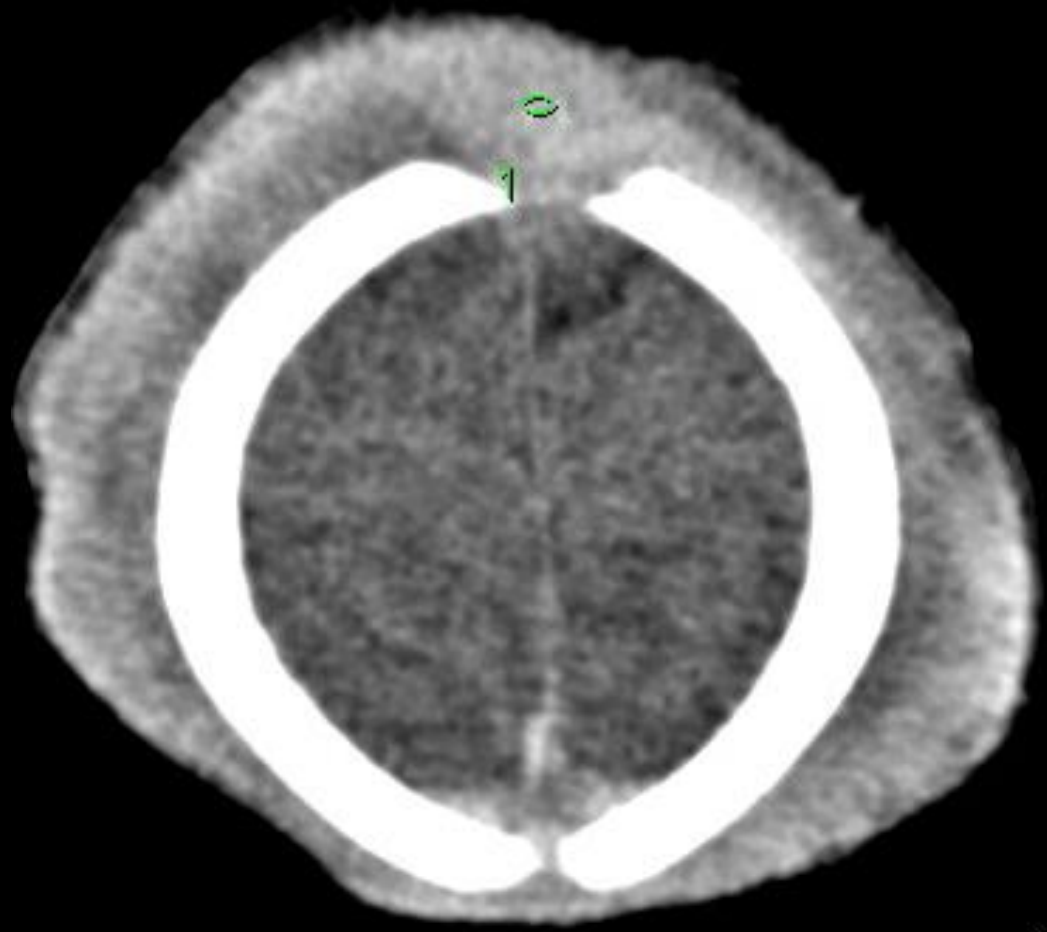
- Baby boy
- DOB: 30th July 2010
- SVD, discharged well
- That night, noted large bruise behind ears and scalp swelling
- Brought to A&E

Case 1 – Clinical suspicion

- Non-accidental injury (NAI)
- Police report made

Case 1 – Investigations & Rx

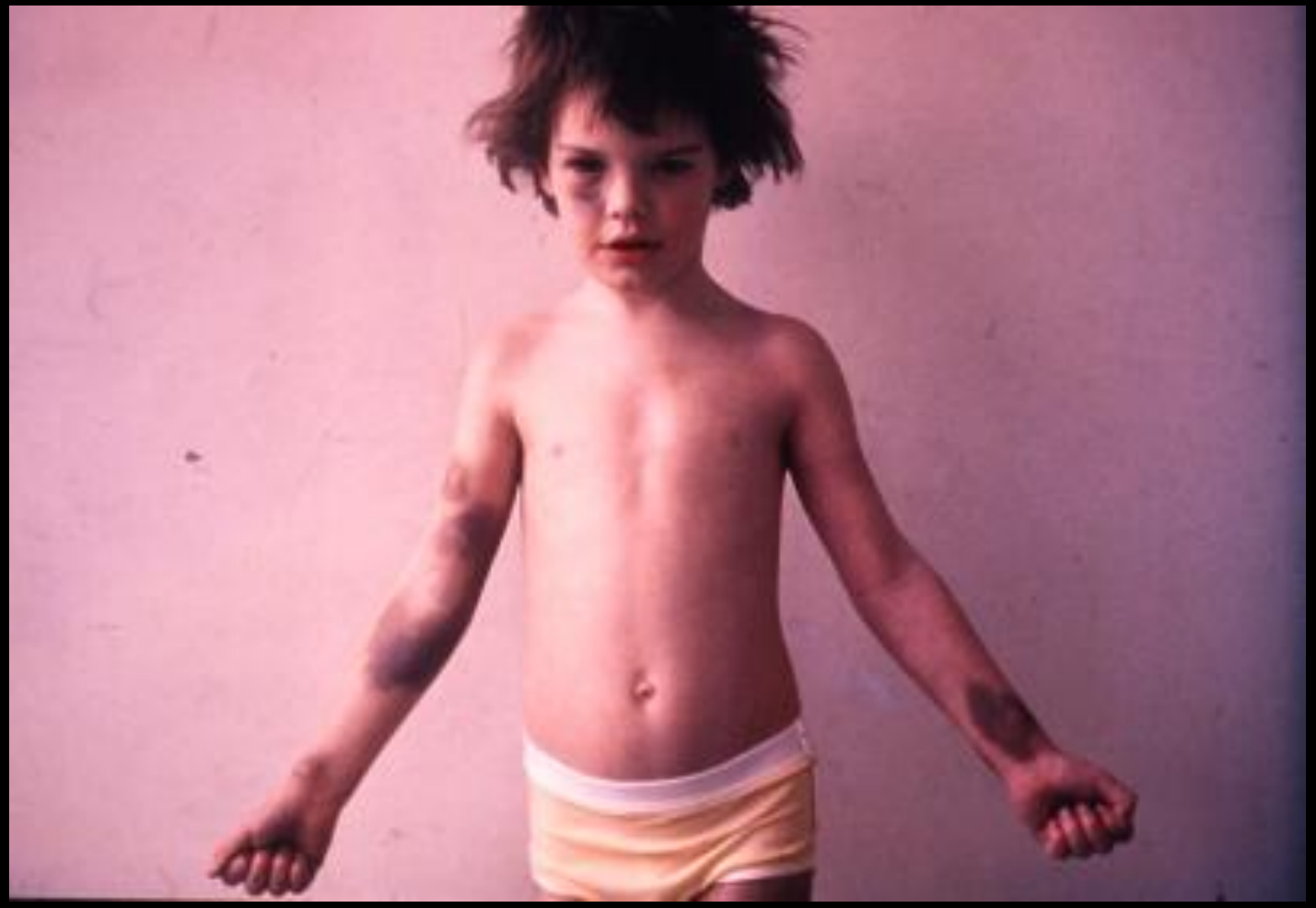
- Hb 4.5 g/dL
- APTT x3 >100 sec
- CT Brain: cephalhematoma & subdural bleed
- Rx: PRBCs + FFP transfused



Case 1 – Factor assay

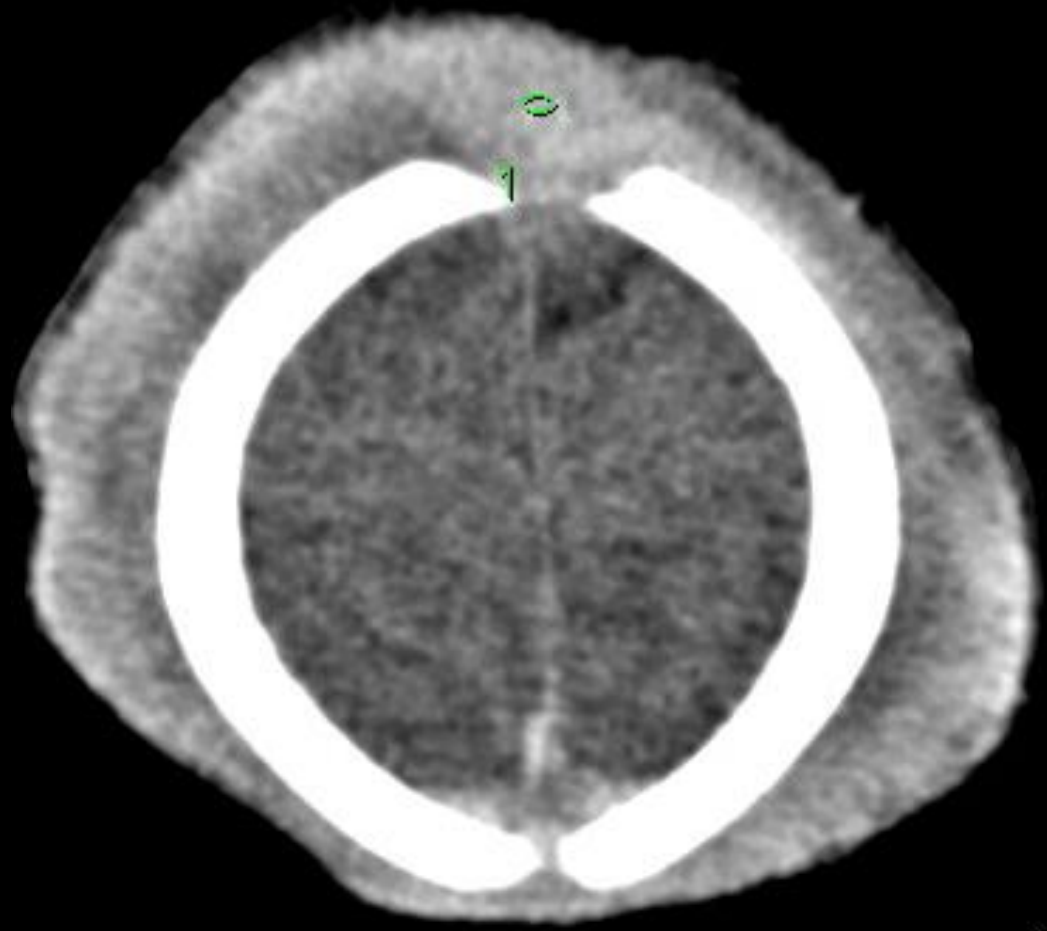
- Sample sent over to haemostasis lab
- Within 1 hour
  - FVIII <1 %
  - VWF 90%
- Δ: Severe haemophilia A

Do not mistake haemophilia for non-accidental injury (NAI)

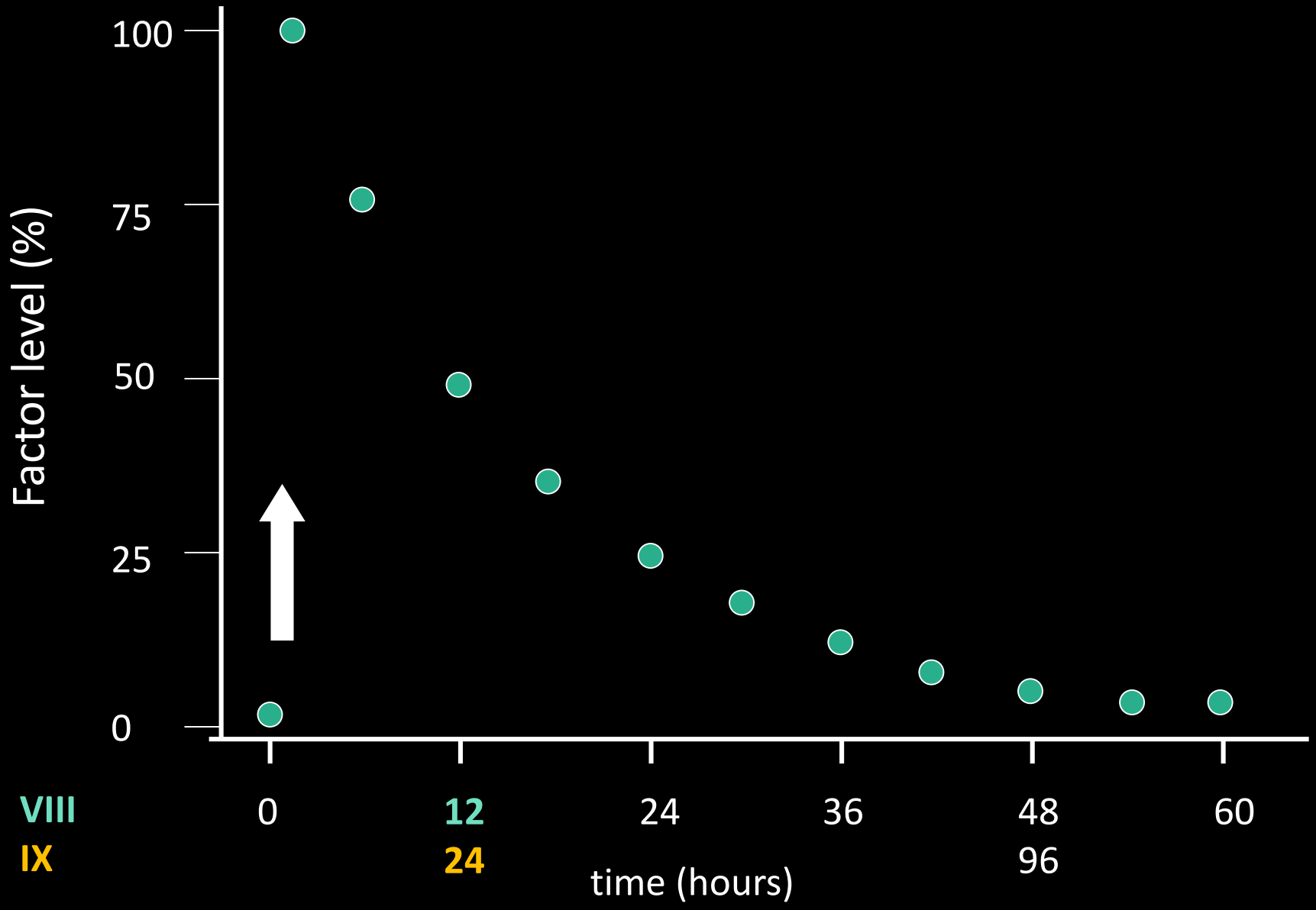


Case 1 – Rx of Intracranial Haemorrhage

- Factor replacement
  - D1 - D2: 100%
  - D3 - D5: 80%
  - D6 - D9: 50%
  - D10 - D14: 30%
- Monitor FVIII levels
  - D1 – post dose, 6 - 8 h later
  - D2, D4, D6 – trough



Factor replacement



Factor dosing

- Formula:

  Dose in units =

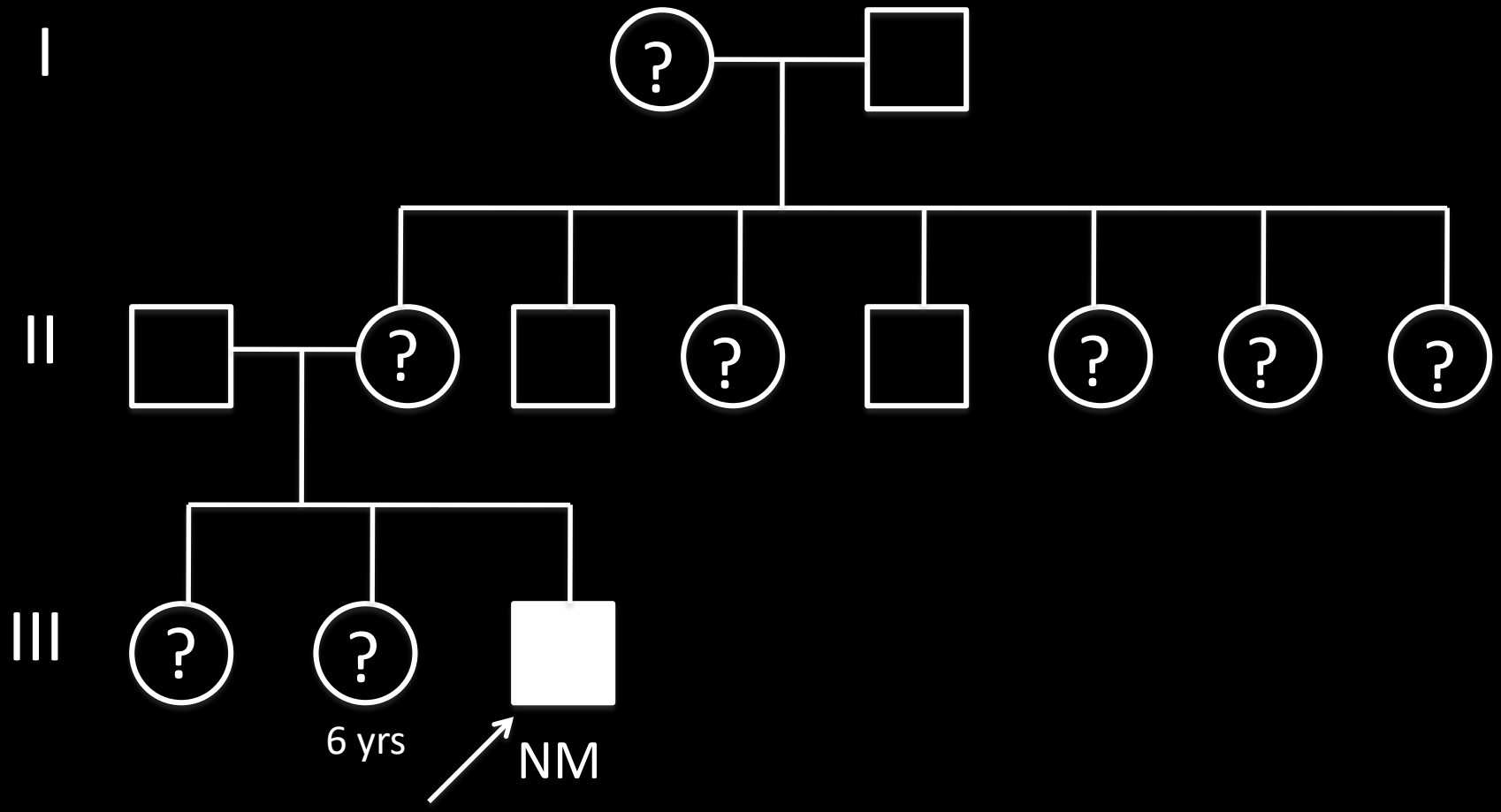
  $$\frac{\text{Weight in kg x \% rise in factor required}}{\text{K factor}}$$

  (K factor for FVIII = 2.0 , FIX = 1.0)

Case 1 – Family history

- Mom
  - 2 daughters (10 and 6 years old)
  - 6 younger siblings
  - No f/h of haemophilia

Case 1 – Family tree



Case 1 – Counseling

- Dr: *Your son has been diagnosed with severe haemophilia A. Have you heard about haemophilia?*
- Mom: *No doctor, but from what I see it must be a serious bleeding disorder*
- Dr: Explain about haemophilia

Haemophilia

- Hereditary bleeding disorder
- X-linked
- Lack a clotting factor
  - factor VIII (HA) or factor IX (HB)
- Blood fails to clot
- Bleeds spontaneously in severe disease
- 20% present at birth

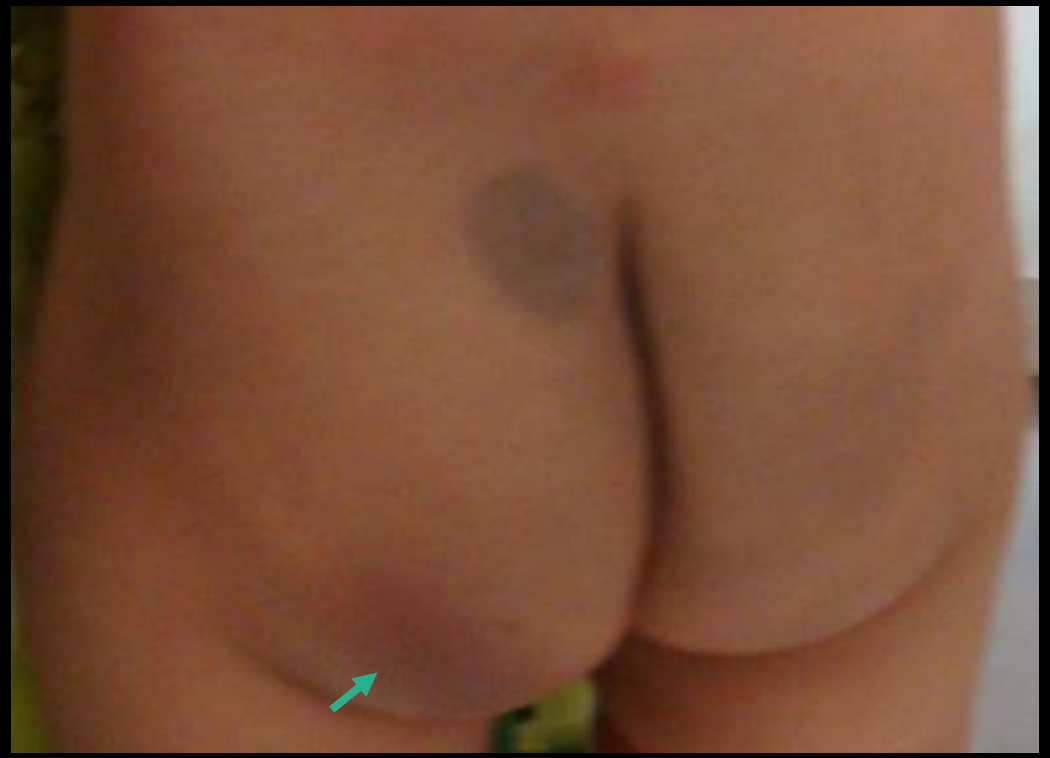
Classification of Haemophilia

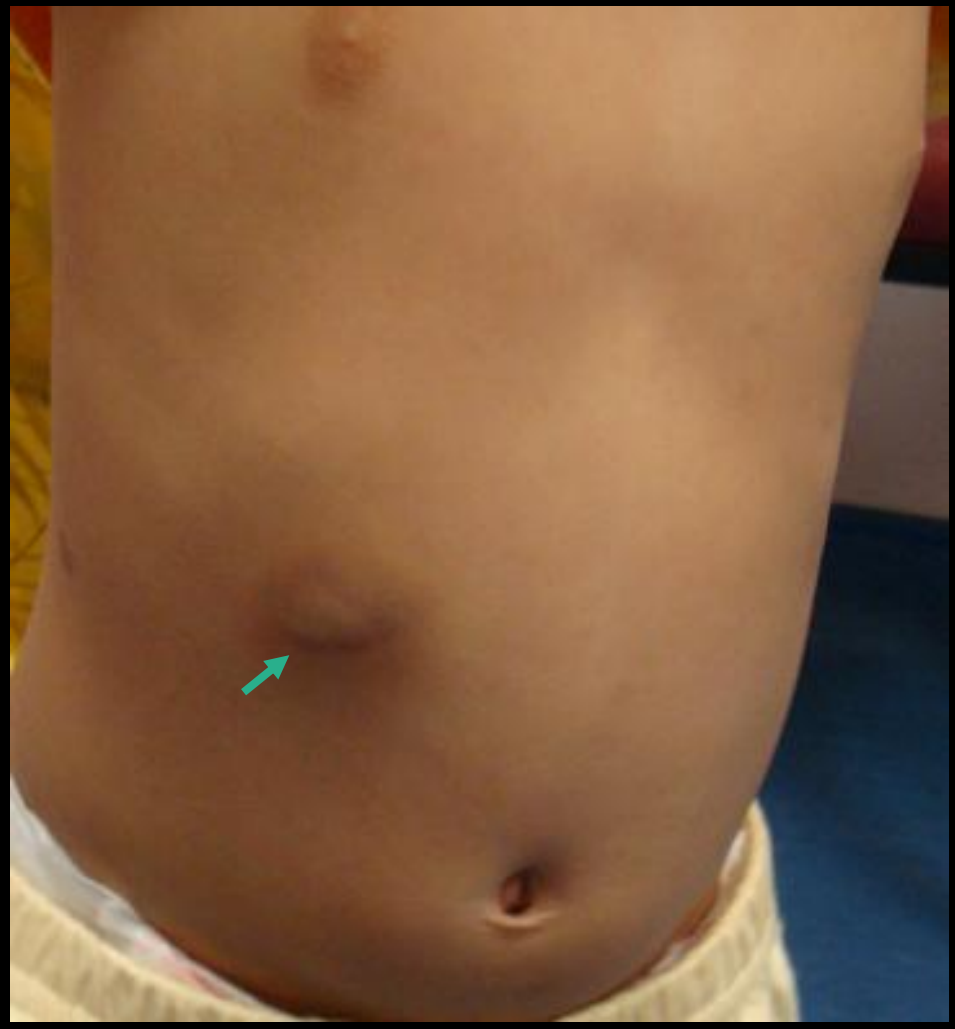
Severity	Factor level %	Bleeding
Severe	< 1	Spontaneous
Moderate	1 – 5	After minor trauma
Mild	>5 – 40	After major trauma or surgery

Management

- Replace the factor that is missing
- Vaccinations are not contraindicated but should be given subcutaneously
- Learn about haemophilia and inhibitor risk
- Learn to recognise bleeds
- Need to report trauma or bleeding

Bruise or haematoma?

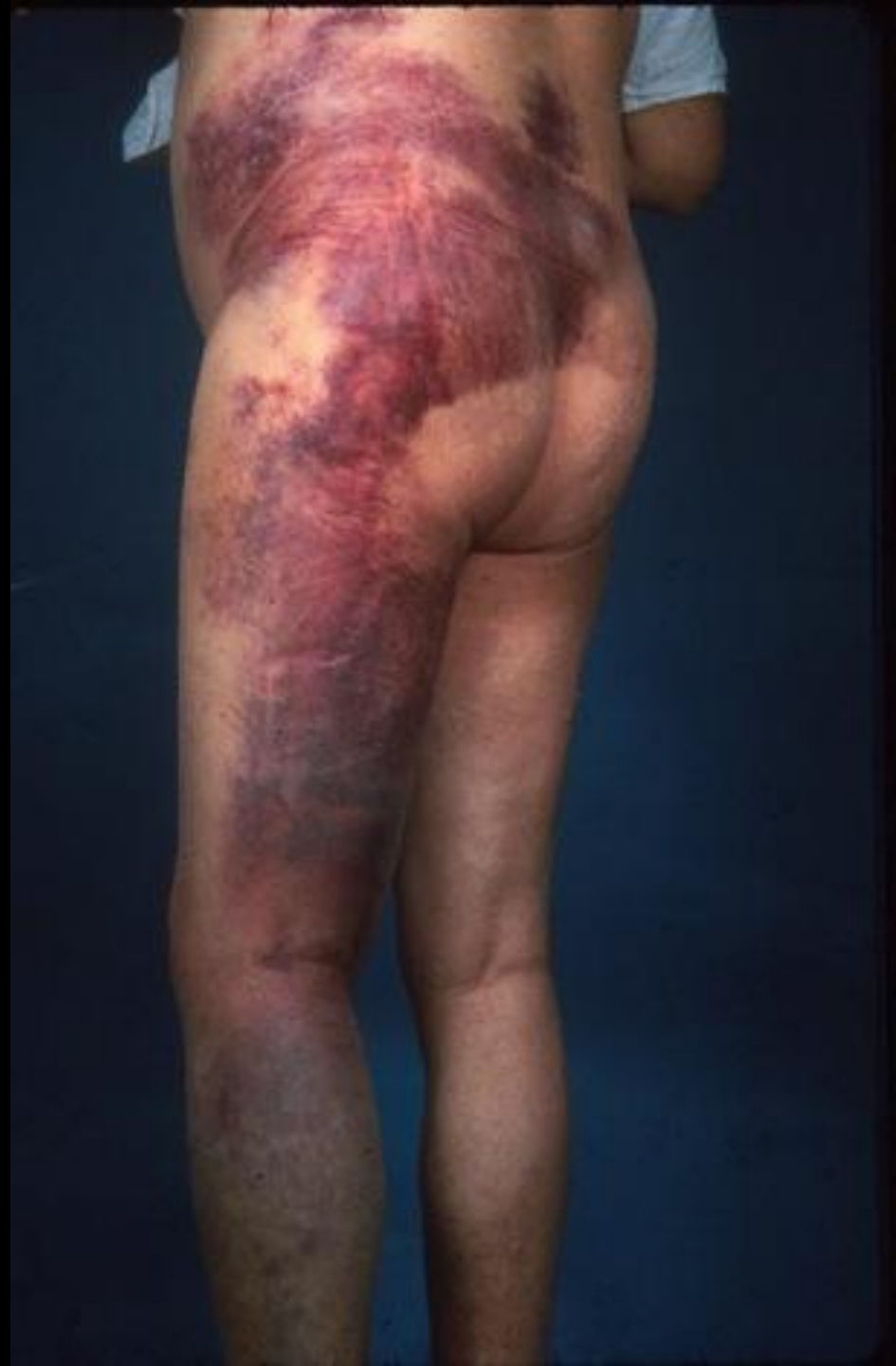




Avoid aspirin / NSAIDs

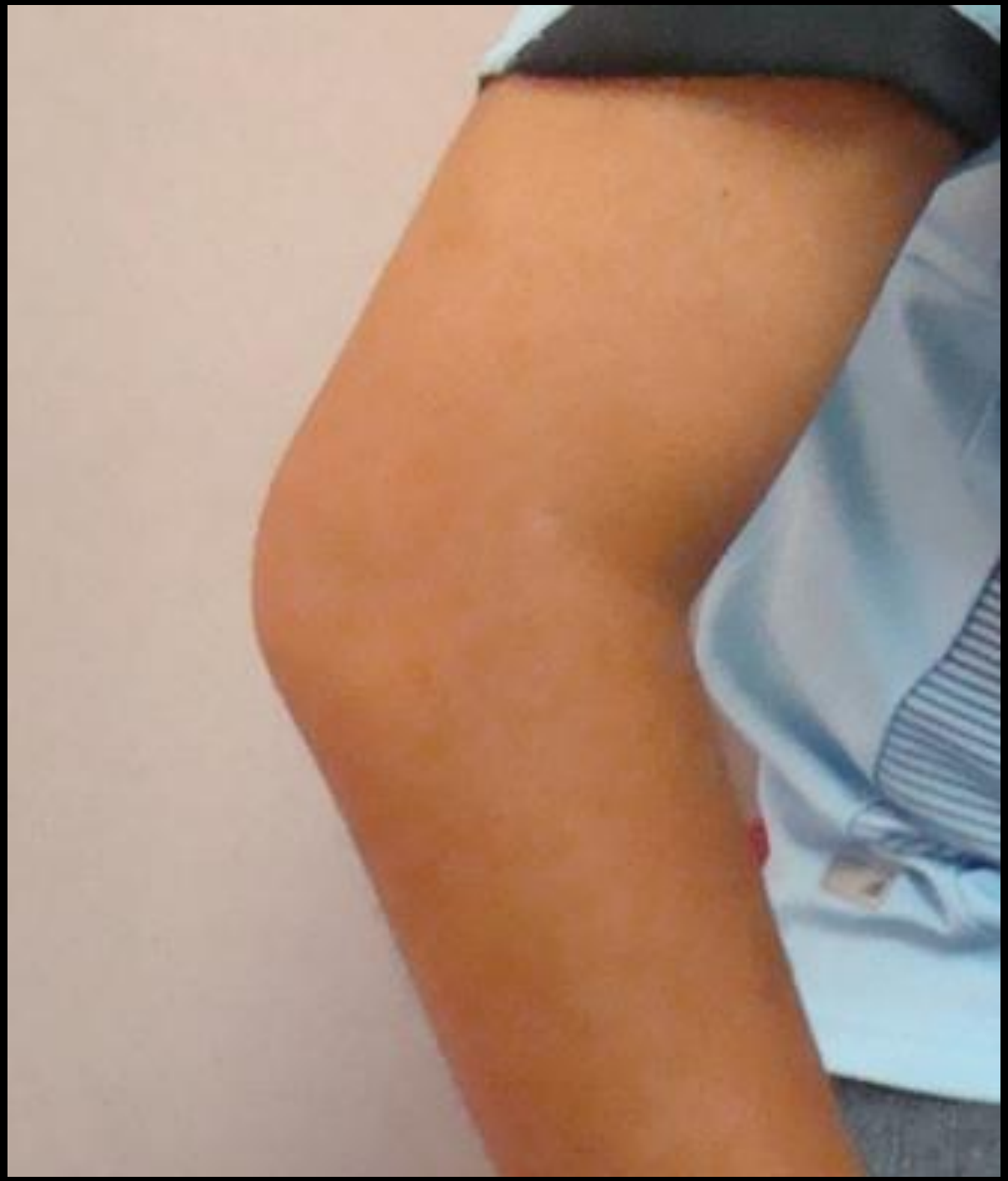
- Superficial cuts – OK
- Platelets → Primary haemostasis

IM injections must be avoided



Haemarrthrosis

the hallmark of haemophilia

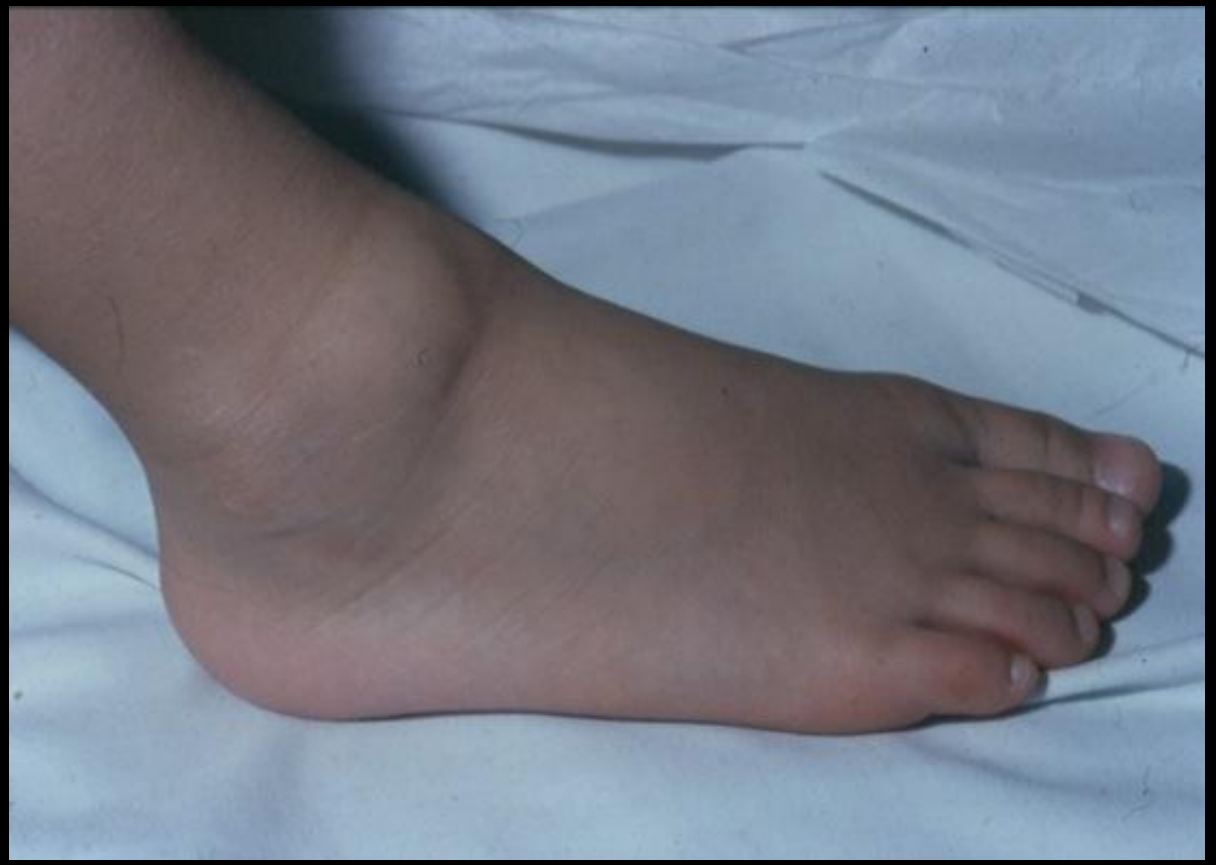


Bleeding in haemophilia

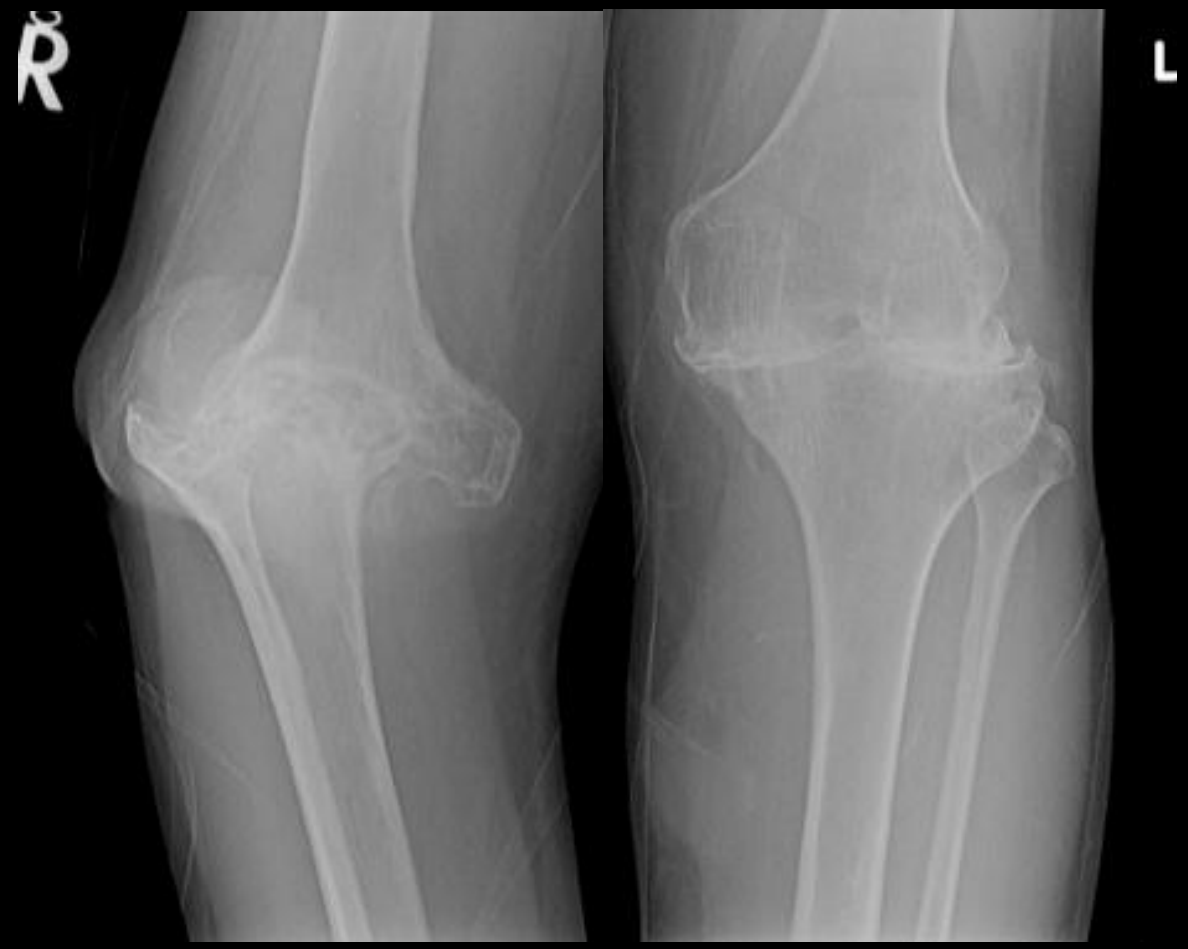
1. Haemarrthrosis
   - Begin approximately 1 year of age
   - Spontaneous
   - May be preceded by ‘tingling’ sensation
   - Blood fills joint cavity
   - Rise in pressure is excruciatingly painful
   - Pressure eventually stops the bleeding
   - Blood damages cartilage
   - Joint becomes prone to recurrent bleeds

Target joint

- Recurrent bleeds into same joint
  - 3 - 4 bleeds in 6 months



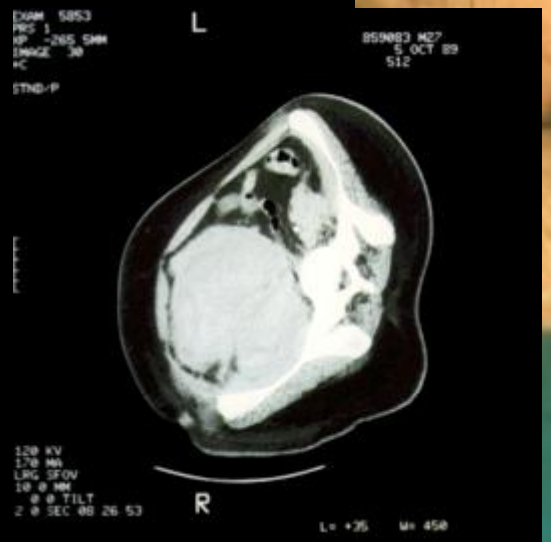
Joint damage



Bleeding in haemophilia

2. Muscle bleeds
   - Often, apparently spontaneous
   - May result from exertion
   - Blood fills muscle capsule or compartment
   - Compartment syndrome may result
   - Pressure eventually stops the bleeding
   - Psoas bleed is a typical example

Psoas bleed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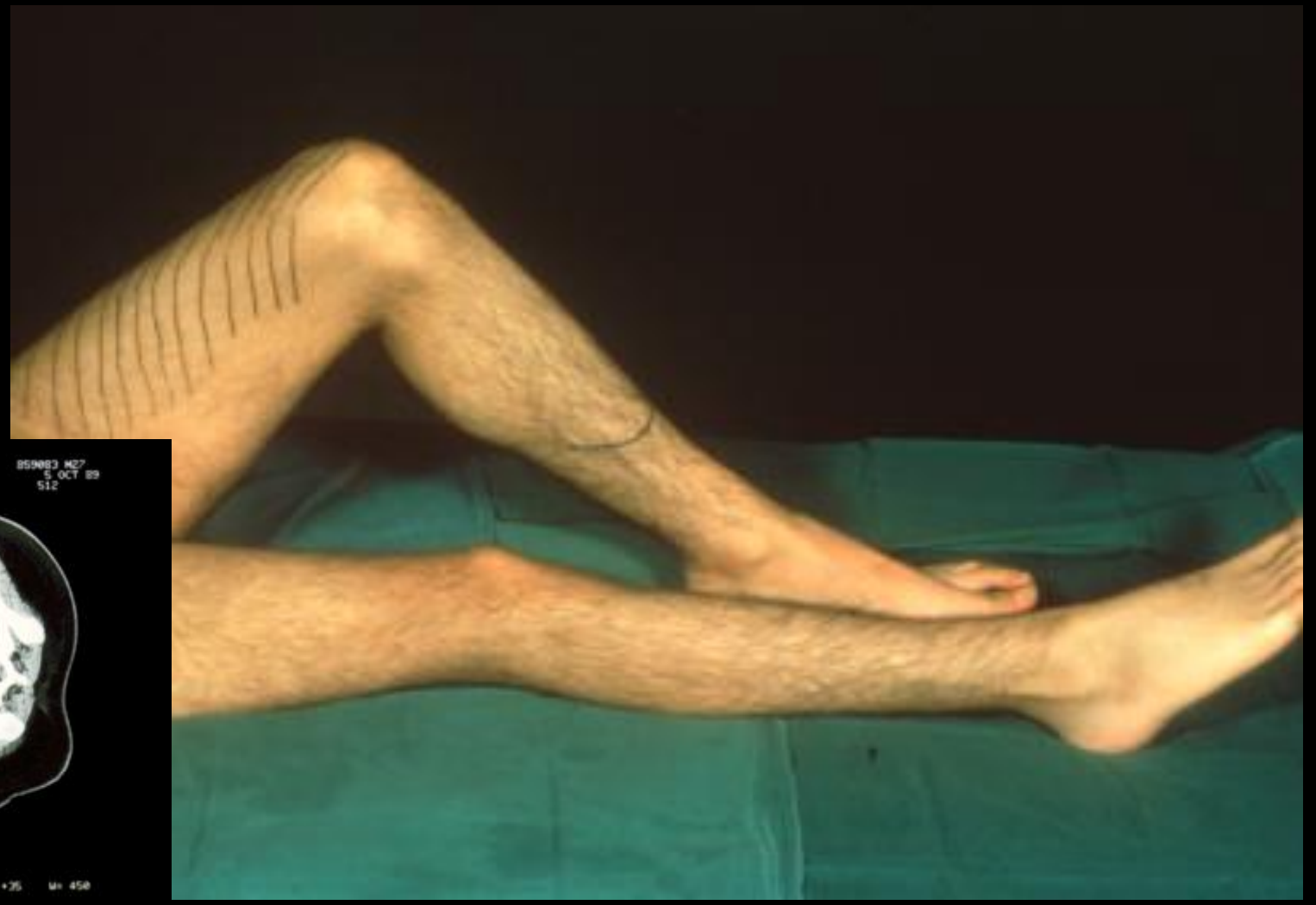
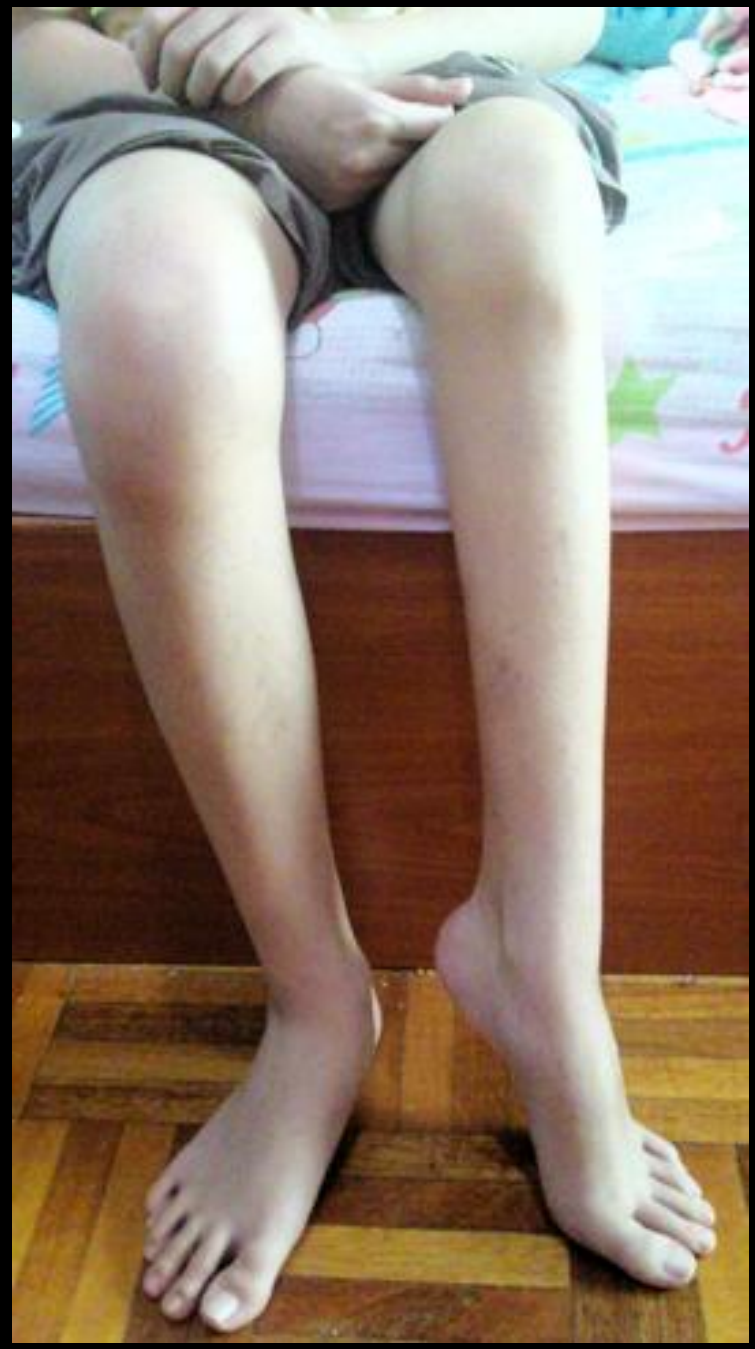
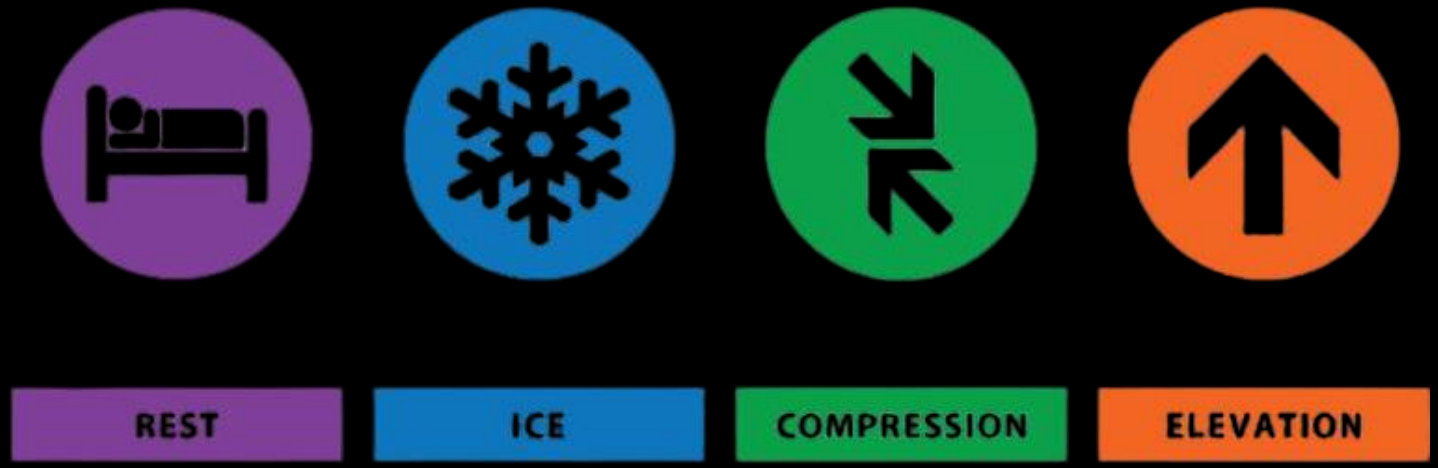


Muscle contractures

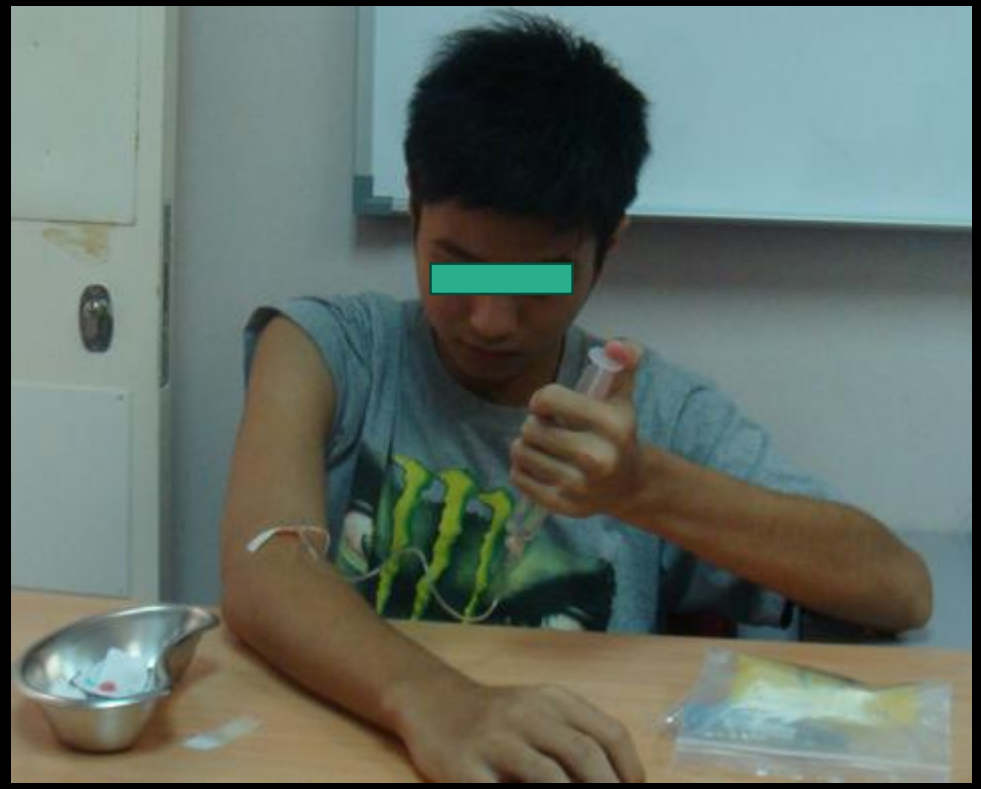


Treatment of joint bleeds



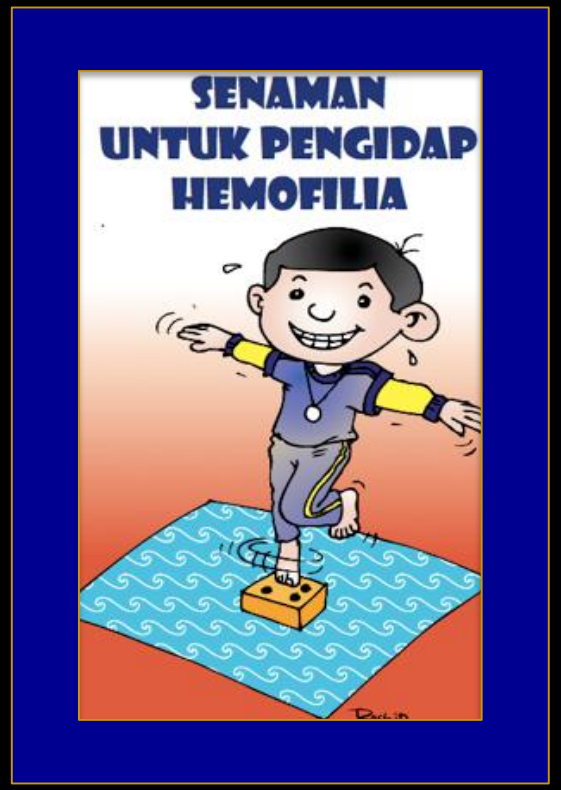
Treatment of joint bleeds

- Prompt factor replacement (within 2 h)
- Treat until pain subsides + 1 extra dose



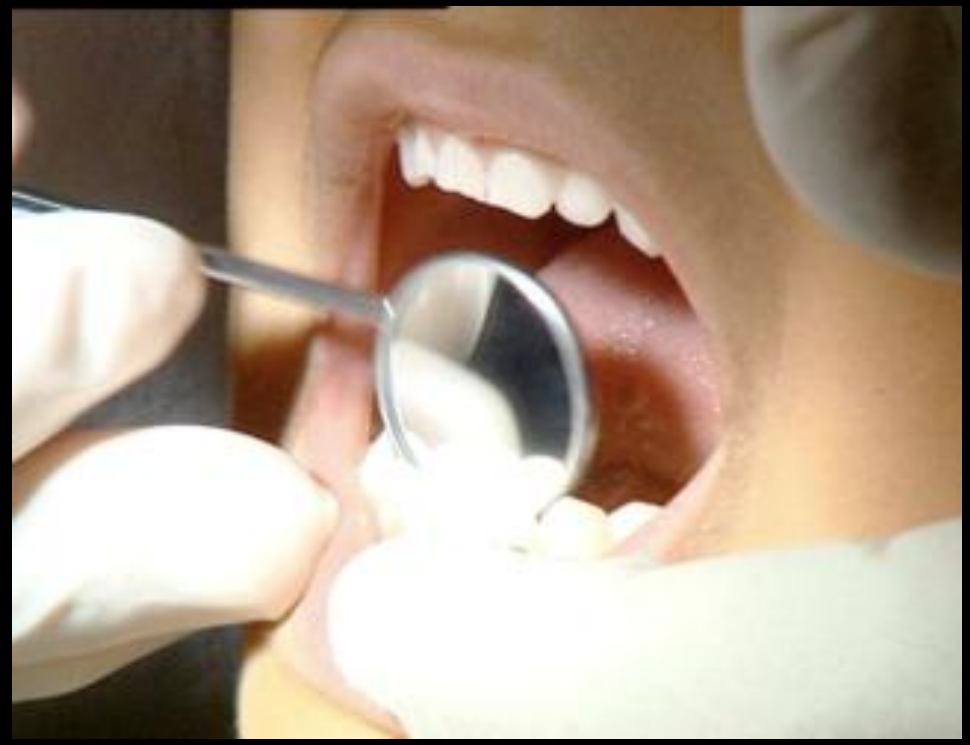
Physiotherapy

- Start exercise once pain subsides
- Early restoration of
  - Full range of motion
  - Strength
  - Proprioception, balance and coordination



Dental check-ups

- ½ yearly
- Prevention is better

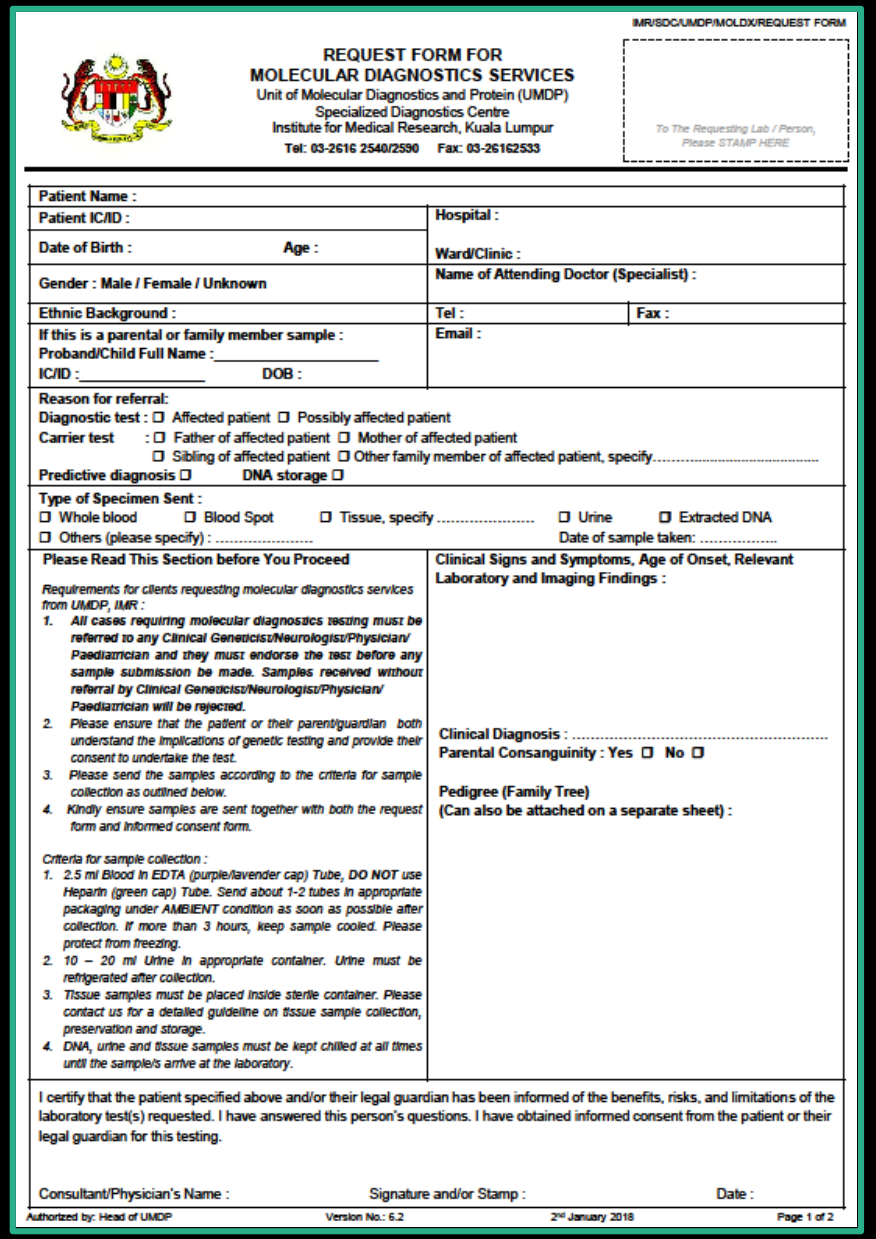


Case 1 – Counseling cont’d

- Mom: *Does that mean I am a carrier?*
- Dr: *Possible as 30% may arise from a spontaneous mutation*
- Mom: *How do I know if I am a carrier?*

Genetic testing

- Index patient (NM)
  - Intron 22 inversion by PCR
- If negative
  - Intron 1 inversion
- If both negative
  - DNA sequencing
- Once mutation detected, screen mom



IMR/SDC/UMDP/MOLDX/REQUEST FORM

REQUEST FORM FOR MOLECULAR DIAGNOSTICS SERVICES

Unit of Molecular Diagnostics and Protein (UMDP)
Specialized Diagnostics Centre
Institute for Medical Research, Kuala Lumpur
Tel: 03-2616 2540/2590 Fax: 03-26162533

To The Requesting Lab / Person, Please STAMP HERE

Patient Name :

Patient IC/ID : | **Hospital :**

Date of Birth : **Age :** | **Ward/Clinic :**

Gender : Male / Female / Unknown | **Name of Attending Doctor (Specialist) :**

Ethnic Background : | **Tel :** **Fax :**

If this is a parental or family member sample :
Proband/Child Full Name :_____
IC/ID :_____ **DOB :** | **Email :**

Reason for referral:
Diagnostic test : ☐ Affected patient ☐ Possibly affected patient
Carrier test : ☐ Father of affected patient ☐ Mother of affected patient
☐ Sibling of affected patient ☐ Other family member of affected patient, specify.....
Predictive diagnosis ☐ **DNA storage** ☐

Type of Specimen Sent :
☐ Whole blood ☐ Blood Spot ☐ Tissue, specify ..... ☐ Urine ☐ Extracted DNA
☐ Others (please specify) : ..... Date of sample taken: .....

Please Read This Section before You Proceed

Requirements for clients requesting molecular diagnostics services from UMDP, IMR :

1. ***All cases requiring molecular diagnostics testing must be referred to any Clinical Geneticist/Neurologist/Physician/ Paediatrician and they must endorse the test before any sample submission be made. Samples received without referral by Clinical Geneticist/Neurologist/Physician/ Paediatrician will be rejected.***
2. *Please ensure that the patient or their parent/guardian both understand the implications of genetic testing and provide their consent to undertake the test.*
3. *Please send the samples according to the criteria for sample collection as outlined below.*
4. *Kindly ensure samples are sent together with both the request form and informed consent form.*

Criteria for sample collection :

1. *2.5 ml Blood in EDTA (purple/lavender cap) Tube, **DO NOT** use Heparin (green cap) Tube. Send about 1-2 tubes in appropriate packaging under AMBIENT condition as soon as possible after collection. If more than 3 hours, keep sample cooled. Please protect from freezing.*
2. *10 – 20 ml Urine in appropriate container. Urine must be refrigerated after collection.*
3. *Tissue samples must be placed inside sterile container. Please contact us for a detailed guideline on tissue sample collection, preservation and storage.*
4. *DNA, urine and tissue samples must be kept chilled at all times until the sample/s arrive at the laboratory.*

Clinical Signs and Symptoms, Age of Onset, Relevant Laboratory and Imaging Findings :

Clinical Diagnosis : .....
Parental Consanguinity : Yes ☐ **No** ☐

Pedigree (Family Tree)
(Can also be attached on a separate sheet) :

I certify that the patient specified above and/or their legal guardian has been informed of the benefits, risks, and limitations of the laboratory test(s) requested. I have answered this person's questions. I have obtained informed consent from the patient or their legal guardian for this testing.

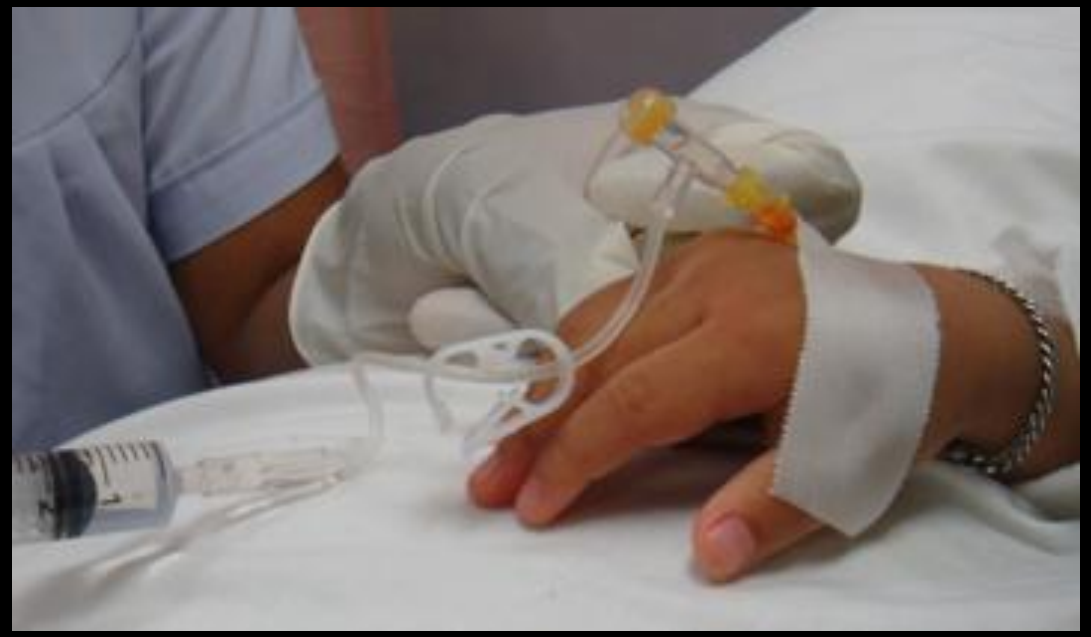
Consultant/Physician's Name : Signature and/or Stamp : Date :

Case 1 – Result

- NM – intron 22 inversion
- Mom – same mutation
- So, mom is a carrier
- At risk of having another child with haemophilia
- 1 daughter is a carrier
- Need to screen mom's sisters

Case 1 – Prevention of bleeds

- Started prophylaxis age 10 months at 50 IU/kg once a week
- Followed by 25 IU/kg 3x/week

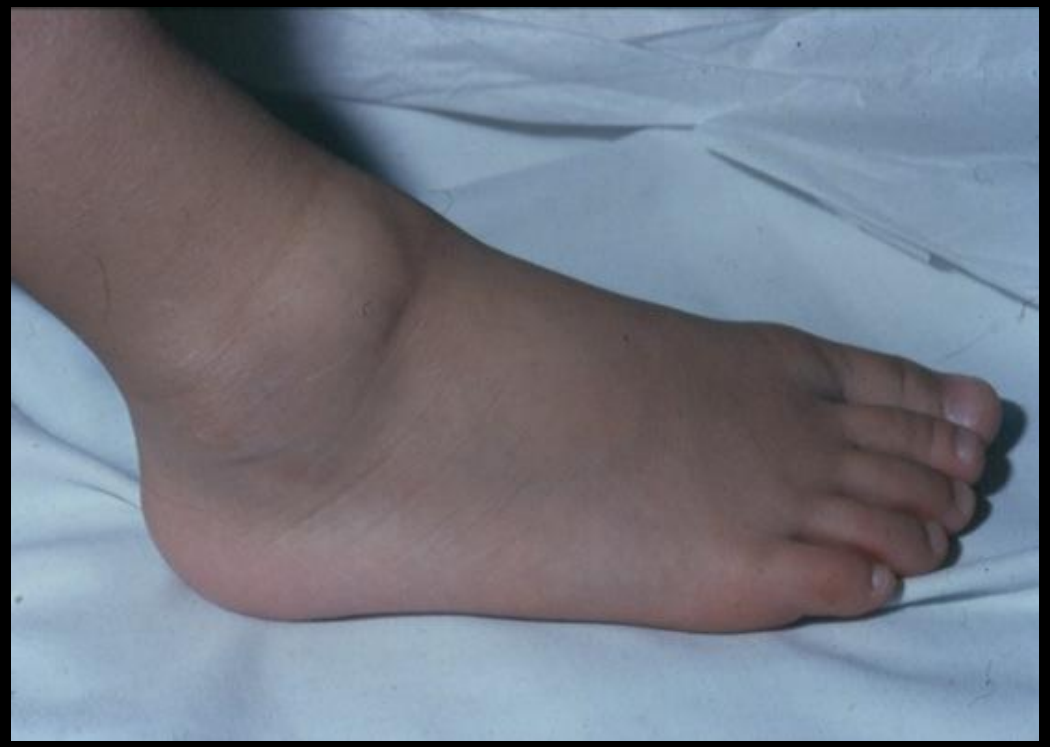


Prophylaxis is the standard of care

- Prevents joint damage
- Prevents intracerebral haemorrhage
- Reduces development of inhibitor
- Improves QOL

When to start prophylaxis?

- Synovium in children are vulnerable to damage by blood
- It may take just one bleed to cause a target joint
- Start prophylaxis before joint bleeds for severe haemophilia
- Between 12 – 18 months of age



Explain about inhibitor risk

- Dr: *There is a 15 – 30% risk of inhibitor development*
- Mom: *What is an inhibitor?*
- Dr: *An inhibitor is an antibody against the infused factor VIII*
- Mom: *Why is it important?*
- Dr: *It will render treatment with FVIII useless*

Inhibitor screening schedule

Exposure days	**Inhibitor screening**
1 – 20	Every 5 days
21 – 50	Every 3 months
>50	Every 6 months
>100	Every year

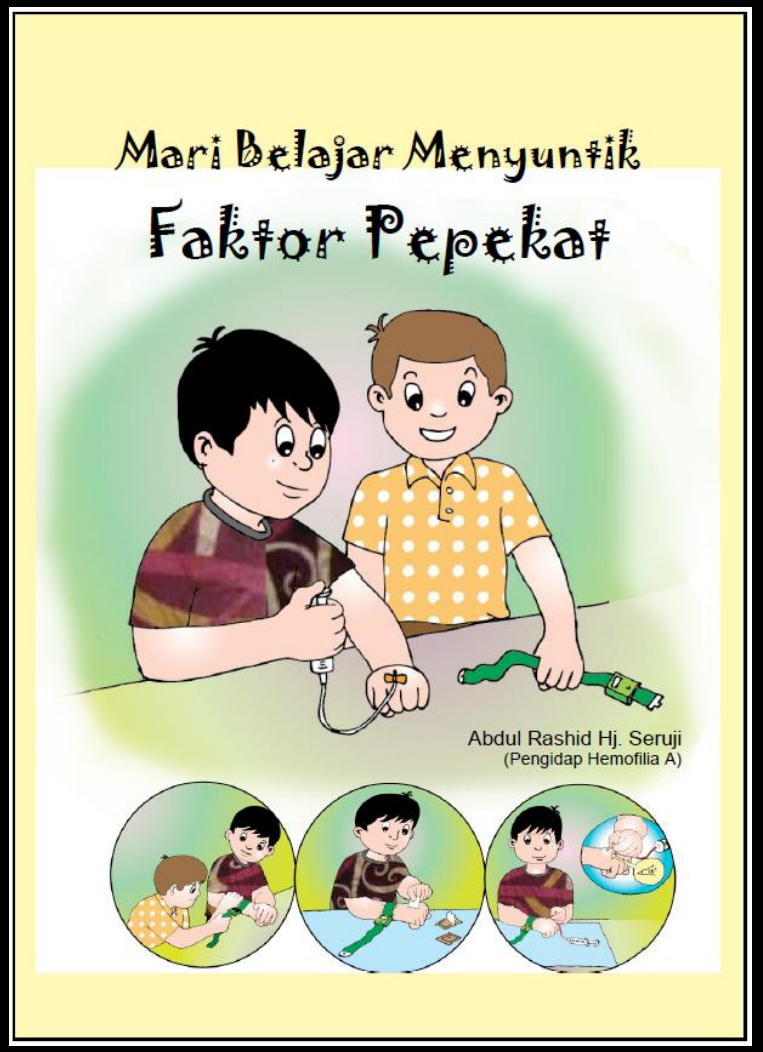
WFH guidelines 2012

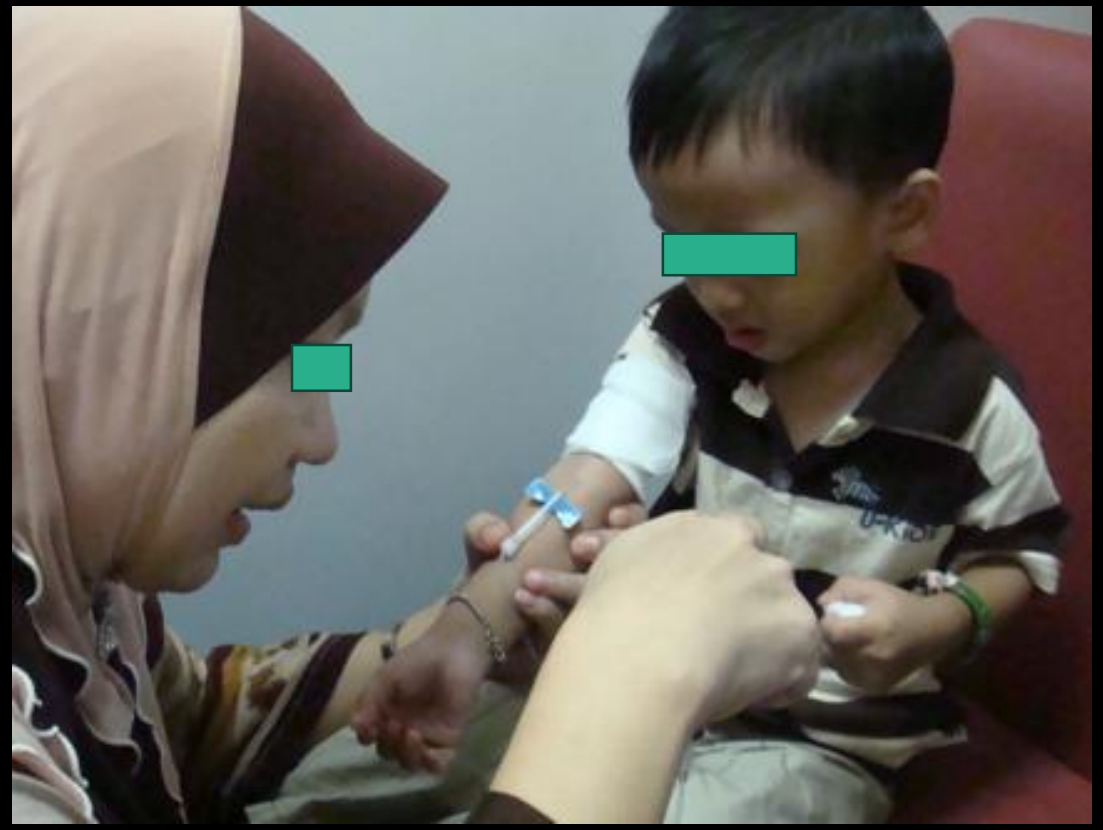
Monitor inhibitor development

14. **Inhibitor measurement should also be done in all patients who have been intensively treated for more than five days, within four weeks of the last infusion. (Level 4) [63,65]**

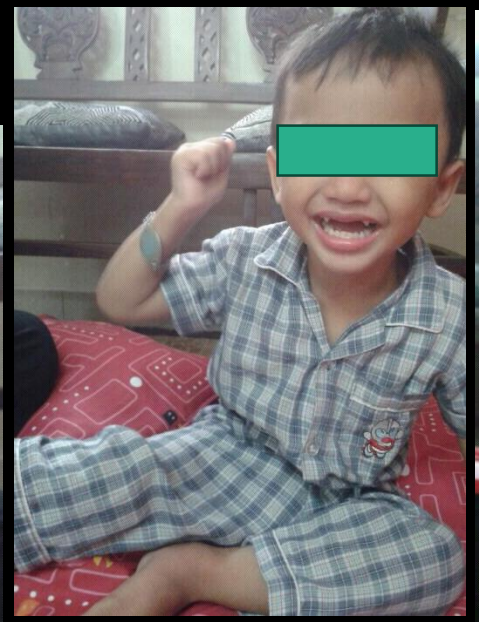
WFH guidelines 2012

Mom taught to infuse factor

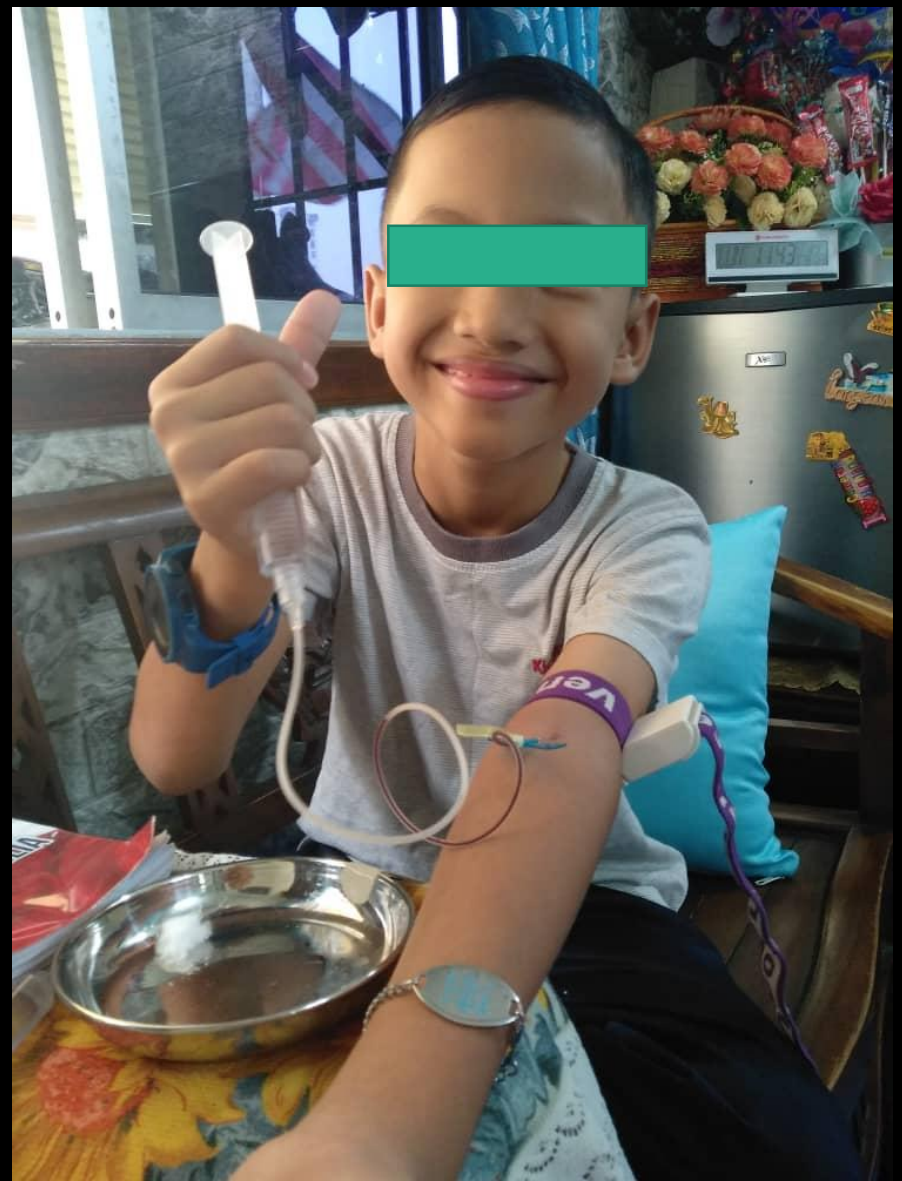




Starting home therapy

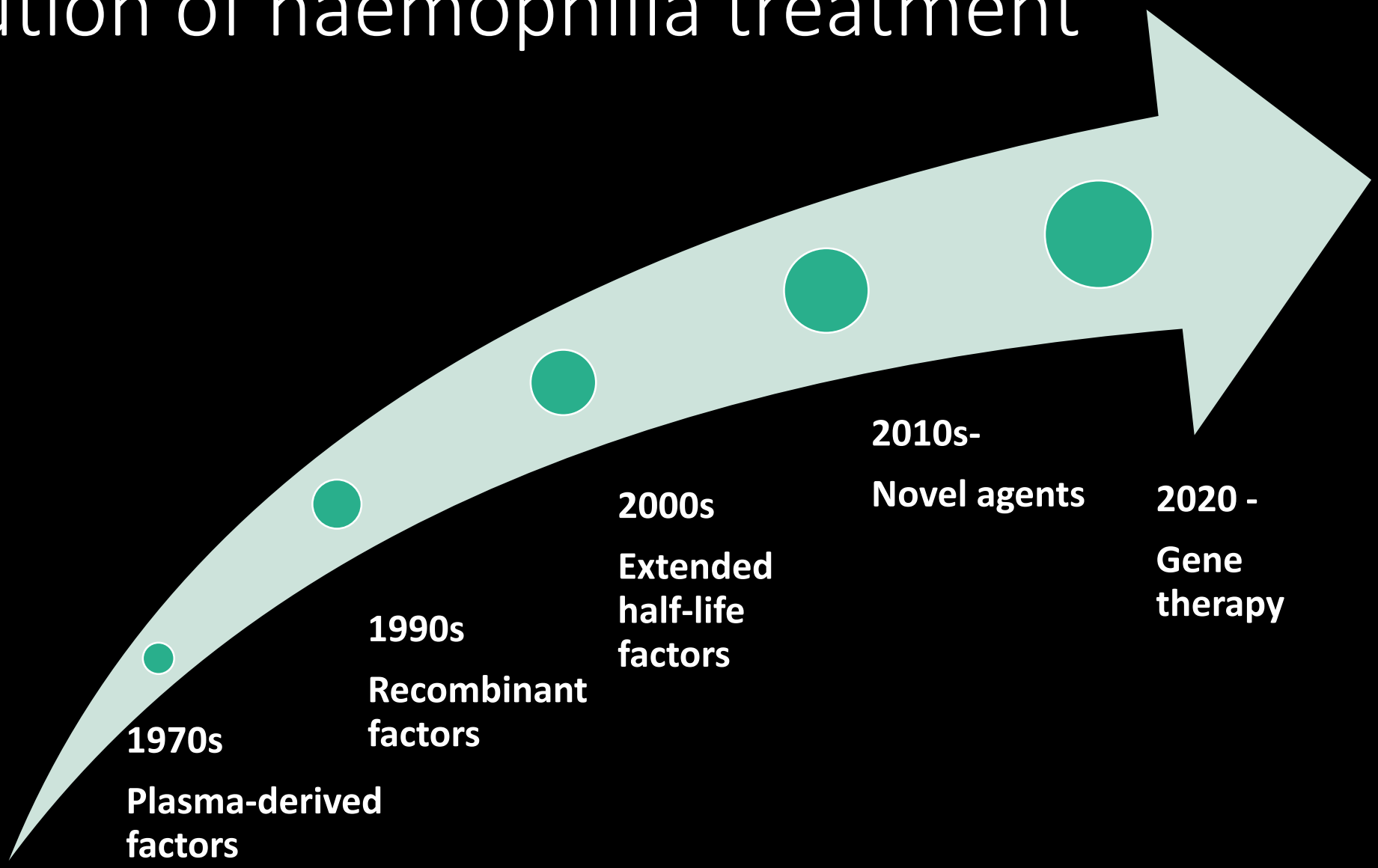


Home therapy



Therapies in haemophilia

Evolution of haemophilia treatment



Therapy Choices

- Plasma-derived (PD) vs. Recombinant
- Standard half-life (SHL) vs. Extended half-life (EHL) factors
- Factor vs. Non-factor

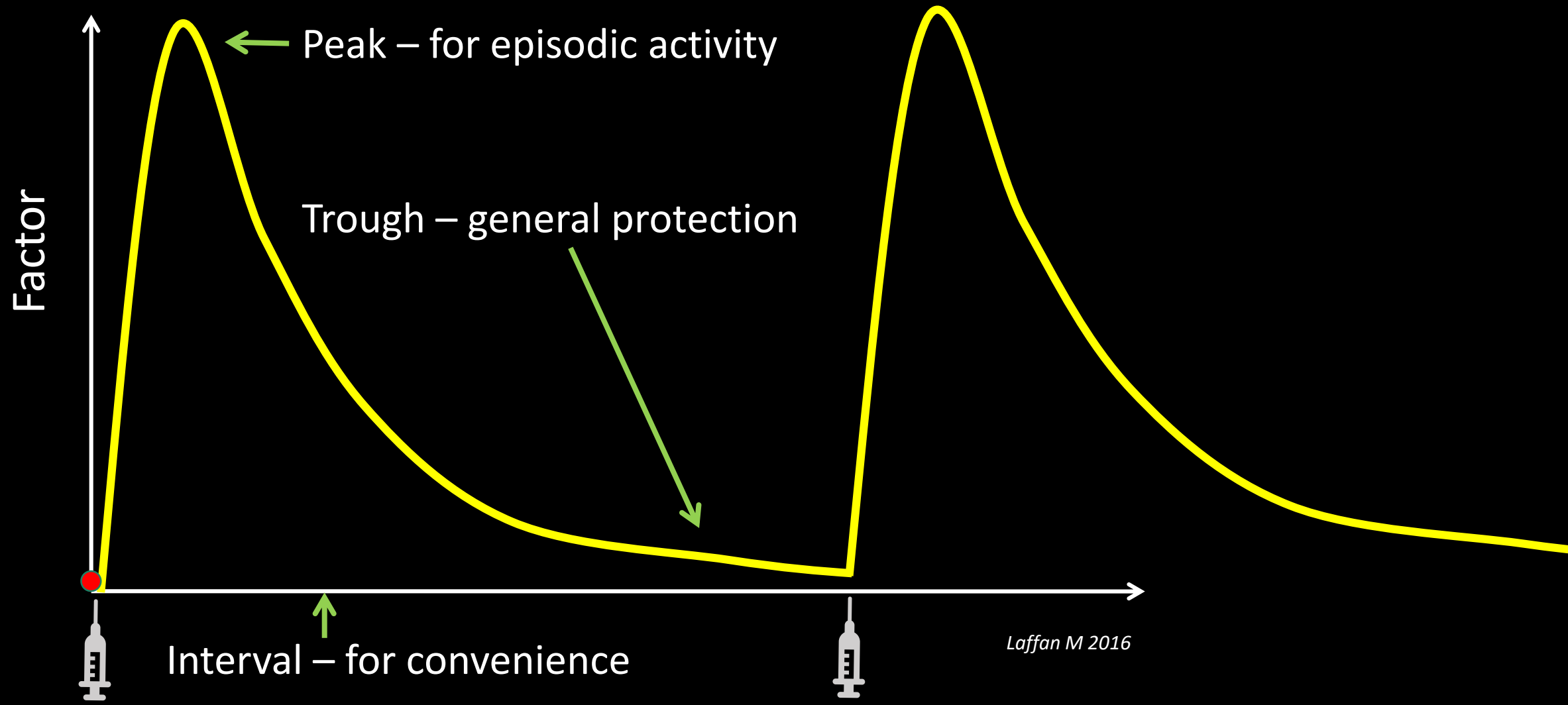
Factor therapies in Haemophilia

- Plasma-derived factor
- Recombinant factor
  - Standard half-life (SHL)
    - FVIII $T_{1/2}$ 11 h
    - FIX $T_{1/2}$ 18 h
  - Extended half-life (EHL)
    - FVIII $T_{1/2}$ 18.8 h
    - FIX $T_{1/2}$ 92 h

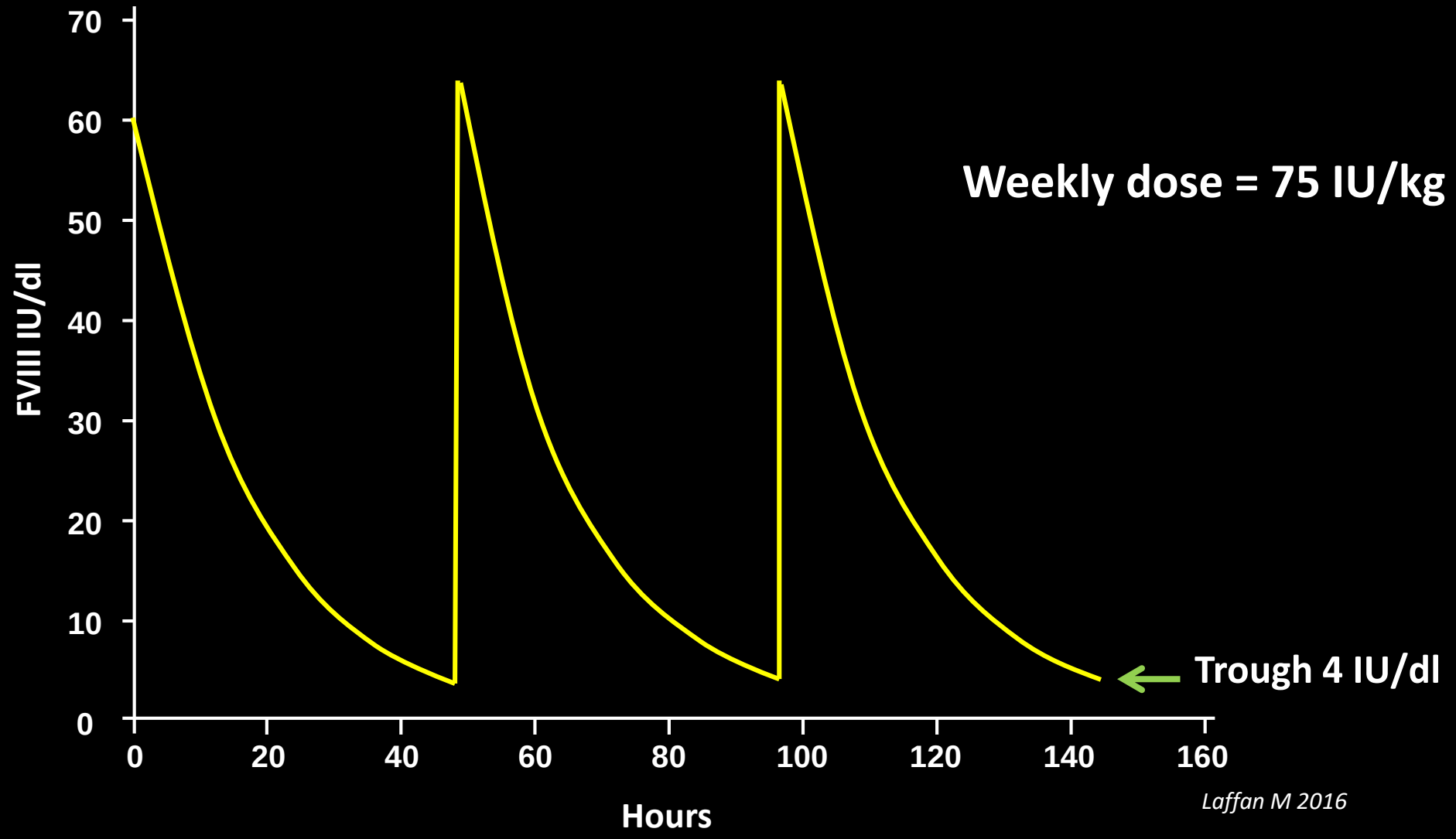
Methods for prolonging half-life

- Couple to PEG (polyethylene glycol)
  - reduced clearance by renal and proteolytic mechanisms
- Couple to albumin
  - albumin $t_{1/2}$ 20 days
- Couple to Fc
  - binds to the FcRn (neonatal Fc receptor) on endothelial cells and is recycled, avoiding lysosomal degradation: prolongs half-life
- Single chain technology
  - Augmenting the stability of the molecule

Treatment Profiles and Prophylaxis

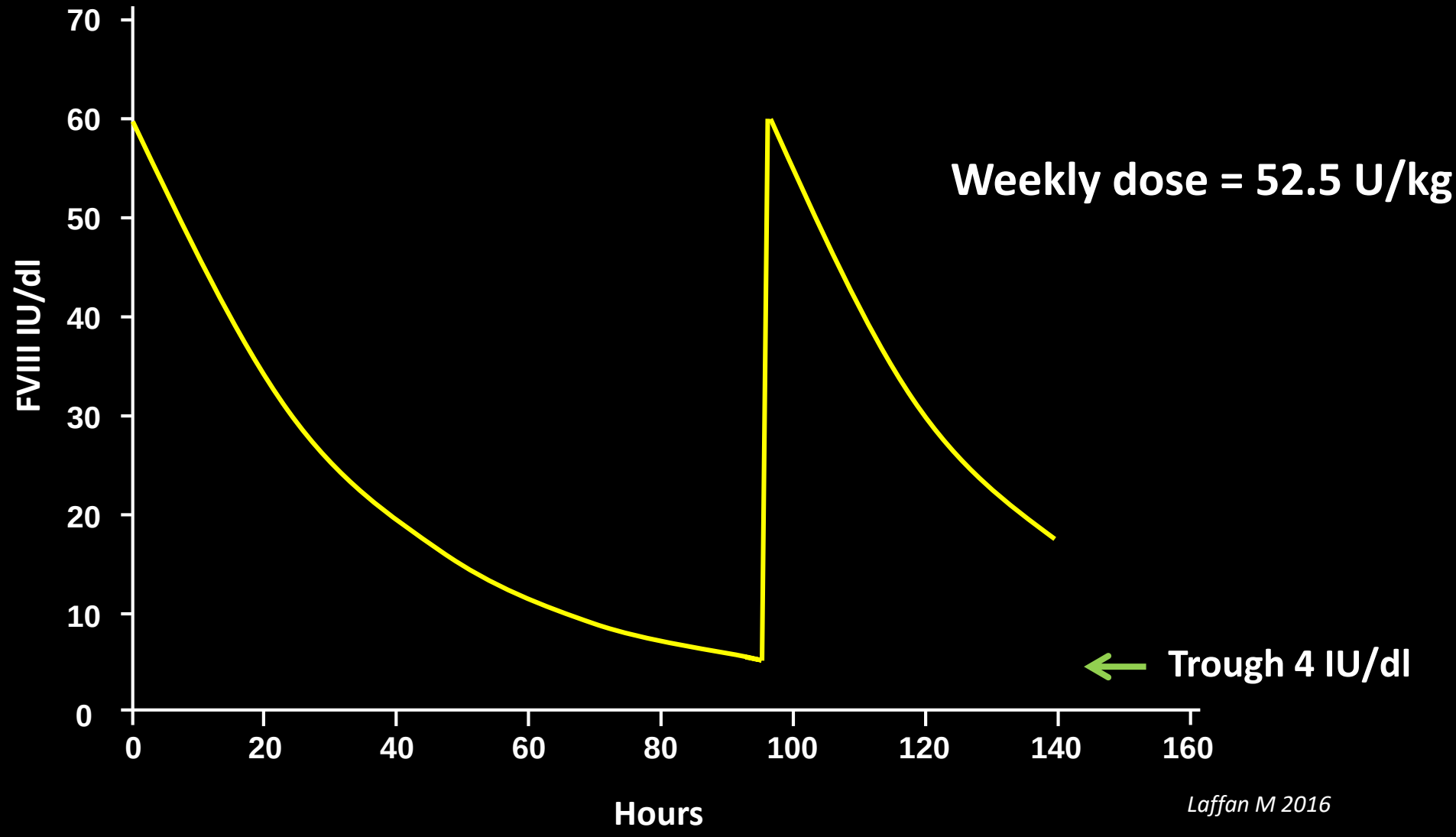


SHL (12 hr $T_{1/2}$) alt. day dosing, 30 IU/kg



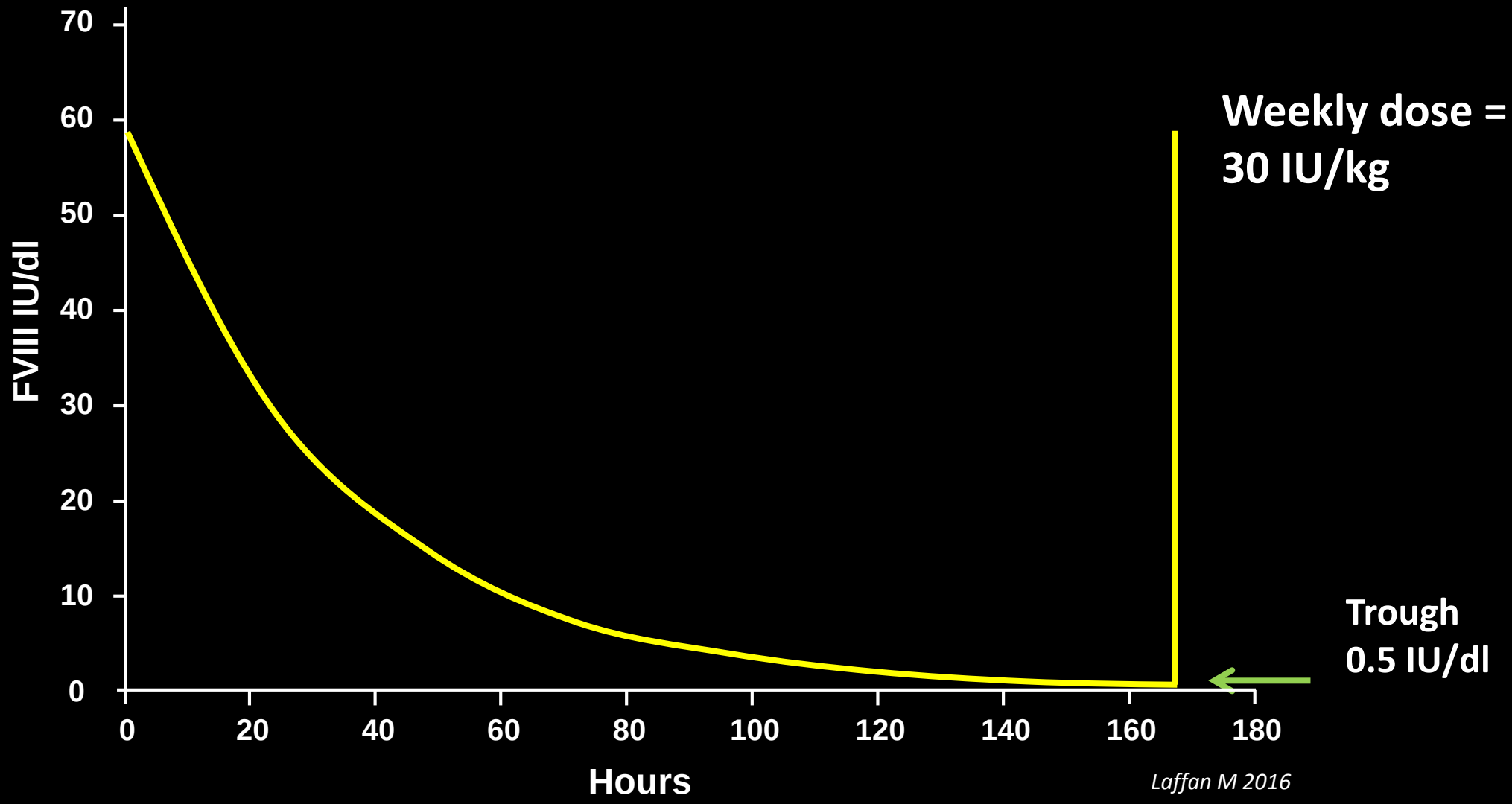
Laffan M 2016

EHL (24 hr $T_{1/2}$) 4-day dosing, 30 IU/kg



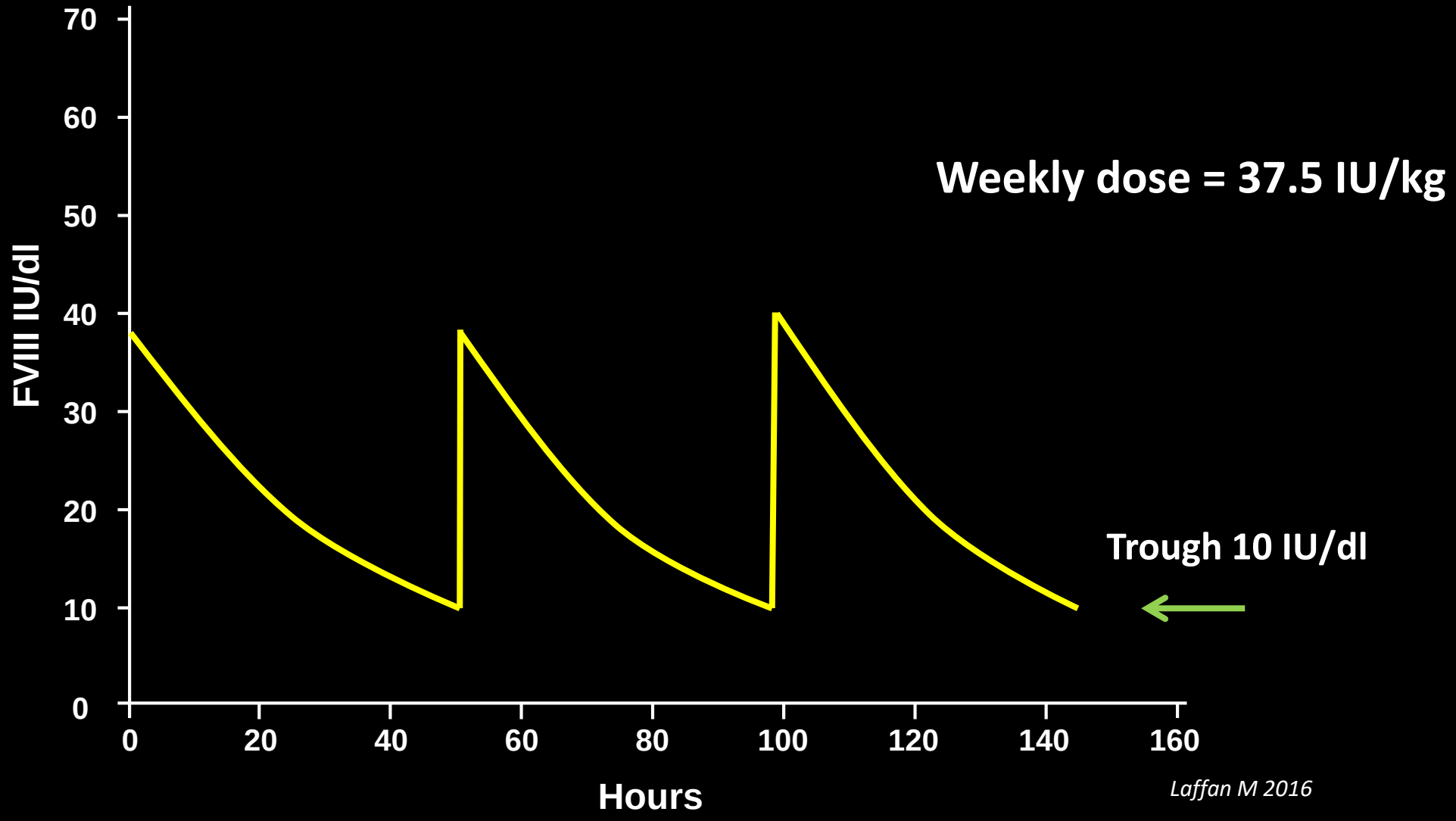
Laffan M 2016

EHL (24 hr $T_{1/2}$) weekly dosing, 30 IU/kg



Laffan M 2016

EHL (24 hr $T_{1/2}$) alt. day dosing, 15 IU/kg



Laffan M 2016

Applications of EHL factors

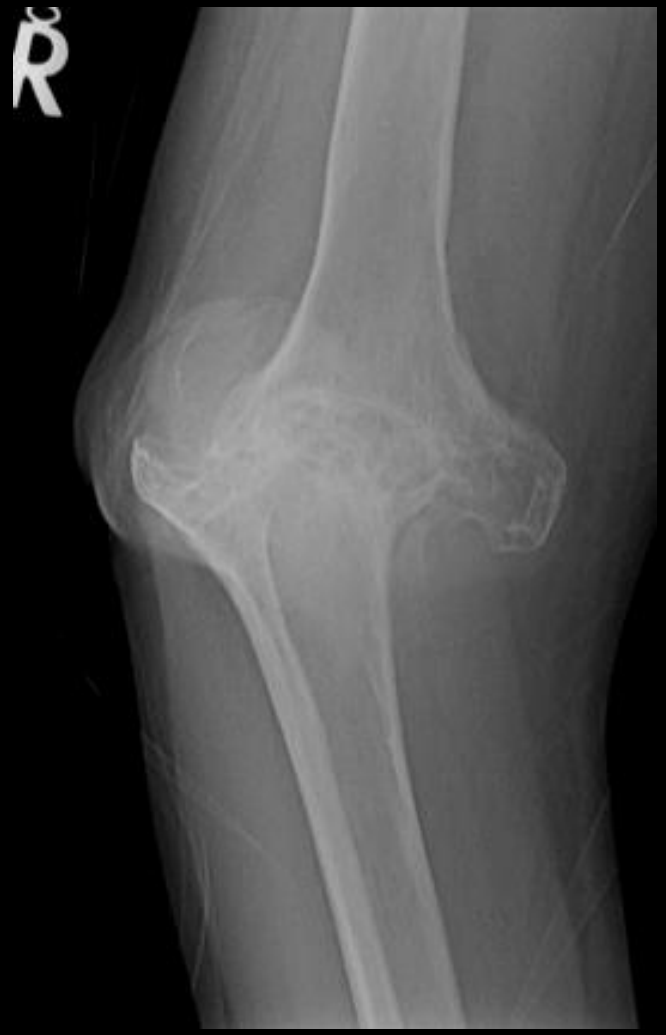
Prophylaxis

- Higher trough levels
  - Better protection from arthropathy
  - More continuous protection
  - May aid target joint resolution
- Reduced/ fewer peaks
  - Less factor – less cost

Surgery

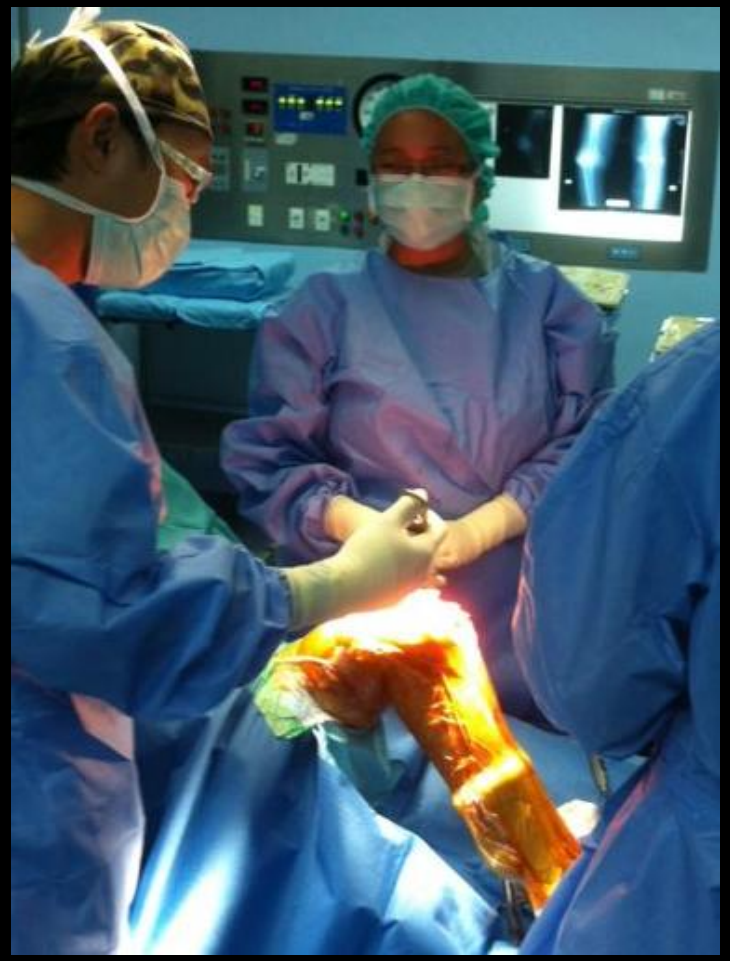
- Less dosing frequency – more convenient
- Less factor level monitoring required
- Physiotherapy sessions less stringent with factor timing
- Shorter hospital stay

Chronic haemophilic arthropathy



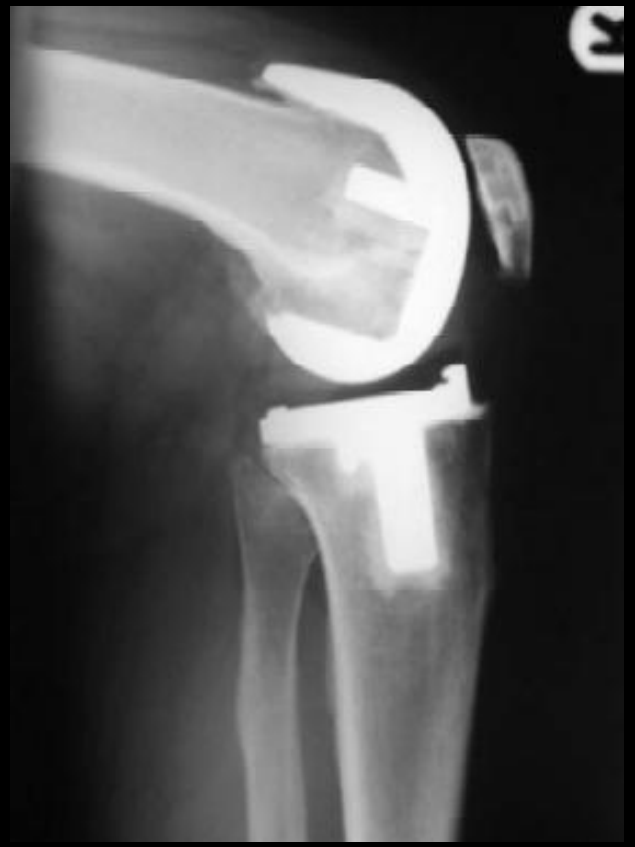
Joint replacement

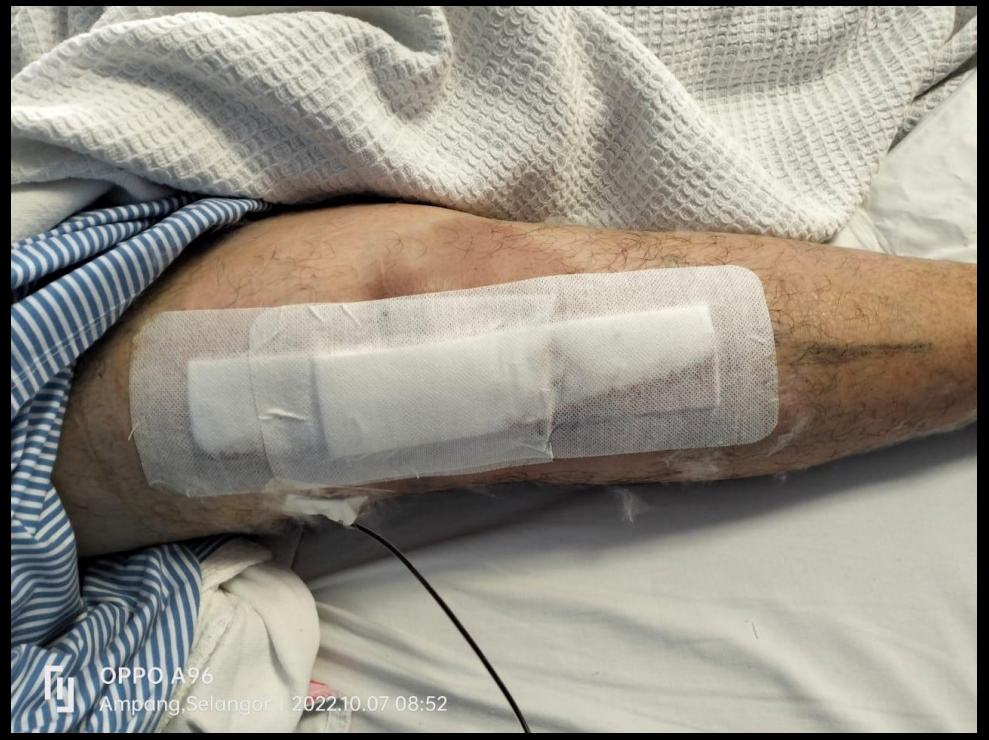
Patient 1 (70 kg) - 10 vials of 1000 IU EHL factor



Joint replacement

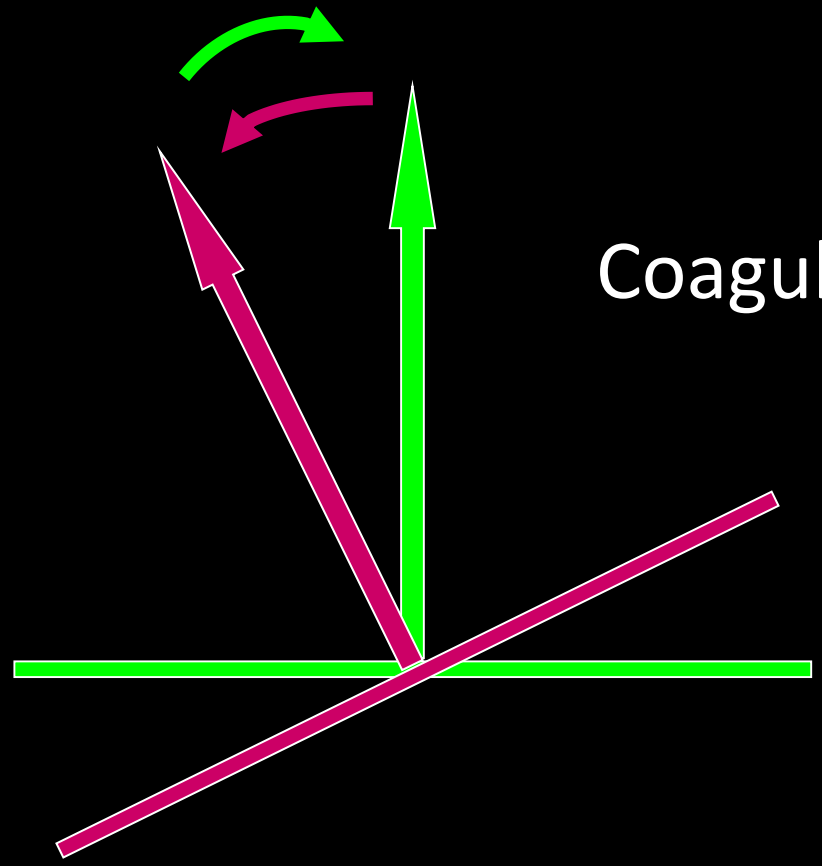
Patient 2 (75 kg) - 34 vials of 1000 IU SHL factor





Novel agents

Re-balancing haemostasis



Coagulation factors ↓

↓ Anticoagulant proteins

Non-factor therapies

- Emicizumab
  - a chimeric bispecific humanised antibody directed against FIXa and FX, which mimics the co-factor function of FVIII
- Anti-AT
  - Fitusuran
- Anti-TFPI
  - Concizumab

Subcutaneous injections

- Non-factor
  - Bispecific antibody (Emicizumab)
  - Anti-TFPI (Concizumab)
  - Anti-AT (Fitusiran)
- FDA- approved
  - Emicizumab for HA and HAwI
  - Concizumab for HBwI

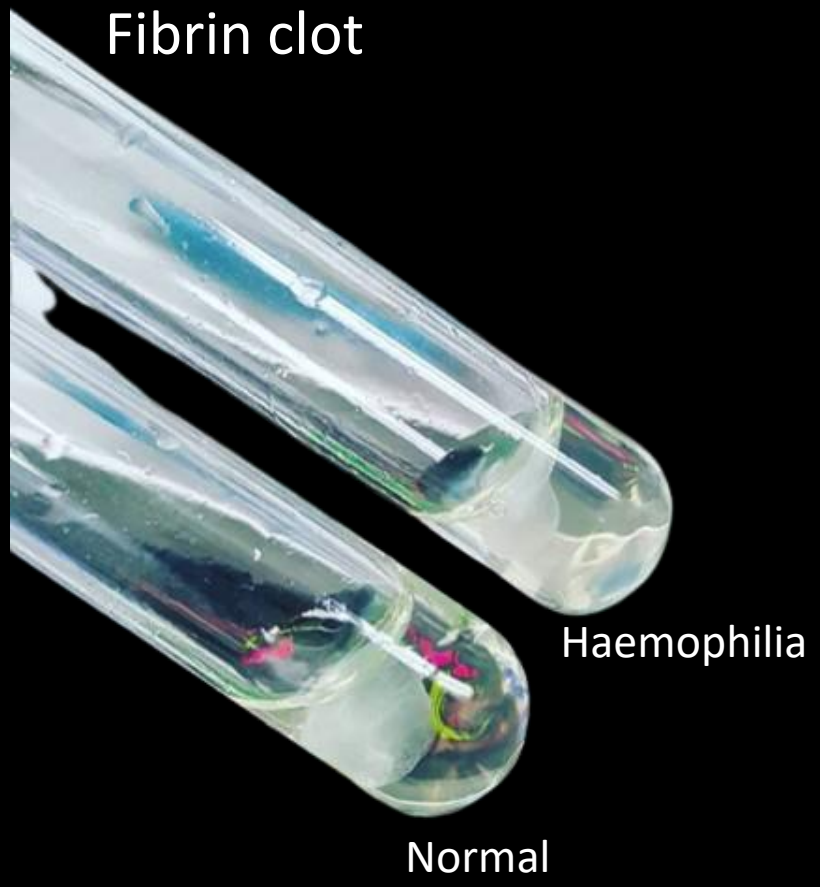
Monitoring new therapies

Monitoring new therapies

- More complex
- One-stage factor assays may under- or over-estimate EHL factor therapies
- APTT-based tests cannot be used to measure factor VIII or inhibitor level when on Emicizumab therapy

Factor assays

- EHL factors
  - Chromogenic factor assay or
  - One-stage assay with validated reagents
- Emicizumab
  - Chromogenic assay with bovine FIX and FX
  - Modified one-stage assay with emicizumab calibrators



Opportunities

Haemophilia Registry

- Malaysia joined WBDR in 2019
- 16 centres have taken part
- Another 3 have registered
- 603 haemophilia; 22 VWD registered

WBDR Malaysia 2023

Not forgetting the women

The women's club

KHWAN = Kelab Hemostasis Wanita

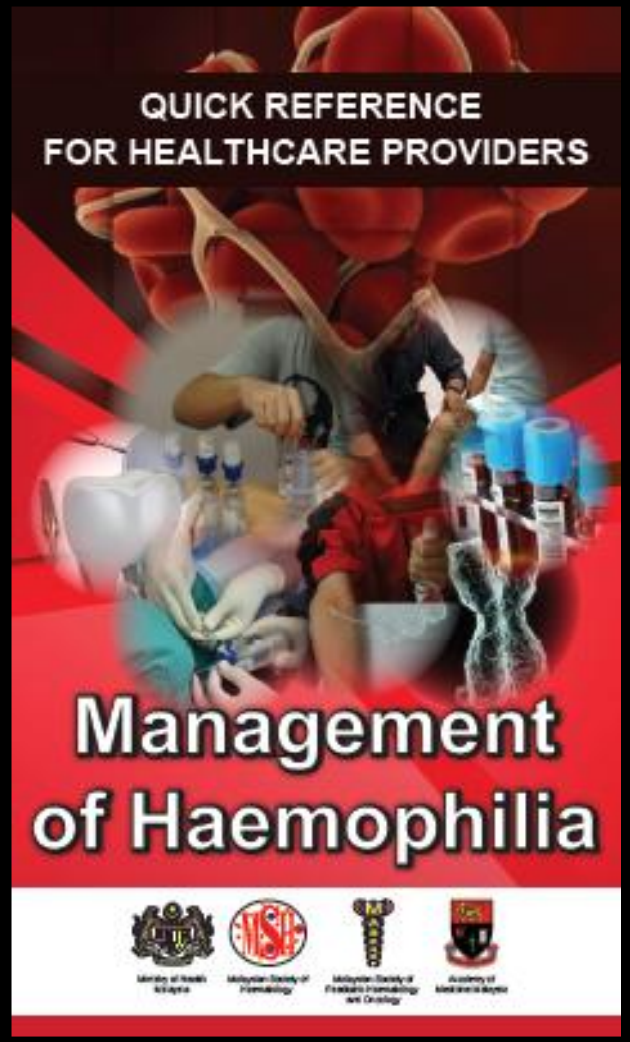
Haemophilia Society Advocacy Group

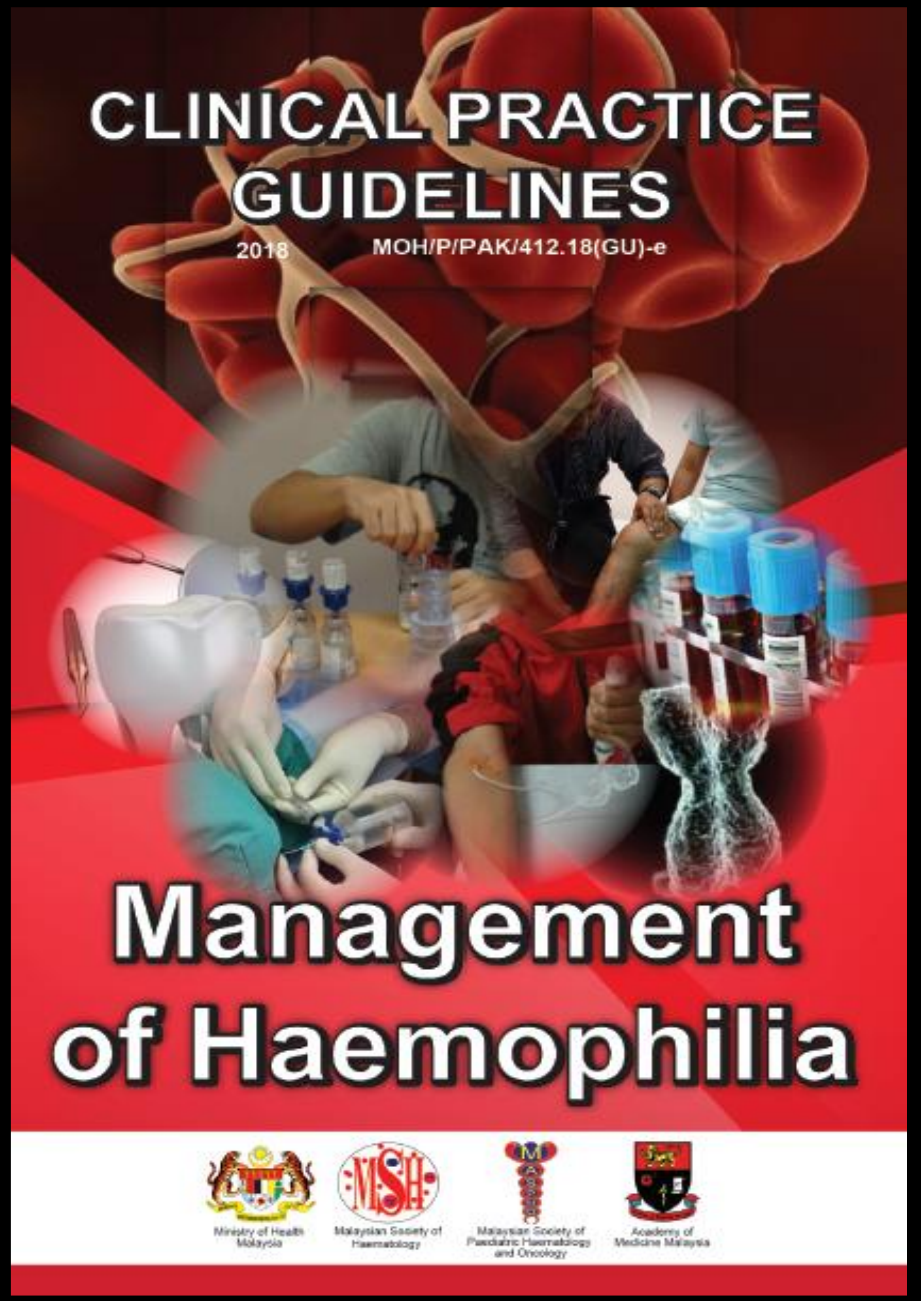
The men’s club

National Haemophilia Technical Advisory Board

- Formed in 2017
- Implement optimal haemophilia care throughout the country

Haemophilia CPG
2018





Per capita factor usage

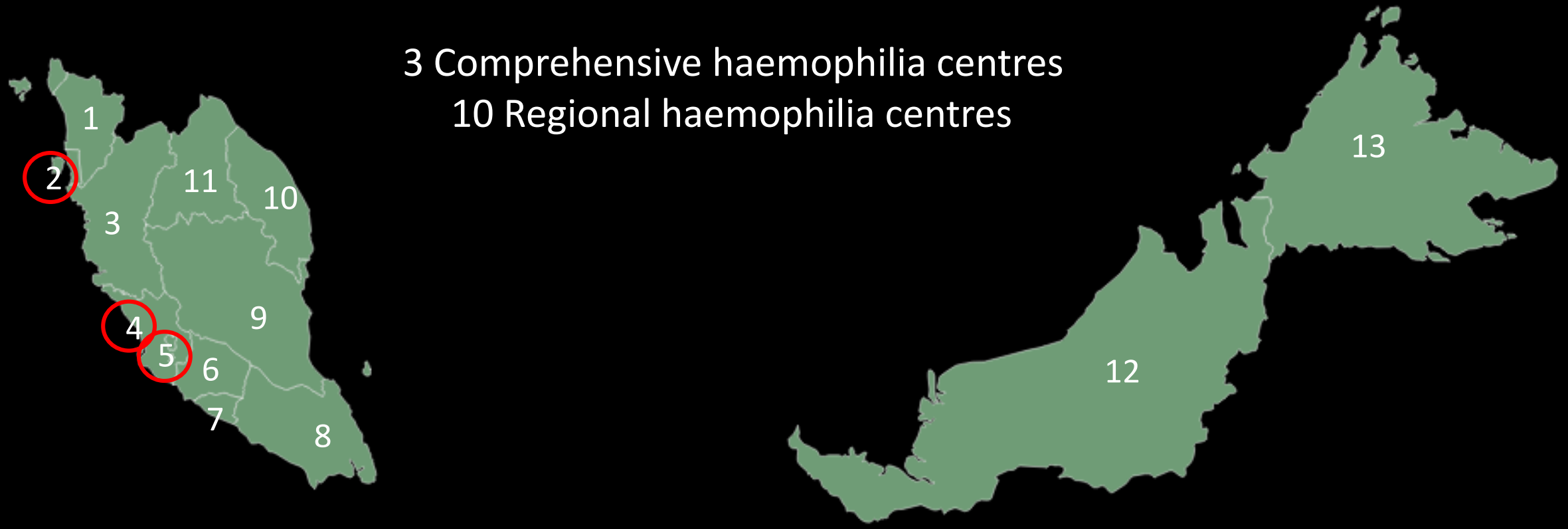
excluding BPA

Year	**2008**	**2010**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2023**
Total factor purchased per year (million IU)	15.5	21.0	30.0	37.6	43.8	51.2	54.7	60.8	62.0	84.5
Population (million)	27.6	28.7	30.1	30.6	31.0	31.5	31.9	32.4	32.8	34.3
IU per capita	0.56	0.73	0.99	1.23	1.41	1.62	1.71	1.87	1.89	2.46
IU per patient per year										87,383

MOH Malaysia

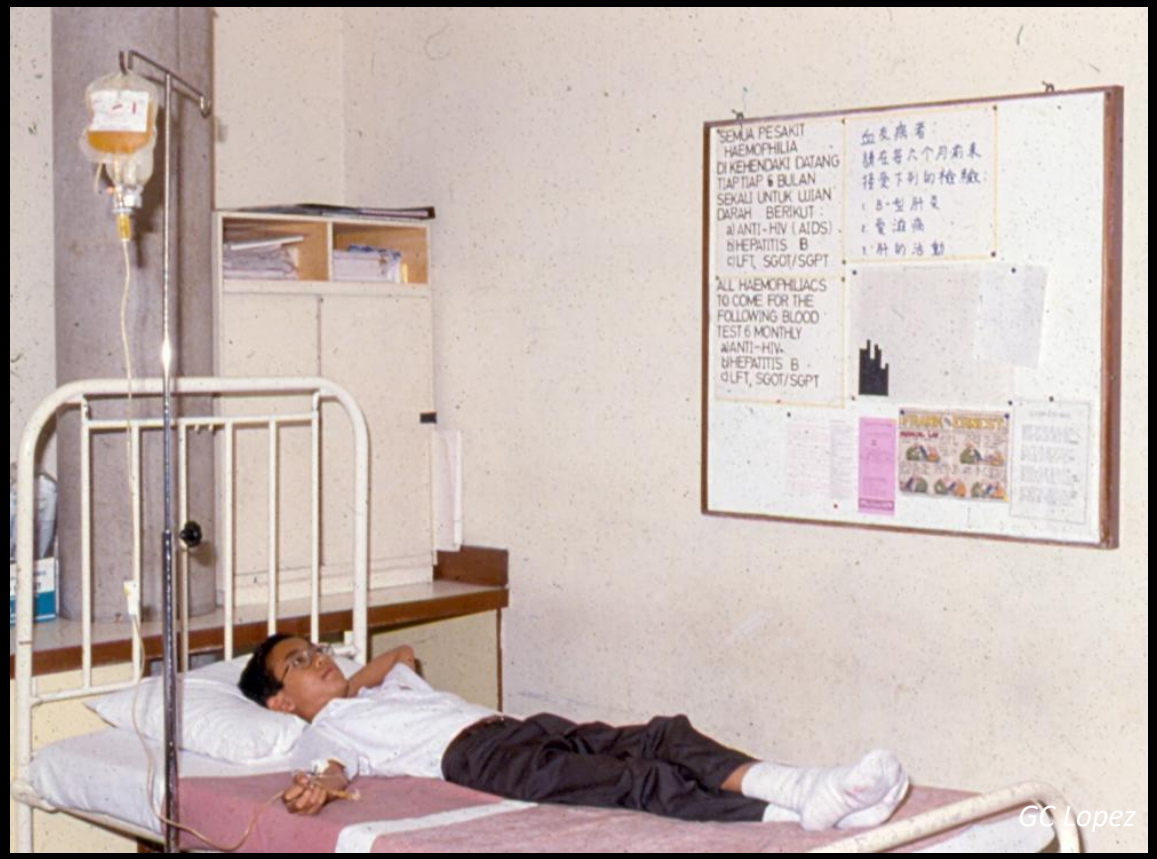
Haemophilia Treatment Centres

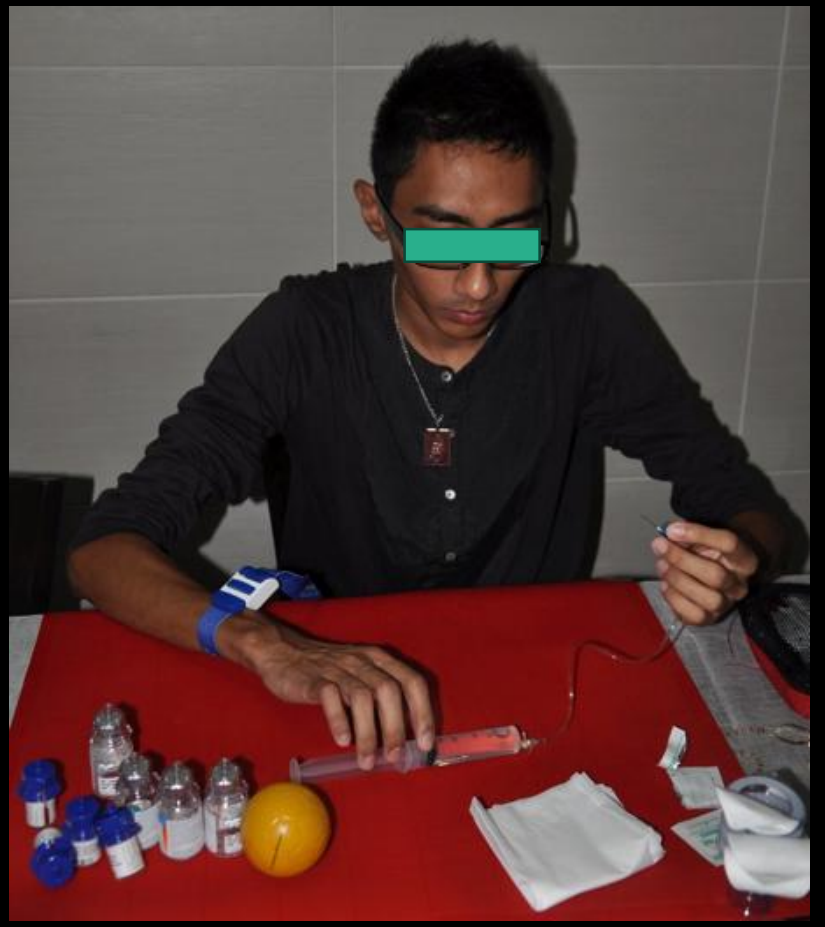
3 Comprehensive haemophilia centres
10 Regional haemophilia centres



Conclusion

We have come a long way





People with Haemophilia

- Their lives have improved tremendously
  - From On-demand to Prophylaxis
  - From Plasma-derived to Recombinant factors
  - From SHL to EHL factors
  - From Factors to Non-factors
  - From IV to SC injections
  - From Breakthrough bleeds to Zero bleeds
  - Towards a cure with Gene therapy

Treatment

On-demand, at hospital

Prophylaxis, at home (Home therapy)

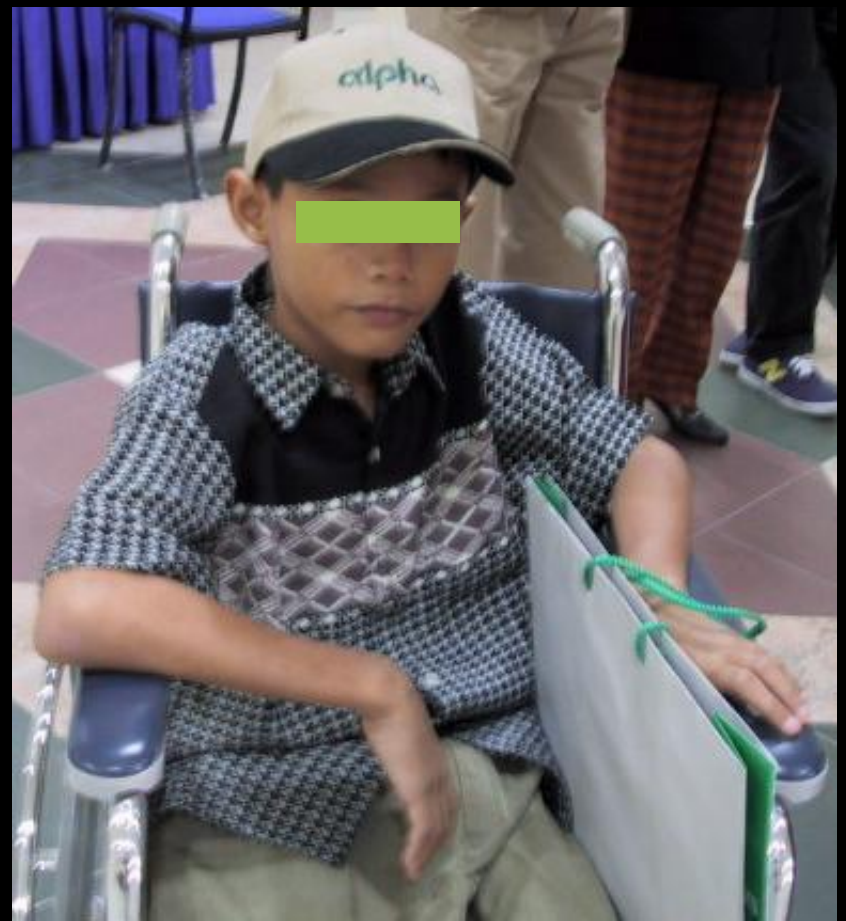
From IV to SC injections

Intravenous (Factor)

Subcutaneous (Non-factor)

Crippled → Normal lives

Past



Present

Life does not get better by chance, it gets better by change

Jim Rohn