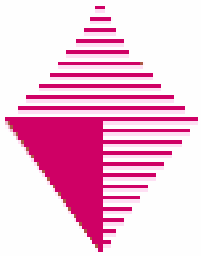

Australian Health Ministers' Advisory Council

Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products

Released June 2006

Disclaimer:

The recommendations in this document are designed to provide information to assist decision-making and have been developed based upon the best available published evidence as at October 2004 to the parties involved in developing the Guidelines [ie, the Jurisdictional Blood Committee (JBC) FVIII & FIX Working Party, the Commonwealth of Australia, the Australian Haemophilia Centres Directors Organization (AHCDO) and Adelaide Health Technology Associates (AHTA)].

However, this document is not a substitute for individual medical advice obtained from the attending clinician. The recommendations in this document should be used subject to the clinician's judgement and the patient's preference in each individual case, with the attending clinician having ultimate responsibility for the appropriate choice of treatment. The recommendations also assume that a correct diagnosis has been made and that the severity of the relevant disorder has been properly ascertained.

Accordingly, each of the parties involved in developing the Guidelines and their employees expressly disclaims, and accepts no responsibility for, any consequences arising from relying upon the information contained in this document.

It is recommended these guidelines be reviewed between 2008 and 2010. After this time, these Guidelines should not be used without first determining their currency. At the time of publication, this can be done by checking the NBA website at www.nba.gov.au or the AHCDO website at www.ahcdo.org.au.

ISBN: 0 – 9775298 - 0 - 0

This systematic literature review and clinical practice guidelines document was developed for the Jurisdictional Blood Committee (JBC) FVIII & FIX Working Party, which was established to oversee the development process.

Reviewers

Petra Bywood BSc (Hons), PhD

Research Officer, Adelaide Health Technology Assessment, Department of Public Health, University of Adelaide, Adelaide, SA 5005

Skye Newton B Psych (Hons)

Research Officer, Adelaide Health Technology Assessment, Department of Public Health, University of Adelaide, Adelaide, SA 5005

Linda Mundy BSc, DPH

Research Officer, Adelaide Health Technology Assessment, Department of Public Health, University of Adelaide, Adelaide, SA 5005

Tracy Merlin BA (Hons), MPH

Manager, Adelaide Health Technology Assessment, Department of Public Health, University of Adelaide, Adelaide, SA 5005

Ben Saxon MBBS, FRACP, FRCPA

Transfusion Medicine Specialist, Australian Red Cross Blood Service-Discovery, Department of Haematology, Women's and Children's Hospital, North Adelaide, SA 5006

Janet Hiller MPH, PhD

Professor of Public Health and Director, Adelaide Health Technology Assessment, Department of Public Health, University of Adelaide, Adelaide, SA 5005

AHTA
Adelaide
Health Technology
Assessment

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

Table of Contents

List of Tables

Foreword

From an historical perspective, these guidelines originated in October 2003 when the Australian Health Ministers' Conference (AHMC) agreed to increase access to recombinant clotting factors and to continued access to plasma-derived products where appropriate for all Australians with haemophilia, and subject to funding. In 2004, all Australian Governments announced their agreement to fund the increased access commencing 1 July 2004, conditional on the development of appropriate clinical practice guidelines and tolerisation protocols.

Australian guidelines for treating people with haemophilia at this stage were still consensus based, and modified from the United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) Executive Committee Guidelines. These new guidelines however, are evidence-based and specifically developed for the Australian situation.

On 5 December 2003, The Jurisdictional Blood Committee (JBC) met and agreed to the development, Terms of Reference and membership of a Working Party to oversee the development of these new guidelines. The Working Party was established in January 2004, and consisted of members from the Australian Haemophilia Centre Directors Organization (AHCDO) for clinical input, the Haemophilia Foundation of Australia (HFA) for consumer representation, and the JBC. The NBA provided secretariat support to the Working Party.

On 18 August 2004, Adelaide Health Technology Assessment (AHTA) was awarded the contract to develop the Guidelines. Their methodology *a-priori* was evidence-based, and evolved from a comprehensive systematic literature review that integrated evidence from empirical research using a systematic and unbiased approach.

Recommendations outlined in these guidelines are based on the highest level of evidence available. In the absence of good quality comparative studies, many recommendations are based on lower levels of evidence such as case series. Where empirical evidence was unavailable, expert opinion relevant to Australia has been included and stated accordingly. The level of evidence is indicated for each recommendation in this document.

A list of reviewers for the literature review is included inside the front cover of this document.

A list of Contractors, JBC FVIII & FIX Working Party members and NBA support staff is available at page 161 of this document.

The content of these guidelines was approved by the JBC on 11 March 2005, and by AHMAC in June 2006. The guidelines were endorsed by AHCDO on 15 July 2005.

These guidelines can be used by both clinicians and their patients to guide treatment of haemophilia in Australia, and are based on the most up-to-date evidence available at the time of development. However, the ultimate responsibility for the care and treatment of patients with haemophilia lies with the attending doctor.

Summary of Guideline Recommendations

Introduction

Rationale for developing clinical practice guidelines

The previous Australian clinical guidelines were modified from the United Kingdom Haemophilia Centre Directors Organisation (UKHCDO) Executive Committee guidelines by the Haemophilia Foundation Australia Medical Advisory Panel in March 2000 (Haemophilia Foundation Australia Medical Advisory Panel 2000). These guidelines were based on a non-systematic review of published evidence and were largely consensus-based.

The Australian Health Ministers' Advisory Council (AHMAC) Blood and Blood Products Committee *Report of the Working Party on the Supply and Use of Factor VIII and Factor IX in Australia* was published in April 2003. This report made several recommendations about the extended use of recombinant factors VIII and IX. These recommendations were endorsed in the R*eport of the Expert Advisory Group on Hepatitis C and Plasma in 1990* (Barraclough Report) tabled in the Senate in May 2003 and later in The Senate Community Affairs References Committee report *Hepatitis C and the blood supply in Australia* in June 2004.

In response to the AHMAC Working Party report, the National Blood Authority was requested by the Jurisdictional Blood Committee (JBC) in December 2003 to commission the development of evidence-based clinical practice guidelines and national tolerisation protocols for the use of recombinant and plasma-derived factor VIII and IX products.

On 30 August 2004, the Australian government announced funding for access to recombinant factors VIII and IX for haemophilia patients (Department of Health and Ageing 2004). The Jurisdictional Blood Committee (JBC) indicated that the new policy would be implemented throughout Australia soon after 1 October 2004. Accordingly, access to recombinant factor VIII and IX has been extended to people who were ineligible under the previous policy, and these evidence-based guidelines refer primarily to the use of recombinant products.

Approach to developing evidence-based clinical practice guidelines

These evidence-based clinical practice guidelines evolved from a systematic literature review that integrated evidence from empirical research using a systematic, unbiased approach. Recommendations outlined in these guidelines are based on the highest level of evidence available. In the absence of good quality comparative studies, many recommendations are based on lower levels of evidence such as case series. Where empirical evidence was unavailable, expert opinion relevant to Australia has been included and stated accordingly.

Plasma-derived factor concentrates remain available to patients who prefer not to transfer to recombinant products or for those with other rare bleeding disorders that do

not have recombinant alternatives. However, due to their higher safety profile concerning transmission of blood-borne agents, recombinant factors are preferred over plasma-derived factors. Since studies that evaluated the safety and effectiveness of plasma-derived products *alone* did not satisfy the criteria for inclusion in the systematic review, plasma-derived products were assessed in terms of their *relative* safety and effectiveness compared to recombinant products.

Previous guidelines have included the use of porcine factor VIII and aminocaproic acid. While the effectiveness and safety of porcine factor VIII was evaluated in the systematic review, all references to the use of porcine factor concentrates have been removed from the evidence-based guidelines, as it is unavailable in Australia. Similarly, aminocaproic acid has become unavailable and was not included in these evidence-based guidelines.

Intended use of guidelines

These guidelines are designed as a general guide to inform clinicians on the safest and most effective treatment strategies using the best evidence available (highest level and quality of evidence) in published and unpublished literature. They take into consideration products that are available in Australia, either registered, or available through the Therapeutic Goods Administration on a 'named patient' basis.

These guidelines do not attempt to cover the cost-effectiveness of different treatments. Despite its rarity, haemophilia is often considered to be the most expensive disease in the community due to the high costs involved with regular replacement of coagulation factors VIII and IX and the life-long nature of the disease (Street & Ekert 1996; World Health Organization 2002). Current treatment may cost up to $110,000 annually per patient, with clotting factor concentrates comprising 90% of these costs (Waymouth Resources Limited 2003; World Health Organization 2002). The Australian Health Ministers' Advisory Council, Blood and Blood Products Committee Working Party (AHMAC 2003) recently estimated that the cost of meeting the recommended quantity and mix of coagulation products in Australia would be $91,950,000 per annum. This estimate was calculated prior to the recent government decision to fund unrestricted access to recombinant products for people with haemophilia (Department of Health and Ageing 2004). Therefore, since recombinant products are approximately 20–50% more expensive than plasma-derived concentrates (Ananyeva et al. 2004), the annual costs are likely to increase.

Due to the high cost of products required for the treatment of coagulation disorders, it is important that resources be used optimally in the safest and most effective manner. Individual treatment strategies should recognise both patient choice and the availability of resources at the time.

General Comments

For each individual case of haemophilia, von Willebrand disease or other rare coagulation disorders, the management of the disease should be associated with a haemophilia treatment centre (see Appendix C, page 160). All aspects of haemophilia disease management, including rheumatology, orthopaedic surgery, dentistry, clinical genetics, infectious diseases, physiotherapy and gynaecology should be managed in consultation with a haemophilia specialist.

Different treatment options should be offered to the patient including information about the advantages and risks of each choice, so that informed decisions may be made.

To minimise risks associated with treatment products, patients should be vaccinated against hepatitis A and B if they have not been previously. Close monitoring of any adverse events such as viral infections or inhibitor formation is essential, particularly after a change in management.

Due to the lack of higher level evidence in some sections of the systematic literature review, ongoing randomised controlled trials should be closely monitored for results and changes to recommendations should be made when new, good quality evidence becomes available.

Haemophilia A, without inhibitors

Products available

- Recombinant factor VIII concentrates (rFVIII)
- Plasma-derived factor VIII concentrates (pdFVIII)
- Desmopressin (1-deamino-D-arginine vasopressin, DDAVP)
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)

Treatment of acute bleeding episodes

- Recombinant FVIII is safe and effective for patients without inhibitors to FVIII (Level II evidence for effectiveness, Level III-2 evidence for safety, page 52).
- Inhibitor testing, particularly in young children and/or those with severe haemophilia, should be performed no earlier than day three after initial administration of factor concentrate, or when the expected response is absent, with re-testing at regular intervals (Level IV evidence, page 57).
- Patients with mild/moderate haemophilia A may be treated using DDAVP, at a dose of 0.3 μg/kg diluted in 50ml of 0.9% saline and infused over ≥30 minutes (Level IV evidence, page 38).
- DDAVP may be administered intravenously or subcutaneously with comparable results (Level II evidence, page 38).
- DDAVP may be administered once every 24 hours. If given for more than three consecutive days, repeated doses may lead to a reduction in responsiveness (tachyphylaxis) (Level IV evidence, page 38). If DDAVP is given more than once in 24 hours, predose monitoring of electrolyte concentrations is recommended (expert opinion).
- A test dose of DDAVP and a FVIII/von Willebrand factor (FVIII/vWF) assay should be performed to demonstrate efficacy (Level IV evidence, page 38).
- Caution should be taken to restrict fluid intake during DDAVP treatment to prevent fluid overload (Level IV evidence, page 42). DDAVP should be used with caution in the elderly; and it is not recommended in those with arteriovascular disease and in young children (<2 years) (expert opinion).

Prophylaxis

- Recombinant FVIII is recommended for prophylaxis in patients without inhibitors to FVIII (Level IV evidence, page 78).

- Prophylaxis should be initiated after bleeding episodes have commenced, rather than at diagnosis, due to potential increased risk of inhibitor development associated with administration of factor concentrates in very young children (Level IV evidence, page 82).

- Central venous access devices may assist in the regular infusion of factor concentrates in children. However, adequate aseptic technique should be taught and routinely reviewed to avoid infection (Level IV evidence). External devices should be avoided due to the higher rate of infection compared to fully implanted devices (Level IV evidence, page 132).

Surgical and dental procedures

- Recombinant FVIII is safe and effective for haemophilia A patients, before or after surgery as required (Level III-2 evidence for safety and Level IV evidence for effectiveness, page 106).

- Tranexamic acid can be used as secondary prophylaxis for surgical or dental procedures (Level IV evidence, page 108).

- Consensus-based recommendations for the management of patients undergoing surgery (Association of Hemophilia Clinic Directors of Canada 1995a) or dental procedures (Stubbs & Lloyd 2001) have been outlined in detail (Table 37 and Appendix G). The available evidence that was evaluated in this review is consistent with the recommendations in these existing guidelines.

Haemophilia A, with inhibitors

Products available

- Recombinant factor VIII (rFVIII)
- Plasma-derived factor VIII (pdFVIII)
- Recombinant factor VIIa (rFVIIa) (e.g. NovoSeven)
- Activated prothrombin complex concentrates (aPCCs) (e.g. FEIBA[a])
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)

Treatment of acute bleeding episodes

- Recombinant FVIIa is recommended for acute bleeding episodes in patients with high titre and/or high responder inhibitors to FVIII (Level II evidence for effectiveness, Level IV evidence for safety, page 90).
- Recombinant FVIIa may be infused as a bolus at a dose of 90 μg/kg for adults (Level IV evidence). An appropriate dose of rFVIIa may be given by continuous infusion as an alternative method of delivery (Level IV evidence, page 90). Paediatric doses of up to 200–250 μg/kg may be required due to the shorter half-life in children (expert opinion).
- There were no available studies with data on the effectiveness of high dose FVIII concentrates alone in patients with inhibitors (page 90). Therefore, recommendations for its use are based on consensus only. Expert opinion indicates that there are no adverse effects at high doses of FVIII.
- Activated prothrombin complex concentrates (aPCCs) may be used to control mild-severe bleeding in patients with high titre inhibitors. However, patients should be closely monitored for adverse reactions that, though rare, may be serious. Standard dose of FEIBA[a] is 60–100 IU/kg twice per day to a maximum daily dose not exceeding 200 IU/kg (Level II evidence, page 90).
- Plasmapheresis (with or without immunoadsorption) may be used to reduce inhibitors in high titre/high responders before infusion with FVIII to control bleeding. However, patients should be monitored for potential anaphylactic reactions (Level IV evidence, page 90).

[a] FEIBA = Factor eight inhibitor bypassing agent

- Immunosuppression therapy, using cyclophosphamide, to reduce inhibitors is not recommended for treating acute bleeding episodes (Level IV evidence, page 90).

Surgical and dental procedures

- Recombinant FVIIa may be considered the first line of treatment for dental and other surgical procedures in patients with high titre and/or high responder inhibitors (Level II evidence for effectiveness and Level IV evidence for safety, page 92).

- Evidence for the use of recombinant FVIII concentrates for surgery or dental procedures is currently awaited.

- Plasma-derived FVIII concentrate may be considered for use during surgery in patients with low titre, low-responding inhibitors, but should be avoided in patients with high-responding inhibitors (Level IV evidence, page 92).

- Activated PCCs may be used for surgical and dental procedures. However, patients should be closely monitored for thrombotic complications, including disseminated intravascular coagulation and thrombophlebitis (Level IV evidence, page 92).

- aPCCs should not be used in conjunction with antifibrinolytic agents, but they may be used in succession (Level IV evidence, page 92).

Tolerisation procedures

In Australia, tolerisation protocols vary widely across haemophilia centres. There is little published evidence of effectiveness, no consensus on procedures and the Bonn and Malmö protocols are not used routinely in Australia. The International Immune Tolerance Induction study, which includes several participating Australian haemophilia centres, is ongoing and results from this study, when available (expected completion in 2007), should provide guidance to tolerisation procedures.

Bonn protocol (modified): Patients are given 150 IU/kg FVIII every 12 hours until the inhibitor level drops below 1 B. Then FVIII concentrate is reduced to 150 IU/kg daily, until inhibitor is no longer detectable.

- The Bonn protocol may be considered for young patients (Level IV evidence, page 95). Treatment is more likely to be successful with low pre-treatment inhibitor titres, and with less time between development and treatment of inhibitors (Level IV evidence, page 95).

Malmö protocol: When inhibitor titres ≥10 BU, extracorporeal immunoadsorption is given until levels are reduced to <10 BU. High doses of FVIII (approximately 200 IU/kg/day) are administered to bring the FVIII concentration to 40-100 IU/dL and to maintain it at 30-80 IU/dL. At the same time, cyclophosphamide is administered at a dose of 12-15 mg/kg intravenously for 2 days, followed by 2-3 mg/kg for 8 days. On day 1 of treatment, immunoglobulin is also used at a dose of 2.5-5 g/kg, followed by 0.4g/kg on days 4-8. Factor VIII is administered until the inhibitor disappears. Patients then receive FVIII for ongoing prophylaxis.

- The Malmö protocol may be considered when patients have long-standing inhibitors (Level IV evidence, page 95).

Haemophilia B, without inhibitors

Products available

- Recombinant factor IX (rFIX) (BeneFIX®)
- Plasma-derived factor IX (pdFIX) (MonoFIX®)
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)

Treatment of acute bleeding episodes

- Recombinant FIX (BeneFIX®) is safe and effective for the treatment of bleeding episodes in haemophilia B patients without inhibitors (Level IV evidence, page 67). Since there is a risk of anaphylaxis occurring within the first 50 days of treatment with rFIX, patients should be closely monitored and early exposure to factor concentrate should occur in a centre equipped to treat anaphylaxis (expert opinion).
- Due to large inter-patient variability, individual dosing regimens should be monitored by FIX recovery assays (Level II evidence, page 65).
- The dosage ratio for rFIX to pdFIX is 1.6:1 for patients aged ≤15 years and 1.2:1 for patients aged 16 years and over (Level III-3 evidence, page 65).

Prophylaxis

- Recombinant FIX is safe and effective for prophylaxis in haemophilia B patients without inhibitors (Level II evidence, page 78).
- Dosing regimens should take into account the lower rFIX recovery compared to pdFIX and the inter-patient variability—see previous recommendations for treatment of bleeding episodes (Level II evidence, page 65).
- Central venous access devices may assist in the regular infusion of factor concentrates in children. However, adequate aseptic techniques should be taught and routinely reviewed to avoid infection (Level IV evidence, page 132). External devices should be avoided due to the higher rate of infection compared to fully implanted devices (Level IV evidence, page 132).

Surgical and dental procedures

- Recombinant FIX is recommended for haemophilia B patients, before or after surgery as required (Level IV evidence for safety and effectiveness, page 106).

- Tranexamic acid can be used as secondary prophylaxis for surgical or dental procedures (Level IV evidence, page 108).

Haemophilia B, with inhibitors

Products available

- Recombinant factor VIIa (rFVIIa) (e.g. NovoSeven)
- Activated prothrombin complex concentrates (aPCCs)
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)
- Recombinant factor IX (rFIX) (BeneFIX®)

Treatment of acute bleeding episodes

- Recombinant FVIIa is safe and effective for acute bleeding episodes in patients with high titre and/or high responder inhibitors to FIX (Level II evidence, page 90).
- Activated prothrombin complex concentrates (aPCCs) may be considered to control mild-severe bleeding in patients with high titre inhibitors. However, patients should be closely monitored for adverse reactions that, though rare, may be serious (Level IV evidence, page 90).

Tolerisation procedures

- There is no evidence to guide tolerisation procedures in patients with haemophilia B with inhibitors. Recombinant FIX may be used for tolerisation protocols, due to the higher safety profile pertaining to transmission of blood-borne agents, but there should be close monitoring to prevent anaphylactic reactions (expert opinion).

von Willebrand disease

Products available

- Desmopressin (1-deamino-D-arginine vasopressin, DDAVP)
- Plasma-derived factor VIII/von Willebrand factor concentrates (pdFVIII/vWF)
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)

Treatment of acute bleeding episodes

- Patients with mild von Willebrand disease (vWD) may be treated using DDAVP at a dose of 0.3 μg/kg diluted in 50ml of 0.9% saline and infused over ≥30 minutes (Level IV evidence, page 38).
- DDAVP may be administered intravenously or subcutaneously with comparable results (Level II evidence, page 38).
- DDAVP may be administered once every 24 hours. If given for more than three consecutive days, repeated doses may lead to a reduction in responsiveness (tachyphylaxis) (Level IV evidence, page 38). If DDAVP is given more than once in 24 hours, predose monitoring of electrolyte concentrations is recommended (expert opinion).
- DDAVP should be used only as an adjunct to factor replacement therapy in patients with severe vWD and not as the primary treatment (Level II evidence, page 38).
- A test dose of DDAVP and a FVIII/von Willebrand factor (FVIII/vWF) assay should be performed to demonstrate efficacy (Level IV evidence, page 38).
- Caution should be taken to restrict fluid intake during DDAVP treatment to prevent fluid overload (Level IV evidence, page 42). DDAVP should be used with caution in the elderly; and it is not recommended in those with arteriovascular disease and in young children (<2 years) (expert opinion).
- Patients unresponsive to (or contraindicated for) DDAVP should receive pdFVIII/vWF concentrate, which may be administered every 8–12 hours (Level IV evidence, page 72).

Prophylaxis

- Prophylaxis may be required for patients with menorrhagia. Limited published evidence suggests that intranasal DDAVP is no better than placebo at reducing subjectively measured menorrhagia (Level II evidence, page 85). Plasma-derived FVIII/vWF concentrates or tranexamic acid are possible alternatives (Level IV evidence, page 71).

Surgical and dental procedures

- DDAVP, which may be used in conjunction with local therapies such as fibrin glue and tranexamic acid, may be considered for use prior to dental extractions or surgery in patients who respond to DDAVP (test dose) (Level IV evidence, page 111).

- Plasma-derived FVIII/vWF concentrates may be used to cover surgical or dental procedures (Level IV evidence, page 112).

Other rare bleeding disorders

Products available

- Recombinant factor VIIa (rFVIIa)—Factor VII deficiency
- Prothrombin complex concentrates—Factor II, IX, or X deficiency
- Fibrinogen—Fibrinogen deficiency
- Plasma-derived factor VII—Factor VII deficiency
- Plasma-derived factor XI—Factor XI deficiency
- Plasma-derived factor XIII—Factor XIII deficiency (e.g. Fibrogammin P)
- Cryoprecipitate—Factor XIII deficiency, afibrinogenaemia, dysfibrinogenaemia
- Fresh frozen plasma—Factor V deficiency
- Adjunctive agents (e.g. fibrin glue)

Acquired haemophilia

Products available

- Desmopressin (1-deamino-D-arginine vasopressin, DDAVP)
- Activated prothrombin complex concentrates (aPCCs)
- Recombinant factor VIIa (rFVIIa) (e.g. NovoSeven)
- Immunosuppressants (e.g. rituximab)
- Antifibrinolytics (e.g. tranexamic acid)
- Adjunctive agents (e.g. fibrin glue)

Treatment of acute bleeding episodes

- Bleeding episodes in patients with acquired haemophilia require prompt treatment (Level IV evidence, page 99).

Inhibitors <5 BU

- DDAVP should be used at the dose recommended above (Haemophilia A, without inhibitors). Plasma-derived factor VIII concentrate may be used at a dose of 20 IU/kg for each BU of inhibitor plus an additional 40 IU/kg and tested after 15 minutes. If response is poor, another bolus injection may be given (Level IV evidence, page100).

Inhibitors >5 BU

- Activated PCCs may be administered at a dose of 50–200 IU/kg/day in divided doses (Level IV evidence, page 100).
- Recombinant FVIIa may be administered at a dose of 90 μg/kg every 2–6 hours until the bleeding stops (Level IV evidence, page 100).
- Due to the risk of thrombotic events, patients should be closely monitored after treatment (Level IV evidence, page 99).

Tolerisation protocols

- Patients with acquired haemophilia should be treated for the underlying disorder before deciding on strategies to eliminate inhibitors (Level IV evidence, page 99).

  Postpartum: Patients may be monitored, without treatment, as inhibitors most frequently disappear spontaneously. Alternatively, immunosuppressive therapy may be considered (Level IV evidence, page 98).

Drug-related: The drug should be withdrawn to allow spontaneous disappearance of inhibitors. Alternatively, immunosuppressive therapy may be considered (Level IV evidence, page 99).

Autoimmune disease: Immunosuppressive therapy should be given, as inhibitors are unlikely to disappear spontaneously (Level IV evidence, page 98).

Malignant neoplasm: Patients should be treated for the primary malignancy. Immunosuppressive therapy should then be given (Level IV evidence, page 99).

Idiopathic: Patients should be given immunosuppressive therapy (Level IV evidence, page 100).

Infant delivery

Unless stated, all recommendations are based on Level IV evidence. Recommendations assume a correct diagnosis and that the severity of the disorder has been ascertained.

Antenatal care

- Counselling pertaining to the potential risks of antenatal testing and the potential complications during pregnancy and delivery should be accessible to all haemophilia carriers and women with von Willebrand disease (page 118).

- If antenatal testing is accepted, chorionic villus sampling is the preferred method. If the levels of FVIII or FIX are low prior to pregnancy, FIX levels in haemophilia B carriers and FVIII levels in haemophilia A carriers should be monitored, particularly in the third trimester and postpartum (page 120).

Delivery of infants

- Invasive fetal monitoring, such as scalp electrodes, instrument deliveries and long labours should be avoided for affected infants (page 121).

- Vaginal delivery is the recommended mode of delivery, unless obstetric factors indicate caesarean section. Vacuum extraction delivery is contraindicated (page 121).

- Use of DDAVP in women with von Willebrand disease is not recommended during labour (expert opinion, page 38).

Postnatal and postpartum care

- Cord or peripheral blood samples should be taken from affected infants of haemophilia carriers and infants with suspected bleeding disorders to ascertain coagulation factor status (page 121).

- All infants with intracranial haemorrhage should be evaluated for the presence of a bleeding disorder, even where there is no family history of haemophilia. DDAVP is contraindicated in neonates (page 121).

- Heel sticks and venipuncture, other than to assess coagulation factor status, should be avoided if possible. Intramuscular vitamin K is associated with bleeding in infants with haemophilia. Oral vitamin K is available as an alternative (page 121).

- Fibrin glue may be used in conjunction with pdFVIII/vWF or pdFIX concentrates to achieve haemostasis if circumcision is performed (Level IV evidence, page 50). The use of rFVIII or rFIX has not been assessed in this context.

- DDAVP may be used for prophylaxis during the first 3–4 days after delivery in women with mild Type 1 von Willebrand disease to increase and maintain factor levels (page 38).

- All Type 2 and 3 von Willebrand patients who fail to reach optimal FVIII:C levels may be treated with pdFVIII/vWF concentrates postpartum (page 125).

Background

Normal haemostasis

When blood vessels are damaged through injury, there are three key mechanisms that promote haemostasis—i.e. to stop any bleeding that occurs. Vasoconstriction, which occurs within seconds following loss of vascular integrity, is the initial mechanism that reduces the flow of blood to the site of injury. This is followed by platelets adhering to the site of the injured vessel wall, forming an aggregate or haemostatic plug. Adhesion of the platelets is mediated by von Willebrand factor, a protein that binds to and stabilises blood coagulation factor VIII (Braunwald et al. 2001). The third phase, which takes place over several minutes, involves a cascade of reactions that culminate in the production of sufficient thrombin to convert fibrinogen to fibrin—a key element in strengthening the haemostatic plug and forming a fibrin clot. Figure 1 illustrates a schematic model of the coagulation cascade. Over 20 proteins are involved in the complete coagulation process and two of these, factors VIII and IX, are central to this process. These two factors activate FX to FXa, a necessary component in the activation of prothrombin to thrombin. Thrombin, in turn, converts fibrinogen to fibrin, which attaches to the platelet plug, forming a fibrin mesh, or blood clot.

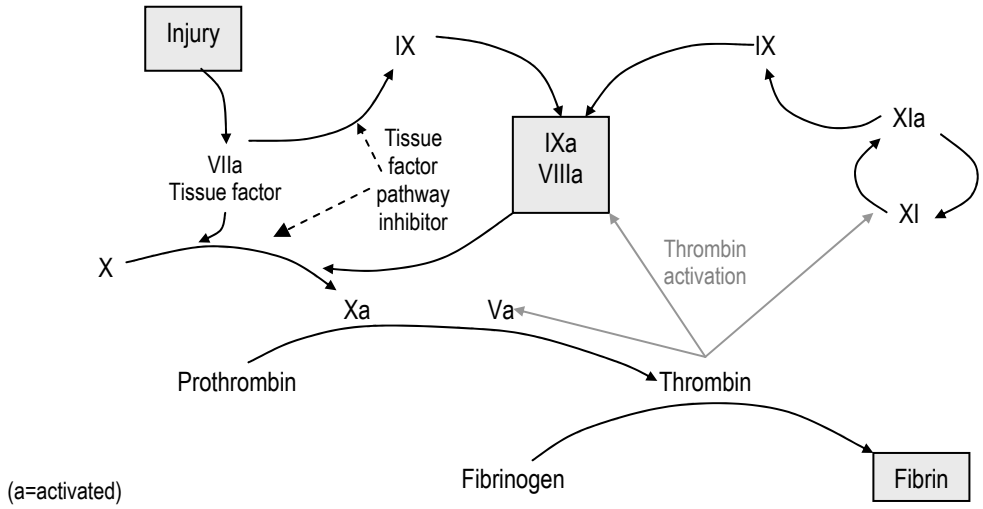

Figure 1. A schematic model of blood coagulation after injury (modified from Bolton-Maggs et al. 2003)

Haemophilia

Haemophilia is an inherited blood coagulation disorder that results from a functional deficiency in specific blood clotting factors. The most common deficiencies are of factor VIII (haemophilia A or Classic haemophilia) or factor IX (haemophilia B or Christmas disease). A deficiency in either factor leads to insufficient activation of thrombin, slower blood clotting and weak, unstable blood clots (Bolton-Maggs & Pasi 2003). The severity of haemophilia is inversely related to the level of circulating functional blood clotting proteins (Table 1).

Table 1. Classification of haemophilia

Concentration of factor (VIII or IX)	Classification	Clinical characteristics
<0.01 IU/ml (<1% of normal[a])	Severe	Spontaneous joint and muscle bleeding; bleeding after injuries, accidents, and surgery
0.01 - 0.05 IU/ml (1-5% of normal)	Moderate	Bleeding into joints and muscles after minor injuries; excessive bleeding after surgery and dental extractions
>0.05 – 0.40 IU/ml (5-40% of normal)[b]	Mild	Spontaneous bleeding does not occur: bleeding after surgery, dental extractions, and accidents

Modified from Bolton-Maggs & Pasi 2003; [a] Normal concentration of factor VIII or IX is defined as 100% or one unit of factor VIII activity per ml of plasma - 100 U/dL (Kasper 2004); [b] levels of FVIII above 40% are considered sufficient for normal haemostasis.

The hallmark of haemophilia is bleeding into organs or muscle tissue (haematoma) or joint spaces (haemarthrosis), which may occur without trauma. Frequent bleeding into joints thickens synovial tissue and produces more friable blood vessels. This cycle of repeated bleeding may lead to chronic arthritis and a steady decrease in joint mobility and function (Bolton-Maggs & Pasi 2003). Haemophilia is also characterised by spontaneous bruising and bleeding gums (World Health Organization 2002). Given that haemophilia A and B are clinically indistinguishable, a diagnosis must be confirmed by a specific factor assay (Hitchens 2004).

Since both haemophilia A and B are determined by recessive mutant genes on the X-chromosome, they predominantly affect males (Hitchens 2004). A female may be a carrier, but have no symptoms of haemophilia as she has another X-chromosome to produce factor VIII and IX. However, a proportion of female carriers, who have very low concentrations of factors, may be predisposed to excessive bleeding, demonstrating a form of haemophilia (Bolton-Maggs & Pasi 2003). In rare cases, if the relevant genes on the normal X-chromosome are switched off (lyonisation), females may develop a more severe form of haemophilia (Kulkarni & Lusher 2001).

Haemophilia is diagnosed most commonly in those with a known family history of haemophilia, or following presentation with bleeding. Although most infants with severe haemophilia are born without incident, intracranial haemorrhage during the neonatal period occurs in 1–4% of cases, particularly after vacuum extraction (Bolton-Maggs & Pasi 2003).

Acquired haemophilia, which is caused by the development of inhibitors to factor VIII in people without a family or personal history of bleeding diathesis, is characterised by the sudden onset of bleeding, usually severe (Baudo et al. 2004; Delgado et al. 2003). In 40–50% of cases the aetiology is unknown, whereas the remainder are associated with conditions such as pregnancy, autoimmune disease, malignant neoplasm and drug administration (Delgado et al. 2003).

Burden of disease

Haemophilia A accounts for approximately 80% of haemophilia while the remaining 20% of people with haemophilia have haemophilia B (Haemophilia Foundation Australia 2004b). Currently, haemophilia affects approximately 1800 people in Australia (one in 7000 males) (Haemophilia Foundation Australia 2004b). In 2001–02, there were 912

hospital separations[b] for haemophilia A and 59 hospital separations for other hereditary coagulation factor deficiencies in Australia (AIHW 2004). Approximately one third of cases are thought to have no known family history of haemophilia (Chalmers 2004). In addition, acquired haemophilia affects approximately one in a million people (Baudo et al. 2004; Delgado et al. 2003).

The prevalence of haemophilia in the community is likely to rise with the increasing longevity of people with haemophilia. For example, in 2000, data from the National Bleeding Disorder Registry (which includes all Australian states except NSW) showed that nearly 45% of people with severe haemophilia A and 50% of those with severe haemophilia B were aged 18 or under (AHMAC 2003). Compared to previous cohorts who had a higher risk of transmission of infectious diseases via blood products that were not adequately screened or heat treated, the life expectancy for current (and future) cohorts of people with haemophilia is greater, leading to a potential increase in the demand for clotting factors.

Treatment regimens

Since there is no cure for haemophilia at the present time, standard treatment for bleeding episodes involves replacing the deficient factors (VIII or IX). Before treatment with appropriate blood clotting factors was available, people with haemophilia had a short life expectancy and were likely to die prematurely from a spontaneous bleeding episode (World Health Organization 2002). A range of different factor replacement methods involving intravenous administration of fresh or commercial factor concentrates has been developed. People with severe haemophilia are likely to receive approximately 14,000 intravenous infusions of factors in a lifetime. Administration of specific doses, adjunctive haemostatic agents, and additional medical intervention depends on the site and severity of the bleeding episode.

The two main forms of treatment for haemophilia are 'on-demand' or 'prophylactic', and factor concentrates may be either plasma-derived or recombinant (genetically engineered product that does not require human blood). For on-demand treatment, patients are treated only when a bleeding episode occurs, either spontaneously or associated with trauma (World Health Organization 2002). Prophylactic treatment is based on the principle of maintaining clotting factor levels above 1% of normal, to convert the bleeding pattern of severe haemophilia to that found in milder levels of the disease and involves regular factor infusions regardless of bleeding status (Nilsson & Hedner 1976). Prophylactic infusions are also administered prior to surgical or dental procedures.

von Willebrand disease

Von Willebrand disease is caused by a deficiency (either quantitative or functional) in von Willebrand factor (vWF). This factor circulates in the blood, acting as a carrier protein to factor VIII and as an adhesive protein involved in platelet-vessel wall interaction (Laffan et al. 2004). Deficiency of vWF causes inadequate platelet adhesion and secondary deficiency of factor VIII. It is characterised by easy bruising, bleeding from mucous

[b] Hospital separations = a hospital transfer, discharge or death (Australian Bureau of Statistics)

membranes, post-operative bleeding and menorrhagia (heavy menstrual bleeding). Unlike haemophilia A and B, which are determined by mutations on the sex chromosome, von Willebrand disease affects males and females equally (Laffan et al. 2004). There are three main types of von Willebrand disease, depending on whether the vWF is partially deficient (Type 1), dysfunctional (Type 2) or completely absent (Type 3, a rare autosomal recessive form) (Laffan et al. 2004). The most common symptoms of von Willebrand disease are epistaxis (bleeding from the nose) and postoperative bleeding in men and women and menorrhagia in women (Ziv & Ragni 2004).

Burden of disease

Approximately 1016 people in Australia have been diagnosed with von Willebrand disease (Australian Bleeding Disorder Registry 2004) (personal communication, Simone Proft, Population Health Division, Department of Health and Ageing). However, since it generally presents in its mild or moderate form, von Willebrand disease frequently goes undiagnosed and untreated (Haemophilia Foundation Australia 2004b). In 2001–02 there were 342 hospital separations for people with von Willebrand disease in Australia (AIHW 2004).

Treatment regimens

Mild to moderate forms of von Willebrand disease (Type 1) are treated primarily with desmopressin (DDAVP), an analogue of vasopressin that stimulates release of von Willebrand factor (vWF) into the plasma. Bleeding episodes in severe Type 1 and in Type 2 and 3 von Willebrand disease are treated by infusion of plasma-derived factor VIII concentrate containing vWF (pdFVIII/vWF concentrate) (Braunwald et al. 2001).

Other rare bleeding disorders

While haemophilia A, B and von Willebrand disease represent the larger proportion of inherited bleeding disorders, a series of rare blood coagulation disorders, which are associated with deficiencies in other clotting factors, make up the balance.

A deficiency in factor V (otherwise known as Owren's disease or parahaemophilia, and distinct from factor V Leiden) in its homozygous state affects approximately one in a million people and affects men and women equally. It is usually associated with easy bruising and mucous membrane bleeding, such as epistaxis or oral cavity bleeding (Bolton-Maggs et al. 2004).

Clotting factor X, or Stuart-Prower factor, is an enzyme in the coagulation pathway and deficiency in this factor may be inherited (autosomal recessive) or acquired (associated with severe liver disease, vitamin K deficiency, or anticoagulant drugs such as warfarin) (Steen & Schwartz 2004). Symptoms of factor X deficiency include severe umbilical stump bleeding in newborn infants, epistaxis, menorrhagia, easy bruising, recurrent miscarriage, postpartum bleeding and excessive bleeding following surgery or trauma.

Inherited factor VII deficiency is a rare autosomal recessive bleeding disorder, which results from mutations in the FVII gene located on chromosome 13 and affects males and females equally (Israels 2004a). Factor VII is a vitamin K-dependent coagulation

factor with a short half-life (3–4 hours). Deficiency or dysfunction of this factor is characterised by mucosal bleeding, such as epistaxis and menorrhagia, post-operative bleeding and intracranial haemorrhaging in the first year of life.

Deficiency in factor XI (also known as haemophilia C) is a milder bleeding disorder, with autosomal inheritance, that occurs predominantly in Ashkenazi Jews (Bolton-Maggs & Pasi 2003). Depending on the severity of the deficiency, the first sign of this bleeding disorder may occur at circumcision, menarche, or during dental extractions, trauma or surgery (Siegel 2004).

Inherited factor XIII deficiency is a rare autosomal recessive disease primarily caused by mutations in the gene located on chromosome 6 (Israels 2004b). Factor XIII is required for the final step in the coagulation cascade and stabilisation of the fibrin plug. Factor XIII deficiency is often detected within the first few days of life due to bleeding from the umbilical cord stump. Common characteristics of this disorder include intracranial haemorrhage in the infant, bruising and soft tissue bleeding, delayed bleeding after trauma, recurrent miscarriages and poor wound healing.

Prothrombin deficiency is an extremely rare autosomal recessive disorder, with approximately 26 cases reported worldwide (Di Paola et al. 2001). Acquired prothrombin deficiency, which is more common, has been associated with severe liver disease, use of prescription drugs to inhibit blood clotting (e.g. warfarin) and vitamin K deficiency (Canadian Hemophilia Society 2004). Prothrombin, or factor II, is converted by factor Xa to thrombin, an essential component in the clotting cascade (see Figure 1). Characteristics of prothrombin deficiency include umbilical cord stump bleeding at birth, epistaxis, easy bruising, menorrhagia, postoperative and/or postpartum bleeding and occasional muscle haematomas.

Complications of treatment

The primary complications associated with treatment for haemophilia are transmission of viral infections, such as human immunodeficiency virus (HIV), hepatitis B and C and the theoretical risk of prion transmission through infected pooled plasma concentrates, and the development of inhibitors to the clotting factors (Street & Ekert 1996). Between 1981 and 1984, 245 people with haemophilia contracted HIV in Australia and the majority of patients who received factor concentrates before 1989 were infected with hepatitis C. After 1989 the safety profile of blood products from plasma improved. Technologies became available to heat treat the plasma products to inactivate blood-borne viruses and donors were screened for HIV and hepatitis C (from 1990) (Street & Ekert 1996; Haemophilia Foundation Australia 2004a). Despite recent advances in creating high purity plasma-derived concentrates there is still anxiety in the haemophilia community about contracting viruses not yet identified through infusions of plasma-derived factors (Haemophilia Foundation Australia 2004a). For example, there remains a theoretical risk of transmission of prions, such as Creutzfeldt-Jakob disease. With the introduction of blood donor screening, donor testing and virus inactivation techniques, there have been no reported events of viral transmission from infected blood transfusions since the early 1990s. At present, however, the risk of transmission of prions is unknown in Australia.

Another serious complication of treatment with clotting factors (both plasma-derived and recombinant) is the development of inhibitory antibodies. This occurs when the

body recognises the therapeutic clotting agents as foreign proteins (Giangrande 1996). Up to one third of people with severe haemophilia A develop neutralising antibodies, or inhibitors, while the incidence in those with haemophilia B is 1–6% (World Health Organization 2002). There are significant clinical implications associated with inhibitor development for a proportion of patients with inhibitors, as the response to treatment becomes uncertain, morbidity increases, and life expectancy is reduced (Hay et al. 2000b). The direct and indirect costs to patients, their families and society increase. To counteract the effects of inhibitor development, a tolerisation procedure may be introduced. Tolerisation (or immune tolerance induction) may be achieved by the regular administration of factor VIII or IX over a period of months or years.

Approach to Guideline Development

How do we develop clinical practice guidelines?

Evidence-based clinical practice guidelines are developed as part of a systematic literature review.

'Systematic reviews provide information about the effectiveness of interventions by identifying, appraising, and summarising the results of otherwise unmanageable quantities of research.' (Khan et al. 2001) The primary focus of systematic reviews in medicine is to integrate empirical research for the purpose of creating generalisations and thus to provide a rational basis for health care decision making and the development of guidelines for clinical practice (Mulrow et al. 1997; Cooper & Hedges 1994).

The key components of a systematic review include: 1) the development of specific research questions or hypotheses; 2) a transparent methodical process defined *a priori* (i.e. a review protocol); 3) an exhaustive search for relevant primary research on the topic; 4) the critical appraisal of this research; 5) an attempt to answer the research questions and to resolve conflicts in the literature; and 6) the identification of issues central to future research on the topic (Mulrow et al. 1997; Cooper & Hedges 1994; Clarke & Oxman 2000). Evidence that has been synthesised can then inform the development of a guideline pertaining to each clinical practice question.

In the light of recent policy initiatives by the Australian Government (Department of Health and Ageing 2004), the main objectives of this guideline document were to develop: 1) national clinical practice guidelines for the use of recombinant factors VIII and IX for patients with Haemophilia A and B; 2) national clinical guidelines for the use of plasma-derived factors for patients with von Willebrand Disease; and 3) national tolerisation protocols for tasks 1) and 2) above.

Since the *Report of the Working Party on the supply and use of Factor VIII and Factor IX in Australia* (AHMAC 2003) recently examined the clinical need and costs of treatment in Australia, this guideline document omits any systematic determination of clinical need and cost-effectiveness.

Although the systematic literature review that underpins the development of these clinical practice guidelines examined the effectiveness and safety of recombinant compared to plasma-derived factors VIII and IX, the new clinical practice guidelines have incorporated recent government policy to provide full access to recombinant factors VIII and IX for haemophilia A and B patients. The evidence-based recommendations also focus on the implications of transferring patients from plasma-derived to recombinant products. Other guidelines sections, which remain unaffected by the new policy, include the use of plasma-derived factors for patients with von Willebrand disease, the use of adjunctive haemostatic agents, and the development of national tolerisation protocols for patients with haemophilia A or B.

Research questions

The main research questions that this report was commissioned to investigate are:

1. What is best practice for the treatment of acute bleeding episodes in patients with haemophilia A, B, von Willebrand disease and other rare coagulation disorders?

2. What is best practice for the prophylactic treatment of patients with haemophilia A, B or von Willebrand disease?

3. What is the best method for treating bleeding episodes in patients with inhibitors to factors VIII or IX?

4. What is best practice for the implementation of tolerisation procedures for patients with inhibitors to factors VIII or IX?

5. What is the best method of managing patients with haemophilia A, B, von Willebrand disease and other rare coagulation disorders undergoing surgical and dental procedures?

6. What is best practice in the delivery of infants with haemophilia A or B and the management of infant delivery in women with von Willebrand disease and other rare coagulation disorders?

Overview of methodology

Inclusion criteria

Criteria for including studies in this systematic review and clinical practice guidelines document are provided in Box 1 (Appendix E). In order to ensure that the selection of studies was not biased, these criteria were delineated prior to collating the literature.

Search strategy

Prevalence data on haemophilia and von Willebrand disease were obtained from the Australian Bleeding Disorder Registry (Australian Bleeding Disorder Registry 2004) and the Population Health Division, Department of Health, NSW.

The medical and health literature was searched to identify relevant studies and reviews to answer the research questions on the management and treatment of patients with haemophilia A, B, von Willebrand disease and other rare blood coagulation disorders. The search period was from 1966 to September 2004. Table 56 (Appendix E) lists the electronic databases that were used for this search. Table 57 (Appendix E) lists other potentially relevant sources of literature that were canvassed, including grey literature.

The search terms used for identification of literature on haemophilia A, haemophilia B and von Willebrand disease, and concerning factors VIII and IX, were developed on an Embase platform, which includes Embase and Medline databases (Table 58, Appendix E). Similar strategies were used for other electronic databases, with the same text words being used along with the relevant alternatives to indexing headings.

The full texts of all articles that were deemed potentially relevant (453) were retrieved for further screening and allocated to different topic areas—haemostatic agents, treatment of bleeding episodes, prophylaxis, inhibitors and tolerisation protocols, surgical and dental procedures, infant delivery and other aspects of management. Three researchers judged the eligibility for inclusion of all retrieved studies according to the inclusion criteria developed in the review protocol. A description of all the studies that met the inclusion criteria for assessing the effectiveness and safety of the different therapies is provided in Appendix I.

Many studies that reported on treatment of patients with haemophilia A, B or von Willebrand disease failed to meet the inclusion criteria. Exclusion was primarily due to inappropriate study design (case reports or expert opinion); assessment of efficacy of plasma-derived products alone in haemophilia A or B; or inability to distinguish between therapies as patients treated with recombinant and plasma-derived factor were combined in the same group.

In order to minimise duplication of data extraction, authors, time period and location of studies, patient characteristics, and methodological details were examined closely. Where multiple publications reported data on the same patient population, data were extracted from the paper providing the most complete follow-up. It should be noted, however, that it was not always clear to what extent data overlapped multiple publications. Time constraints precluded contacting authors for missing data or clarification of methodology.

Critical appraisal

The evidence presented in the included studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000a). These dimensions (Table 2) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 3. Only the highest level of evidence was reported for each research question.

Table 2. Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 3

Table 3. Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well designed quasi-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from (NHMRC 2000a).

Appraisal of the included papers was undertaken using several checklists appropriate to each particular study design—systematic reviews (Khan et al. 2001); intervention studies (Downs & Black 1998); or non-comparative studies, such as uncontrolled before-and-after studies and case series (Young et al. 1999) (Appendix H).

Statistical precision was determined using standard statistical principles. Small confidence intervals and p-values give an indication of the probability that the reported effect is real (NHMRC 2000b). Clinically important benefits of the effect size associated with outcomes and the clinical relevance of the evidence were assessed using appropriate checklists (Appendix H). A greater than 20% difference, compared to a baseline measure or the control group performance, was used as an arbitrary measure of clinical importance.

Data Extraction and Analysis

The process of study selection went through six phases and the number of literature citations retrieved and retained at each phase was documented (Figure 2, Appendix E).

Evidence tables, as described in Appendix I, were used as a guide to summarise the extraction of data (NHMRC Guidelines Assessment Register Consultants Working Party 2004). Definitions of specific safety and effectiveness outcomes were provided in the review protocol. All data extraction was checked by another researcher for face validity.

Information on each of the relevant outcomes was extracted, tabulated and summarised in the body of the report—including numerator and denominator information, means and standard deviations, and summary measures of effect, where appropriate. All statistical calculations and testing were undertaken using the statistical computer package, Stata version 8.2 (Stata Corporation 2004).

Meta-analysis was not feasible due to the paucity of high level evidence, the heterogeneous nature of the available randomised crossover trials, and the potential for duplication of data in multiple publications.

The quantity and quality of evidence varied across the different sections of this report. For each section, the highest level of evidence is presented and, where possible, data were extracted from comparative studies. For the most part, however, the evidence base consisted of low level evidence (case series) and a 'best evidence' approach was used.

Selection of Products

The key advantage to using recombinant products over plasma-derived products is believed to be their higher safety profile with a lower transmission of blood-borne pathogens. Therefore, recombinant products should be used preferentially over plasma-derived products for patients with haemophilia A or B. Since the Australian Government announced unrestricted access to recombinant factors VIII and IX for all individuals with haemophilia A or B, this review focuses on the effectiveness, safety and appropriate use of *recombinant* factor concentrates for the management of haemophilia A and B. The effectiveness and safety of other products, such as plasma-derived factor concentrates and adjunctive haemostatic agents, are also evaluated in relation to their use in the treatment of patients with von Willebrand disease and other rare coagulation disorders, or in patients with inhibitors to factors VIII or IX.

Table 4 to Table 9 list products that are registered in Australia and include those that are available, not currently available, and those available on the Special Access Scheme[c], for use in patients with haemophilia A, B, von Willebrand disease and other rare bleeding disorders. All statements on the therapeutic use of these products are based on Level IV evidence (Haemophilia Foundation Australia Medical Advisory Panel 2000).

Fresh plasma products

The first successful treatment of haemophilia A, using whole blood, was reported in 1840. In 1929, a technique was developed that enabled plasma to be separated from whole blood. Until the 1960s whole blood and blood plasma were the only therapeutic options for people with haemophilia A and B. In 1965, cryoprecipitate was developed for the treatment of haemophilia A, enabling local blood banks to stock this effective and portable treatment (Kingdon & Lundblad 2002). Both fresh frozen plasma and cryoprecipitate are still available for treatment of some blood coagulation disorders (see Table 4), but safer products have superseded their use for haemophilia A and B.

Table 4. Fresh plasma products not virally inactivated*

Product	Manufacture of product	Therapeutic use of product
Fresh frozen plasma	Plasma is separated from whole blood through centrifugation, and then snap frozen in a mechanical freezer. Fresh frozen plasma contains approximately 200 units of FVIII coagulant activity in 150–300ml volume.	For use in treatment of patients with FV deficiencies. May be used for FXI deficiency when FXI concentrate is contraindicated.
Cryoprecipitate	Fresh frozen plasma is thawed over 24 hours at 4°C and the cold insoluble precipitate is separated through centrifugation. Cryoprecipitate contains 100 units of FVIII coagulant activity per bag.	For use in some circumstances for vWD and hypofibrinoginemia patients.

* modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000; FV= factor V; FXI= factor XI; vWD= von Willebrand Disease

[c] The Special Access Scheme refers to arrangements that provide for the import and/or supply of an unapproved therapeutic good for a single patient, on a case-by-case basis.

Plasma-derived coagulation factor concentrates

In 1968, the first clotting factor concentrate (Hemofil®) was produced on an industrial scale. Between 1985 and 1992, all available plasma-derived factor concentrates became virally inactivated against lipid-enveloped viruses, including hepatitis C, hepatitis B and HIV (Kingdon & Lundblad 2002). Von Willebrand factor, which is not present in recombinant or immuno-affinity purified FVIII concentrates, is preserved in the plasma-derived FVIII concentrate, Biostate®. Human plasma-derived factors available in Australia are listed in Table 5.

Table 5. Plasma-derived coagulation factor concentrates*

Type of product	Product (Manufacturer)	Manufacture of product	Therapeutic use of product
pdFVIII	Biostate® (CSL)	Dried factor VIII preparation, which is fractionated from cryoprecipitate, contains von Willebrand factor. Fibrinogen and fibronectin are removed by precipitation with heparin and by gel filtration. Factor VIII is precipitated with glycine sodium chloride and lyophilised after albumin is added. Viral inactivation is by solvent detergent plus dry superheating for 72 hours at 80°C. Each vial of FVIII concentrate contains 250 units of FVIII and 500 units of von Willebrand factor: ristocetin cofactor activity.	For the control and prevention of haemorrhagic episodes and for surgical prophylaxis in patients with haemophilia A and von Willebrand Disease.
pdFIX	MonoFIX®-VF (CSL)	Factor IX concentration is chromatographically purified, with two viral inactivation or removal steps, solvent detergent and nanofiltration. Heparin and human antithrombin III are added. Each vial of FIX concentrate contains 500 units of FIX.	For the treatment of haemorrhages and for use in minor surgery and as prophylaxis in patients with haemophilia B.

*modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000; pdFVIII= plasma-derived factor VIII; pdFIX= plasma-derived factor IX,

Recombinant coagulation factor concentrates

In 1987, the first recombinant factor VIII product was infused into a haemophilia A patient. From December 1992, Recombinate™ was available in the United States, and Kogenate® followed in 1993. In 1999, a B-domain-deleted recombinant factor VIII concentrate became available in Europe (ReFacto®) and was licensed in the United States in 2000 (Kingdon & Lundblad 2002). The smaller, more stable B-domain-deleted recombinant FVIII molecule precludes the need for human albumin as a stabiliser (Fijnvandraat et al. 1997). Prompted by the desire to improve their efficacy and safety profile, recombinant factors have developed through several generations, listed in Table 6.

First generation products were manufactured using animal and human proteins in the cell culture medium and with albumin to stabilise the product. Second generation products are manufactured without albumin, which has been replaced with a non-protein stabiliser, such as sucrose. Third generation products do not have human or animal proteins added to the cell culture. Excluding human or animal products from the recombinant products reduces the risk of transmission of infectious agents (United Kingdom Haemophilia Centre Doctors' Organisation 2003).

In 1997, the first recombinant factor IX for haemophilia B was developed (BeneFix®), based on the technologies used for recombinant factor VIII (Kingdon & Lundblad 2002). Activated recombinant factor VII (rFVIIa, NovoSeven®) is the most recent development in treatments for haemophilia patients with inhibitors (Kingdon & Lundblad 2002).

Table 6. Recombinant coagulation factor concentrates[a]

Type of product	Product (Manufacturer)[b]	Manufacture of product	Therapeutic use of product
1st generation rFVIII	Recombinate™ (Baxter)	Factor VIII and vWF genes are inserted into Chinese hamster ovary cell lines. The vWF is used as a stabiliser for FVIII. The secreted rFVIII is purified by single immunoaffinity chromatography using a murine monoclonal antibody, and by two ion-exchange chromatography steps. Purified rFVIII is stabilised with pasteurised human albumin.	The treatment of choice for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A.
	Kogenate® (Bayer), Helixate® (Bayer)	Factor VIII genes are inserted into baby hamster kidney cell lines. The secreted rFVIII is purified with two ion-exchange gel filtration/size exclusion chromatography and double immunoaffinity chromatography using a murine monoclonal antibody. Purified rFVIII is stabilised with pasteurised human albumin and contains trace hamster protein, trace murine immunoglobulin and trace von Willebrand factor. Viral inactivation is achieved through heat treatment.	
2nd generation rFVIII	ReFacto® (Wyeth Pharmaceuticals)	B-domain deleted FVIII genes are inserted into Chinese hamster ovary cell lines. Purification involves five chromatographic steps and one virus inactivation step by solvent detergent. Human albumin is not added. Trace amounts of hamster protein and murine protein are included.	
	Kogenate® FS (Bayer), Helixate Nexgen® (Bayer)	Different to Kogenate, Kogenate FS- expressing cells are cultured in a medium containing recombinant insulin and a human plasma protein solution. Sucrose is used as a stabiliser rather than human albumin. The purification process includes two viral inactivation steps by solvent/detergent treatment and high salt treatment.	
3rd generation rFVIII	Advate® (Baxter)[c]	Factor VIII genes are inserted into Chinese hamster ovary cells. The rFVIII is purified using a series of chromatography columns, using an immunoaffinity chromatography step with a monoclonal antibody to isolate the rFVIII from the medium. This is further purified with a viral inactivation solvent detergent. No animal or human products are used in the cell culture or purification processes.	
3rd generation rFIX	BeneFIX® (Wyeth Pharmaceuticals)	Factor IX genes are inserted into Chinese hamster ovary cells. The secreted FIX is purified with four chromatographic steps and three (nanofiltration, ultrafiltration and diafiltration) membrane based filtration steps, the final of which is a viral retention filtration step. Human albumin and immunoaffinity chromatography are not used.	The treatment of choice for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia B.
2nd generation rFVIIa	NovoSeven® (Novo Nordisk)	Baby hamster kidney cells are genetically transformed to produce factor VII as a single-chain glycoprotein (406 amino acids, 50kDa). This is purified by ion exchange and immunoaffinity chromatography using murine monoclonal antibodies. The rFVII is converted to the two-chain activated form, and freeze dried. Trace amounts of hamster proteins, mouse proteins, bovine IgG and other bovine products are included.	For the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A or B and inhibitors to FVIII or FIX. May also be used for patients with FVII deficiency.

[a] modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000 and information from the Therapeutic Goods Administration (accessed 2004); [b]Manufacturers are current as at January 2005, but are subject to change; [c]Advate® (Baxter) is currently registered as an Orphan drug by the Therapeutic Goods Administration; FVII= factor VII; FVIII factor VIII; FIX= factor IX; IgG=Immunoglobulin G; rFVIIa= activated recombinant factor VII; rFVIII= recombinant factor VIII; rFIX= recombinant factor IX; vWF= von Willebrand factor

Prothrombin complex concentrates (PCCs)

Activated prothrombin complex concentrates, which directly activate prothrombin by stimulation of activated factor X (Xa), are useful in treating patients with inhibitors to factor VIII or IX (Kingdon & Lundblad 2002) (Table 7).

Table 7. Prothrombin complex concentrates (PCCs)*

Type of product	Product (Manufacturer)	Manufacture of product	Therapeutic use of product
PCCs	Prothrombinex®-HT (CSL)	This concentrate of factors II, IX and X is prepared from cryoprecipitate supernatant and purified by ion exchange chromatography. It is lyophilised and then heat-treated for 72 hours at 80°C for viral inactivation. Prothrombinex® contains approximately 500 units each of factors II, IX and X.	Traditionally used for treatment in haemophilia B, but now replaced by BeneFIX® and MonoFIX®. Treatment of choice for FII or FX deficiencies.
aPCCs	FEIBA® (Baxter)	This activated prothrombin complex concentrate is prepared from cryoprecipitate supernatant which then generates FEIBA. This is purified with adsorption and filtration and then vapour heated for 10 hours at 60°C then 80°C for 1 hour before being lyophilised.	For the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A or B and inhibitors to FVIII or FIX.

* modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000 ; aPCC= activated prothrombin complex concentrates; FEIBA= factor eight inhibitor bypassing agent; FII= factor II; FVIII= factor VIII; FIX= factor IX; FX= factor X; PCC= prothrombin complex concentrates

Coagulation factor concentrates for less common disorders

Haemophilia A and B and von Willebrand disease account for the majority of inherited bleeding disorders. The remainder include deficiencies of fibrinogen, prothrombin, and deficiencies of factor V, combined V/VIII, VII, X, XI, and XIII. While treatments for haemophilia have improved over the last 15 years, treatments for more rare deficiencies traditionally have used fresh frozen plasma and cryoprecipitate. For deficiencies in factor V, fresh frozen plasma remains the only treatment option since cryoprecipitate does not contain any factor V, and factor V concentrate is not available. However, for other deficiencies, plasma-derived concentrates are now available. Since factor XI has a half-life of two to three days and has been associated with thrombosis, factor XI concentrates are generally used in low doses for surgical procedures and control of bleeding associated with trauma (Kasper 2004). People with a deficiency in factor XIII are at risk of intracranial bleeding and pregnant women have a high risk of miscarriage. Factor XIII has a long half-life of 10 to 20 days and monthly prophylactic infusions with factor XIII concentrates may be a convenient and effective way of preventing spontaneous bleeding.

Due to the small demand for concentrates for rare bleeding disorders, it is unlikely that recombinant products will be developed or become available in the near future. Therefore, plasma-derived factor concentrates are likely to remain the treatment of choice for these conditions until gene therapy is available (Di Paola et al. 2001). Table 8 lists the coagulation factor concentrates that are available for the less common coagulation disorders.

Table 8. Coagulation factor concentrates for less common disorders*

Type of product	Product (Manufacturer)	Manufacture of product	Therapeutic use of product
Fibrinogen	Fibrinogen (Immuno)	Cryoprecipitate supernatant is treated with DEAE-sephadex to produce fibrinogen, which is then virally inactivated with vapour heating.	For use in patients with fibrinogen deficiency.
	Haemocomplettan P (ZLB Behring)	The glycine supernatant from the intermediate-purity FVIII process produces fibrinogen which is pasteurised for 10 hours at 60°C.	
pdFVII	Factor VII (Baxter)	This high purity concentrate is manufactured using two-step vapour heat inactivation for 10 hours at 60°C then 80°C for 1 hour, both under excess barometric pressure. A PCR test for HIV, HBV and HCV is carried out.	To be used for FVII deficiency at a dose of 5–10 IU/kg.
	Factor VII (Bio Products Laboratory)	This high purity concentrate is manufactured with a dedicated viral inactivation procedure. Plasma is sourced from FDA approved USA sites.	
	Facteur VII (LFB)	Fractionated by DEAE adsorption and anion exchange chromatography. Virally inactivated by TNBP/polysorbate 80; no albumin added (Kasper 2004)	
pdFXI	Factor XI (Bio Products Laboratory)	This high-purity concentrate is dry heated at 80ºC for 72 hours to inactivate viruses. Since 1993, this product has included heparin and antithrombin to minimise thrombogenicity (Bolton-Maggs 2000).	For use in FXI deficient people to treat excessive bleeding due to trauma or surgery. Due to the long half-life (2–3 days), the dosage required for surgery is low. Restraint in dosage is recommended due to possible thrombogenicity, particularly in the elderly and/or those with pre-existing cardiovascular disease. Factor XI should not be given at doses exceeding 30 U/kg (product information).
	Hemoleven (LFB)	This product, which is similar to the BPL factor XI, is manufactured in France. It contains smaller amounts of heparin and antithrombin than in the BPL product and viral inactivation is by solvent/detergent and nanofiltration.	
pdFXIII	Factor XIII (Bio Products Laboratory)	This high purity concentrate is manufactured with a dedicated viral inactivation procedure. Plasma is sourced from FDA approved USA sites.	For use in FXIII deficient patients. Patients should be monitored for development of inhibitors to FXIII under clinical observation and laboratory tests. Patients on a low sodium diet should be closely monitored as FXIII concentrate contains sodium chloride. May be used every 21 days in individuals with a history of spontaneous abortions (Di Paola et al 2001)
	Fibrogammin® P (ZLB Behring)	This FXIII concentrate is prepared from cryoprecipitate supernatant and then purified by ion exchange chromatography. It is then pasteurised for 10 hours at 60°C, and albumin is added as stabiliser.	

* modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000 ; DEAE= diethylaminoethyl; FDA= Food and Drug Administration (USA); FVII= factor FVII; HBV= hepatitis B; HCV= hepatitis C; HIV= human immuno-deficiency virus; LFB= Laboratoire Francais du Fractionnement et des Biotechnologies; PCR= polymerase chain reaction; pdFVII= plasma-derived factor VII; pdFXI= plasma-derived factor XI; pdFXIII= plasma-derived factor XIII; TNBP= tri(n-butyl)phosphate

Gene therapy

Gene therapy involves insertion of the factor VIII/IX gene or an active derivation into the cells of a patient, allowing expression and secretion of factor proteins into the blood stream (Kingdon & Lundblad 2002). Although research in gene transfer is progressing

(Powell et al. 2003; Roth et al. 2001b), this field is still in its infancy and results have been limited. Therefore, factor replacement therapy remains the mainstay of haemophilia care.

Adjunctive haemostatic agents

Due to the risks associated with viral transmission and the high cost of factor concentrates, a range of haemostatic agents (Table 9) have been trialled for use in patients with haemophilia A, B or von Willebrand disease (vWD). While the routine use of viral inactivation techniques and the development of recombinant products has alleviated most of the anxieties about the safety of factor concentrates, they are still expensive and other products may be considered if necessary (Saulnier et al. 1994; Warrier & Lusher 1983).

Table 9. Adjunctive haemostatic agents*

Type of product	Product (Manufacturer)	Description of product	Therapeutic use of product
DDAVP	Desmopressin acetate Octostim (Fisons Pharmaceuticals), Minirin (Ferring)	Desmopressin acetate is a synthetic analogue of the anti-diuretic hormone 8-D-arginine vasopressin.	DDAVP is for use in mild/moderate haemophilia A or mild vWD. Contraindicated in those with arteriovascular disease, those under two years of age, and should be used with caution in the elderly or in pregnant women.
Fibrin sealant	Tisseel Duo (Baxter)	This fibrin sealant contains human fibrinogen, fibronectin, FXIII and plasminogen. The product is double steam heat-treated and PCR tested for HIV, HBV and HCV. The end product is deep-frozen.	To be used locally as an adjunct to haemostasis during surgical procedures, when control of bleeding by conventional surgical techniques is ineffective or impractical.
Tranexamic acid	Cyklokapron (Pfizer)	Tranexamic acid inhibits activation of plasminogen and plasmin, and is available in both suspension and tablet form.	Particularly useful for treating bleeding from gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP. Treatment of choice for patients with FXI deficiency for mild bleeding episodes.

*modified from Haemophilia Foundation Australia Medical Advisory Panel guidelines 2000; DDAVP= 1-deamino-8-D-arginine vasopressin; FXI= factor XI; HBV= hepatitis B; HCV= hepatitis C; HIV= human immuno-deficiency virus; PCR= polymerase chain reaction; vWD= von Willebrand Disease

Desmopressin (1-deamino-D-arginine vasopressin, DDAVP)

DDAVP, which is a synthetic analogue of the natural anti-diuretic hormone arginine vasopressin, induces the release of factor VIII and von Willebrand factor into the bloodstream. Plasma levels peak 30–60 minutes after administration and the half-life is comparable to levels found after administration of factor concentrates (Association of Hemophilia Clinic Directors of Canada 1995b).

Previous Australian consensus-based guidelines

DDAVP should be considered for all patients with mild/moderate haemophilia A or mild vWD. DDAVP is generally administered intravenously at a dose of 0.3 mcg/kg diluted in 50 mL of 0.9% saline and infused over at least 30 minutes. Efficacy should be demonstrated irrespective of the route employed, by measuring FVIII/vWF. DDAVP should be used with caution in elderly individuals, pregnant women and avoided in those with evidence of arteriovascular disease and in children younger than 2 years of age. (see Appendix G for full details) (Haemophilia Foundation Australia Medical Advisory Panel 2000).

Three randomised controlled trials and one non-randomised controlled trial (Level II and III-2 evidence) examining effectiveness and/or safety of DDAVP were included in the systematic review for assessment. The other included studies on DDAVP were case series (Level IV evidence) (Table 10).

Effectiveness of DDAVP

DDAVP is generally available in Australia in two strengths in both intravenous and subcutaneous form. The different modes of administration are comparable at the same 0.3 μg/kg dose (Level II evidence) (Mannucci et al. 1987). One study compared the effectiveness and safety of a 0.3 μg/kg dose with a 0.4 μg/kg dose and concluded that the 0.3 μg/kg dose had the same efficacy as the 0.4 μg/kg dose (Level IV evidence) (Mariana et al. 1984).

One good quality case series had one patient who was given DDAVP by mistake during labour. It was found that DDAVP appeared to stop the process of labour when administered when the cervix was fully dilated (Schulman et al. 1991). While it is unclear whether it was the DDAVP or a natural occurrence in a primipara, similar observations have been made in case reports (below the level of evidence examined in this review). Consequently, if DDAVP is to be given to prevent blood loss in labour, it should be given postpartum to prevent interference in labour, at least until stronger evidence refutes the recommendation (expert opinion) (Schulman et al. 1991).

One good quality randomised crossover trial (Level II evidence) showed that a DDAVP nasal spray alleviated menorrhagia in women with inherited bleeding disorders (subjective assessment). However, statistically the effect was no greater than that of placebo due to the small sample size (statistically underpowered) (Level II) (Kadir et al. 2002). In Australia, the intranasal spray is available only through individual importation.

The best evidence available on the effectiveness of DDAVP showed that in multi-transfused patients with severe vWD (bleeding time over 30 minutes) receiving cryoprecipitate for joint or muscle haemorrhages, DDAVP assisted in further reducing bleeding time to within the normal range (upper limit seven minutes), showing a statistically significant improvement in haemostatic control and a clinical benefit[d] compared to saline placebo (Level II evidence) (Cattaneo et al. 1989).

Lower levels of evidence have shown that DDAVP alone is unsuitable for use in severe vWD, since only 18–27% of patients with severe Type 1 and Type 2 vWD met the criteria for response to DDAVP (Level IV) (Federici et al. 2004). Although the criteria for minimum response and definition of a positive haemostatic effect differed slightly between studies, generally they referred to the increase of factor concentrates and reduction of bleeding time to within the normal range[e].

---

[d] Clinical importance of statistically significant effects was ranked according to the checklist provided in Appendix H. More than 20% improvement in haemostasis—vs baseline—indicated a clinical benefit.

[e] The normal range is defined according to the results found in individual laboratories. Normal factor concentrate levels found by Nolan et al. 2000 were FVIII:C=0.5-1.5 IU/dl, vWF:Ag=0.5-1.5 IU/dl, and vWF:Ac=0.5-1.5 IU/dl. Normal bleeding time as defined by Federici et al. 2004 was 12 minutes or less.

DDAVP was clinically effective in the majority of mild and moderate vWD and haemophilia A patients. However, a significant number of patients did not meet the minimum response criteria (Level IV evidence) (Nolan et al. 2000; Federici et al. 2004; Schulman et al. 1991). Response to DDAVP depends on both the severity[f] and the subtype of disease, and the mode of administration. While the sample size of study participants within particular subgroups, other than for Type 1 vWD, were small, the available evidence suggests that Type 1 and mild Type 2 vWD patients are likely to respond to DDAVP. In contrast, severe Type 2 and Type 3 vWD are unlikely to respond measurably unless DDAVP is used as an adjunctive agent after factor concentrates have reduced bleeding (Schulman et al. 1991; Federici et al. 2004; Nolan et al. 2000; Cattaneo et al. 1989). Thus, since approximately 20–30% of patients are non-responsive to DDAVP, it is suggested that a test dose should be administered initially to establish efficacy.

When patients repeatedly receive DDAVP in a short space of time, they may become less responsive or unresponsive to its effects (tachyphylaxis). A low level study by Mannucci et al. 1992 found that when DDAVP was administered on four consecutive days, the response to DDAVP on the second day was 30% lower than on the first and continued to decline over the subsequent three days. The development of tachyphylaxis limits the usefulness of DDAVP over a long period of time (Level IV evidence).

DDAVP has also been effective in preventing, stopping or reducing excessive bleeding in dental extractions and surgery. Data from studies using DDAVP in surgical/dental procedures are presented in the Surgical and Dental Procedures section.

[f] Severe vWD was defined by participating centres as a lifelong history of bleeding, including ≥ 2 episodes requiring replacement therapy and at least one of the following laboratory abnormalities: bleeding time > 15 minutes; vWF:RCo < 10 IU/dL; or FVIII:C < 20 IU/dL (Federici et al. 2004).

Table 10. Effectiveness of DDAVP for haemostatic control

Study	Level and quality of evidence	Population	Effectiveness		
(Kadir et al. 2002)	Level II: randomised crossover trial Quality score: 24/27 External validity uncertain Bias minimised Confounding avoided	39 women with mild-moderate vWD, heterozygote FXI-deficiency, and carriers of haemophilia, aged 18–60 Prophylaxis for menorrhagia	PBAC Scores	DDAVP (300µg) 140 Mean difference= -8 No statistically significant difference, p=0.51	Placebo 148
(Mannucci et al. 1987)	Level II: randomised crossover trial Quality score: 23/27 External validity uncertain Bias minimised Confounding avoided	14 mild and moderate haemophilia A (median FVIII:C level 7 U/dL, range 2-31) Test dose		Intravenous DDAVP (0.3 µg/kg) mean±SD	Subcutaneous DDAVP (0.3 µg/kg) mean±SD
			Peak FVIII:C (pg/mL)	2363[d]	582±158
			Half-life of FVIII:C (hr)	4.4±1.1	4.7±1.6
			Significant difference in peak FVIII:C (p<0.02) Non-significant difference in half life of FVIII:C		
(Cattaneo et al. 1989)	Level II: randomised crossover trial Quality score: 20/27 Clinical importance[c]: 1/4 External validity uncertain Bias minimised Confounding avoided	10 PTPs with severe vWD, (type not specified) with prolonged bleeding time (>30 minutes) Test dose		Cryoprecipitate + DDAVP (0.3 µg/kg) mean±SD	Cryoprecipitate + saline mean±SD
			Bleeding time (minutes)	Post cryo=14±2 Post DDAVP=9±2 p<0.01	Post cryo=15±3 Post saline=15±3 NS
			vWF:Ag (IU/dL)	Post cryo=75±7 Post DDAVP=69±6 NS	Post cryo=92±9 Post saline=83±1 NS
			vWF:RCo (IU/dL)	Post cryo=64±7 Post DDAVP=64±7 NS	Post cryo=76±8 Post saline=63±7 NS
(De Sio et al. 1985)	Level III-2: non randomised controlled trial Quality score: 17/27 External validity uncertain Bias possible Confounding possible	26 patients, 21 mild haemophilia A, 5 moderate haemophilia A 8 patients had both treatments Test dose	Within subjects	Intravenous DDAVP (0.3 µg/kg) mean±SD	Subcutaneous DDAVP (0.3 µg/kg) mean±SD
			FVIII:C (IU/dl)	24.9±12.4 Range= 9.5-50.0	25.5±12.4 Range= 12.8-48.0
			Ratio post/pre	3.7±1.4 Range= 1.7-5.9	3.1±1.4 Range= 1.7-5.1

(cont.)

Table 10. (cont.) (Schulman et al. 1991)	Level IV: before and after study Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate Uncontrolled	370 patients with disorders of primary haemostasis. 133 vWD, 237 platelet function defects, aged 3–80 years Test dose	No. responsive[a] to DDAVP (0.2–0.3 µg/kg) Total vWD 120/133 (90%) Type 1 (mild) vWD 110/113 (97%) Type 1 (moderate) vWD 6/10 (60%) Type 2A vWD 3/3 Type 2B vWD 1/4 Type 3 (severe) vWD 0/3 Platelet function disorder 202/237 (85%)
(Federici et al. 2004)	Level IV: before and after study Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate Uncontrolled	66 patients with severe[b] Type 1 or 2 vWD, BT more than 15 minutes, aged 12–65 years Exclusions: Type 2B and type 3 vWD Test dose	No. responsive[a] to DDAVP (0.3 µg/kg) Type 1 vWD 7/26 (26.9%) Type 2A vWD 1/15 (0.1%) Type 2M vWD 3/21 (14.2%) Type 2N vWD 3/4 (75.0%)
(Nolan et al. 2000)	Level IV: before and after study Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate Uncontrolled	133 patients with bleeding disorders. 91 Type 1 vWD, 20 mild haemophilia A, 22 platelet function disorders Test dose	No. responsive[a] to DDAVP (0.3 µg/kg) Type 1 vWD 82/91 (90.1%) Mild haemophilia A 15/20 (75.0%) Platelet function disorders 15/22 (68.2%)
(Mannucci et al. 1992)	Level IV: before and after study Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	37 patients, 22 with mild haemophilia A, 15 with mild Type 1 vWD, aged 16–63 years Test doses	DDAVP (0.3 µg/kg) — Day 1 / Day 2 / Day 3 / Day 4 Haemophilia — FVIII:C post/pre‡: 3.0±0.7 / 2.0±2.5* / 2.0±0.6* / 1.9±0.5* vWD — FVIII:C post/pre‡: 4.3±1.9 / 3.4±2.7* / 3.5±2.8* / 2.8±1.2* vWF:Ag post/pre‡: 4.8±2.4 / 3.1±1.8* / 3.4±1.8* / 3.3±2.3* RCo post/pre‡: 5.1±3.0 / 4.3±3.3* / 3.8±2.4* / 3.5±1.8* BT post/pre‡: 0.6±0.2 / 0.6±0.2 / 0.7±0.2 / 0.7±0.2 ‡ Data are expressed as a post/pre DDAVP ratio. *significantly less response than Day 1 (p<0.001)

(cont.)

Table 10 (cont.) Study	Level and quality of evidence	Population	Effectiveness
(Warrier & Lusher 1983)	Level IV: before and after study Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	3 vWD patients 3 cases of menorrhagia	DDAVP via intranasal drip (2–4 µg/kg) or intravenous (0.2–0.3 µg/kg) All reported decreased menstrual bleeding within 24 hours after receiving DDAVP
(Leissinger et al. 2001)	Level IV: before and after study Quality score: 1/3 Measurement bias minimised Selection bias possible Follow-up inadequately stated Uncontrolled	172 Type 1 vWD patients: 135 mild 37 moderate 254 bleeding episodes	DDAVP (150 µg) intranasal Mild type 1 vWD: 211/254 (83%) rated haemostasis 'Excellent'; 35/254 (14%) rated 'Good' Moderate type 1 vWD: 55/78 (71%) rated haemostasis 'Excellent', 14/78 'Good'.
(Mariana et al. 1984)	Level IV: before and after study Quality score: 1/3 Measurement bias possible Selection bias likely Follow-up adequate Uncontrolled	5 vWD patients (Types 1 and 2) 7 spontaneous bleeding episodes	DDAVP (0.3–0.4 µg/kg) intravenous + tranexamic acid Bleeding or pain ceased promptly in 6/7 episodes, 1 progressive reduction in bleeding.

[a] the definition of responsiveness in the normal range varies across laboratories. Normal factor concentrate levels found by Nolan et al. 2000 were FVIII:C=0.5-1.5 IU/dl, vWF:FVIIIB, and vWF:Ag=0.5-1.5 IU/dl; Normal bleeding time was defined by Federici et al. 2004 as 12 minutes or less; [b] Severe vWD was defined by participating centres as a lifelong history of bleeding, including ≥ 2 episodes requiring replacement therapy and at least one of the following laboratory abnormalities: bleeding time > 15 minutes; vWF:RCo < 10 IU/dL; or FVIII:C < 20 IU/dL (Federici et al, 2004); [c] Rank scores for the clinical importance of the benefit/harm (1/4 ranked highest and 4/4 ranked lowest); [d] Information on population source not provided; BT= bleeding time, in minutes; cryo= cryoprecipitate; FVIII:C= factor VIII coagulant activity; FXI= factor XI; PBAC= Pictorial Blood Assessment Chart, a commonly used tool to measure menstrual loss where a score of ≥100 is equivalent to more than 80 mL of blood loss (definition of menorrhagia); PTPs= previously treated patients; RCo= ristocetin cofactor; SD= standard deviations; vWD=von Willebrand Disease; vWF:Ag= von Willebrand factor antigen; [d] Standard deviation provided by the authors was not meaningful

Safety of DDAVP

The majority of studies on the safety of DDAVP were too small to be able to identify uncommon side effects (Table 11). The best evidence addressing the side effects of DDAVP found that while there were numerous adverse events related to the use of a DDAVP intranasal spray to reduce menorrhagia in women with vWD and other rare bleeding disorders, there were a similar number of adverse events related to the use of placebo (Level II evidence) (Kadir et al. 2002).

With the exception of transient headaches and/or mild facial flushing, the majority of papers reported few side effects from DDAVP (Rose & Aledort 1991; Warrier & Lusher 1983; Chuansumrit et al. 1993; Rodeghiero et al. 1996; Dewald et al. 1980; Ghirardini et al. 1988; Mariana et al. 1984). In some cases, more severe, but less common, side effects related to DDAVP included dizziness, nausea, vomiting, asthenia, and side effects associated with excess fluid, such as oedema and hyponatraemia (Schulman et al. 1991; Ghirardini et al. 1987; Dunn et al. 2000; Gill et al. 2002; de la Fuente et al. 1985; Leissinger et al. 2001).

DDAVP has an anti-diuretic effect, which means patients must restrict their fluid intake to avoid the adverse events associated with low levels of sodium in the blood. Fluid restriction may be based on the following calculation: 100 mL/kg for the first 10 kg of body weight + 50 mL/kg for the second 10 kg of body weight + 20 mL for each additional kilogram of body weight (Gill et al. 2002). A simpler restriction is the limit of 1.5-2 L of fluid per day for adults (Kadir et al. 2002). For the most part, side effects associated with DDAVP are minimised when patients adhere to fluid restrictions (Level IV evidence) (Dunn et al. 2000). Alternatively, close observation of sodium and symptom status may be adequate (expert opinion) (Palmer et al. 2003). If DDAVP is given more than once in 24 hours, predose monitoring of electrolyte concentrations is recommended (JBC FVIII/FIX working party & National Blood Authority 2004).

No studies included in this systematic review evaluated the safety of DDAVP in children less than two years of age. Therefore, any such recommendation would be based on expert opinion. Previous recommendations have suggested DDAVP should be avoided in those younger than two years of age due to risk of fluid overload (Haemophilia Foundation Australia Medical Advisory Panel 2000).

Table 11. Adverse events associated with use of DDAVP

Study	Level and quality of evidence	Population	Adverse events to DDAVP
(Kadir et al. 2002)	Level II: randomised crossover trial Quality score: 24/27 External validity uncertain[a] Bias minimised Confounding unlikely	39 women with menorrhagia. Mild-moderate vWD, heterozygote FXI-deficiency, and carriers of haemophilia Prophylaxis for menorrhagia	24/29 (83%) adverse events. Headache, facial flushing, weight gain Total: DDAVP (300µg) 18/26 (69%); Placebo 15/29 (52%) Headache: DDAVP (300µg) 23%; Placebo 24% Weight gain: DDAVP (300µg) 12%; Placebo 0%
(De Sio et al. 1985)	Level III-2: non randomised controlled trial Quality score: 17/27 External validity uncertain Bias possible Confounding possible	26 patients, 21 mild haemophilia A, 5 moderate haemophilia A Test dose	DDAVP (0.3 µg/kg) intravenous Moderate increase in pulse rate and/or blood pressure, frequently associated with mild facial flushing DDAVP (0.3 µg/kg) subcutaneous Immediate swelling caused by injection, disappeared within a few minutes No other adverse events reported
(Nolan et al. 2000)	Level IV: prospective case series Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate Uncontrolled	133 patients with bleeding disorders. 91 Type 1 vWD, 20 mild haemophilia A, 22 platelet function disorders Test dose	DDAVP (0.3 µg/kg) intravenous infusion 2/133 minor side effects: Facial flushing and palpitations—resolved by decreasing infusion rate
(Schulman et al. 1991)	Level IV: case series Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate Uncontrolled	370 patients with disorders of primary haemostasis. 133 vWD, 237 platelet function defects, aged 3–80 years 127 patients given DDAVP on 173 occasions, either prophylaxis for surgery or treatment for bleeding	DDAVP (0.2–0.3 µg/kg, route of administration not specified) Two patients had side effects after surgery, relating to fluid retention. Mild side effects such as nausea, dizziness, or moderate fatigue in patients undergoing general anaesthesia could not solely be attributed to desmopressin
(Rodeghiero et al. 1996)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	79/169 patients, 43 vWD, 36 haemophilia A 219 bleeding episodes—including menorrhagia, tooth extraction, epistaxis, muscle haematoma and haemarthrosis	DDAVP (20 µg for >70 kg or 40 µg for <70 kg) subcutaneous in home treatment 30% of patients reported mild flushing, with or without headache. One patient had mild chest pain unlikely to be related to treatment

(cont.)

Table 11 (cont.) (de la Fuente et al. 1985)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	68 patients, 32 mild and 8 moderate–severe haemophilia A, 13 Type 1 vWD, 7 Type 2A vWD, 1 Type 2B vWD, aged 2–66 years 26 test doses, 17 bleeding episodes, 12 dental extractions, 24 surgical interventions	DDAVP (0.3 µg/kg) intravenous 24/68 adverse events: A 'warm feeling' or mild facial erythema. Other possible side effects may have been due to pre-existing medical problems, ie headaches (n=4), fatigue (n=2), oedema with transient rash (n=1). One patient was hyponatraemic and had a grand mal seizure after vomiting
(Dunn et al. 2000)	Level IV: case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	40 patients, 24 Types 1 and 2 vWD, 16 mild–moderate haemophilia A and symptomatic haemophilia A carriers aged 5–58 years Test dose	DDAVP intranasally, 150 µg if under 50k g, 300 µg if over 50 kg 27/40 side effects. 75% of vWD patients and 56% of haemophilia A patients. 78% had no or mild reactions (facial flushing, transient headache, burning/itching eyes) while 23% had moderate to severe adverse events (nausea, fatigue, moderate-severe headache, abdominal cramping, weight gain, vomiting, vertigo, ataxia, weakness)
(Warrier & Lusher 1983)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	38 patients, 31 vWD, 7 mild–moderate haemophilia A and 3 normal subjects 8 surgical events, 3 cases of menorrhagia, 4 patients with bleeding episodes	DDAVP via intranasal drip (2–4 µg/kg) or intravenous (0.2–0.3 µg/kg) No side effects
(Ghirardini et al. 1987)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias likely Follow-up adequate Uncontrolled	25 patients, 23 mild haemophilia A, 2 moderate haemophilia A Test dose	DDAVP (0.3 µg/kg) subcutaneous 5/25 adverse events: Modest facial flushing, transient headache, brief nausea
(Gill et al. 2002)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	25 patients, 9 haemophilia A, 16 vWD, Test dose	DDAVP intranasal (150 µg for under 50 kg) 12/25 (48%) 16 adverse events. Headache, congestion, fatigue, flushing, difficulty breathing, insomnia, generalised leg aches and stiff neck
(Ghirardini et al. 1988)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	24 patients, 16 mild haemophilia A, 2 moderate haemophilia A, 6 Type 1 vWD patients, 10 bleeding episodes, 6 dental extractions, 11 surgical interventions	DDAVP subcutaneous (0.3 µg/kg) A few reports of mild and transient facial flushing (cont.)

Table 11 (cont.) Study	Level and quality of evidence	Population	Adverse events to DDAVP
(Rose & Aledort 1991)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	22 patients, 11 vWD, 8 mild haemophilia A, 3 symptomatic carriers of haemophilia A Test doses	DDAVP (300 µg for adults, 150 µg for children-unspecified age) intranasally Approximately 50% nasal spray administrations resulted in facial flushing and/or transient headache. No other adverse events
(Chuansumrit et al. 1993)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	22 patients, 13 haemophilia A, 1 Type 1 vWD, 8 with inherited or acquired platelet dysfunction, aged 2–26 years 31 administration episodes, either treatment of bleeding episode or test dose	DDAVP (0.3–0.4 µg/kg) intravenous No adverse events
(Dewald et al. 1980)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	5 patients, 4 haemophilia A, 1 vWD 10 test doses	DDAVP (0.4 µg/kg) intranasal No side effects
(Mariana et al. 1984)	Level IV: case series Quality score: 1/3 Measurement bias possible Selection bias likely Follow-up adequate Uncontrolled	43 patients, 21 mild haemophilia A, 2 moderate haemophilia A, 20 vWD (Types 1 and 2) 29 dental extractions, 12 surgical procedures, 12 spontaneous bleeding episodes	DDAVP (0.3 µg/kg) intravenous 52 infusions, no side effects DDAVP (0.4 µg/kg) intravenous 13 infusions, no side effects
(Leissinger et al. 2001)	Level IV: case series Quality score: 1/3 Measurement bias minimised Selection bias possible Follow-up inadequately stated Uncontrolled	333 patients enrolled. 124 mild haemophilia A, 135 mild Type 1 vWD, 37 moderate Type 1 vWD, 23 haemophilia carriers, 14 other bleeding disorders, aged 5–64 years 45% of doses treated 748 episodes of bleeding, 19% prophylaxis, 35% for menorrhagia	DDAVP (150 µg) intranasal Overall 80 patients reported 272 adverse events. 80 had headaches, 59 had vasodilation/flushing, 33 had nausea, 23 had dizziness, 14 had asthenia, 8 vomited, 6 had peripheral oedema, and 49 had less common adverse events No. of adverse events/ no. of patients Mild Haemophilia A 80/124 Mild Type 1 vWD 117/135 Moderate Type 1 vWD 37/37 Haemophilia A carrier 24/23 Other bleeding disorders 14/14

[a] Information on population source not provided; DDAVP, 1-deamino-D-arginine vasopressin; vWD= von Willebrand Disease

Evidence-based clinical practice guidelines

On the basis of the available research, there are several modifications to the existing recommendations:

- DDAVP may be considered for all patients with mild/moderate haemophilia A or mild vWD. DDAVP is generally administered intravenously at a dose of 0.3 µg/kg diluted in 50 mL of 0.9% saline and infused over at least 30 minutes. Subcutaneous administration of DDAVP is comparable (Level II evidence). Efficacy should be demonstrated with a test dose irrespective of the route employed, by measuring FVIII/vWF. DDAVP should be used with caution during pregnancy and in elderly individuals (Level IV evidence). It is not recommended in those with evidence of arteriovascular disease and in young children (<2 years) (expert opinion).

- DDAVP is not recommended during labour. The evidence suggests that it is clinically effective in reducing bleeding when administered immediately postpartum (Level IV evidence).

- DDAVP may be considered for use prior to dental extractions or surgery in patients who respond to DDAVP (Level IV evidence).

- DDAVP should not be used as first treatment for patients with severe vWD. Type 1 and Type 2A vWD patients are deemed *likely* to respond, whereas Type 2B and Type 3 vWD are deemed *unlikely* to respond (Level IV evidence). However, DDAVP may assist as an adjunct to factor replacement therapy (Level II evidence).

- Caution should be taken to restrict fluid intake during DDAVP treatment to prevent fluid overload, leading to hyponatraemia (Level IV evidence). Daily measurement of serum sodium levels may be taken (expert opinion).

- DDAVP may be administered once during every 24 hours. If given for more than three consecutive days, repeated doses may lead to tachyphylaxis (Level IV evidence). If DDAVP is given more than once in 24 hours, predose monitoring of electrolyte concentrations is recommended (expert opinion).

Tranexamic acid

Previous Australian consensus-based guidelines

- Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin and is available in an intravenous or oral preparation. Tranexamic acid is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP.
- The recommended intravenous dose is 10 mg/kg 2–3 times daily and the oral dose 25 mg/kg 2-3 times daily. Tranexamic acid is contraindicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with Factor Eight Inhibitory Bypass Agents (FEIBA) or other prothrombin complex concentrates. Tranexamic acid can be used in conjunction with recombinant human coagulant factor VIIa bypassing agent.

See Appendix G for full details (Haemophilia Foundation Australia Medical Advisory Panel 2000)

Tranexamic acid is usually used in conjunction with other treatments, such as DDAVP, fibrin glue or factor replacement. Very few studies have evaluated the effects of tranexamic acid alone in individuals with coagulation disorders. One average quality randomised controlled trial (Level II evidence) investigated the effectiveness, and three case series (Level IV evidence) reported on the safety, of tranexamic acid (Table 12 and Table 13). Tranexamic acid was found to reduce the amount of factor concentrates needed in a group of patients with severe haemophilia A, but this difference was not statistically significant (Schiavoni et al. 1983). This study, however, was underpowered to detect benefits of the size observed.

The sample sizes of the studies that assessed safety were too small to detect less common side effects. While it appears safe (Level IV evidence), there is little evidence to support the effectiveness of tranexamic acid. Therefore, the literature does not provide enough information on which to change the consensus-based recommendations.

Table 12. Effectiveness of tranexamic acid

Study	Level and quality of evidence	Population	Effectiveness of tranexamic acid	
(Schiavoni et al. 1983)	Level II: randomised controlled trial Quality score: 13/27 External validity low Bias minimised Confounding avoided Reporting poor	26 patients, 17 severe haemophilia A, 2 mild haemophilia A, 7 severe haemophilia B	Tranexamic acid 25 mg/kg 3x daily as prophylaxis	Placebo
			11 traumatic bleeds	14 traumatic bleeds
			6 spontaneous bleeds	4 spontaneous bleeds
			589 units FVIII used per bleeding episode	825 units FVIII used per bleeding episode
			533 units FIX used per bleeding episode	637 units FIX used per bleeding episode
			No statistically significant differences between groups reflecting small sample sizes	

FVIII= factor VIII, FIX= factor IX

Table 13. Safety of tranexamic acid

Study	Level and quality of evidence	Population	Adverse events to tranexamic acid
(Sindet-Pedersen et al. 1988)	Level IV: case series Quality score: 1.5/3 Measurement bias partially minimised Selection bias possible Follow-up adequate Uncontrolled	15 patients, 13 haemophilia A, 2 haemophilia B 21 occasions of gingival haemorrhage	Tranexamic acid orally (25 mg/kg 4x daily) or as mouthwash (10 ml of 5% tranexamic acid solution, 4x daily for 2 minutes) No adverse events reported
(Ong et al. 1998)	Level IV: case series Quality score: 1/3 Measurement bias possible Selection bias possible Follow-up adequate Uncontrolled	4 patients with menorrhagia, 1 Type 1 vWD, 2 Type 2A vWD, 1 Type 2B vWD, aged 17–42 years. Previous treatments with DDAVP, oral contraceptives and regular dosing with tranexamic acid had failed	Single dose tranexamic acid (4 g for 3-5 days) 1 patient complained of occasional diarrhoea
(Mohri 2002)	Level IV: case series Quality score: 1/3 Measurement bias possible Selection bias possible Follow-up adequate Uncontrolled	2 patients with menorrhagia, 1 Type 1 vWD, 2 Type 2A vWD, aged 23–43 years	Single dose tranexamic acid (3 g for 1-5 days) No adverse events reported

DDAVP=1-deamino-D-arginine vasopressin; vWD= von Willebrand Disease

Evidence-based clinical practice guidelines

There was no evidence on which to base changes to the previous consensus-based recommendations. Dosing regimens provided in the current guidelines are consistent with manufacturer's recommendations. No paediatric dosages are provided.

Fibrin glue

There were no available studies that satisfied the inclusion criteria to assess the effectiveness of fibrin glue, although two studies provided data on safety. While conclusions need to be interpreted with caution as the sample sizes in the included studies were too small to report less common side effects, fibrin glue appears to be a very safe product, without any side effects, that can be used in conjunction with other products (Level IV evidence).

Table 14. Safety of fibrin glue

Study	Level and quality of evidence	Population	Adverse events after use of fibrin glue
(Avanoglu et al. 1999)	Level IV: prospective case series Quality score: 2/3 Measurement bias unlikely Selection bias possible Follow up uncertain Uncontrolled	22 patients, 21 haemophilia A, 1 haemophilia B, aged 6–17 years 22 circumcisions, 11 with fibrin glue, 11 without	Fibrin glue used with pdFVIII or pdFIX and tranexamic mouth wash One bleeding episode due to erection No other adverse events noted
(Rakocz et al. 1993)	Level IV: case series Quality score: 2/3 Measurement bias unlikely Selection bias possible Follow-up adequate Uncontrolled	80 patients with bleeding disorders, 37 severe haemophilia A/B, 4 mild haemophilia A/B, 10 mild/moderate vWD, 29 other 135 dental extractions	Fibrin glue used with aprotinin concentration 1000 KIU/ml Secondary bleeding in 9/12 severe haemophilia patients due to insufficient effectiveness Fibrin glue used with aprotinin concentration 10,000 KIU/ml and tranexamic acid mouthwash No adverse events

KIU= Kallikrein Inhibitor Units; vWD= von Willebrand Disease

Prothrombin Complex Concentrates (PCCs)

Prior to the development of high-purity plasma derived factor IX and recombinant factor IX, PCCs were used predominantly for the treatment of haemophilia B patients. Given the availability of safer products, PCCs are now used rarely in patients *without inhibitors,* as they have been associated with an increased incidence of thrombotic events, such as disseminated intravascular coagulation (DIC) and thromboembolism (Scharrer 1995). Moreover, they are made from pooled human plasma, which has a theoretical risk of viral transmission. For evaluation of studies on the use of PCCs in patients *with inhibitors*, see section on Inhibitors and Tolerisation.

Treatment of Bleeding Episodes

Frequent, persistent and prolonged haemorrhage, either spontaneous or trauma-induced, is the main indication requiring immediate attention in patients with coagulation disorders. Treatment may take place in a variety of settings—emergency rooms, clinics, specialist haemophilia care centres and home treatment. The development and introduction of recombinant factors obviates the need to rely on plasma as the sole source of antihaemophilic factors and provides a potentially unlimited resource.

For an evaluation of the treatment of bleeding episodes in haemophilia A or B patients *with inhibitors*, see section on Inhibitors and Tolerisation.

Haemophilia A, without inhibitors

In Australia, the factor replacement products used for the treatment of patients with haemophilia A, without inhibitors, are recombinant or plasma-derived factor VIII products. The recombinant factor VIII (rFVIII) products are: Recombinate™ (Baxter), Helixate® and Kogenate® (Bayer), and ReFacto® (Wyeth Pharmaceuticals). The only plasma-derived factor VIII product available in Australia is Biostate® (CSL). These factors, which vary due to differences in manufacturing processes, are detailed above (see section on Selection of Products).

Previous Australian consensus-based guidelines

- Haemophilia A (without inhibitors): Recombinant factor VIII is the treatment of choice for all patients.
- Mild-moderate haemophilia A (without inhibitors): Intravenous DDAVP (0.3 mcg/kg) may be considered. Use with caution in elderly patients and pregnant women.

See Appendix G for details (Haemophilia Foundation Australia Medical Advisory Panel 2000)

Are treatments effective?

Thirteen studies—ranging from Level II to Level IV evidence—investigated the effectiveness of rFVIII concentrates in haemophilia A patients.

In general, the effectiveness of treatments for haemophilia (A or B) is measured using specific pharmacokinetic analyses, including the factor coagulant activity, half-life and response or recovery. These indicate the rate at which the plasma factor levels rise after treatment. The commonly used measures of factor activity are defined as follows:

FVIII:C*	Coagulant activity of FVIII—refers to specific levels or concentration of plasma FVIII. eg FVIII:C<1 IU/dL = severe haemophilia A IU = International Units—1 IU, as defined by the World Health Organization standard for human blood coagulation FVIII is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma (Bayer Healthcare). 1 IU FVIII/kg body weight is expected to raise plasma FVIII activity by 2%. A ratio of actual to predicted FVIII recovery ≥0.66 is considered within normal limits (Bray et al. 1994).
Incremental Recovery	Increase of FVIII:C/Actual dose (IU) of FVIII/body weight (kg) (Yoshioka et al. 2001)
In vivo recovery (%)	(FVIII:C after infusion of FVIII – FVIII:C before infusion of FVIII (IU/dL)/ expected rise in plasma FVIII:C x 100 (Yoshioka et al. 2001)

*Official abbreviation for the factor VIII functional assay is now FVIII (Kasper 2004)

To obtain plasma FVIII recovery data, blood samples are drawn before infusion of factor concentrate (to obtain a baseline measure) and 10 minutes after infusion for comparison. Clearly, this procedure is less likely to occur for more serious acute bleeding episodes and/or in young children. Therefore, the available studies provide data on FVIII recovery from patients in a non-bleeding state and include a mixture of patients undergoing treatment for bleeding episodes, prophylaxis, surgery or dental procedures.

Comparison of recombinant products

One good quality randomised double-blinded crossover trial (Level II evidence) showed equivalent efficacy between a newly developed recombinant antihaemophilic factor (rAHF-PFM) and a recombinant FVIII (Recombinate™). The former was produced by a plasma/albumin-free method and the latter was processed by a better known method using genetically engineered cells cultured in the presence of human/animal plasma proteins or stabilised with human albumin (Tarantino et al. 2004).

Comparison of recombinant and plasma-derived products

One good quality randomised crossover trial (Level II evidence) showed the mean FVIII activity was equivalent after infusion of either plasma-derived or recombinant factor concentrate (Fijnvandraat et al. 1997; Berntorp 1997). In three studies, including one study conducted in a paediatric population (Kelly et al. 1997), there appeared to be an advantage in FVIII recovery after infusion with rFVIII compared to pdFVIII in non-bleeding previously treated patients (PTPs) (Kelly et al. 1997; Morfini et al. 1992; Schwartz et al. 1990) (Level III-1 and III-2 evidence) (Table 15). However, inadequate randomisation or incomplete blinding of outcomes in the lower level studies may have yielded an overestimate of effect.

Overall, the higher-level evidence indicates that there is no difference or, at the most, a slightly better factor VIII recovery after infusion with rFVIII compared to pdFVIII (Table 15).

Table 15. FVIII recovery following treatment with rFVIII in haemophilia A patients

Study	Level and quality of evidence	Population	Incremental FVIII recovery (IU/kg^{-1})		
(Tarantino et al. 2004)	Level II: double-blinded randomised crossover trial Quality score: 25/27 Selection bias minimised Confounding avoided Follow-up adequate Patients representative	56 PTPs with moderate-severe haemophilia A, aged 10–65 years, without inhibitors, with ≥150 exposure days	rAHF-PFM[a] (50 IU/kg) 2.6±0.5	rFVIII (50 IU/kg) 2.4±0.5	% change 8.3% NS
(Fijnvandraat et al. 1997; Berntorp 1997)	Level II: randomised single-blinded (patient) crossover trial Quality score: 21/27 Selection bias minimised Confounding avoided Follow-up adequate Patients representative	12 PTPs with severe haemophilia A, aged 17–64 years, without inhibitors	rFVIII SQ[b] (50 IU/kg) 2.4±0.21	pdFVIII (50 IU/kg, Octonativ) 2.4±0.26	% change 0
(Kelly et al. 1997)	Level III-1: quasi-randomised single-blinded (investigator) controlled trial Quality score: 21/27 Clinical importance[e]: 2/4 Selection bias minimised Confounding avoided Follow-up adequate Patients representative	10 non-bleeding PTPs with severe haemophilia A, aged 6–12, without inhibitors	rFVIII (50 IU/kg, Recombinate™) 1.91±0.14%	pdFVIII (50 IU/kg, Hemofil® M) 1.5±0.15%	% change 27.3% p=0.007
(White et al. 1997)	Level III-2: non-randomised crossover trial Quality score: 20/27 Selection bias unclear Confounding avoided Follow-up adequate Patients representative	69 PTPs with moderate-severe haemophilia A, without inhibitors	rFVIII (50 IU/kg, Recombinate™) 2.40±0.97	pdFVIII (50 IU/kg, Hemofil® M) 2.47±0.33	% change 2.9% p=0.59
(Schwartz et al. 1990; Seremetis et al. 1999)	Level III-2: non-randomised crossover trial Quality score: 19/27 Clinical importance[e]: 3/4 Selection bias unclear Confounding avoided Follow-up adequate Patients representative	17 non-bleeding PTPs with moderate-severe haemophilia A, without inhibitors	rFVIII (50 IU/kg) 2.68±0.52	pdFVIII (50 IU/kg, Koate HS) 2.42±0.33	% change 10.7% p=0.026

(cont.)

Table 15 (cont.) Study	Level and quality of evidence	Population	Incremental FVIII recovery (IU/kg^{-1})		
(Morfini et al. 1992)	Level III-2: non-randomised crossover trial Quality score: 16/27 Clinical importance[e]: 3/4 Selection bias possible Confounding avoided Follow-up adequate Patients representative	47 PTPs with severe haemophilia A, without inhibitors	rFVIII (50 IU/kg, Recombinate™) 2.31[c] In vivo recovery (%) 107.1±45.6	pdFVIII (50 IU/kg, Hemofil® M) 1.99[c] 92.2±32.0	% change 16.1% 14.9% p<0.019
(Arkin et al. 1991)	Level III-3: historical control study Quality score: 5/27 Selection bias likely Confounding likely Follow-up uncertain External validity uncertain[d]	14 non-bleeding PTPs with moderate-severe haemophilia A, aged 4–72, without inhibitors Historical controls: no description provided	rFVIII (20–40 IU/kg, 3 x week) 2.7±0.6	pdFVIII 2.5±0.33	% change 8.0% p=0.29
(Aygoren-Pursun et al. 1997)	Level IV: uncontrolled before-and-after study Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	39 PTPs with mild-severe haemophilia A, aged 2–62 years, treated for bleeding episodes, prophylaxis and surgery		rFVIII (50 IU/kg, Kogenate®) Month 0 Month 12	 2.4±0.83 2.12±0.61
(Yoshioka et al. 2001)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	20 PTPs with moderate-severe haemophilia A, aged 12–55 years, without inhibitors, treated for bleeding episodes		rFVIII-FS[d] (10-50 IU/kg, Kogenate®) Week 0 Week 12 Week 24	 1.73±0.40 1.84±0.40 1.95±0.55

[a] recombinant antihaemophilic factor, plasma albumin-free; [b] recombinant B-domain deleted FVIII; [c] calculated by authors from data provided; [d] recombinant FVII formulated with sucrose; [e] Rank scores for the clinical importance of the benefit/harm (1/4 ranked highest and 4/4 ranked lowest); [d] Information on population source not provided; MTPs = minimally treated patients; PTPs = previously treated patients; PUPs = previously untreated patients

Effectiveness of treatment of bleeding episodes with rFVIII was also assessed according to the number of infusions needed to control haemostasis. Seven before-and-after studies or case series (Level IV evidence) consistently reported that approximately 90% of bleeding episodes were managed with 1–2 infusions and were rated as excellent or good by patients or physicians, using a four- or five-point Likert scale, ranging from excellent to no or less effect (Table 16).

Table 16. Number of infusions required to control haemostasis in haemophilia A patients

Study	Level and quality of evidence	Population	Control of haemostasis	
			Number of infusions per bleeding episode	% of bleeding episodes
(Gringeri et al. 2004)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	25 PTPs with severe haemophilia A, aged 6–60 years, without inhibitors, treated for bleeding episodes	1 2 3 4 >4	76.7 12.2 6.6 2.8 1.7
(Schwartz et al. 1990; Seremetis et al. 1999)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	58 PTPs with moderate–severe haemophilia A, without inhibitors, treated	1 2 ≥2	82.0 12.0 6.0
(Aygoren-Pursun et al. 1997)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	39 PTPs with mild-severe haemophilia A, aged 2–62 years, treated with rFVIII (Kogenate®) for bleeding episodes, prophylaxis and surgery	1 2 3 4 ≥5	75.5 14.5 5.6 1.4 3.1
(Yoshioka et al. 2003)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	43 PUPs and MTPs with mild-severe haemophilia A, aged 3–386 months, treated with rFVIII (Kogenate®) for bleeding episodes	1 2 3	98.5 1.4 0.1
(Lusher et al. 2004)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	102 PUPs with mild-severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	1 2 3 4 ≥5	82.2 10.9 3.2 1.3 2.3
(Yoshioka et al. 2001)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	20 PTPs with moderate-severe haemophilia A, aged 12–55 years, without inhibitors, treated for bleeding episodes	Mean number of infusions per bleeding episode	1.4±1.2
(Giangrande 2002)	Level IV: case series Quality score: 1/3 Selection bias uncertain Follow-up uncertain Uncontrolled	31 PUPs and MTPs with severe haemophilia A, aged ≤ 4 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	1-2	88.1

MTPs = minimally treated patients; PTPs = previously treated patients; PUPs = previously untreated patients

Are treatments safe?

In the early 1980s, up to 80% of haemophilia patients became infected with HIV through transfusion of infected plasma-derived products. Since then, the safety of plasma-derived factor concentrates has improved substantially with the introduction of two virus inactivation procedures: 1) solvent/detergent treatment, which inactivates lipid-enveloped viruses; and 2) heat treatment, which targets non-lipid enveloped viruses (Ananyeva et al. 2004). There have been no reports of HIV in Australia since the introduction of heat and solvent/detergent (SD) treatment of coagulation factor concentrates (Haemophilia Foundation Australia Medical Advisory Panel 2000).

More recently, nanofiltration, which filters out lipid-enveloped viruses and prions, has been developed. For example, the Pall Corporation has developed membrane filtration technology to remove prions, such as those associated with variant Creuztfeldt-Jakob disease (vCJD) in humans and Bovine Spongiform Encephalopathy in cattle (Pall Corporation 2004). Late stage testing of the Leukotrap® Affinity prion reduction filter has shown effective removal of different strains of infectious prions, including vCJD and scrapie, from red blood cell concentrates. However, there remains a theoretical risk that previously unrecognised infective agents may still gain access to the donor pool. For example, although there has been no reported transmission of blood-borne viral agents in Australia since 1990 (JBC FVIII/FIX working party & National Blood Authority 2004), confidence in plasma-derived products was seriously undermined in Japan when 1) plasma-derived products produced from pooled plasma were withdrawn after donors were diagnosed with Creutzfeld Jacob disease; and 2) evidence of hepatitis A transmission through pdFVIII products was revealed (Yoshioka et al. 2001). Therefore, methods used to purify plasma-derived products are a direct function of the accuracy of information concerning novel infectious agents.

Recombinant products, which contain no components from the donor pool, are believed to offer substantial protection from viral transmission. However, the use of human albumin as a stabiliser during the production of recombinant products has the theoretical potential to introduce pathogens, such as prions or unknown agents, into these products. Only the complete exclusion of *all* human or animal proteins would eliminate that possibility. Recombinant products are continuously in development and the potential immunogenicity of recombinant factors is still in question. Further, the transfer of patients to different blood coagulation products was thought to increase the potential risk for inhibitor development following a cluster of cases with inhibitors after patients were switched to products that had undergone newly developed viral inactivation processes (Ewenstein et al. 2004). The viral inactivation methods were thought to have modified the tertiary structure of the FVIII molecule, thereby exposing neoantigens.

The key safety outcomes reported in the studies included in this review are: the transmission of viral infections, the development of inhibitors to FVIII and adverse reactions to the treatment. Several studies also reported immunogenic responses to proteins used in the recombinant manufacturing process, including murine immunoglobulins and hamster proteins, and seroconversions for human immunodeficiency virus (HIV), hepatitis (A, B, or C) or parvovirus (B19).

Transmission of viral infections

One good quality retrospective cohort study (Level III-2 evidence) evaluated the risk of human parvovirus B19 transmission in rFVIII, a combination of rFVIII and pdFVIII,

and pdFVIII alone (Soucie et al. 2004). The patients who received pdFVIII had 7.6 times the odds of B19 antibody seropositivity compared to patients who had never received blood or blood components (OR= 7.6, 95% CI 3.6, 15.9). Patients who received only rFVIII had an equivalent risk to patients who had never received blood or blood components (OR= 0.8, 95% CI 0.4, 1.5) (Level III-2 evidence).

No included studies reported new cases of viral transmission such of HIV, hepatitis A, B or C, after treatment with either plasma-derived or recombinant factor concentrate. In addition, there were no reports of adverse reactions in patients with a positive antibody reaction to animal proteins, even in cases with detectable pre-existing antibodies to these proteins (White et al. 1997) (Level IV evidence).

One average quality historically controlled study (Level III-3 evidence) examined the immune status of HIV seropositive and seronegative haemophilia A patients treated with rFVIII (Mannucci et al. 1994). The percentage of CD4 and CD8 cells, a surrogate measure of HIV infection, showed no significant change in seronegative or seropositive patients over a period of 3.5 years. However, a small but significant decrease in the *absolute* count of CD4 cells was apparent in HIV seropositive patients (p=0.001). The clinical significance of this difference is unclear.

Development of inhibitors

Inhibitor detection is conducted using the Bethesda assay, with or without the Nijmegen modification (Verbruggen et al. 1995), and results are expressed in Bethesda units (BU)[g]. If the inhibitor titre is high (>5 BU/ml), factor replacement therapy is ineffective and bleeding persists. With low titre inhibitor (<5 BU/ml), haemostasis may be achieved with higher doses. Patients with severe haemophilia A with high-titre inhibitors are most at risk for recurrent bleeds and chronic haemarthroses.

The best available evidence to determine the rate of inhibitor development in recombinant compared to plasma-derived products was provided by one average quality non-randomised controlled trial (Level III-2 evidence) in which patients were transferred from plasma-derived factors to recombinant factor products (Giles et al. 1998) and two good-average quality case series (Level IV evidence) in patients who had previously been treated with plasma-derived factors (Gringeri et al. 2004). After two years and six months follow-up, respectively, neither study showed evidence of increased incidence in FVIII inhibitors following transfer. Results are shown in Table 17.

Of four case series that included patients previously treated with pdFVIII, two studies reported low-level transient inhibitors in one patient (0.9% and 1.4%) (Schwartz et al. 1990; Tarantino et al. 2004; White et al. 1997; Yoshioka et al. 2001). One patient had severe haemophilia (Tarantino et al. 2004) while the other had a history of inhibitor development with use of pdFVIII (White et al. 1997). However, previously treated patients (PTPs) without inhibitors are thought to be at lower risk of inhibitor development—compared to previously untreated patients (PUPs)—since PTPs failed to develop inhibitors with previous replacement therapy (Lusher et al. 1993; Yoshioka et al. 2003).

---

[g] Bethesda units (BU) = a measure of inhibitor activity – the amount of inhibitor that inactivates 50% or 0.5 units of a coagulation factor during the incubation period

One poor quality historically controlled study (Level III-3 evidence) and six case series (Level IV evidence) assessed the development of inhibitors in PUPs or minimally treated patients (MTPs)[h] following treatment with rFVIII. Slightly higher levels of both high-titre and low-titre inhibitors were detected in pdFVIII-treated patients compared to rFVIII-treated patients. However, results from this study are subject to considerable selection and measurement biases.

In the lower level evidence (Level IV evidence) studies that assessed development of inhibitors in haemophilia A patients receiving rFVIII products, the proportion of patients developing high or low titre inhibitors varied widely across studies (0–23%). The characteristics of patients (severity of disease, previous treatments), factor products, and differences in study methodology (length of follow-up, frequency of inhibitor testing) may influence the reported rate of inhibitor development. For example, transient or low concentration inhibitors were more likely to be detected if patients were tested for inhibitors—whether clinically indicated or not—compared to studies that performed tests only when presence of inhibitors was clinically indicated. The latter studies tend to underestimate the incidence of inhibitor formation (Lusher et al. 1993).

Therefore, since the available evidence indicates that recombinant factors, which provide a higher safety profile with respect to viral transmission, do not induce higher rates of inhibitor development, they should be the first line of treatment (Level III-2 evidence).

[h] MTPs—minimally treated patients who have received ≤ 2 prior infusions with either recombinant or plasma-derived products

Table 17. Development of inhibitors in haemophilia A patients treated with recombinant factor VIII

Study	Level and quality of evidence	Population	No. of patients with inhibitor development
Patients transferred from pdFVIII to rFVIII			
(Giles et al. 1998)	Level III-2: non randomised controlled trial Quality score: 15/27 Selection bias not minimised (patient self-selection) Confounding unclear Follow-up adequate External validity uncertain[a]	872 PTPs with mild–severe haemophilia, transferred from plasma-derived products to recombinant or affinity-purified FVIII	rFVIII (N=339) / AP-FVIII (N=32) High-titre inhibitors: 17 (5.0%) / 2 (6.3%) Low-titre inhibitors: 52 (15.3%) / 5 (15.6%)
(Gringeri et al. 2004)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	25 PTPs with severe haemophilia A, aged 6–60 years, without inhibitors, treated for bleeding episodes	High-titre inhibitor: 1 (4.0%) Low-titre inhibitor: 0
	Level IV: case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	94 PTPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes or prophylaxis	High-titre inhibitor: 1 (1.1%) Low-titre inhibitor: 0

(cont.)

Table 17 (cont.) Previously treated patients (PTPs)				
(Tarantino et al. 2004)	Level IV: case series Quality score: 3/3 Selection bias minimised Confounding avoided Follow-up adequate Uncontrolled	108 PTPs with moderate-severe haemophilia A, aged 10–65, without inhibitors, with ≥150 exposure days	High-titre inhibitor Low-titre inhibitor	0 1 (0.9%) transient
(White et al. 1997)	Level IV: case series Quality score: 2/3 Selection bias uncertain Confounding avoided Follow-up adequate Uncontrolled	69 PTPs with moderate–severe haemophilia A, without inhibitors	High-titre inhibitor Low-titre inhibitor	0 1 (1.4%) transient
(Schwartz et al. 1990; Seremetis et al. 1999)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	58 PTPs with moderate–severe haemophilia A, without inhibitors, treated	None detected	
(Yoshioka et al. 2001)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	20 PTPs with moderate–severe haemophilia A, aged 12–55 years, without inhibitors, treated for bleeding episodes	None detected	
Previously untreated patients (PUPs)				
(Kreuz et al. 2002)	Level III-3: historical control study Quality score: 11/27 Selection bias likely Confounding possible Follow-up unclear Patients representative	72 PUPs with moderate–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis, or surgery	rFVIII (N=21) High-titre inhibitors Low-titre inhibitors Total	pdFVIII (N=51) 4 (19.0%) 13 (25.5%) 0 5 (9.8%) 4 (19.0%) 18 (35.3%)
(Lusher et al. 2004)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate	102 PUPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	High-titre inhibitor Low-titre inhibitor	12 (11.8%) 9 (8.8%) 8 transient
(Lusher et al. 1993)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate	95 PUPs with mild–severe haemophilia A, aged 0–658 months, treated for bleeding episodes or prophylaxis	High-titre inhibitor Low-titre inhibitor	5 (5.3%) 11 (11.6%) 4 transient

(cont.)

Table 17 (cont.) Study	Level and quality of evidence	Population	Inhibitor development associated with factor replacement therapy	
(Bray et al. 1994)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate	73 PUPs with moderate–severe haemophilia A, aged 2 days–50 months, without inhibitors, treated for bleeding episodes or prophylaxis	High-titre inhibitor Low-titre inhibitor	8 (11.0%) 9 (12.3%) 5 transient
(Rothschild et al. 1998)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate	50 PUPs with severe haemophilia A, aged 1–43 months, treated for bleeding episodes or prophylaxis	High-titre inhibitor Low-titre inhibitor	7 (14.0%) 7 (14.0%) 2 transient
(Yoshioka et al. 2003)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate	43 PUPs and MTPs with mild–severe haemophilia A, aged 3–386 months, treated with rFVIII (Kogenate®) for bleeding episodes	High-titre inhibitor Low-titre inhibitor	5 (11.6%) all severe 10 (23.3%) 8 severe 2 moderate 7 transient
(Giangrande 2002)	Level IV: case series Quality score: 1/3 Selection bias uncertain Follow-up uncertain	31 PUPs and MTPs with severe haemophilia A, aged ≤ 4 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	High-titre inhibitor Low-titre inhibitor	1 (3.2%) 3 (9.7%) 2 transient

[a] Information on population source not provided; AP-FVIII= affinity-purified factor VIII; MTPs = minimally treated patients; PTPs = previously treated patients; PUPs = previously untreated patients

Eight low level studies (Level IV evidence) measured the number of days of exposure (ED) to factor concentrates prior to inhibitor development. The median ED varied between five and 17 days across studies (Table 18). It is suggested that inhibitors be tested for no earlier than three days after administration of factor concentrates, or when the expected response is absent (Level IV evidence).

Table 18. Exposure days prior to inhibitor development in haemophilia A patients treated with recombinant factor VIII

Study	Level and quality of evidence	Population	Number of exposure days (ED) prior to inhibitor development	
			Inhibitor positive	Median ED (range)
Previously treated patients (PTPs)				
(Gringeri et al. 2004)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	25 PTPs with severe haemophilia A, aged 6–60 years, without inhibitors, treated for bleeding episodes	1 (4.0%)	5
	Level IV: case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	94 PTPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes or prophylaxis	1 (1.1%)	10
Previously untreated patients (PUPs)				
(Lusher et al. 2004)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	102 PUPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	21 (20.6%)	9 (3–54)
(Bray et al. 1994)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	73 PUPs with moderate–severe haemophilia A, aged 2 days–50 months, without inhibitors, treated for bleeding episodes or prophylaxis	17 (23.9%)	9 (3–45)
(Rothschild et al. 1998)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	50 PUPs with severe haemophilia A, aged 1–43 months, treated for bleeding episodes or prophylaxis	14 (28.0%)	17 (3–69)
(Yoshioka et al. 2003)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	43 PUPs and MTPs with mild–severe haemophilia A, aged 3–386 months, treated with rFVIII (Kogenate) for bleeding episodes	15 (34.9%)	12 (1–48)
(Kreuz et al. 2002)	Level IV: case series Quality score: 1/3 Selection bias likely Confounding possible Follow-up unclear Uncontrolled	72 PUPs with moderate–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis, or surgery	22 (31%)	15 (4–195)

(cont.)

Table 18 (cont.) Study	Level and quality of evidence	Population	Number of exposure days (ED) prior to inhibitor development	
			Inhibitor positive	Median ED (range)
(Giangrande 2002)	Level IV: case series Quality score: 1/3 Selection bias uncertain Follow-up uncertain Uncontrolled	31 PUPs and MTPs with severe haemophilia A, aged ≤ 4 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	4 (12.9%)	8 (3–12)

MTPs = minimally treated patients; PTPs = previously treated patients; PUPs = previously untreated patients

Adverse events and complications

A broad range of adverse events were found to be associated with rFVIII infusions—but in a relatively small proportion of patients (<1.0%). Reactions were mild to moderate in severity, transient or reversible, and none resulted in discontinuation of treatment. Results are shown in Table 19.

Table 19. Adverse events in haemophilia A patients treated with recombinant factor VIII

Study	Level and quality of evidence	Population	Adverse events	Ratio of adverse events to total number of infusions
(Tarantino et al. 2004)	Level IV: case series Quality score: 3/3 Selection bias minimised Confounding avoided Follow-up adequate Patients representative Uncontrolled	108 PTPs with moderate–severe haemophilia A, aged 10–65, without inhibitors, with ≥150 exposure days	19 mild–moderate adverse events related to AHF-PFM: Taste perversion, headache, fever, diarrhoea, dizziness, hot flushes, pain (upper abdomen, lower chest), shortness of breath, sweating, nausea, itching	Adv. events = 19 Total number of infusions = 12,597 Ratio = 0.15%
(Schwartz et al. 1990; Seremetis et al. 1999)	Level IV: case series Quality score: 3/3 Selection bias minimised Follow-up adequate Uncontrolled	58 PTPs with moderate–severe haemophilia A, without inhibitors, treated for bleeding episodes or surgical procedures	42 mild-moderate adverse events associated with Kogenate®: Burning/erythema at infusion site, nausea, pruritis, dizziness, rash, dyspnea, chest tightness, dry mouth	Adv. events =42 Total number of infusions =17,922 Ratio = 0.23%
(Lusher et al. 2004)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	102 PUPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	16 mild–moderate adverse events associated with Kogenate®: Urticaria, flushing, erythema, rash	Adv. events =16 Total number of infusions =13,464 Ratio = 0.12% (cont.)

Table 19 (cont.) (Lusher et al. 1993)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	95 PUPs with mild–severe haemophilia A, aged 0–658 months, treated for bleeding episodes or prophylaxis	3 minor adverse events associated with Kogenate®: Urticaria, flushing, erythema at infusion site	Adv. Events =3 Total number of infusions =3,315 Ratio = 0.09%
(Bray et al. 1994)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	73 PUPs with moderate–severe haemophilia A, aged 2 days–50 months, without inhibitors, treated for bleeding episodes or prophylaxis	1 transient adverse event, which existed prior to infusion, worsened by Recombinate™: Erythematous rash	Adv events =1 Total number of infusions =1,785 Ratio = 0.06%
(White et al. 1997)	Level IV: case series Quality score: 2/3 Selection bias uncertain Confounding avoided Follow-up adequate Uncontrolled	69 PTPs with moderate–severe haemophilia A, without inhibitors	13 mild transient adverse events: Slight flushing, nausea, tiredness, epistaxis, brief dizziness	Adv events =13 Total number of infusions =13,591 Ratio = 0.10%
(Aygoren-Pursun et al. 1997)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	39 PTPs with mild–severe haemophilia A, aged 2–62 years, treated for bleeding episodes, prophylaxis and surgery	3 mild and transient adverse events associated with Kogenate®: Flushing, paraesthesia at infusion site, headache	Adv. Events =3 Total number of infusions =3,679 Ratio = 0.08%

AHF-PFM = antihaemophilic factor, plasma/albumin free; PTPs = previously treated patients; PUPs = previously untreated patients

Overall, the data evaluated in this review suggest that rFVIII is safe and effective for the treatment of haemophilia A patients (without inhibitors) and that inhibitor development is equally likely with rFVIII treatment or prophylaxis as with pdFVIII.

Evidence-based clinical practice guidelines

Based on the evidence, it is recommended that bleeding episodes be treated according to the existing guidelines, with modifications:

- Haemophilia A: Recombinant FVIII is the treatment of choice for patients with haemophilia A without inhibitors to FVIII (Level II evidence for effectiveness; Level III-2 evidence for safety). Inhibitor development is equally likely with rFVIII treatment or prophylaxis, as with pdFVIII (Level III-2 evidence).

- Patients should be tested for inhibitors no earlier than day three after initial administration of factor concentrate, particularly in young children and/or those with severe haemophilia A. Given the wide range in exposure days prior to inhibitor development, re-testing should be performed at regular intervals (Level IV evidence) or when expected response is absent (expert opinion).

Haemophilia B, without inhibitors

In Australia, the product used for treatment of patients with haemophilia B, without inhibitors, is recombinant factor IX (rFIX), BeneFIX® (Wyeth Pharmaceuticals). A purified plasma-derived FIX concentrate, MonoFIX-VF (CSL) is also available.

Previous Australian consensus-based guidelines

Haemophilia B: High purity FIX concentrates are preferred over prothrombin complex concentrates (PCCs).

See Appendix G for details (Haemophilia Foundation Australia Medical Advisory Panel 2000)

Are treatments effective?

Several studies (Bjorkman et al. 2001; Roth et al 2001a; White et al. 1998) provided data on the same group of patients and, where possible, the most comprehensive and up-to-date data were extracted.

Two good-to-average quality randomised crossover trials (Level II evidence) (White et al. 1998; Ewenstein et al. 2002) and one average quality historically controlled study (Level III-3 evidence) (Poon et al. 2002) showed lower factor recovery after rFIX infusion than for pdFIX in patients with haemophilia B ($p<0.0001$) (Table 20). The reduction in FIX recovery with rFIX was not only statistically significant, but also indicated clinical harm[i]. Importantly, two studies reported large inter-patient variability in pharmacokinetic analyses in both rFIX and pdFIX concentrates (Ewenstein et al. 2002; Poon et al. 2002). In addition, both rFIX and pdFIX showed lower recovery in young children (<16 years) compared with older children and adults.

However, dosage multiplication factors of 1.57 [95% CI 1.48-1.66] and 1.19 [95% CI 1.13-1.26] were recommended when treating haemophilia B patients aged ≤15 and >15 years, respectively, with rFIX (Poon et al. 2002). Findings from these studies suggest that patients with haemophilia B should be closely monitored for FIX activity/recovery after treatment with rFIX concentrate to optimise individual treatment regimens.

[i] Clinical importance of statistically significant effects was ranked according to the checklist provided in Appendix H. More than 20% reduction in FIX recovery—vs control group FIX recovery—indicated a clinical harm.

Table 20. FIX recovery following treatment of bleeding episodes in haemophilia B patients

Study	Level and quality of evidence	Population	Incremental FIX recovery, % IU/kg^{-1}		
(Ewenstein et al. 2002)	Level II: randomised crossover trial Quality score: 22/27 Clinical importance[a]: 1/4 Selection bias minimised Confounding avoided Follow-up adequate Patients representative	38 non-bleeding PTPs with severe haemophilia B, aged 7–75 years, without inhibitors	rFIX (50 IU/kg) 0.86±0.31	pdFIX (50 IU/kg) 1.71±0.73	% change p-value 49.7% p≤0.0001
(White et al. 1998)	Level II: randomised crossover trial Quality score: 17/27 Clinical importance[a]: 2/4 Selection bias minimised Confounding avoided Follow-up adequate External validity uncertain[b]	11 PTPs with haemophilia B	rFIX (50 IU/kg) 0.8±0.3	pdFIX (50 IU/kg) 1.2±0.3	% change p-value 33.3%
(Poon et al. 2002)	Level III-3: historical control study Quality score: 15/27 Clinical importance[a]: 1/4 Selection bias uncertain Confounding possible Follow-up adequate Patients representative	PTPs with mild–severe haemophilia B, aged 1–74 years	rFIX (N=126) (50 IU/kg) 0.77±0.19	pdFIX (N=74) (50 IU/kg) 1.05±0.26	% change p-value 26.7% p<0.0001
(Roth et al. 2001a; Bjorkman et al. 2001)	Level IV: uncontrolled before-and-after study Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery		rFIX (50 IU/kg)	
			Mean FIX activity increase	0.75 (range 0.34-1.38)	

[a] Rank scores for the clinical importance of the benefit/harm (1/4 ranked highest and 4/4 ranked lowest); [b] Information on population source not provided; PTPs = previously treated patients

One uncontrolled before and after study (Level IV evidence) showed that over 90% of bleeding episodes were controlled by 1–2 infusions of rFIX (Roth et al. 2001a; White et al. 1998) (Table 21).

Table 21. Number of FIX infusions required to control haemostasis in haemophilia B patients

Study	Level and quality of evidence	Population	Control of haemostasis	
			Number of infusions per bleeding episode	% of bleeding episodes
(Roth et al. 2001a) (White et al. 1998)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	1 2 3 4 >4	80.9 11.6 3.6 1.8 2.1

PTPs = previously treated patients

Are treatments safe?

Transmission of viral infections

The preparation of rFIX occurs without the use of animal or human plasma-derived products, thereby eliminating potential transmission of viruses or other known or unknown pathogens (Roth et al. 2001a). There were no reported cases of transmission of viral infections in patients treated with rFIX products.

Development of inhibitors

One uncontrolled before-and-after study (Level IV evidence) reported a transient low titre inhibitor in one patient with severe haemophilia (1.8%) after 39 days of treatment with rFIX (Roth et al. 2001a) (Table 22 and Table 23).

Table 22. Development of inhibitors in haemophilia B patients treated with recombinant factor IX

Study	Level and quality of evidence	Population	Inhibitor development associated with treatment	
(Roth et al. 2001a) (White et al. 1998)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	High-titre inhibitor Low-titre inhibitor	0 1 (transient)

PTPs = previously treated patients

Table 23. Exposure days prior to inhibitor development in haemophilia B patients treated with recombinant factor IX

Study	Level and quality of evidence	Population	Number of exposure days (ED) prior to inhibitor development	
			Inhibitor positive	Median ED (range)
(Roth et al. 2001a)	Level IV: uncontrolled before-and-after study Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	1 (1.8%)	39

PTPs = previously treated patients

Adverse events and complications

The majority of adverse events associated with rFIX were minor allergic reactions (Table 24). Data from the Canadian registry of haemophilia patients reported anaphylactic reactions to rFIX in two patients after 1–5 years of exposure (Poon et al. 2002).

Table 24. Adverse events in haemophilia B patients treated with recombinant factor IX

Study	Level and quality of evidence	Population	Adverse events	Ratio of adverse events to total number of infusions
(Roth et al. 2001a) (White et al. 1998)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	55 adverse events associated with rFIX: Minor allergic reaction	Adv. Events =55 Total number of infusions =7362 Ratio = 0.75%
(Poon et al. 2002)	Level IV: case series Quality score: 1/3 Selection bias uncertain Confounding possible Follow-up adequate Uncontrolled	244 PTPs with mild–severe haemophilia B	Anaphylactic reaction From Canadian registry data: 2 patients (of 244) exposed to rFIX for 1–5 years developed anaphylactic reactions	Not estimable

PTPs = previously treated patients

Evidence-based clinical practice guidelines

Based on the evidence, it is recommended that bleeding episodes in haemophilia B patients, without inhibitors, be treated in the following manner:

Haemophilia B: Recombinant FIX is safe for treatment of patients with haemophilia B without inhibitors (Level IV evidence). Due to the lower rFIX recovery compared to pdFIX, and the large inter-patient variability, individual dosing regimens should be monitored by FIX recovery/activity assays (Level II evidence). The recommended rFIX dosage, compared to pdFIX, should be increased by a multiplication factor of 1.6 for patients aged ≤15 years and 1.2 for patients aged 16 years and over (Level III-3 evidence).

Von Willebrand disease

Von Willebrand disease is caused by either quantitative or qualitative abnormalities of von Willebrand factor (vWF), which is required for coagulation. The three main types of von Willebrand disease are classified as 1, 2 or 3 and these are further divided into subtypes. The types listed in Australia on the Australian Bleeding Disorders Registry (ABDR)[j] are shown in Table 25.

Table 25. Number of patients listed on Australian Bleeding Disorders Registry for vWD subtypes

Type of vWD	Number of patients on the ABDR	Description (adapted from Kasper, 2004)
1	301	vWF is normal in structure; mild-moderate quantitative deficiency of vWF; ristocetin-induced platelet aggregation is normal
2 (undefined)	24	vWF is abnormal in structure; qualitative deficiency of vWF
2A	10	Decreased platelet-dependent vWF function; absence of high molecular weight multimers; ristocetin-induced platelet aggregation is reduced or absent; bleeding time is prolonged; collagen binding is low
2B	11	Increased platelet-dependent vWF function; absence of high molecular weight multimers; ristocetin-induced platelet aggregation is high at low concentrations of ristocetin cofactor
2M	16	Decreased platelet dependent vWF function, with normal multimeric structure; ristocetin cofactor is deficient
2N	3	Decreased vWF affinity for factor VIII
3	21	Patients are unable to synthesise vWF; virtual absence of vWF; usually severe deficiency; ristocetin cofactor levels are undetectable
Unrecorded	435	
Total	821	

ABDR= Australian Bleeding Disorders Registry, includes data from all states except NSW; vWD= von Willebrand Disease; vWF= von Willebrand factor

The goal of therapy in patients with von Willebrand disease is to correct the dual defect of abnormal platelet adherence and abnormal coagulation due to low factor VIII levels.

The methods of testing the effectiveness of treatments for von Willebrand disease differ from the methods appropriate with haemophilia. Effectiveness of treatments for von Willebrand disease may be tested by measuring the vWF antigen, vWF activity—ristocetin cofactor or collagen binding and bleeding time (See Table 26). High purity plasma concentrates have been found to return FVIII:C[k] to normal, without a reduction in bleeding time, therefore FVIII:C should not be used as the sole indicator of efficacy with von Willebrand patients (Berntorp 1994).

Platelet function analysers such as the PFA-100® (Dade) have been used for therapeutic monitoring of patients with vWD treated with DDAVP or FVIII/vWF concentrates (Franchini et al. 2002). However, a recent study indicates the PFA-100® has limited benefit in evaluating the effectiveness of treatment (Level II) (Favaloro et al. 2005).

[j] Including data on all Australian states except NSW

[k] FVIII:C= factor VIII coagulant activity

While it may detect changes in blood flow after DDAVP treatment, it was not useful in detecting improvements after treatment with pdFVIII/vWF concentrate.

Table 26. Methods of testing efficacy of treatments for von Willebrand disease*

Measure	Definition
BT	Bleeding time— time for the bleeding to stop from a superficial incision on the forearm. There are several different methods that result in different normal ranges. None of these measures of bleeding time are very sensitive or specific. Ivy method= less than 5 minutes Template method= less than 10 minutes Duke method= less than 3 minutes
PFA-100®	Platelet function analyser—measures blood flow through a capillary device and calculates the time to capillary occlusion, ie closure time. Measure of closure time is more sensitive than bleeding time, but it is also non-specific.
FVIII:C	Coagulant activity of FVIII—refers to specific levels/concentration of plasma FVIII
vWF:Ag	von Willebrand factor antigen—immunologic test, measured by ELISA, for the overall level of vWF:Ag in test plasma; expressed as a percentage of that in pooled, normal plasma (50–200% of the level in pooled normal plasma, sometimes expressed as 0.5-2.0 U/mL); levels of vWF:Ag are reduced in classical von Willebrand disease, usually to a similar extent as the reduction in factor VIII and vWF:Rco
vWF:FVIIIB	von Willebrand factor-factor VIII binding—measured by ELISA, which tests the ability of von Willebrand Factor (vWF) to bind factor VIII
vWF:CB	Functional assay that reflects the ability of von Willebrand factor to bind collagen; vWF:CB is low in all types except 2M. This test is used commonly in Australia.
Ristocetin cofactor tests	Functional assays that reflect the ability of vWF to aggregate normal platelets in the presence of ristocetin cofactor; commonly used as the initial test for von Willebrand factor activity as it is low in all but Type 2N von Willebrand disease
vWF:Rco	Uses 3 reagents: multiple dilutions of plasma, standard amount of normal platelets, and standard amount of ristocetin. Patient platelet aggregation times are compared to a standard curve to quantitate von Willebrand factor activity as vWF:Rco
RIPA	Ristocetin induced platelet aggregation uses 2 reagents: fresh platelet-rich plasma and 2 concentrations of ristocetin cofactor. While high concentration ristocetin always stimulates aggregation of normal platelet-rich plasma, low concentration ristocetin reveals any over-response, such as that seen in Type 2B.

*Methods are described for the purposes of interpreting literature and may not reflect current official tests and abbreviated terms (Kasper, 2004); ELISA= enzyme linked immunosorbent assay

Previous Australian consensus-based guidelines

- The use of desmopressin (DDAVP), which is preferred over plasma-derived products and is usually administered by intravenous infusion, in a dose of 0.3 µg/kg of body weight, diluted in 50 mL of 0.9% saline and infused over 30 minutes.
- Where DDAVP is not likely to be effective, or is contraindicated (i.e. patients with Type 2B von Willebrand disease), then factor VIII concentrate or purified von Willebrand factor is the treatment of choice.
- Cryoprecipitate is not recommended, as it cannot be virally inactivated and, therefore, carries a risk of viral infection. However, there are some circumstances where the administration of cryoprecipitate is justified.

See Appendix G for details (Haemophilia Foundation Australia Medical Advisory Panel 2000)

What treatments are used?

Recombinant products with von Willebrand factor are still in the research phase. Therefore, there are two main treatment options for the treatment of bleeding episodes: desmopressin (DDAVP) or transfusion with plasma-derived products. DDAVP is the treatment of choice for Type 1 patients, who account for 70–80% of cases (Mannucci 2001). However, DDAVP is contraindicated in Type 2B as it may cause thrombocytopenia and platelet aggregation due to the release of abnormal platelet aggregating multimers (Berntorp 1994). DDAVP may also be ineffective in patients with the more severe Type 3 von Willebrand disease (Level IV evidence) (Schulman et al. 1991). DDAVP should be used with caution in elderly patients and individuals with a history of heart disease, hypertension or stroke (expert opinion). For more information on the general recommendations on the use of DDAVP see section on Adjunctive haemostatic agents.

Patients contraindicated for DDAVP should be treated with a pdFVIII concentrate containing von Willebrand factor (Mannucci 2001). Biostate® (CSL) is the only pdFVIII/vWF concentrate for the treatment of von Willebrand disease that is registered for use in Australia (JBC FVIII/FIX working party & National Blood Authority 2004).

Are treatments effective?

DDAVP

Overall effectiveness of DDAVP for treating bleeding episodes and/or prophylaxis for patients with von Willebrand disease or mild haemophilia is assessed under the Adjunctive haemostatic agents section.

Plasma derived factor VIII and von Willebrand factor concentrates

Purified von Willebrand factor concentrates have been in use in France since 1989 (e.g. Wilfactin®, LFB) for the treatment of von Willebrand disease, but are currently unavailable in Australia. Therefore, only combined pdFVIII/vWF concentrates like Biostate® have been assessed for this review.

One randomised crossover trial (Level II evidence) and four case series studies (Level IV evidence) met our inclusion criteria for assessing the effectiveness of pdFVIII/vWF concentrates in patients with von Willebrand Disease for bleeding episodes (See Table 27).

The highest level of evidence was a randomised crossover pharmacokinetic study assessing the effectiveness and safety of two variations of plasma-derived concentrates in a group of Type 3 von Willebrand disease patients (Level II evidence). This study reported that Alphanate®, a product not currently available in Australia, reduced median bleeding time from over 30 minutes to 10.5 minutes. These results suggest that pdFVIII/vWF concentrates are effective in reducing prolonged bleeding time in patients with severe von Willebrand disease (Level II evidence) (Mannucci et al. 2002).

Several large case series (Level IV evidence) reported subjective data on the effectiveness of pdFVIII/vWF concentrates for treating bleeding episodes in von Willebrand patients. Haemostasis was rated by the clinician as 'excellent/good' in the majority of patients

after treatment (Level IV evidence) (Lillicrap et al. 2002; Dobrkovska et al. 1998; Auerswald et al. 2002; Gill et al. 2003).

Dobrkovska et al. (1998) reported that in a group of six patients with prolonged bleeding time, bleeding times for all patients had normalised at six and 22 hours after infusion (data not shown). These findings support the recommendation that pdFVIII/vWF concentrates can be administered every 8–12 hours depending on the individual response (Level IV evidence) (Dobrkovska et al. 1998).

The retrospective case series by Lillicrap et al. (2002) reported on the efficacy of Haemate® P in patients where DDAVP was known to be inadequate and where prophylaxis prior to surgery was indicated. The median dose given to patients to control bleeding episodes was 55.3 IU vWF:Rco/kg (range 17.1–227.5), the wide range indicating that individual assessment and monitoring of patients is essential. The minimum, haemostatically effective dose could not be ascertained from these data (Lillicrap et al. 2002).

Table 27. Effectiveness of plasma-derived factor VIII/von Willebrand factor concentrates in controlling bleeding episodes

Study	Level and quality of evidence	Population	Effectiveness
(Mannucci et al. 2002)	Level II: randomised crossover trial Quality score: 22/27 Selection bias minimised Confounding minimised Follow-up adequate External validity uncertain[c]	12 patients with Type 3 von Willebrand disease, treated with Alphanate® Solvent Detergent (A-SD) and Alphanate® Solvent Detergent/Heat-Treated (A-SD/HT)	Efficacy FVIII:C vWF:Ag vWF:Rco Mean in vivo half lives (hours) A-SD 20.9 12.4 7.1 A-SD/HT 23.8 12.9 6.5 Mean in vivo incremental recoveries (per IU/kg) A-SD 2.0% 2.5% A-SD/HT 2.1% 2.9% Median bleeding time Baseline 1 hour post treatment >30 minutes 10.5 minutes (Range=4.5-20.8 minutes)
	Level IV: case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	14 patients with von Willebrand disease, treated with 135 infusions of Alphanate® for 87 bleeding episodes 3 x Type 1 7 x Type 2A 4 x Type 3	All bleeding episodes controlled by treatment, no patients required alternative therapy 75% of bleeding episodes were controlled after 1 infusion
(Gill et al. 2003)	Level IV: prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	33 patients with von Willebrand disease, treated with 290 infusions of Haemate® P for 53 bleeding episodes—both surgical and spontaneous bleeding episodes 9 x Type 1 4 x Type 2A 7 x Type 2B 27 x Type 3 6 x Other	52/53 (98%) bleeding episodes had 'excellent/good' haemostasis after treatment
(Auerswald et al. 2002)	Level IV: before and after case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	14 patients with vWD, treated with Immunate® for 14 acute bleeds or surgical events	Haemostasis after treatment of bleeding episodes considered 'Excellent' or 'Good' in all patients Perioperative bleeds normal in most cases 3/14 patients experienced post operative complications, 2 related to insufficient cover (cont.)

Table 27 (cont.) (Lillicrap et al. 2002; Dobrkovska et al. 1998)	Level IV: retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	97 patients with von Willebrand disease, 344 bleeding events treated with Haemate® P 32 x Type 1 5 x Type 2A 18 x Type 2B 28 x Type 3 14 x Other	Type 1 vWD: 'Excellent/good' haemostasis in 32/32 (100%) bleeding episodes Type 2A vWD: 'Excellent/good' haemostasis in 17/17 (100%) bleeding episodes Type 2B vWD: 'Excellent/good' haemostasis in 60/60 (100%) bleeding episodes Type 3 vWD: 'Excellent/good' haemostasis in 198/208 (95%) bleeding episodes, 'Poor' haemostasis in 10/208 (5%) bleeding episodes Other types vWD: 'Excellent/good' haemostasis in 25/27 (93%) bleeding episodes, 'Poor' haemostasis in 2/27 (7%) bleeding episodes FVIII:C (IU dL^{-1} per IU kg^{-1}) Median in vivo recovery= 1.94, Range= 1.21-4.58 vWF:RCo (IU dL^{-1} per IU kg^{-1}) Median in vivo recovery= 1.23, Range= 0.59-2.44
(Dobrkovska et al. 1998)	Level IV: case series Quality score: 2/3 Measurement bias unlikely Selection bias possible Follow-up adequate Uncontrolled	6 patients with von Willebrand disease, given a bolus infusion of Haemate® P (80 IU vWF:RCo kg^{-1} bw and 32 IU FVIII:C kg^{-1} bw) Test dose 2 x Type 1B 2 x Type 2A 2 x Type 3	Efficacy vWF:RCo [a] vWF:Ag [a] FVIII:C [a] In vivo recovery (IU dl/kg) 2.10 (1.10-2.74) 1.88 (1.67-2.90) 2.69 (1.94-3.65) In vivo recovery (%) 73 (50-96) 69 (51-102) 99 (66-168) Half-life (hours) 11.3 (6.4-13.3) 15.2 (13.2-17.4)
(Federici et al. 2002)	Level IV: retrospective case series Quality score: 1/3 Measurement bias possible Unable to assess selection bias Follow-up adequate Uncontrolled	10/22 patients with von Willebrand disease, treated with Fanhdi®[b] for 12 bleeding episodes 9 x Type 1 7 x Type 2B 6 x Type 3	'Excellent/good' haemostasis in 11/12 (92%) episodes In 7/12 (58%) cases bleeding episodes were controlled after one infusion

[a] values expressed as median (range); [b] not available in Australia; [c] Information on population source not provided; A-SD = Alphanate® Solvent/detergent treated; A-SD/HT = Alphanate® solvent/detergent, heat-treated; FVIII:C = factor VIII coagulant activity; IVR= in vivo recovery; RCoF = ristocetin-cofactor activity; vWF:Ag = von Willebrand factor antigen; vWF = von Willebrand factor

Are treatments safe?

DDAVP

The safety of DDAVP is discussed under the Adjunctive haemostatic agents section.

Plasma-derived factor VIII and von Willebrand factor concentrates

Recombinant factor VIII concentrates contain no von Willebrand factor and high purity pdFVIII concentrates contain less von Willebrand factor than intermediate-purity pdFVIII concentrates. Therefore, although intermediate-purity factor concentrates are preferred for von Willebrand disease patients, they may increase their risk of contracting blood borne viruses (Berntorp 1999). The safety issues surrounding treatment with

Haemate® P[1] or Biostate® are similar to those associated with other intermediate-purity plasma derived factor concentrates (See Treatment of Bleeding Episodes).

One small case series (Level IV evidence) reported adverse effects in 33.3% of patients administered Haemate® P (Dobrkovska et al. 1998). Although these side effects were mild, they occurred after only one administration of factor.

In a larger retrospective case series (Level IV evidence), 17% of patients experienced adverse events after the administration of Haemate® P (Lillicrap et al. 2002; Dobrkovska et al. 1998). However, neither study distinguished between patients experiencing these adverse events in the surgical, bleeding episodes or prophylaxis groups.

Overall, with the exception of isolated cases of deep vein thrombosis, paraesthesia, and virus transmission (not assessed by the included studies), it appears that most of the side effects associated with use of pdFVIII/vWF concentrates in von Willebrand disease were mild in nature (Level IV evidence).

Table 28. Safety of plasma-derived products for von Willebrand Disease for treating bleeding episodes

Study	Level and quality of evidence	Population	Adverse events
(Mannucci et al. 2002)	Level IV: prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	81 patients with vWD, treated with Alphanate®-Solvent Detergent (A-SD) or Alphanate®Solvent Detergent/Heat-Treated (A-SD/HT) for 71 surgical or invasive procedures, or 87 bleeding episodes 15 x Type 1 29 x Type 2A 5 x Type 2B 32 x Type 3	A-SD A-SD/HT 9/66 (13.6%) 5/36 (13.9%) Most adverse events were mild–moderate: Reduced in vivo recovery, B19 parvovirus transmission, thrombophlebitis, deep vein thrombosis
(Gill et al. 2003)	Level IV: prospective case series Quality of evidence: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	33 patients with von Willebrand disease, treated with Haemate® P for 53 bleeding episodes 9 x Type 1 4 x Type 2A 7 x Type 2B 27 x Type 3 6 x Other	24/53 (45%) bleeding episodes associated with adverse events, but none considered related to treatment: Nausea, vomiting, anaemia, insomnia
(Auerswald et al. 2002)	Level IV: case series Quality of evidence: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	14 patients with von Willebrand disease treated with Immunate® for surgical or bleeding episodes	No serious adverse events One phlebitic reaction at venous access site after 102 hours of continuous infusion (cont.)

[1] Haemate® P is not available in Australia

Table 28 (cont.) (Dobrkovska et al. 1998)	Level IV: prospective case series Quality score: 2/3 Measurement bias unlikely Selection bias possible Follow-up adequate Uncontrolled	6 patients with von Willebrand disease, given a bolus infusion of Haemate® P (80 IU vWF:RCo kg^{-1} b.w. and 32 IU FVIII:C kg^{-1} b.w.) 2 x Type 1B 2 x Type 2A 2 x Type 3	2/6 (33.3%) patients suffered mild adverse effects including urticaria, rash, hives, cough, fever, weakness and nausea.
(Lillicrap et al 2002; Dobrkovska et al. 1998)	Level IV: retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	97 patients with von Willebrand disease, treated with Haemate® P for 530 different treatment events: 73 surgery, 344 bleeding events, 20 prophylaxis prior to surgery, 93 other events 32 x Type 1 5 x Type 2A 18 x Type 2B 28 x Type 3 14 x Other	16/97 (16.5%) patients suffered adverse effects including chills, phlebitis, paraesthesia, vasodilation, pruritis, rash and urticaria.
(Federici et al. 2002)	Level IV: retrospective case series Quality score: 1/3 Measurement bias possible Unable to assess selection bias Follow-up adequate Uncontrolled	10/22 patients with von Willebrand disease, treated with Fanhdi® for 12 bleeding episodes 9 x Type 1 7 x Type 2B 6 x Type 3	No adverse events

A-SD= Alphanate® Solvent/Detergent; A-SD/HT= Alphanate® Solvent Detergent/Heat-Treated

Evidence-based clinical practice guidelines

- Based on the available evidence, DDAVP may be used in von Willebrand patients who are responsive to DDAVP and when it is not contraindicated (e.g. DDAVP should not be used during pregnancy or labour, in children under two years, or in patients with Type 2B von Willebrand disease) (Level IV evidence).
- Patients unresponsive to DDAVP or those contraindicated for DDAVP should be treated with pdFVIII/vWF concentrates (Level IV evidence).
- Since the optimal dose of Biostate® cannot be determined, close monitoring is required (Level IV evidence).
- Plasma-derived FVIII/vWF concentrates may be administered every 8–12 hours depending on the individual response (Level IV evidence).

Other rare bleeding disorders

There were no studies available that met the predetermined criteria for inclusion in this review to assess the safety and effectiveness of treatment of bleeding episodes in patients with other rare bleeding disorders.

Prophylaxis

Prophylaxis is defined as 'treatment by intravenous injection of factor concentrate in anticipation of and in order to prevent bleeding' (Berntorp et al. 2003). Instead of simply using factor concentrates reactively for acute bleeding episodes, a more premeditated approach of prophylactic administration of factors has been introduced to prevent acute bleeding episodes and cover surgical procedures. Prophylactic treatment may be further categorised into primary or secondary prophylaxis. According to the European Network for Paediatric Haemophilia Management, primary prophylaxis is defined as regular, continuous treatment started before the age of two years or after the first joint bleed. Secondary prophylaxis is the regular, continuous (long-term) treatment started at the age of ≥ two years or after two or more joint bleeds; or, periodic treatment (short-term), due to frequent bleeds (Petrini 2001).

Young boys with a severe form of haemophilia (A or B) may experience frequent bleeding into soft tissues (haematomas) or joints (haemarthrosis), leading to joint damage (arthropathy) and disability by early adult life (Carcao & Aledort 2004). Haemarthrosis induces acute inflammation and swelling that presents as pain and loss of function. Acute haemarthrosis may predispose patients to repeated cycles of bleeding in a joint, leading to chronic joint damage and significant disability. The most widely used measure of haemophilic arthropathy is the Pettersson radiological score, which classifies roentgenograms of knees, elbows, and ankles on a scale from 0 to 13 (Pettersson et al. 1981). Scores are given for several changes, which are listed in Table 29. The minimum score of 0 signifies no arthropathy and the maximum score is 78.

Table 29. Pettersson radiological score of haemophilic arthropathy

Type of change	Finding	Score
Osteoporosis	Absent Present	0 1
Enlarged epiphysis	Absent Present	0 1
Irregular subchondral bone	Absent Surface partly involved Surface totally involved	0 1 2
Narrowing of joint space	Absent Joint space <1mm Joint space >1mm	0 1 2
Subchondral cyst formation	Absent 1 cyst >1 cyst	0 1 2
Erosions at joint margins	Absent Present	0 1
Incongruence of joint surfaces	Absent Slight Pronounced	0 1 2
Joint deformity	Absent Slight Pronounced	0 1 2

Modified from (Rodriguez-Merchan et al. 2003)

Two alternative expanded instruments for measuring arthropathy have been developed in Colorado—the Colorado Physical Examination full point instrument (Colorado PE-1) and the Colorado Physical Examination half-point instrument (Colorado PE-0.5) (Manco-Johnson et al. 2000). These instruments have been designed to detect early structural and functional abnormalities and to classify the severity of joint impairment. A third instrument, the Child Physical Examination instrument (Child PE), has been tailored to reflect the developmental changes in children.

The rationale for prophylaxis in patients with severe haemophilia is underpinned by two concepts: 1) patients with mild–moderate haemophilia have fewer bleeding episodes with mild or no arthropathy (Gringeri 2003); and 2) maintaining plasma clotting factor levels >1% is expected to reduce the number of spontaneous bleeding episodes in patients with severe haemophilia and prevent secondary arthropathy from recurrent joint haemorrhages.

The majority of patients undergoing prophylactic treatment are young boys with severe congenital haemophilia A. Effective prophylaxis depends on sustaining adequate plasma levels of FVIII to minimise the risk of haemorrhage (Gruppo et al. 2003). Frequent prophylactic treatment in young children requires adequate access to veins. While regular, frequent venipuncture may be painful and traumatic in young children, intravenous access devices may also be associated with complications, such as infections and thrombosis. For evaluation of the safety and effectiveness of intravenous access devices, see section on Other Aspects of Management.

Haemophilia

The products used for prophylactic treatment of patients with haemophilia A, without inhibitors, are the same as those used for treatment of acute bleeding episodes (See section on Treatment of Bleeding Episodes).

Previous Australian consensus-based guidelines

- FVIII and FIX prophylaxis is recommended for all children with severe haemophilia A or B up to the age of 18 years.
- Haemophilia A: The recommended dosage range for FVIII prophylaxis is 25–40 IU/kg, three times per week or more frequently as required.
- Haemophilia B: The recommended dosage range for FIX prophylaxis is 40–60 IU/kg, twice a week or more frequently as required. See Appendix G for details

(Haemophilia Foundation Australia Medical Advisory Panel 2000).

Are prophylactic treatments effective?

The 'gold standard' of prophylaxis is thought to be the Malmö approach, which has been used in Sweden since 1958 (Carcao & Aledort 2004). The Malmö regimen recommends prophylaxis in boys with severe haemophilia at 1–2 years of age, before joints are affected by repeated bleeds, using 25–40 IU/kg pdFVIII every second day (haemophilia

A) or pdFIX twice a week for boys with haemophilia B. Follow-up of 60 patients (52 haemophilia A; 8 haemophilia B) over 25 years showed almost no spontaneous bleeds, regular joints (assessed by Pettersson scores), and good quality of life in boys treated early (1–2 years), while those given lower doses or treated later showed some breakthrough bleeding and minor joint defects (Level IV evidence) (Nilsson et al. 1992). On the basis of these results, the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (USA) recommended prophylactic treatment as optimal for children with severe haemophilia A or B (Medical and Scientific Advisory Council (MASAC) 2001).

To date, few good quality randomised controlled trials have assessed prophylaxis in patients with haemophilia and even fewer have investigated the effectiveness and/or safety of recombinant factors for prophylaxis.

In this review, several studies on prophylactic treatment were not included for evaluation as it was impossible to distinguish between patients treated with recombinant and those treated with plasma-derived factors, or else the type of factor was not stated.

One average quality systematic review of 13 observational studies (Level III-2, III-3 and IV evidence) compared the effectiveness of full-length FVIII (FL-FVIII), which included both recombinant and plasma-derived factor, to B-domain-deleted recombinant FVIII (BDD-rFVIII)[m] in prophylactic treatment (Gruppo et al. 2003). Meta-analysis showed that breakthrough bleeding episodes[n] were more than twice as likely to occur with BDD-rFVIII (16.8 bleeds per patient-year [95% CI 9.5-24.2]) than FL-FVIII (6.6 bleeds per patient-year [4.7-8.5], $p<0.0005$) at equivalent doses and ages (incidence rate ratio = 2.10 [1.98-2.24]). Pharmacokinetic analysis revealed biochemical differences, such as a shorter half-life of BDD-rFVIII, which may partly account for the lower prophylactic effectiveness of BDD-rFVIII. Subsequent analysis of pooled data, using a median-to-mean conversion statistic[o], confirmed the robustness of increased incidence of bleeding in patients treated with BDD-rFVIII compared to FL-rFVIII (Gruppo et al. 2004). However, although the investigators used a random effects model to accommodate heterogeneity when pooling data from the observational studies, these study designs are prone to selection bias, observer bias and confounding. As such, the results should be confirmed by well-designed randomised clinical trials that make *direct* comparisons between BDD-rFVIII and FL-FVIII groups.

Apart from one good quality randomised crossover trial on prophylaxis in haemophilia B patients (Level II evidence), current evidence of the effectiveness of prophylactic treatment is derived primarily from poor–average quality uncontrolled studies (Level IV

[m] BDDrFVIII: The reduced size of the molecule means it is less prone to proteolytic degradation and, therefore, stabilising with human albumin is not necessary (Fijnvandraat et al. 1997)

[n] Pooled incidence of bleeding was calculated from the mean annual total of bleeding episodes reported in studies

[o] A median-to-mean conversion factor of 2.6 is based on clinical data compiled by the Universal Data Collection Program of the US Centers for Disease Control and Prevention

evidence) that include heterogeneous study populations (haemophilia A or B; children/adults; PUPs/PTPs[p]).

The good quality randomised double-blinded crossover trial (Level II evidence) measured the recovery of plasma FIX following a single infusion of 50 IU/kg rFIX (BeneFIX®) or pdFIX (Mononine®) in boys with haemophilia B (Kisker et al. 2003). The aim of this study was to determine the level of dosing necessary to maintain a prophylactic level of FIX ≥2%. Results are provided in Table 30 and show a twofold greater recovery with pdFIX compared to rFIX, despite a significantly better median half-life for rFIX (13.7 vs. 12.9, p=0.016). Pharmacokinetic analysis indicates the median concentrate required to maintain ≥2% plasma FIX for 30 days, when administered every third day is 677 IU/kg pdFIX (388-6005 IU/kg/month) compared to 1168 IU/kg rFIX (268-13085 IU/kg/month). This statistically significant reduction in FIX recovery following treatment with rFIX also indicated clinical harm[q]. However, the large overlap in products, and wide inter-patient variability in recovery and half-life suggests that individual pharmacokinetic evaluation with different products may be necessary to tailor appropriate products and dosing schedules to individual needs.

One good quality uncontrolled before-and-after study (Level IV evidence) assessed the effectiveness of prophylaxis compared with baseline (on-demand treatment) of patients with severe haemophilia A or B, using recombinant factors VIII or IX (Panicker et al. 2003). While receiving prophylaxis, all patients showed statistically significant reductions —from baseline—and clinical benefit[r] in the mean number of bleeding episodes, hospital admissions, length of hospital stay, and number of emergency room visits (p<0.001) (Table 30). As expected, there was a concomitant increase in the mean annual dose of factor when children were on prophylaxis.

[p] PUPs = previously untreated patients; PTPs = previously treated patients

[q] Clinical importance of statistically significant effects was ranked according to the checklist provided in Appendix H. More than 20% reduction in FIX recovery—vs control group FIX recovery—indicated a clinical harm.

[r] More than 20% improvement (reduction in annual number of major bleeds vs baseline) indicated a clinical benefit.

Table 30. Factor recovery following prophylactic treatment with recombinant factors in haemophilia A or B patients

Study	Level and quality of evidence	Population	Effectiveness		
(Kisker et al. 2003)	Level II: randomised double-blinded crossover trial Quality score: 21/27 Clinical importance[a]: 1/4 Selection bias minimised Confounding avoided Follow-up adequate Good external validity	15 non-bleeding severe haemophilia B patients, aged >12 years, without inhibitors	Incremental factor recovery, IU/kg^{-1} (range)		
			rFIX (50 IU/kg, BeneFIX®)	pdFIX (50 IU/kg, MonoFIX®)	% change
			0.86 (0.39-1.48)	1.67 (0.86-4.66)	48.5% p=0.002
(Panicker et al. 2003)	Level IV: uncontrolled before-and-after study Quality score: 2/3 Clinical importance[a]: 1/4 Selection bias minimised Follow-up adequate	22 patients with severe haemophilia A and 3 children with severe haemophilia B, aged 1.7–20.4 years, on prophylaxis Haemophilia A: Recombinate™ or Kogenate® Haemophilia B*: BeneFIX® * 1 patient received plasma-derived FIX		Before prophylaxis mean±SD (range)	After prophylaxis mean±SD (range)
			Annual number of major bleeds	15.5±8.3 (6.6-43.5)	1.9±1.2 (0-5.2) p<0.001
			Annual hospital admissions	1.2±1.5 (0-6.6)	0.1±0.2 (0-0.8) p<0.001
			Annual number of days in hospital	7.1±11.6 (0-57.4)	0.4±0.8 (0-2.9) p<0.001
			Annual ER visits	4.2±3.9 (0-16.2)	0.3±0.4 (0-1.1) p<0.001
			Mean doses FVIII per year	44.2 (14.1-254.1)	157.6 (105.4-167.6) p<0.001
			Mean doses FIX per year	17.7 (16.9-18.6)	112.6 (108.1-115.4) p<0.001

[a] Rank scores for the clinical importance of the benefit/harm (1/4 ranked highest and 4/4 ranked lowest); MTPs = minimally treated patients; PTPs = previously treated patients; PUPs = previously untreated patients

Ongoing clinical trials

Three clinical trials of prophylactic treatment are currently ongoing:

ESPRIT (Evaluation Study on Prophylaxis Italian Trial): A prospective randomised trial (Level II evidence) that compares the efficacy and safety of prophylaxis and on-demand regimens in reducing the number of bleeding episodes and preventing joint deterioration in patients with haemophilia A (Gringeri 2003). A one-year follow-up to this study has been provided in a conference abstract (Gringeri 1998). All patients in the prophylaxis arm of the study (N=20) maintained FVIII >2%, and no breakthrough bleeding episodes were reported. One patient developed an infection at the site of the in-dwelling catheter and one patient, who developed inhibitors to FVIII, was withdrawn from the study. It is not clear whether the factor concentrates used were plasma-derived or recombinant.

US study: A randomised controlled trial (Level II evidence) that aims to determine whether preventing bleeding into joints is necessary for preventing joint damage in patients with haemophilia A. This study compares standard prophylaxis (25 IU/kg FVIII every other day) with an aggressive episode-based regimen for acute joint haemorrhages (40 IU/kg FVIII at time of haemorrhage onset, 20 IU/kg FVIII at 24 and 72h, and 20 IU/kg FVIII every 48h up to 4 weeks until joint function is completely restored). Thus far, 65 children from 15 haemophilia centres have been enrolled. The type of FVIII (plasma-derived or recombinant) is not reported (Manco-Johnson & Blanchette 2003).

Canadian cohort study: A single-arm open-label study (Level III-2 evidence) that examines whether escalating prophylaxis successfully maintains haemostatic control in children with severe haemophilia A. All children begin with an initial dose of 50 IU/kg rFVIII per week. Dosage escalates to 30 IU/kg twice weekly or 25 IU/kg thrice weekly if a threshold of bleeding episodes (≥3 haemorrhages within 3 months) is exceeded. To date, 25 children have been followed up for five years, with no losses to follow-up, and no evidence of safety concerns (Manco-Johnson & Blanchette 2003).

Are prophylactic treatments safe?

Development of inhibitors

The first bleeding episodes in patients with severe haemophilia occur at very different ages. While evidence suggests that prophylaxis is effective at preventing joint damage, prophylaxis given before bleeding episodes start is costly and the age of first FVIII exposure may influence the risk of inhibitor development (Pollmann et al. 1999). Two retrospective case series found that patient age at initial treatment with factor concentrates predicted inhibitor development in patients with severe haemophilia (Table 31). Those who were treated before six months of age had a much higher risk of developing inhibitors than those who were treated between 6–12 months or over 12 months of age. This relationship was not related to cumulative exposure days and no difference was found between baseline FVIII levels. These results suggest that the risk of inhibitor development is decreased if the first exposure to factor concentrates is delayed until there is a clinical need (Level IV evidence) (Lorenzo et al. 2001; van der Bom et al. 2003).

Table 31. Inhibitor development in young children undergoing prophylaxis

Study	Level and quality of evidence	Population	Age at first FVIII exposure		
			0–6 months	7–12 months	>12 months
(Lorenzo et al. 2001)	Level IV: retrospective case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	62 consecutive severe haemophilia A patients (FVIII<2 IU/dl)	Cumulative incidence of inhibitors at 3 years from first FVIII exposure	41%	29% p=0.03	12%
(van der Bom et al. 2003)	Level IV: retrospective case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	81 consecutive severe haemophilia A patients (FVIII<1 IU/ml)	Cumulative incidence of inhibitors at 100 days from first FVIII exposure	4/13 (31%)	5/29 (17%) p=0.03	3/27 (11%)
			Mean number of infusions before antibodies	14 IQR=9,44	25 IQR=10,34 p=0.96	40 IQR=10,40

FVIII = factor VIII; IQR= Inter quartile range

Adverse events

One very poor quality historically controlled study (Level III-3 evidence) reported mild-severe adverse events in <1% of haemophilia A patients undergoing prophylaxis (Arkin et al. 1991).

Table 32. Adverse events in haemophilia A or B patients undergoing prophylactic treatment with recombinant factors

Study	Level and quality of evidence	Population	Adverse events
(Arkin et al. 1991)	Level III-3: historical control study Quality score: 5/27 Selection bias likely Confounding likely Follow-up uncertain External validity uncertain[a]	14 non-bleeding PTPs with moderate–severe haemophilia A, aged 4–72, without inhibitors Historical controls: no description provided	< 1% of 821 infusions of rFVIII resulted in adverse reactions Mild chest twinge, cold hands and feet, erythema/burning at infusion site, unusual taste in mouth, dry mouth Severe dizziness, hypotension, rash, shortness of breath

[a] Information on population source not provided; PTPs = previously treated patients; rFVIII= recombinant factor VIII

Evidence-based clinical practice guidelines

Based on the evidence, it is recommended that prophylactic treatment is available to patients with severe haemophilia, without inhibitors (Level II and IV evidence):

- Haemophilia A: Recombinant FVIII—as in consensus guidelines (Level IV evidence).
- Haemophilia B: Recombinant FIX is safe for prophylaxis in patients with haemophilia B without inhibitors. Due to the lower rFIX recovery compared to pdFIX, and the large inter-patient variability, individual dosing regimens should be monitored by FIX recovery/activity assays (Level II evidence). The recommended rFIX dosage, compared to pdFIX, should be increased by a multiplication factor of 1.6 for patients aged ≤15 years and 1.2 for patients aged 16 years and over (Level III-3 evidence, see section on treatment of bleeding episodes).
- Prophylaxis with factor concentrates should be initiated after bleeding episodes have commenced, due to an increased risk of inhibitor development when factors are administered at a young age (Level IV evidence).

von Willebrand disease

Previous Australian consensus-based guidelines

There are currently no Australian consensus guidelines for primary prophylaxis in patients with von Willebrand disease.

Effectiveness of prophylaxis

Although short-term prophylaxis may be given to von Willebrand patients who are expecting to undergo a serious surgical or dental procedure (see section on Surgical and Dental Procedures), it is not usually required for long-term management. The exception to this is the prophylactic treatment of women with menorrhagia, which occurs in over 50% of women with von Willebrand disease (Kadir et al. 2002).

DDAVP and Tranexamic acid

The highest level of evidence on the effectiveness of DDAVP for prophylaxis in von Willebrand disease was a randomised controlled trial, which found that intranasal DDAVP was no better than placebo at reducing subjectively measured excessive bleeding from menorrhagia (Level II evidence) (Kadir et al. 2002).

While there is insufficient evidence to make recommendations based on the effectiveness of tranexamic acid for treating menorrhagia, two low level studies reported positive effects in seven patients with von Willebrand disease who were treated for menorrhagia with a single or daily dose of tranexamic acid (Ong et al. 1998; Mohri 2002). More good quality research is required in this area before strong recommendations can be made.

Expert opinion suggests that a combination of DDAVP and antifibrinolytics should be investigated for menorrhagia in von Willebrand disease patients (Kadir et al. 2002).

Plasma-derived factor concentrates

Two low level studies (Level IV evidence) reported on the use of plasma-derived concentrates for prophylaxis in 20 patients with Type 3 von Willebrand disease—mostly to prevent recurrent gastrointestinal bleeding. All patients received Haemate® P as prophylaxis for at least three days and approximately nine patients received prophylaxis for ≥20 days. A physician efficacy rating of 'excellent/good' indicated that there was an effective reduction in the number of bleeding episodes observed. The median dose for patients undergoing prophylaxis was 41.6 IU vWF:RCo/kg (range 34.6–81.0). While there is insufficient evidence for firm recommendations, it appears that prophylaxis with Haemate® P may be effective for prophylaxis in patients with von Willebrand Disease.

Table 33. Effectiveness of prophylaxis in von Willebrand Disease

Study	Level and quality of evidence	Population	Effectiveness
(Kadir et al. 2002)	Level II: randomised crossover trial Quality score: 24/27 Unable to assess external validity Bias minimised Confounding avoided	39 women with mild–moderate vWD, heterozygous FXI-deficiency, and carriers of haemophilia, aged 18–60, treated for menorrhagia Median pre-treatment PBAC score= 250	DDAVP nasal spray Median PBAC score= 148 Placebo Median PBAC score= 140 p=0.51
(Lillicrap et al. 2002; Dobrkovska et al. 1998)	Level IV: retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate	97 patients with von Willebrand disease, of which 20 patients with Type III were given prophylaxis, mainly to prevent gastrointestinal bleeding.	Haemate® P[a] 20/20 (100%) reported a physician efficacy rating of 'excellent/good'
(Ong et al. 1998)	Level IV: retrospective case series Quality score: 1/3 Measurement bias possible Selection bias possible Follow-up adequate	4 women with von Willebrand disease and menorrhagia, after oral contraceptive pills and regular dosing of tranexamic acid had failed to reduce bleeding 1 x Type 1 2 x Type 2A 1 x Type 2B	High dose tranexamic acid 4/4 (100%) had menorrhagia controlled
(Mohri 2002)	Level IV: retrospective case series Quality score: 1/3 Measurement bias possible Selection bias possible Follow-up adequate	3 women with von Willebrand disease and menorrhagia, after DDAVP or pdFVIII/vWF concentrates had minimal effect 1 x Type 1 2 x Type 2A	High dose tranexamic acid 3/3 (100%) had menorrhagia well controlled

[a] Haemate® P is not available in Australia; FXI= factor XI; PBAC= Pictorial Blood Assessment Chart, a commonly used tool to measure menstrual loss where a score of ≥100 is equivalent to more than 80 mL of blood loss (definition of menorrhagia); vWD= von Willebrand disease

Safety of prophylaxis

The safety of all three of the prophylactic treatments - DDAVP, tranexamic acid and pdFVIII/vWF concentrates - was assessed in other sections (Adjunctive haemostatic agents; Treatment of Bleeding Episodes and Surgical and Dental Procedures). The same safety issues apply for this population and for this purpose.

Evidence-based clinical practice guidelines

Based on limited published evidence, DDAVP administered intranasally is ineffective as prophylaxis to prevent menorrhagia in women with von Willebrand disease (Level II evidence). Plasma-derived FVIII/vWF concentrates or tranexamic acid are possible alternatives (Level IV evidence).

Other rare bleeding disorders

There were no studies that met the predetermined criteria for inclusion in this review to assess effectiveness and safety of prophylaxis in patients with other rare bleeding disorders.

Inhibitors and Tolerisation

With the advent of donor screening and sophisticated processes to inactivate viruses, such as HIV and hepatitis, and eliminate prions and parvovirus (e.g. Creutzfeld-Jakob disease; parvovirus B19) with nanofiltration techniques, blood coagulation products of increasing purity have become available and the risk of transmission of viruses has been almost eliminated. However, the development of inhibitory antibodies to FVIII or FIX remains one of the greatest challenges to physicians treating patients with FVIII or FIX deficiency, particularly in those with severe haemophilia. Therapeutically administered factor is recognised as a foreign protein by the immune system, thus stimulating the production of antibodies (inhibitors). Inhibitors react with and neutralise FVIII rendering it ineffective in the clotting process. If the inhibitor titre is high, factor replacement therapy is totally ineffective and bleeding persists. With low titre inhibitor haemostasis may still be achieved, though higher doses of factor concentrates may be needed. Prophylaxis is not an option for high-titre inhibitor patients and those with severe haemophilia and high-titre inhibitors are most at risk for recurrent bleeds and chronic haemarthroses.

The development of inhibitors to FVIII or FIX occurs: 1) in patients with congenital haemophilia A or B who develop alloantibodies when treated with FVIII or FIX concentrates; or, more rarely 2) in patients with normal haemostasis who develop autoantibodies to FVIII or FIX ('acquired haemophilia'). While the development of inhibitors to FIX in haemophilia B is relatively rare (1–6%) and usually associated with a gross gene deletion or nonsense mutation, FVIII inhibitor formation in haemophilia A patients is more common (up to 33%) (World Health Organization 2002). The prevalence of inhibitors to FVIII in haemophilia A patients varies widely (4–20% in moderate-severe patients; up to 50% in study populations with severe haemophilia) (Manno 1999) depending on the frequency of inhibitor measurement, the study population (age, ethnicity, immune status), the product used and methods of data collection. According to the Australian Bleeding Disorder Registry, approximately 8% of registered patients have inhibitors (Australian Bleeding Disorder Registry 2004).

In patients with severe haemophilia A, inhibitors generally develop after a median of 9–12 days of exposure to treatment (Hay et al. 2000b). Screening for inhibitors may be conducted by two methods: activated partial thromboplastin time (aPTT) assay[s] or the Bethesda method, which is more sensitive and routinely used in Australia. Inhibitor titre is measured in Bethesda Units (BU)[t]—a measure of the extent to which plasma with inhibitor inactivates FVIII in normal human plasma (Paisley et al. 2003). A similar Bethesda method is used to quantify inhibitors to FIX in haemophilia B patients.

The level of inhibitors varies not only between individuals but also within individuals over time. Inhibitors are measured on two dimensions: 1) the concentration of inhibitor—low titre (≤5 BU) and high titre (>5 BU); and 2) the response to factor—low

[s] Activated partial thromboplastin time (aPTT) = detects the presence of substances in the blood that inhibit the activity of coagulation factors

[t] Bethesda units (BU) = a measure of inhibitor activity—the amount of inhibitor that inactivates 50% or 0.5 units of a coagulation factor during the incubation period

responders show no increase in inhibitors, while high responders show a large increase in inhibitor production (anamnestic response). Clinically, low responders can be treated with FVIII concentrate, usually at high doses, whereas high responders cannot.

In most cases the antibody is at a low level (<5 BU/ml) and tends to disappear spontaneously. However, for approximately 20% of patients, the inhibitor persists, making prophylaxis and routine treatment with factor concentrates ineffective, which increases the risks associated with surgical or dental procedures.

Although the frequency and site of bleeding episodes in haemophilia patients is similar whether or not inhibitors are present, management of the condition is more challenging and requires different treatment strategies. In general, ad hoc treatment for acute bleeding episodes in patients with inhibitors requires the use of the alternative therapies listed in Table 34. Additionally, procedures have been developed to eliminate inhibitors. These include immune tolerance induction (tolerisation) or immune suppression therapy, which is used mainly in acquired haemophilia. Evidence on the safety and effectiveness of tolerisation protocols is addressed in the following section.

Table 34. Products used for haemophilia patients with inhibitors

Type of product	Mechanism of action	Product (Manufacturer)	Disadvantages	Advantages
rFVIII	FVIII replacement	Recombinate™ (Baxter Hyland Immuno)[a] Kogenate® (Bayer)[a] Bioclate™ (Aventis Behring)[a] Helixate® (Aventis Behring)[a] ReFacto® (Genetics Institute)	Not effective for high titre inhibitors Anamnestic response	No known risk of viral transmission Measured by laboratory assay Used for maintenance and prophylaxis after successful tolerisation
rFIX	FIX replacement	BeneFIX® (Genetics Institute)	Not effective for acute bleeding episodes in high titre inhibitors	As for rFVIII Devoid of human serum or proteins
rFVIIa	Bypassing agent	NovoSeven® (NovoNordisk)	Short half-life Thrombosis risk	No known risk of viral transmission No human serum or proteins No anamnestic response
Plasma-derived FVIII	FVIII replacement	Hemophil® M (Baxter Hyland Immuno)	Pooled plasma product Unknown risk of viral transmission	Measured by laboratory assay Used for maintenance and prophylaxis after successful tolerisation
Plasma-derived FIX	FIX replacement	Alphanine® (Alpha) MonoFIX (Aventis Behring)	Pooled plasma product Anaphylaxis and nephritic syndrome reported when used for tolerisation Unknown risk of viral transmission	Can be measured by laboratory assay
aPCCs (with FIIa, FVIIa, FXa)	Bypassing agent	Autoplex® T (Nabi) FEIBA VH® (Baxter Hyland Immuno)	Pooled plasma product Risk of thrombosis Anamnestic response Allergic reaction Cannot be assayed	Long half-life Virally inactivated More effective than PCCs
PCCs (with FII, FVII, FIX)	Bypassing agent	Prothrombinex®-HT Proplex T; Bebulin VH (Baxter Hyland Immuno) Konyne 80 (Bayer) Profilnine SD (Alpha)	Pooled plasma product Less effective than aPCCs Risk of thrombosis Factor content variable between lots and products Anaphylaxis and nephritic syndrome reported when used for tolerisation Cannot be assayed	Long half-life Virally inactivated

Modified from (Kulkarni et al. 2001); [a] Product contains albumin; [b] Due to a series of corporate changes since this reference article was published in 2001, some product manufacturers in this table may differ from those listed previously in the section under Selection of Products; aPCCs = activated prothrombin complex concentrates; FEIBA= factor eight inhibitor bypassing agent; PCC = prothrombin complex concentrates

Previous Australian consensus-based guidelines

These guidelines are for the treatment of haemophilia A in patients with inhibitors to FVIII. There are no existing guidelines for the treatment of haemophilia B in patients with inhibitors to FIX.

Low titre inhibitor (<5 BU/ml), low responder	
Minor bleeding	FVIII (50–100 IU/kg every 8–12 hours). Assess clinically and monitor FVIII levels.
Major bleeding	FVIII (50–150 IU/kg every 8–12 hours). Assess clinically. Monitor FVIII levels and maintain at >50% until healing has completed.
Low titre inhibitor (<5 BU/ml), high responder	
Minor bleeding	Recombinant FVIIa (90 µg/kg—adult dose; up to 200–250 µg/kg—paediatric dose) every 2 hours. Assess clinically and follow up with a further single dose. If no response is observed, consider treatment with aPCC. Alternative treatment with FEIBA: 60–80 IU/kg FEIBA bd (max = 200 IU/kg/day)
Major bleeding	Recombinant FVIIa (90 µg/kg—adult dose; up to 200–250 µg/kg—paediatric dose) every 2 hours for minimum 2 doses. Assess clinically. If no response is observed, consider treatment with aPCC. Alternative treatment with FEIBA: 60–100 IU/kg FEIBA as a single dose
High titre inhibitor (>5 BU/ml)	
Minor bleeding	Recombinant FVIIa (90 µg/kg—adult dose; up to 200–250 µg/kg—paediatric dose) every 2 hours for minimum 2 doses. Assess clinically and follow up with a further single dose. If no response is observed, consider treatment with aPCC. Alternative treatment with FEIBA: 60–80 IU/kg FEIBA as a single dose
Major bleeding	Recombinant FVIIa (90 µg/kg—adult dose; up to 200–250 µg/kg—paediatric dose) every 2 hours for 12 hours; increase to 3 hourly intervals depending on clinical response. Increase dose interval to 4 hours if necessary to maintain dosage. Duration may extend to 14 days if major surgery has been performed. Alternative dosing regimen: 320 µg/kg every 6 hours. If no response is observed, consider treatment with aPCC. Alternative treatment with FEIBA: 60–100 IU/kg FEIBA bd (max = 200 IU/kg/day).

* Modified from guidelines by AHCDO (2004) See Appendix G; aPCCs = activated prothrombin complex concentrates; bd = twice per day; FEIBA = Factor Eight Inhibitor Bypassing Agent

Treatment of bleeding episodes in patients with inhibitors

The highest level of evidence was provided by one good quality systematic review of 52 studies (Lloyd Jones et al. 2003). Overall, the study design, therapy and methodology of included studies, which were predominantly low level evidence (Level IV), were highly variable and of poor quality. Few randomised controlled trials with appropriate comparators or placebo were available (8 of 52). The target population in the included studies was predominantly patients with inhibitors to FVIII (haemophilia A), although some studies included those with inhibitors to FIX (haemophilia B). A wide range of therapies was used in haemophilia patients with inhibitors, including: 1) high-dose human FVIII concentrate (plasma-derived); 2) highly purified porcine FVIII[u]; 3) inhibitor bypassing agents—activated prothrombin complex concentrates (aPCCs) and prothrombin complex concentrates (PCCs); 4) plasmapheresis or immunoadsorption plus high-dose FVIII; 5) cimetidine plus high-dose FVIII; and 6) immunosuppression plus plasma-derived FVIII. Data from this systematic review are summarised in Table 35.

Due to the discontinuation of a poor quality randomised controlled trial and the absence of data from case series, there was no available evidence to support the use of high-dose plasma-derived FVIII alone for controlling acute bleeding in patients with high titre

[u] Since porcine FVIII is not used in Australia, data has not been presented in this report

inhibitors or in high responder patients. There was no evidence assessing the safety or effectiveness of rFVIII for treating bleeding episodes in patients with inhibitors, however, due to reports of equivalent effectiveness between rFVIII and pdFVIII in patients without inhibitors, and the higher safety profile of rFVIII, it is suggested that rFVIII may be a better alternative (Lloyd Jones et al. 2003) (expert opinion). Higher-level evidence (Level II) indicates that PCCs[v] and aPCCs are effective in controlling mild to severe bleeding in patients with inhibitors (≥4 BU/ml). However these inhibitor-bypassing agents may be unpredictable, with a potential for serious adverse reactions—including thrombosis, disseminated intravascular coagulation (DIC), myocardial infarction and pulmonary embolism. Therefore, they are not recommended for first-line treatment in life-threatening haemorrhages. In addition, the maximum daily dose of FEIBA should not exceed 200 IU/kg (Level II evidence, Lloyd Jones et al. 2003).

In terms of both safety and efficacy, the evidence (Level II) suggests that rFVIIa is the best option as the first line of treatment for high responder patients, particularly if used early rather than late. Controlling 70–90% of mild–severe bleeding episodes in high responder patients, rFVIIa does not provoke anamnesis, side effects are generally minor, and it is suitable for home treatment (Lloyd Jones et al. 2003). Evidence from a systematic review by Lloyd Jones suggests that acute haemorrhages of mild to moderate severity are best treated using 90 μg/kg of rFVIIa (Level IV evidence). While the standard method of rFVIIa administration is by bolus injection, low level evidence suggests that continuous infusion is also effective (Level IV evidence) (Lloyd Jones et al. 2003). There is evidence that the half life of rFVIIa is shorter in children than in adults (Level IV evidence, Lloyd Jones et al. 2003). Therefore, the recommendation from previous consensus guidelines, that children may require as much as 200-250 μg/kg rFVIIa, should remain.

Limited low-level evidence (Level IV) shows successful reduction of inhibitors by plasmapheresis (with or without immunoadsorption) and subsequent infusion of pdFVIII to control bleeding in patients with high titre or high responder inhibitors (80–100%). In contrast, immunosuppression with cyclophosphamide to prevent anamnesis combined with factor replacement is largely unsuccessful.

[v] The formulation of PCCs tested in the Level II evidence is different to what is currently available in Australia; therefore, while results are presented, recommendations on the use of PCCs have not been given

Table 35. Summary of efficacy of interventions to control bleeding in haemophilia A patients with inhibitors*

Intervention	Population	Level of evidence	Haemostasis control (%)	Adverse events
Acute bleeding episodes				
pdFVIII	Any	No evidence[a]	No evidence	No evidence
PCCs	High titre/ high responders	Level II: RCT Level IV: uncontrolled before-and-after study	83% 81%	Mainly minor Potential for DIC, DVT, MI
aPCCs	High titre/ high responders	Level II: RCT Level IV: uncontrolled before-and-after studies	64% 88–100%	
rFVIIa	High responders or high titre	Level II: RCT Level IV: uncontrolled before-and-after studies	71–90% 62–100%	Mainly minor. Occasional thrombophlebitis or DIC
Plasmapheresis + high-dose pdFVIII	Intermediate-high responders	Level IV: case series	100%	Anaphylactic reactions, headache, fever, vomiting
Extracorporeal protein A adsorption + high-dose pdFVIII	High titre	Level IV: uncontrolled before-and-after study	80%	All minor
Cimetidine + FVIII	High responders	Level IV: uncontrolled before-and-after study	100%	None reported
Immunosuppression + pdFVIII	Any	Level IV: uncontrolled before-and-after study	27%	Increased susceptibility to infection, impaired wound healing
Surgical procedures				
pdFVIII	High titre/ high responders	Level IV: case series	78%	None reported
aPCCs	Not clear	Level IV: uncontrolled before-and-after study	86–93%	Mainly minor. Occasional thrombophlebitis or DIC
rFVIIa	High titre	Level II: RCT Level IV: uncontrolled before-and-after studies	55–100%	Mainly minor. Occasional thrombophlebitis or DIC
Plasmapheresis + high-dose pdFVIII	High titre	Level IV: case series	67%	Anaphylactic reactions, headache, fever, vomiting
Dental surgery				
PCCs	High and low titre	Level IV: case series	33%	Mainly minor. Potential for DIC, DVT, MI
aPCCs	High titre	Level IV: case series	100%	Mainly minor. Potential for DIC, DVT, MI
rFVIIa	Not stated	Level IV: uncontrolled before-and-after study; case series	86–92%	Mainly minor. Occasional thrombophlebitis or DIC

*Modified from (Lloyd Jones et al. 2003) [a] One poor quality RCT was discontinued (non-compliance) and a case series failed to provide data for effectiveness; aPCCs = activated prothrombin complex concentrates; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; MI = myocardial infarction; PCCs = prothrombin complex concentrates, (a different formulation than is currently available in Australia); RCT = randomised controlled trial; rFVIIa= activated recombinant factor VII, pdFVIII = plasma-derived factor VIII

Surgical and dental procedures in haemophilia patients with inhibitors

The best evidence for the management of patients with inhibitors during surgery or dental procedures is also provided in the systematic review by Lloyd Jones et al. 2003 (Table 35). In surgery, high-dose plasma-derived FVIII was successful for patients with low-titre, low-responding inhibitors (100%). It was less reliable for controlling peri- and post-operative bleeding in patients with high-responding inhibitors (80%); only effective when the inhibitor titre was below 10 BU/ml and only for 5–7 days before an anamnestic response occurred. Bypassing agents (PCCs, aPCCs, and rFVIIa) are the only available options for patients who cannot be treated with plasma-derived FVIII. Low-level evidence indicates that PCCs, even when combined with antifibrinolytic agents, have limited success in controlling bleeding associated with dental surgery (33%), with variable results on different occasions in the same patient. In contrast, aPCCs were

successful in controlling bleeding in approximately 90% of surgical and 100% of dental procedures (with antifibrinolytic agents). However, although most side effects were minor, there is the potential for serious complications and evidence suggests that antifibrinolytic products should be used consecutively with aPCCs rather than simultaneously during dental surgery. The highest level of evidence for use of rFVIIa in surgery is derived from one randomised controlled trial (Level II evidence), which demonstrated 93% success. The majority of remaining studies included patients enrolled in a 'compassionate use' program[w], which comprises patients who have not or are unlikely to respond to other treatments. In most cases, their clinical condition is complicated by disordered haemostasis, advanced age, or general poor health.

Evidence-based clinical practice guidelines

Based on the evidence, it is recommended that haemophilia A patients with inhibitors be treated in the following manner:

- Recombinant FVIIa may be considered the first line of treatment for acute bleeding episodes or dental and other surgical procedures in patients with high titre and/or high responder inhibitors (Level II evidence).
- aPCCs may be used to control mild to severe bleeding in patients with high titre inhibitors. Due to their unpredictable effects, patients should be closely monitored for severe reactions, such as disseminated intravascular coagulation, myocardial infarction, or thrombotic complications. Activated PCCs are preferred over PCCs, particularly for controlling bleeding in dental and other surgical procedures. During dental surgery, aPCCs should be used consecutively with antifibrinolytic agents, rather than in combination (Level IV evidence). The maximum daily dose of FEIBA should not exceed 200 IU/kg (Level II evidence).
- Plasmapheresis (with or without immunoadsorption) may be considered to reduce inhibitors in high titre/high responders prior to infusion with FVIII concentrate to control bleeding. However, patients should be closely monitored for anaphylactic reactions (Level IV evidence).
- Plasma-derived FVIII concentrate may be considered for use during surgery in patients with low titre, low-responding inhibitors, but should be avoided in patients with high-responding inhibitors (Level IV evidence). There was no evidence to support its use for the treatment of acute bleeding episodes. The evidence on recombinant FVIII concentrate is awaited.
- Immunosuppression therapy with cyclophosphamide to reduce inhibitors should be avoided (Level IV evidence).

Tolerisation protocols

For the most part, if inhibitors develop they are most likely to do so within a few exposure days (median 9–12 days) in young boys with severe haemophilia A. In addition, most low titre inhibitors disappear over time. For a small proportion, however, inhibitors persist and strategies for eradication of inhibitors need to be employed.

[w] Compassionate use program—manufacturer allows physicians to use rVIIa on patients with special needs

Currently, the only method of removing inhibitors in patients with haemophilia A or B is by immune tolerance induction (DiMichele 1998). Several different methods of immune tolerance induction (tolerisation) have attempted to abolish inhibitors with varying success, but there is no consensus on the optimum approach of tolerisation.

In Australia, tolerisation protocols are highly variable across haemophilia centres, with no consensus on procedures. Dosages of FVIII concentrate for tolerisation of haemophilia A patients with inhibitors to FVIII range from 25 IU/kg three times a week to 100 IU/kg/day (JBC FVIII/FIX working party & National Blood Authority 2004). Since the current Australian consensus-based guidelines are recently developed, there is no available evidence of the effectiveness of this approach.

Previous Australian consensus-based guidelines

Tolerisation should be considered in all those patients with recent persisting inhibitors. Written informed consent should be obtained before starting. Intensive replacement therapy for immune tolerance usually requires central venous access.

Haemophilia A

- The International Registry on Tolerisation identifies better results in those patients with lower age at the start of Immune Tolerance Induction (ITI); shorter elapsed time of inhibitor presence before ITI; lower maximum pre-treatment inhibitor titres and treatment with higher doses of FVIII.
- AHCDO strongly recommends participation in an international randomised trial of high dose versus low dose factor VIII tolerisation protocols. All patients considered eligible for the trial should be involved.
- For patients who do not enter an international trial, there are a number of published tolerisation protocols that describe a variety of doses of factor VIII (e.g. 50 IU/kg three times a week up to 200 IU/kg daily) as well as the use of immune suppression. Tolerisation should continue until eradication of the inhibitor demonstrated by a greater than 60% recovery and normal half-life of factor VIII. Tolerisation should only be attempted in consultation with a physician experienced in the management of patients with haemophilia and inhibitors.
- It is recommended that adults with severe haemophilia A who have had an inhibitor for many years, and in some instances decades, should be managed with treatment of haemorrhage by infusion of recombinant factor VIIa. Adult patients with mild or moderate haemophilia A who develop inhibitors often have mild inhibitors, which may decline with time. These patients should be treated with desmopressin (DDAVP) for minor bleeds and recombinant factor VIIa for more serious haemorrhages. Tolerisation may be considered if haemorrhages cannot be controlled by recombinant factor VIIa.

Acquired Haemophilia A

Immunosuppression is recommended for eradication of inhibitors in Acquired Haemophilia A.

Haemophilia B

There are no existing Australian clinical practice guidelines for ITI in patients with inhibitors to factor IX.

See Appendix G for details (Australian Haemophilia Centre Directors' Organisation 2004).

Effectiveness of tolerisation

The best information on the effectiveness and safety of tolerisation protocols for haemophilia A with inhibitors comes from one good quality systematic review of level IV evidence (Wight et al. 2003). No studies of tolerisation in patients with haemophilia B, von Willebrand disease or other rare bleeding disorders satisfied our inclusion criteria for an evaluation of effectiveness.

High dose protocols

Bonn protocol: The original Bonn regime involved giving 100 IU/kg FVIII plus 40–60 IU/kg FEIBA every 12 hours until the inhibitor level dropped below 1 BU and FEIBA was discontinued. Then FVIII was reduced to 150 IU/kg daily until inhibitor was no longer detectable. Recently, the protocol was modified so that people with a tendency to bleed are given 150 IU/kg FVIII every 12 hours, rather than FEIBA (Wight et al. 2003). After completing the Bonn protocol or other high dose protocols, 90% of patients had complete elimination of inhibitors and partial success in two others (Level IV evidence) (Wight et al. 2003). In a large case series (Level IV evidence) it was found that lower initial inhibitor titres were associated with shorter treatment time on the Bonn protocol (Wight et al. 2003).

Malmö protocol: The Malmö protocol utilises extracorporeal immunoadsorption when inhibitor titres are above 10 BU, until levels are brought down to less than 10 BU. High doses of FVIII (around 200 IU/kg/day) are then administered to bring FVIII concentration up to 40–100 IU/dL and to maintain it at 30–80 IU/dL. At the same time, cyclophosphamide (an immunosuppressant) is administered at a dose of 12–15 mg/kg intravenously for two days, followed by 2–3 mg/kg for eight days. On day one of treatment, immunoglobulin is also used at a dose of 2.5–5 g/kg, followed by 0.4 g/kg on days 4–8. Factor VIII is administered until the inhibitor disappears and patients receive FVIII for ongoing prophylaxis. Of the 32 patients who were treated by the Malmö protocol or slight variants of it, 47% successfully had inhibitors removed (Wight et al. 2003). One case series (Level IV evidence) found that treatment of young children tended to be unsuccessful with the Malmö protocol, and success was more likely in patients with long standing inhibitors who had been exposed to multiple doses of FVIII since inhibitor development (Wight et al. 2003). These results are contrary to those found in the Bonn protocol, which suggests that while the Malmö protocol may be less effective overall, it may be more effective than other protocols in patients with long standing inhibitors (Wight et al. 2003).

The Bonn and Malmö protocols are not used routinely in Australian practice. In particular, the Malmö protocol requires specific equipment not readily available outside Sweden and is, consequently, not practical for use in Australia (JBC FVIII/FIX working party & National Blood Authority 2004).

Other protocols have been developed, aiming to reduce the cost and complexity of the Bonn and Malmö protocols (Wight et al. 2003). However, there is insufficient evidence relating to these variations for adequate evaluation.

Low dose protocols

A variety of low dose protocols have also been developed for use in haemophilia patients. Dose regimens using FVIII varied from 175 IU/kg/week to 100 IU/kg/day,

with or without additional immunosuppressive drugs (Wight et al. 2003). For example, from a total of 107 patients following a low dose protocol (maximum of 100 IU/kg/day of factor VIII), immune tolerance was successful in 67% of patients, and partially successful in 8% of others (Level IV evidence).

Low dose regimes may be more cost-effective and may be administered more readily without the use of a central line (Level IV evidence) (Hay et al. 2000a).

Registry data

The International, North American, German and Spanish registries on haemophilia patients with inhibitors were analysed in univariate and multivariate analysis. The results suggest that tolerisation is more likely to be successful when patients are younger, maximum pre-treatment inhibitor titres are low, and when there is a shorter period of time between development of inhibitor and treatment of inhibitors (Level IV evidence) (Wight et al. 2003).

The International Immune Tolerance Study—ongoing

A randomised controlled trial (Level II evidence) of the effectiveness, morbidity and cost effectiveness of two types of immune tolerance induction in severe haemophilia A was started late in 2002 and aims to include 150 patients. The study was delayed due to a shortage of rFVIII and no results have been published to date. Based on the lack of evidence regarding optimum treatment for eradicating inhibitors, it is suggested that patients with severe haemophilia A, an inhibitor for 12 months or less, a historical peak inhibitor titre of > 5 but < 200 BU, and currently an inhibitor titre of less than 10 BU be enrolled in the International Immune Tolerance Study so future treatment may be guided by clinical evidence (Hay et al. 2000a). The International Immune Tolerance Study is expected to be completed by July 2007.

Immunosuppressive drugs

Based on poor quality studies, immunosuppressive drugs used to date are ineffective in reducing inhibitors in haemophilia patients (Level IV evidence). A survey on the use of immunosuppressive drugs in 56 patients found that the drugs were ineffective in the majority of cases (61%), partially effective in 28% of patients and successful in only 13% of patients (Lloyd Jones et al. 2003). It is possible that newer immunosuppressive drugs, such as rituximab, may be more effective than those used previously, but there is no evidence available at present to recommend this treatment.

Choice of products

There is no strong evidence that any particular type or brand of product is more effective than another in immune tolerance induction. An uncontrolled study on a small group of people found that an intermediate-purity factor VIII concentrate was more effective than high-purity factor. However, similar response rates have been reported with high-purity or recombinant products (Hay et al. 2000a). Therefore, it is recommended that rFVIII products be used due to the higher safety profile compared with plasma-derived factor.

Safety of tolerisation

No available studies reported on the safety of immune tolerance protocols, although the International Immune Tolerance Study is currently collecting information on adverse events related to the tolerisation and data should be available in the future.

If tolerisation is performed on patients with haemophilia B using FIX, patients should be closely monitored to prevent anaphylactic reactions (expert opinion, AHCDO Executive Committee 2005).

Evidence-based clinical practice guidelines

In Australia, the tolerisation protocols vary widely across haemophilia treatment centres, with little published evidence of effectiveness, no consensus on protocols, and the Bonn and Malmö protocols are not routinely used. Doses of FVIII concentrate for tolerisation range from 25 IU/kg three times per week, to 100 IU/kg/day. Guidelines should be revised after publication of results from the International Immune Tolerance Study.

- The Bonn protocol may be considered for young patients (Level IV evidence).

  Bonn protocol (modified): People with a tendency to bleed are given 150 IU/kg FVIII every 12 hours until the inhibitor level drops below 1 BU. Then FVIII is reduced to 150 IU/kg daily, until inhibitor is no longer detectable.

- Treatment is more likely to be successful with lower pre-treatment inhibitor titres and less time between development and treatment of inhibitors (Level IV evidence).

- When patients have long standing inhibitors, the Malmö protocol may be considered (Level IV evidence).

  Malmö protocol: When inhibitor titres ≥10 BU extracorporeal immunoadsorption is given until levels are reduced to <10 BU. High doses of FVIII (around 200 IU/kg/day) are then administered to bring FVIII concentration up to 40–100 IU/dL and to maintain it at 30–80 IU/dL. At the same time, cyclophosphamide is administered at a dose of 12–15 mg/kg intravenously for two days, followed by 2–3 mg/kg for eight days. On day one of treatment, immunoglobulin is also used at a dose of 2.5–5 g/kg, followed by 0.4 g/kg on days 4–8. Factor VIII is administered until the inhibitor disappears and patients receive FVIII for ongoing prophylaxis.

- When factor concentrates are used, recombinant factors are preferred rather than plasma-derived factors, due to their higher safety profile regarding transmission of blood-borne agents (Level IV evidence).

- There is no evidence to guide tolerisation procedures in patients with haemophilia B with inhibitors. Recombinant FIX is preferred over plasma-derived FIX due to the higher safety profile pertaining to transmission of blood-borne agents, but there should be close monitoring to prevent anaphylactic reactions (expert opinion).

Treatment of patients with acquired haemophilia

Acquired haemophilia is a very rare disease (about one in a million people) in which people without haemophilia develop antibodies to factor VIII. The bleeding complications associated with acquired haemophilia can be life threatening, so prompt diagnosis and treatment are vital. While most people with acquired haemophilia have idiopathic autoantibodies, 40–50% of cases are associated with other conditions, such as the postpartum state, autoimmune disease, underlying malignancies and drug administration (Delgado et al. 2003). Due to the rarity of acquired haemophilia, information regarding its treatment and prognostic factors is derived solely from case series (Level IV evidence) or from an average quality systematic review of case series with five or more patients (Level IV) (Delgado et al. 2003). Due to the lack of appropriate studies for evaluation of effectiveness recommendations must rely on case series.

Pregnancy

Antibodies to factor VIII usually develop 1–4 months after infant delivery, but some patients show inhibitors during pregnancy or up to one year after delivery. In the majority of cases, the level of postpartum inhibitors is low and they disappear spontaneously after a mean of 30 months (Level IV evidence). However, it is advisable that patients are evaluated for lupus or rheumatoid arthritis since patients with these disorders require a different approach to treatment (Delgado et al. 2003).

An important issue in managing pregnancy-related acquired haemophilia is the risk of inhibitor recurrence in subsequent pregnancies. While most case series reported little risk in those who achieved complete remission, one study, which included three patients and six subsequent pregnancies, reported an anamnestic response of the inhibitor in four of the pregnancies. Therefore, it is considered essential to counsel women about this risk in subsequent pregnancies (Delgado et al. 2003).

Autoimmune diseases

Inhibitors to factor VIII have been associated with the following derangements of the immune system:

- rheumatoid arthritis
- systemic Sjögren's syndrome
- dermatomyositis
- graft-versus-host disease after allogenic bone marrow transplantation
- myasthenia gravis
- multiple sclerosis
- Grave's disease

- autoimmune haemolytic anaemia.

Patients with autoimmune disease-related inhibitors usually have high titre inhibitors that require immediate treatment, as they do not spontaneously disappear. Prednisolone, a synthetic corticosteroid with potent anti-inflammatory activity, shows a greater effect with the addition of an alkylating agent that has immunosuppressant action (Delgado et al. 2003).

Malignant neoplasms

There are inconsistencies between studies on whether the association between malignant neoplasms (either solid or haematologic) and acquired haemophilia is causal, or whether the appearance of solid neoplasms is simply common in elderly people in whom inhibitors usually appear. After a review of case reports of 41 cancer-associated inhibitors, the following recommendations were made: The primary malignancy should be treated, as the antibodies are easier to eradicate when the tumour is controlled. If the tumour is still present or has failed to respond to treatment, immunosuppressive therapy should be considered. The decision to administer immunosuppressive therapy should take into account the age, type of malignancy and severity of bleeding (Level IV evidence) (Delgado et al. 2003).

Drug administration

The association between acquired haemophilia and drug administration is often unclear, particularly in elderly people who are on multiple medications, including antibiotics and anticonvulsants that have well-established associations with inhibitors. In most cases, the inhibitor disappears when the drug is withdrawn (Delgado et al. 2003).

Previous Australian consensus-based guidelines

Currently there are no Australian guidelines on treatment of acquired haemophilia.

Effectiveness and safety of treatment of bleeding episodes

The treatment of acquired haemophilia is similar to that used for congenital haemophilia with inhibitors. There are two fundamental issues: 1) immediate treatment of acute bleeding episodes, as they can be life threatening; and 2) ultimate treatment to remove inhibitors and thus, eradicate the disease (Stasi et al. 2004).

Current options for treating bleeding episodes in patients with inhibitors include the use of high doses of factor VIII (plasma-derived or recombinant) or DDAVP if the inhibitor levels are low (<5 BU). If the inhibitor levels are high (>5 BU) bypassing agents such as aPCCs or rFVIIa should be used. See Table 34 for full details of products used in patients with inhibitors.

Desmopressin (1-deamino-D-arginine vasopressin, DDAVP)

In a systematic review of low level evidence, desmopressin was shown to be effective in patients with low titre inhibitors (<3 BU; Level IV evidence). However, a trial of desmopressin in patients with high titre inhibitors or severe bleeding only delayed the commencement of more effective treatments (Delgado et al. 2003).

Human FVIII concentrates

Human factor VIII (recombinant or plasma derived; rFVIII or pdFVIII) may be useful in large doses for patients with low inhibitor titres (<5 BU), in a recommended dose of 20 IU/kg for each BU of inhibitor plus an additional 40 IU. If the initial dose is not adequate after 10–15 minutes, another bolus injection may be administered. Some clinicians used triple the dose of regular treatment with factor concentrates for haemophilia and found clinical benefit despite poor post-infusion assay results. Response to human factor VIII is highly variable in the presence of inhibitors and should be closely monitored (Delgado et al. 2003). This finding is consistent with that reported in a systematic review on the treatment of haemophilia A patients with inhibitors (Lloyd Jones et al. 2003).

Activated prothrombin complex concentrates (aPCCs)

A recent retrospective case series (Level IV evidence) of 34 acquired haemophilia patients found that a dose of 75 IU/kg of FEIBA every 8–12 hours was successful in curbing bleeding episodes in 76% of severe and 100% of moderate episodes (Sallah 2004). The recommended dose for both FEIBA and Autoplex® is 50–200 IU/kg/day in divided doses. To date, there is no available assay to measure the efficacy of aPCCs (Delgado et al. 2003).

Overall, aPCCs appear to be well tolerated with very few side effects. However, patients should be closely monitored as larger doses may cause thrombotic events, including myocardial infarction, disseminated intravascular coagulation and thrombosis (Delgado et al. 2003).

Activated recombinant FVII (rFVIIa)

The largest case series (Level IV evidence) that investigated the use of rFVIIa in patients with acquired haemophilia reported that it was effective as a 'good' salvage therapy in 75% or 'partial' salvage therapy in 17% of bleeding episodes once other therapies had failed. When used as first-line therapy, there was a 100% success rate. The average dose of rFVIIa was 90 μg/kg every 2–6 hours for a median of 3.9 days (Delgado et al. 2003).

From a study of 180 000 standard doses of rFVIIa, it was concluded that rFVIIa is very well tolerated, with few side effects. Close monitoring of patients is required as adverse events (though rare) may be serious.

Eradication therapy

Immunosuppressants

In approximately 36% of acquired haemophilia cases, inhibitors disappear spontaneously without immunosuppressive therapy (Delgado et al. 2003). However, complete remission is unpredictable and it is recommended that patients be treated with immunosuppressive therapy to assist in removal of inhibitors. However, specific recommendations cannot be made about the safest and most effective type of immunosuppressive therapy for acquired haemophilia due to the lack of quality evidence (Table 36).

Prednisolone in a dose of 1 mg/kg/day has been shown to abolish inhibitors in approximately 30% of patients (Delgado et al. 2003). With the addition of

cyclophosphamide (1–2 mg/kg/day) the success rate increases to 60–100%. Combinations of prednisolone with other immunosuppressants, such as azathioprine, cyclophosphamide, or vincristine have also been effective. Cyclosporin A (200–300 mg/day) was found to be successful as a salvage therapy, alone or with prednisolone. More recently, rituximab (375 mg/m^2/week) has been reported to show effectiveness after other treatments failed. All patients with inhibitor levels <100 BU achieved complete remission, while the two patients with inhibitors >100 BU achieved partial remission (Level IV evidence) (Stasi et al. 2004).

Immunosuppressive therapy may have multiple side effects in an elderly population (the majority of acquired haemophilia cases). In a consecutive series of 18 patients with acquired haemophilia (Level IV evidence), it was reported that one patient died from bleeding, while three patients died from complications associated with immunosuppressive treatment (Collins et al. 2004). Cyclophosphamide may cause bacterial sepsis from neutropaenia, fibrotic lung disease, and a combination of cyclophosphamide, prednisolone and vincristine has been reported to cause alopecia. Prednisolone and cyclophosphamide have been associated with the development of herpes zoster, cataracts, myelodysplasia and severe osteoarticular infections. A meta-analysis of case series of 249 patients found that, while cyclophosphamide was superior to prednisolone for eliminating inhibitors, it was inferior in terms of survival. That is, a substantial number of patients died from neutropaenia-related infections as a side effect of cyclophosphamide treatment (Delgado et al. 2003). A more recent study (Level IV evidence) on rituximab found it was associated with fewer adverse events than cyclophosphamide, but these treatments have not been compared in a systematic way. A total of 15 patients with acquired haemophilia have been treated with rituximab, with very few side effects (Level IV evidence) (Stasi et al. 2004; Wiestner et al. 2002). Early treatment and a combination of rituximab and prednisolone achieved optimal benefit (Level IV evidence) (Wiestner et al. 2002).

Table 36. Adverse events associated with immunosuppressant therapy

Study	Level and quality of evidence	Population	Adverse events after immunosuppression
(Collins et al. 2004)	Level IV: case series Quality score: 3/3 Measurement bias unlikely Selection bias avoided Follow-up adequate Uncontrolled	18 acquired haemophilia: 14 no underlying disorder, 1 gastric carcinoma, 1 polymyalgia rheumatica, 1 Castlemanns disease, 1 Depoxil; aged 38–87, median 70 years	4 patients died: 1 from intracranial haemorrhage, and 3 from immunosuppressive-related treatment
(Sallah & Wan 2003)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	6 acquired haemophilia: 2 no underlying disorder, 1 chronic lymphocyctic leukaemia, 1 scleroderma, 1 systemic lupus erthematosus, 1 colon cancer; aged 59–78 years	2-chlorodeoxyadenosine as salvage therapy Treatment was well tolerated, no grade 4 toxicity or death from treatment observed: 1 case of mild neutropaenia 1 case with atypical pneumonia and lymphopaenia
(Delgado et al. 2002)	Level IV: case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	17 acquired haemophilia: 7 no underlying disorder, 4 postpartum, 1 acute hepatitis B, 1 lymphoma, 1 lung cancer, 1 refractory anaemia with ringed sideroblasts, 1 rheumatoid arthritis, 1 colon cancer; aged 8–86 years, median 67 years	9/17 (52%) had immunosuppressive therapy-related side-effects: 3 died of immunosuppressive related side effects—2 with pneumonia, 1 with unspecified bacterial sepsis Cyclophosphamide Cytopaenia, hair loss, toxic hepatitis Alkylating agent Two episodes pancytopaenia, one cutaneous reaction, one toxic hepatitis Prednisolone Steroid myopathy Prednisolone + cyclophosphamide 3/7 had side effects, femoral nerve palsy, neutropaenia, varicella zoster 2 deaths from pneumonia/septicaemia and pulmonary fibrosis

(cont.)

Table 36 (cont.) (Stasi et al. 2004)	Level IV: case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	10 acquired haemophilia: 6 with no underlying disorder, 1 with rheumatoid arthritis, 1 with prostate carcinoma, 1 with low-grade non-Hodgkin lymphoma, and one after pregnancy; aged 27–78 years, median 61 years	Rituximab 3/10 patients had first-infusion reactions of fever (1 patient), chills (2 patients), and nausea (1 patient). Reactions were brief and mild.
(Wiestner et al. 2002)	Level IV: case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	4 acquired haemophilia: 1 chronic renal failure, 1 ascites and lymphadenopathy, 1 with polymyalgia and ecchymoses, and 1 with no underlying disorder. Aged 38–70 years, median 54 years	Rituximab No side effects

High-dose intravenous immunoglobulin G

The literature on the effectiveness of intravenous immunoglobulin G (IVIg) in patients with acquired haemophilia reported an overall patient response rate of 12–50%. The current clinical evidence does not support the use of IVIg as first-line therapy (Level IV evidence). Reported positive effects following the addition of IVIg to steroids were probably due to publication bias (expert opinion) (Delgado et al. 2003).

Plasmapheresis and immunoadsorption

Plasmapheresis and immunoadsorption (extracorporeal removal of antibodies) may be an option when severe bleeding results in the need for rapid removal of inhibitors. With few exceptions, these methods have been evaluated in conjunction with immunosuppression therapy and their specific contribution to haemostasis is unclear. These methods have not been found to reduce time to complete remission and should only be used with immunosuppressive therapy to prevent the recurrence of inhibitors (expert opinion) (Delgado et al. 2003).

Immune tolerance induction

While immune tolerance induction may be effective in patients with congenital haemophilia and factor VIII alloantibodies, tolerisation is rarely if ever used in patients with acquired haemophilia. Some studies have combined the use of factor VIII concentrates and immunosuppressive agents to reduce inhibitors, but others found that the immunosuppressive agents alone were as successful as when used in combination with factor concentrates (Level IV evidence) (Delgado et al. 2003).

Evidence-based clinical practice guidelines

Treatment of bleeding episodes (All Level IV evidence)

- It is recommended that bleeding episodes in patients with acquired haemophilia receive prompt treatment.

  When inhibitors <5 BU, DDAVP or FVIII concentrate should be used:

  – DDAVP may be used in a dose 0.3 µg/kg body weight, either intravenously or subcutaneously. It should be diluted in 50 mL of 0.9% saline and infused over at least 30 minutes.

  – FVIII concentrate may be used in a recommended dose of 20 IU/kg for each BU of inhibitor plus an additional 40 IU and tested after 15 minutes. If response is poor, another bolus injection may be given.

  – Activated recombinant factor VII (rFVIIa) may be given in a dose of 90 µg/kg every 2–6 hours until bleeding has stopped.

  When inhibitors >5 BU, activated prothrombin complex concentrates (aPCCs) or rFVIIa should be used:

  – aPCCs may be given in a dose of 50–200 IU/kg/day in divided doses.

  – rFVIIa may be given in a dose of 90 µg/kg every 2–6 hours until bleeding has stopped.

- Regardless of treatment option taken, it is recommended that the patient be closely monitored due to the risk of adverse thrombotic events.

Elimination of inhibitors (All Level IV evidence)

- It is recommended that patients with acquired haemophilia be examined for underlying disorders before deciding on treatment strategies. The decision to administer immunosuppressive therapy should take into account the age, type of malignancy and severity of bleeding.

  – Patients with postpartum acquired haemophilia (without lupus or rheumatoid arthritis) may receive immunosuppressive therapy, or may simply be monitored, due the high rate of spontaneous disappearance of inhibitors within this group.

  – Patients with drug-related acquired haemophilia should have the drug withdrawn, in the first instance, and be treated with immunosuppressive therapy or simply monitored for spontaneous disappearance of inhibitor.

  – Patients with autoimmune disease-related inhibitors usually have high titre inhibitors that require treatment with immunosuppressants.

  – Patients with acquired haemophilia associated with a malignant neoplasm should have the primary malignancy treated initially, as the antibodies are easier to eradicate once the tumour is controlled. Immunosuppressive therapy should be considered while the tumour is still present or has failed to respond to treatment.

  – Patients without underlying disorders should receive immunosuppressive therapy.

- Due to the lack of quality evidence on effectiveness and safety of particular immunosuppressants, no recommendation can be made regarding the best treatment, but patients should be treated on an individual basis with close monitoring for adverse events.

Surgical and Dental Procedures

Haemophilia A and B

Surgical procedures

Before the 1960s, the mortality rates for haemophilia patients undergoing surgery were very high (25–50%) (Bastounis et al. 2000). Mortality decreased with the use of plasma (to <10%), cryoprecipitate (to <2%), and the more recent introduction of factor concentrates (to <1%).

Major surgical procedures in patients with coagulation disorders, particularly in those with inhibitors, carry substantial risks and should be undertaken in a haemophilia care centre with careful individual management after consultation with a haemophilia specialist.

There were no studies available that formally looked at the optimal duration of treatment after surgical procedures.

Previous Australian consensus-based guidelines

There are no existing Australian guidelines for the management of patients undergoing surgical procedures. Recommendations from the Canadian guidelines are listed in Table 37.

Table 37. Management of patients undergoing surgical procedures

Before surgery • If the risk of bleeding is very high, elective surgery should be postponed • Screening for inhibitors should be performed shortly before the day of surgery (Bethesda assay) • The patient should avoid using antiplatelet medication before and after surgery • Surgery should be scheduled for early in the week and early in the day to ensure availability of laboratory services and consultants • Adequate amounts of replacement factor product required before and after surgery should be available • A pharmacokinetic analysis to determine recovery/response to a challenge dose of factor product should be conducted before surgery
During surgery • Caution should be taken to avoid medications or procedures that provoke haemorrhages (e.g. analgesics, anaesthetics; ligation of all visible bleeding, cautery only for capillary bleeding) • Keep operation time to a minimum • Use pressure bandages for soft tissue injuries
After surgery • Careful monitoring (factor activity levels) to maintain plasma factor levels >30% for the period of recovery after surgery (2–3 weeks) • Remove sutures after factor replacement given

Modified from Association of Hemophilia Clinic Directors of Canada 1995a; Bastounis et al. 2000. These guidelines do not match with current Australian practice (AHCDO Executive Committee 2005)

Are treatments effective?

Comparisons between patients and across studies are difficult because of considerable variability in surgical procedures (minor/major; elective/emergency), duration of therapy, dosing requirements (pre-operative/additional doses, bolus/continuous dosing).

All available studies (Table 38) relevant to the use of rFVIII or rFIX in patients undergoing surgery were low level evidence (Level IV). Haemostatic control was described by physicians as 'good' or 'excellent' in all patients, without need for additional treatment. Overall, blood loss was estimated to be within the normal range expected in patients without a coagulation disorder for the type of surgery performed.

Table 38. Haemostatic control in haemophilia patients undergoing surgery

Study	Level and quality of evidence	Population	Haemostatic control		
(Scharrer 2002; Scharrer et al. 2000)	Level IV: before-and-after study Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	15 PTPs and 7 PUPs with severe haemophilia A, without inhibitors, undergoing 30 surgical procedures		PTPs	PUPs
			Haemostasis control	18/23 excellent 5/23 good	7/7 excellent
			Median post-surgical duration of therapy	12 days (1–89)	8 days (5–12)
			Median number of infusions	18 (1–75)	12 (6–44)
			Daily dose	52.8 IU/kg/day (10.6–149.4 IU/kg/day)	93 IU/kg/day (51–235 IU/kg/day)
			Blood loss	0–250ml within normal range expected in patients without coagulation disorder	within normal range
(Schwartz et al. 1990; Seremetis et al. 1999)	Level IV: case series Quality score: 2/3 Selection bias unclear Confounding avoided Follow-up adequate Uncontrolled	26 PTPs with moderate–severe haemophilia A, without inhibitors, undergoing 32 surgical procedures, or with serious haemorrhages rFVIII treatment as required	100% rated 'excellent'—no additional treatment required		
(Ragni et al. 2002)	Level IV: before-and-after study Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	26 PTPs with mild–severe haemophilia B and 2 female haemophilia B carriers, undergoing 32 surgical procedures	Intra-operative blood loss: 0–1500ml Post-operative blood loss: 0–2676ml Haemostatic control: excellent/good 34/35		
(White et al. 1997)	Level IV: case series Quality score: 2/3 Selection bias uncertain Confounding avoided Follow-up adequate Uncontrolled	13 PTPs with moderate-severe haemophilia A, without inhibitors undergoing surgical procedures	Blood loss: 0–200ml, as expected for the type of surgery in patients without coagulation disorder		
(Stieltjes et al. 2004)	Level IV: retrospective case series Quality score: 1/3 Selection bias uncertain Follow-up adequate Uncontrolled	16 PTPs with mild-severe haemophilia A, without inhibitors, undergoing 20 surgical procedures	Haemostasis control: excellent 11/20 good 5/20 moderate 4/20 Blood loss: <500ml 6/20 >500ml 3/20 Excessive bleeding required red blood cell transfusion in 8 procedures		

PTPs = previously treated patients; PUPs = previously untreated patients; rFVIII= recombinant factor FVIII

Dental surgery

Dental procedures for patients with bleeding disorders require consultation between the patient's dentist and a haemophilia specialist.

> Previous Australian consensus-based guidelines
>
> Protocols for the dental management of coagulation disorders, haemophilia A, B and von Willebrand disease have been developed and implemented at the Adelaide Dental Hospital in South Australia (Stubbs & Lloyd 2001) (Appendix G).

Are treatments effective?

Data on treatment effectiveness is limited. Over a two year period, 30 haemophilia A, one haemophilia B, and 15 von Willebrand patients were managed successfully according to the protocol devised at the Adelaide Dental Hospital in South Australia (no data provided) (Stubbs & Lloyd 2001). The extent of treatment for controlling haemostasis was based on the expected degree of trauma to oral soft tissue during dental procedures and the severity of disease in the patient. The management of dental extractions was not included in the protocol.

One average quality randomised controlled trial (Level II evidence) investigated the effect of suturing the tooth extraction wound compared to leaving it open in two groups of patients with haemophilia A (Stajcic et al. 1989). Although there was no significant difference between groups in the incidence of post-operative bleeding, the clot size, which was measured subjectively (unvalidated measure), was significantly larger in the group with open wounds ($p<0.01$), making the post-operative period more uncomfortable for patients.

Table 39. Haemostatic control in haemophilia patients undergoing dental procedures

Study	Level and quality of evidence	Population	Haemostatic control		
(Stajcic et al. 1989)	Level II: randomised controlled trial Quality score: 14/27 Selection bias minimised Confounding uncertain Follow-up adequate Patients representative	62 patients with mild-severe haemophilia A, undergoing dental extractions		Open wound (N=25)	Closed wound (N=25)
			Clot size large	15/25	1/22
			Post-operative bleeding	2/25	0/25
			Post-operative dose FVIII	2.7 IU/kg	0

Are treatments safe for surgery or dental surgery?

Inhibitor development following treatment with rFVIII or rFIX was either low titre and transient or not detected in two low level studies described in Table 40.

Table 40. Development of inhibitors in haemophilia patients undergoing surgical procedures

Study	Level and quality of evidence	Population	Development of inhibitors associated with treatment
(Ragni et al. 2002)	Level IV: case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	26 PTPs with mild–severe haemophilia B and 2 female haemophilia B carriers, undergoing 32 surgical procedures	None detected
(Scharrer 2002; Scharrer et al. 2000)	Level IV: case series Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	15 PTPs and 7 PUPs with severe haemophilia A, without inhibitors, undergoing surgical procedures	High-titre inhibitor 0 Low-titre inhibitor 2/7 PUPs 2 transient (prior to surgery)

PTPs = previously treated patients; PUPs = previously untreated patients

Overall, there were few adverse events following surgery (Table 41). Although most adverse events were mild and reversible, Stieltjes et al. 2004 reported four serious post-operative bleeding complications following major surgery (Level IV evidence).

Some dental patients treated according to the protocol developed by Stubbs and Lloyd (2001) reported nausea following the use of tranexamic acid. Generally, there were no post-operative bleeding complications following dental treatment. In the majority of patients, gingival ooze stopped within 60 minutes; some patients with severe haemophilia A experienced mild gingival ooze for several hours post-operatively.

Table 41. Adverse events in haemophilia patients undergoing surgical or dental procedures

Study	Level and quality of evidence	Population	Adverse events
(Zanon et al. 2000)	Level III-2: cohort study Quality score: 16/27 Selection bias uncertain Confounding uncertain Follow-up adequate Patients representative	71 haemophilia A and 6 haemophilia B patients undergoing dental extractions Controls: 184 non-haemophilic patients undergoing dental extractions	No. of bleeding complications/No of dental extractions Haemophilia patients (N=75): 2/98 (2.0%) Non-haemophilia controls (N=184): 1/239 (0.4%)
(Ragni et al. 2002)	Level IV: before-and-after study Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	26 PTPs with mild–severe haemophilia B and 2 female haemophilia B carriers, undergoing 32 surgical procedures	4 patients experienced ≥1 adverse event Rash, flushing, hives, headache, teichopsia, sneezing, dry cough, local phlebitis
(Scharrer 2002; Scharrer et al. 2000)	Level IV: before-and-after study Quality score: 2/3 Selection bias minimised Follow-up adequate Uncontrolled	15 PTPs and 7 PUPs with severe haemophilia A, without inhibitors, undergoing surgical procedures	No adverse events or complications No adjunctive agents required
(Djulbegovic et al. 1996)	Level IV: case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Uncontrolled	8 patients with haemophilia B undergoing dental extraction	4/8 patients reported adverse effects of EACA treatment: Nausea, vomiting, transient creatine phosphokinase elevation
(Stieltjes et al. 2004)	Level IV: retrospective case series Quality score: 1/3 Selection bias uncertain Follow-up adequate Uncontrolled	16 PTPs with mild–severe haemophilia A, without inhibitors, undergoing 20 surgical procedures	5 mild–moderate and 4 serious adverse events associated with BDDrFVIII treatment Mild–moderate: haematoma, obturation of the vein at infusion site, local thrombophlebitis at infusion site Serious: severe postoperative bleeding

BDDrFVIII = recombinant B-domain deleted FVIII; EACA = ε-aminocaproic acid, an antifibrinolytic agent; PTPs = previously treated patients; PUPs = previously untreated patients

von Willebrand disease

One of the most common symptoms of von Willebrand disease is excessive post-operative bleeding. Therefore, dental and surgical procedures should be performed with caution in this population (Ziv & Ragni 2004). Bleeding episodes in people with von Willebrand disease (vWD) may be treated either with DDAVP or factor VIII concentrates enriched with von Willebrand factor (pdFVIII/vWF). Optimal treatment

depends on the type of vWD and the patient's responsiveness to DDAVP (see Adjunctive haemostatic agents section).

Are treatments effective?

Local therapies and DDAVP

There were seven low level research papers included in this systematic review that evaluated the effectiveness of the use of DDAVP plus local therapies for dental or surgical procedures (See Table 42 and Table 43). Overall, it was found that a combination of DDAVP and local therapies[x] such as tranexamic acid and fibrin glue was highly effective for minimising post-operative bleeding (Level IV evidence) (Mariana et al. 1984; Ghirardini et al. 1988; de la Fuente et al. 1985; Warrier & Lusher 1983; Nitu-Whalley et al. 2001; Saulnier et al. 1994).

Table 42. Effectiveness of adjunctive haemostatic agents in surgical and dental procedures for patients with von Willebrand disease

Study	Level and quality of evidence	Population	Effectiveness of DDAVP + local therapies
(Saulnier et al. 1994)	Level IV: before and after study Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	14 vWD, mean age 24 years 16 treatments, 14 dental extractions	DDAVP (0.3 µg/kg) + tranexamic acid + fibrin glue Number without bleeding complications: 100% FVIII:C mean increase post/pre treatment X4.6 vWF:Ag mean increase post/pre treatment X3.22 RcoF mean increase post/pre treatment X4.08 BT mean decrease (measured by Duke method) post/pre treatment 0.27
(Nitu-Whalley et al. 2001)	Level IV: case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	27 patients with Types 1 (93%) and 2 (7%) vWD most of whom had responded to DDAVP, aged 14–57 years 35 surgical events, including major, minor and dental	Intravenous DDAVP (0.3 µg/kg) + tranexamic acid for mucosal surgery Haemostasis rated as 'Excellent' after 32/35 surgical events, 'Moderate' after 2/35, and 'Poor' after 1/35 surgical event.
(de la Fuente et al. 1985)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	11 vWD patients: 8 x Type 1 vWD, 3 x Type 2A vWD 6 dental procedures, 9 surgical interventions	DDAVP (0.3 µg/kg) intravenous + epsilon aminocaproic acid Excellent haemostasis achieved in all 5 patients who had dental extractions 4/6 patients who had surgical procedures had no need for factor concentrates 2/6 patients required fresh frozen plasma or cryoprecipitate due to low FVIII:C levels after surgery.

(cont.)

[x] Local therapies—application of a treatment to the bleeding site

Table 42 (cont.) Study	Level and quality of evidence	Population	Effectiveness of DDAVP + local therapies
(Warrier & Lusher 1983)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	7 patients with vWD 7 surgical events, including 3 dental extractions, 3 tonsillectomies, 1 nasal polypectomy	DDAVP via intranasal drip (2–4 µg/kg) or intravenous (0.2–0.3 µg/kg) + epsilon aminocaproic acid No unusual bleeding from any of the 7 surgical events 6/15 had prolonged BT at baseline All 6 had normal values 15 and 90 minutes post DDAVP 5/6 had prolonged BT at 180 minutes
(Ghirardini et al. 1988)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow-up adequate Uncontrolled	5 Type 1 vWD patients 1 dental extraction, 4 surgical interventions	DDAVP subcutaneous (0.3 µg/kg) + tranexamic acid + fibrin glue for dental No bleeding observed in any dental or surgical procedure
(Mariana et al. 1984)	Level IV: case series Quality score: 1/3 Measurement bias possible Selection bias likely Follow-up adequate Uncontrolled	20 vWD (Types 1 and 2) 9 patients had 12 dental extractions, 6 patients had 8 surgical procedures	DDAVP (0.3–0.4 µg/kg) intravenous + tranexamic acid No bleeding observed in vWD patients for dental procedures No intra-operative bleeding in 5/6 patients post surgery. One patient had a bleeding episode on the 7th day after surgery

BT= bleeding time; DDAVP= 1-D-deamino-8D-arginine vasopressin; FVIII:C= factor VIII coagulant activity; RcoF = ristocetin-cofactor activity; vWF:Ag= von Willebrand factor antigen; vWD= von Willebrand disease

Table 43. Effectiveness of local therapies, local therapies with DDAVP, and local therapies with factor concentrates for dental surgery in von Willebrand disease patients

Study	Level and quality of evidence	Population	Effectiveness of tranexamic acid ± fibrin glue + DDAVP or factor VIII/vWF concentrates		
			Local therapies alone	Local therapies + DDAVP	Local therapies + pdFVIII/vWF
(Federici et al. 2000)	Level IV: retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	63 patients with vWD, for 117 dental extractions or periodontal surgery episodes 31 x Type 1 22 x Type 2 10 x Type 3	1/30 patients experienced bleeding complications	0/66 patients experienced bleeding complications	1/21 patients experienced bleeding complications

DDAVP= 1-D-deamino-8D-arginine vasopressin; vWD= von Willebrand disease; vWF = von Willebrand factor

Plasma-derived factor VIII/von Willebrand factor concentrates

Seven case series (Level IV evidence) evaluated the effectiveness of using pdFVIII/vWF concentrates for haemostasis cover during surgical or dental procedures in patients with von Willebrand disease. The studies varied in amount of factor product used prior to and

after surgery but, overall, pdFVIII/vWF concentrates were found to provide excellent/good haemostatic cover for surgical or dental procedures (Table 44).

One low level study reported that all of the 73 surgical cases received Haemate® P in a single dose prior to surgery and, by day seven, only 11/73 (15%) of cases required further treatment (Lillicrap et al. 2002; Dobrkovska et al. 1998). An 'excellent/good' physician rating was achieved in 99% of cases, indicating that haemostasis and adequate control of bleeding had been achieved. Individual assessment and monitoring of the patient was found to be essential during surgical procedures, due to the wide range of doses required for haemostasis (Level IV evidence) (Lillicrap et al. 2002; Dobrkovska et al. 1998).

As reported in Thompson et al. 2004, a pre-operative loading dose of 60–80 IU vWF:Rco/kg (27-36 IU FVIII:C/kg) was administered every 8–12 hours for three days (Level IV evidence). Maintenance doses were usually administered for seven days post-surgery but treatment was extended in 10/32 (31.3%) patients for more than seven days. Patients treated for longer periods tended to be given lower, less frequent doses. The wide range in dose, number of infusions and duration of treatment indicate that treatment must be assessed on an individual basis, and levels of von Willebrand factor activity and factor VIII need to be measured to tailor individual treatment programs. No consistent pattern was observed for loading or maintenance doses by von Willebrand disease type. However, Type 3 patients appeared to receive a greater number of infusions (13). In addition, the majority of patients with Type 1 and 2 von Willebrand disease completed treatment within seven days (Thompson et al. 2004).

Table 44. Effectiveness of plasma-derived factor VIII/von Willebrand factor concentrates for surgery or dental procedures in von Willebrand patients

Study	Level and quality of evidence	Population	Effectiveness
(Auerswald et al. 2002)	Level IV: before-and-after study Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	14 patients with vWD, treated with Immunate® for 14 acute bleeds or surgical events	Haemostasis 'Excellent' or 'Good' in all patients after treatment Normal perioperative bleeding in most cases 3/14 patients experienced post operative complications, 2 related to insufficient cover and were resolved by further factor concentrate administration
(Mannucci et al. 2002)	Level IV: prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	39 patients with vWD, treated with Alphanate® for 71 surgical or invasive procedures 6 x Type 1 17 x Type 2A 2 x Type 2B 14 x Type 3	Antifibrinolytic required in 8/71 (11.3%) procedures, mainly in oral cavity Median number of infusions= 3 Median treatment interval across all infusions= 24 hours Prolonged bleeding time corrected 30 minutes post infusion in 25/63 patients (39.7%) and partially corrected in 25/63 patients (39.7%), no correction in 12/63 (19/0%)

(cont.)

Table 44 (cont.) Study	Level and quality of evidence	Population	Effectiveness
(Gill et al. 2003)	Level IV: prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	33 patients with vWD, treated with 290 infusions of Haemate® P for 53 bleeding episodes—both surgical and spontaneous bleeding episodes 9 x Type 1 4 x Type 2A 7 x Type 2B 27 x Type 3 6 x Other	52/53 (98%) bleeding episodes had 'excellent/good' haemostasis after treatment
(Lillicrap et al. 2002; Dobrkovska et al. 1998)	Level IV: retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	97 patients with vWD treated for 73 surgical events 32 x Type 1 5 x Type 2A 18 x Type 2B 28 x Type 3 14 x Other	72/73 (98.6%) surgical cases had an 'excellent/good' outcome
(Thompson et al. 2004)	Level IV: prospective case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow up adequate Uncontrolled	39 patients with vWD with 42 surgical events: 17 minor and 25 major surgeries 16 x Type 1 4 x Type 2A 5 x Type 2B 8 x Type 3 6 x Other	Overall physician-rated effectiveness was 'excellent/good' for 39/39 (100%) Daily physician ratings were 'excellent/good' for 38/39 (97.4%) Number of infusions 39 patients required 354 infusions of Haemate® P Median average daily maintenance dose per infusion = 52.8 IU kg^{-1} (range 24.2–196.5 IU kg^{-1}) Median number of infusions per surgical event = 6 (range 1–67 infusions) Median number of days with treatment = 3 days (range 1–50 days) Median treatment duration = 3 (range 1–75 days)

Number of Infusions by von Willebrand Type

	Mean per patient (range)	Mean per day per patient
Type 1 (n=17)	3 (1–20)	0.97
Type 2A (n=4)	4 (3–19)	0.86
Type 2B (n=5)	7 (2–9)	1.53
Type 3 (n=9)	13 (1–67)	1.18
Other (n=4)	8 (1–13)	1.0

(cont.)

<table>
<tr><td>Table 44 (cont.)
(Franchini et al. 2003)</td><td>Level IV: retrospective case series
Quality score: 1/3
Measurement bias possible
Selection bias possible
Follow-up adequate
Uncontrolled</td><td>26 patients with von Willebrand disease, treated for 43 surgical or invasive procedures
19 x Type 1
7 x Type 2B</td><td>
<table>
<tr><th>vWF:Rco [a]</th><th>vWF:Ag [a]</th><th>FVIII:C [a]</th></tr>
<tr><td>Mean pre-infusion IU/dL (range)
12.4 (0–36)</td><td>Mean pre-infusion IU/dL (range)
17 (0–76)</td><td>Mean pre-infusion IU/dL (range)
30 (6–78)</td></tr>
<tr><td>1-hour after pre-operative infusion IU/dL (range)
134.7 (78–265)</td><td>1-hour after pre-operative infusion IU/dL (range)
166.6 (90–299)</td><td>1-hour after pre-operative infusion IU/dL (range)
112.7 (62–226)</td></tr>
<tr><td>Mean IVR (range)
2.0 (1.4–2.7)</td><td></td><td></td></tr>
</table>
Amount of Haemate® P used
Mean (range)
<table>
<tr><th>Type of procedure</th><th>Total dose (IU vWF:Rco/kg)</th><th>Days of treatment</th><th>Daily dose (IU vWF:Rco/kg/day)</th></tr>
<tr><td>Major surgery</td><td>284.1 (125.0–976.4)</td><td>9.7 (5–23)</td><td>39.3 (25.0–52.5)</td></tr>
<tr><td>Minor surgery</td><td>120.8 (42.9–173.3)</td><td>4.2 (2.7)</td><td>28.7 (21.4–34.8)</td></tr>
<tr><td>Dental extractions</td><td>38.4 (23.5–100.0)</td><td>1.6 (1–5)</td><td>24.0 (23.5–25.0)</td></tr>
<tr><td>Invasive procedures</td><td>87.3 (27.3–160.0</td><td>2.7 (1–5)</td><td>32.3 (27.3–37.0)</td></tr>
<tr><td>Total</td><td>183.2 (23.5–976.4)</td><td>5.7 (1–23)</td><td>31.5 (21.4–52.5)</td></tr>
</table>
</td></tr>
<tr><td>(Federici et al. 2002)</td><td>Level IV: retrospective case series
Quality score: 1/3
Measurement bias possible
Unable to assess selection bias
Follow-up adequate
Uncontrolled</td><td>13/22 patients with von Willebrand disease, treated with Fanhdi® for 14 invasive procedures
9 x Type 1
7 x Type 2B
6 x Type 3</td><td>
<table>
<tr><th>Type of procedure</th><th>Subjective clinician rated haemostasis</th></tr>
<tr><td>Major surgery</td><td>‘Excellent/good’ in 7/7 procedures</td></tr>
<tr><td>Minor surgery</td><td>‘Excellent/good’ in 5/5 procedures</td></tr>
<tr><td>Dental extractions</td><td>‘Excellent/good’ in 1/2 procedures
One Type 3 vWD patient had poor outcome</td></tr>
</table>
</td></tr>
</table>

[a] results expressed as mean (range); FVIII:C = factor VIII; IVR = in vivo recovery (IU dl^{-1} per IU kg^{-1}); RcoF = ristocetin-cofactor activity; vWD= von Willebrand disease; vWF:Ag = von Willebrand factor antigen; vWF = von Willebrand factor

Are treatments safe?

DDAVP

The safety of DDAVP is discussed in an earlier section (See Adjunctive haemostatic agents).

Plasma-derived factor concentrates

The safety of pdFVIII/vWF concentrates for von Willebrand disease was reported in eight low level studies (Level IV evidence) that concluded that factors such as Haemate® P, Immunate® and Fanhdi® (not currently available in Australia) are safe in preventing excessive bleeding after major and minor surgery or invasive procedures (See Table 45). However, due to the nature of plasma-derived concentrates, they still pose a theoretical risk of viral and prion transmission.

Table 45 Adverse events associated with the use of plasma-derived factor VIII/vWF concentrates

Study	Level and quality of evidence	Population	Adverse events
(Mannucci et al. 2002)	Level IV: Prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	81 vWD patients treated with Alphanate®-Solvent Detergent (A-SD) or Alphanate®Solvent Detergent/Heat-treated (A-SD/HT) for 71 surgical/invasive procedures or 87 bleeding episodes 15 x Type 1 29 x Type 2A 5 x Type 2B 32 x Type 3	A-SD: 9/66 (13.6%) patients had adverse events A-SD/HT: 5/36 (13.9%) patients had adverse events Most adverse events were mild: Reduced in vivo recovery, B19 parvovirus transmission, thrombotic complications
(Gill et al. 2003)	Level IV: Prospective case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	33 vWD patients, treated with 290 infusions of Haemate® P for 53 bleeding episodes—both surgical and spontaneous bleeding episodes 9 x Type 1 4 x Type 2A 7 x Type 2B 27 x Type 3 6 x Other	24/53 bleeding or surgical events were associated with adverse events One mild allergic reaction was related to treatment
(Auerswald et al. 2002)	Level IV: case series Quality score: 3/3 Measurement bias unlikely Selection bias minimised Follow-up adequate Uncontrolled	14 vWD patients treated with Immunate® for surgical or bleeding episodes	No serious adverse events One phlebitic reaction at venous access site after 102 hours of continuous infusion
(Thompson et al. 2004)	Level IV: case series Quality score: 2/3 Measurement bias minimised Selection bias possible Follow up adequate Uncontrolled	39 vWD patients with 42 surgical treatment events 16 x Type 1 4 x Type 2A 5 x Type 2B 8 x Type 3 6 x Other	55 adverse events were reported in 24/42 (57.1%) of surgical treatments 4/55 (7.3%) included abdominal pain, infection and abnormal wound healing not related to treatment 8/55 (14.5%) related to Haemate® P, including paraesthesia, allergic reaction, vasodilation, peripheral oedema, extremity pain, pseudo-thrombocytopenia and pruritus
(Dobrkovska et al. 1998)	Level IV: Prospective case series Quality score: 2/3 Measurement bias unlikely Selection bias possible Follow-up adequate Uncontrolled	6 vWD patients treated with Haemate® P 2 x Type 1B 2 x Type 2A 2 x Type 3	2/6 patients experienced mild adverse events, including rash, hives, cough, fever, weakness and nausea

(cont.)

Table 45 (cont.) (Lillicrap et al. 2002; Dobrkovska et al. 1998)	Level IV: Retrospective case series Quality score: 2/3 Measurement bias possible Selection bias minimised Follow-up adequate Uncontrolled	97 vWD patients treated with Haemate® P for 73 surgical procedures, 344 bleeding episodes, 20 prophylaxis and 93 other events 32 x Type 1 5x Type 2A 18 x Type 2B 28 x Type 3 14 x Other	16/97 (16.5%) patients experienced adverse events within 24 hours of Haemate® P administration
(Franchini et al. 2003)	Level IV: Retrospective case series Quality score: 1/3 Measurement bias possible Selection bias possible Follow-up adequate Uncontrolled	26 vWD patients treated with Haemate® P for 43 surgical or invasive procedures 19 x Type 1 7 x Type 2B	5/43 (11.6%) interventions (all major surgery) required red blood cell transfusion No adverse events associated with Haemate® P treatment
(Federici et al. 2002)	Level IV: Retrospective case series Quality score: 1/3 Measurement bias possible Unable to assess selection bias Follow-up adequate Uncontrolled	13/22 vWD patients treated with Fanhdi® for 14 invasive procedures 9 x Type 1 7 x Type 2B 6 x Type 3	No adverse events associated with Fanhdi® treatment

A-SD = Alphanate® solvent/detergent treated; A-SD/HT = Alphanate® solvent/detergent, heat-treated; vWD=von Willebrand disease

Evidence-based clinical practice guidelines

On the basis of the available evidence, surgical and dental procedures in patients with haemophilia A, B or von Willebrand disease should be managed as follows:

- Recombinant FVIII is safe (Level III-2 evidence) and effective (Level IV evidence) for patients with haemophilia A before and after surgery as required.
- Recombinant FIX is safe and effective for patients with haemophilia B before and after surgery as required (Level IV evidence).
- Tranexamic acid may be used to control bleeding during surgical or dental procedures (Level IV evidence).
- DDAVP may be used alone or in conjunction with local therapies such as fibrin glue. A test dose of DDAVP should be performed to determine responsiveness (Level IV evidence).
- Plasma-derived FVIII/vWF concentrates may be used to control bleeding in patients with von Willebrand disease who do not respond to DDAVP (Level IV evidence).

Delivery of Infants

Pregnancy, labour and delivery pose risks of bleeding complications to both the mother, if she has von Willebrand disease or is a carrier of haemophilia A or B, and the newborn infant with haemophilia. A variety of ethical and haemostatic challenges are presented throughout the pregnancy, delivery and postpartum period, including invasive antenatal diagnostic procedures, management of miscarriage, termination of pregnancy and the risk of haemorrhage during labour and delivery. Carriers of haemophilia are defined as obligate (father had haemophilia), presumed (more than one son has haemophilia), potential (maternal relative has haemophilia), or sporadic (no family history—identified through an affected child) (Kulkarni & Lusher 2001). Since congenital haemophilia is linked to the X-chromosome, carriers usually have one normal gene that expresses sufficient clotting factor to maintain normal haemostasis. However, in approximately 10–20 per cent of carriers, extreme lyonisation may occur and very low levels of FVIII or FIX (to <10% of normal) increase the risk of haemorrhage during delivery and/or postpartum.

The main challenges are: 1) antenatal testing; 2) management of maternal coagulation disorder during pregnancy; 3) management and method of delivery to prevent haemorrhage in both mother and affected infant; and 4) control of haemorrhage (mother and newborn) during postpartum period.

These guidelines assume a correct diagnosis and that the severity of the disorder has been ascertained.

Previous Australian consensus-based guidelines

Currently, there are no Australian guidelines for the management of haemophilia carriers, pregnant women with von Willebrand disease, or for the delivery of infants with haemophilia.

No available studies concerning the delivery of infants in other rare bleeding disorders, such as fibrinogen abnormalities, or deficiencies in factors V, VII, X, XIII or prothrombin, met the inclusion criteria for an evaluation of effectiveness or safety in this review. In addition, no studies examining the safety of epidural analgesia (for the haemophilia carrier or affected infant) during infant delivery met the inclusion criteria.

Effectiveness of antenatal diagnosis

The decision to have children is complex for carriers of the haemophilia gene due to the well established genetic inheritance of haemophilia. Antenatal diagnosis can aid decision making regarding pregnancy termination or guide the management of the pregnancy and delivery. However, the uptake of antenatal diagnostic procedures in mothers with a known risk is relatively low (approximately 35%) (Kadir et al. 1997).

There are several antenatal diagnostic procedures available at different stages of pregnancy (Table 46).

Table 46. Antenatal diagnosis of haemophilia*

Stage	Procedure	
First trimester	Pre-implantation DNA diagnosis of embryonic blast cells	8-cell stage
	Chorionic villus sampling	11–13 weeks
	DNA analysis of fetal cells in maternal circulation	
	Transvaginal scanning for fetal gender	
Second trimester	Amniocentesis	16 weeks
	Cordocentesis—fetal umbilical cord sampling for clotting factor assay	
	Fetal gender determination	
Third trimester (and at delivery)	Fetal gender determination	
	Umbilical cord blood sampling	

Adapted from (Kulkarni & Lusher 2001)

Three studies reported on the effectiveness of antenatal diagnosis for maternal carriers of haemophilia A or B, or women with von Willebrand disease (Level IV evidence) (Table 47) (Daffos et al. 1988; Hoyer et al. 1985; Kadir et al. 1997).

The good quality study by Hoyer et al. 1985 (Level IV evidence) performed a foetoscopy, which visualises the umbilical cord and samples the fetal blood supply by direct puncture of the umbilical vein. Of 92 pregnancies, 80 foetoscopies obtained satisfactory[y] fetal blood samples. Of the 80 satisfactory samples, 51 pregnancies were diagnosed as normal. However, post-natal testing revealed that one of these infants was positive for haemophilia A (false negative=2%). The majority of the remaining 29 pregnancies, which were diagnosed as positive for haemophilia A, were either terminated or miscarried. Post-mortem analysis in 23 foetuses (82%) confirmed an abnormal result in all 23 cases.

One average quality case series (Level IV evidence) used chorionic villus sampling, the current most commonly used method, to determine not only the sex of the foetus but also whether a male foetus was affected by haemophilia A or B. The procedure is performed at 11–13 weeks gestation and usually yields a result in 24–48 hours, but could take as long as two weeks. Restriction fragment length polymorphisms or polymerase chain reaction is applied to the sample. Sequencing of a known mutation may take 5–7 days. Kadir et al. 1997 recommend antenatal gender diagnosis by chorionic villus sampling, but for those parents unwilling to undergo this procedure, ultrasound at 18 weeks gestation may be performed to ascertain gender.

Neither of the studies by Kadir et al. or Daffos et al. presented post-mortem results of terminated foetuses to confirm the original diagnosis of an affected foetus. Consequently, the accuracy of the antenatal testing is unknown in these studies.

[y] Samples contain a proportion of amniotic fluid, which dilutes the sample. Satisfactory samples = >10% fetal blood; Unsatisfactory samples = <10% fetal blood

Table 47. Effectiveness of antenatal diagnosis

Study	Level and quality of evidence	Population	Fetal sampling
(Hoyer et al. 1985)	Level IV: retrospective case series Quality score: 3/3 Selection bias minimised Follow-up adequate Patients representative	92 pregnancies at risk of haemophilia A	Foetoscopy: 80/92 (87%) satisfactory fetal samples Normal 51/80 (63.8%) 1/51 2.0%) haemophilia A 3/51 (5.9%) fetal loss 47/51 (92.1%) normal males post-natal test 46/47 (97.9%) confirmed normal 1/47 (2.1%) infant with reduced levels of factor VIII Haemophilia A 29/80 (36.2%) 26/29 (89.7%) terminated 1/29 (3.4%) haemophilia A carried to term 2/29 (6.9%) fetal loss post mortem [a] 23/28 (82.1%) abnormal result confirmed 12/92 (13%) unsatisfactory samples 11/12 (91.7%) terminated 1/12 (8.3%) unaffected male
(Kadir et al. 1997)	Level IV: retrospective case series Quality score: 2/3 Selection bias minimised Follow-up adequate Patients representative	32 women, 82 pregnancies 24 haemophilia A and 8 haemophilia B obligate carriers	32/82 (39%) miscarriage or termination 17/48 (35%) had antenatal screening Chorionic villus sampling: 10/17 (58.8%) 4/10 (40%) females 2/10 (20%) unaffected males 4/10 (40%) affected males 2/4 (50%) terminated pregnancy Ultrasound gender screening: 7/17 (41.2%) 3/7 (42.9%) females 4/7 (57.1%) males Cordocentesis: 4 males 3/4 (75%) unaffected males 1/4 (25%) affected male, terminated
(Daffos et al. 1988)	Level IV: case series Quality score: 1/3 Selection bias likely Follow-up adequate Patients representative	93 pregnant women with haemorrhagic disorders Haemophilia A 35 obligate and 44 putative carriers Haemophilia B 8 women obligate and 4 putative carriers vWD 1 Type 1; 1 Type 2A	25/91 (27.5%) foetuses haemophilia A or B 24/25 (96%) terminated 1/2 (50%) of women with vWD (Type 2A) administered cryoprecipitate prior to fetal sampling 2/2 (100%) foetuses were affected by vWD

[a] Only 23/28 terminations were made available for testing at post mortem; vWD = von Willebrand disease

Safety of antenatal diagnosis

Although there is minimal physical maternal risk, antenatal testing is not without physical risk to the foetus. Only one good quality study reported on safety outcomes associated with antenatal testing for haemophilia A (Level IV evidence) (Hoyer et al. 1985) (Table

48). There were five miscarriages (5%) within seven days of foetoscopy (of 92 pregnancies). In addition, there were five premature births in those pregnancies carried to term (10%). However, authors report that this is equivalent to that seen in normal pregnancies without foetoscopy.

Table 48. Safety of antenatal diagnosis

Study	Level and quality of evidence	Population	Complications
(Hoyer et al. 1985)	Level IV: retrospective case series Quality score: 3/3 Selection bias minimised Follow-up adequate Patients representative	92 pregnancies at risk of haemophilia A	5/92 (5.4%) miscarriage within seven days of foetoscopy 5/50 (10%) premature births in the pregnancies that continued past foetoscopy

Overall, it appears that antenatal diagnosis by foetoscopy increases the risk of termination to the foetus and may carry psychosocial consequences for the parent(s). Although chorionic villus sampling is now used routinely for antenatal diagnosis, no studies have directly compared the safety of foetoscopy and chorionic villus sampling methods. Prior to invasive procedures, prophylaxis with factor concentrates may be required (JBC FVIII/FIX working party & National Blood Authority 2004).

Haemophilia

Infants with severe haemophilia A or B may present with haemorrhage in the early neonatal period (Kulkarni & Lusher 2001) and the delivery itself may be a time of potential blood loss to the mother.

There were no studies that reported on the effectiveness of administering clotting factors to pregnant women who were carriers for haemophilia A or B.

One study reported separate results for both haemophilia A and B (Greer et al. 1991) and two large case series reported combined results for haemophilia A and B, for safety outcomes associated with the delivery of infants (Kadir et al. 1997; Ljung et al. 1994) (Level IV evidence) (Table 49).

Haemophilia A

Hormonal changes associated with pregnancy induce a rise in FVIII:C levels during the second trimester, followed by a rapid drop after delivery. Therefore, carriers rarely require prophylaxis for delivery, but they are at risk of bleeding during the first trimester and 3–5 days after delivery (Economides et al. 1999). Two retrospective case series (Level IV evidence) evaluated this occurrence.

It was reported that the majority of women who were carriers of haemophilia A had increased levels of Factor VIII:C and von Willebrand antigen over the course of their

pregnancies, until they were far in excess of normal values at 28–36 weeks gestation (normal values >45 IU/dl), with only two of 18 (11.1%) women failing to attain normal levels of factor VIII:C (Greer et al. 1991). Similarly, Kadir et al. 1997 reported that levels of factor VIII rose significantly in the second or third trimester compared to levels measured in the first trimester in 37.5% of women who had measurements taken ($p< 0.001$).

No cases of primary[z] postpartum haemorrhage were reported in the small case series (Greer et al. 1991), however 8.8% of all pregnancies resulted in secondary[aa] postpartum haemorrhage, which was treated with cryoprecipitate or a blood transfusion.

Haemophilia B

Greer et al. 1991 reported that the majority of obligate carriers of haemophilia B have normal levels of factor IX:C, therefore pregnant carriers of haemophilia B are unlikely to experience major bleeding problems during labour. However, levels of factor VIII and IX should be monitored throughout pregnancy because some women may not experience an increase in factors during the course of their pregnancy and may be at risk of prolonged postpartum bleeding (Level IV evidence). Kadir et al. 1997 reported that there was no significant increase in levels of factor IX during pregnancy in 37.5% of women who had measurements taken (no data given).

Greer et al. 1991 reported no cases of primary postpartum haemorrhage in their small case series (nine term pregnancies) of obligate carriers of haemophilia B and only one case of secondary postpartum haemorrhage, which required a blood transfusion. The remaining eight pregnancies were treated with frozen fresh plasma as a precautionary measure.

Haemophilia A and B

Kadir et al. 1997 reported that 36 (of 82) pregnancies in obligate carriers of haemophilia A or B resulted in miscarriages, spontaneous abortions or terminations (Level IV evidence). The remaining 46 pregnancies were predominantly normal vaginal deliveries (70%). Primary (22%) and secondary postpartum haemorrhages (11%) required treatment, including blood transfusion, or administration of frozen fresh plasma, or infusion of factor VIII concentrates. A number of fetal or neonatal complications were also reported, including fetal distress and bleeding complications. Kadir et al. 1997 recommended antenatal haemophilia diagnosis for the successful management of labour or, at the very least, gender determination.

One large retrospective case series (Level IV evidence) of 117 deliveries reported a significantly higher risk of fetal and neonatal complications in vaginal births with vacuum extraction (64.7%) compared to normal vaginal delivery (8.7%) or caesarean section (23%) (Ljung et al. 1994). In addition, 21% of neonates experienced a bleeding episode

---

[z] Primary postpartum haemorrhage refers to bleeding >500ml during the 24 hours after delivery

[aa] Secondary postpartum haemorrhage refers to bleeding >500ml after the first 24 hours to six weeks after delivery

associated with procedures such as blood sampling and vitamin K injections. Ljung et al. 1994 recommended that the initial approach to delivery in a known haemophiliac should be governed by obstetric factors and that vaginal delivery is *not* contraindicated. Instrument delivery should be avoided (forceps and vacuum extraction), as should the use of fetal scalp electrodes. Early recourse to caesarean is recommended when there is a failure of labour to progress. Caesarean section for all cases where haemophilia is expected is not likely to eliminate intracranial haemorrhage or other bleeding manifestations.

Table 49. Infant delivery and haemophilia

Study	Level and quality of evidence	Population	Outcomes
(Greer et al. 1991)	Level IV: retrospective case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Patients representative	18 obligate carriers of haemophilia A, 34 pregnancies	Vaginal deliveries: 23/34 Secondary PPH: 2/23 (8.7%) Treatment: Evacuation of uterus and blood transfusion Forceps deliveries: 7/34 Caesarean sections: 4/34 Secondary PPH: 1/4 (25%) Treatment: cryoprecipitate for 7 days post-partum; 4 weeks later same patient, secondary PPH, received cryoprecipitate and tranexamic acid
(Greer et al. 1991)	Level IV: retrospective case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Patients representative	5 obligate carriers of haemophilia B, 11 pregnancies 1 missed miscarriage (evacuation), treated with FFP	Vaginal deliveries: 5/11 (45.5%) Perineal haematoma: 1/5 (20%) Secondary PPH: 1/5 (20%) Blood transfusion: 1/5 (20%) Treatment: 4/5 (80%) FFP Forceps deliveries: 2/11 (18.2%) No PPH Treatment: 2/2 (100%) FFP Caesarean sections: 2/11 (18.2%) No PPH Treatment: 2/2 (100%) FFP
(Kadir et al. 1997)	Level IV: retrospective case series Quality score: 2/3 Selection bias minimised Follow-up adequate Patients representative	32 women, 82 pregnancies 24 haemophilia A and 8 haemophilia B obligate carriers Mean gestation 39.2 weeks, (range 34–42 weeks)	Miscarriage, spontaneous abortion, termination: 36/82 (43.9%) Vaginal deliveries: 32/46 (69.6%) Primary PPH: 7/32 (21.9%) Blood loss: 700–1500mls Treatment: 2/7 (28.6%) FFP 2/7 (28.6%) factor VIII concentrate 1/7 (14.3%) recombinant factor VIII Blood transfusion: 2/7 (28.6%) Secondary PPH: 3/32 (9.4%) Treatment: 1/3 (33.3%) FFP 1/3 (33.3%) factor VIII concentrate Instrument deliveries: 6/46 (13%) Primary PPH: 1/6 (16.7%) Blood loss: 600mls No treatment required Caesarean sections: 8/46 (17.4%) Primary PPH: 2/8 (25%) Blood loss: 1200 and 1500 mls Treatment: FFP + factor VIII concentrate; factor VIII concentrate Secondary PPH: 1/8 (12.5%) No treatment required (cont.)

Table 49 (cont.) Study	Level and quality of evidence	Population	Outcomes
(Ljung et al. 1994) Sweden	Level IV: retro-spective case series Quality score: 2/3 Selection bias minimised Follow-up adequate Patients representative	117 pregnant women, 117 deliveries of haemophilic children 101 haemophilia A (77 severe, 24 moderate) 16 haemophilia B (12 severe, 4 moderate)	Bleeding episodes: 23/117 (19.7%) associated with delivery 24/117 (20.5%) neonates (<2 weeks of age) had bleeding episodes associated with procedures eg blood sampling, vitamin K injections, bleeding post-surgery. 6/117 (5.1%) neonates required blood transfusion Vaginal deliveries: 104/117 (88.9%) Primary PPH: 3/104 (2.9%) Fetal/neonatal complications: 9/104 (8.7%) Subgaleal /cephalic 1/104 (0.9%) Intracranial 2/104 (1.9%) Umbilical 3/104 (2.9%) Retro-orbital 1/104 (0.9%) Oral 1/104 (0.9%) Haematuria 1/104 (0.9%) Vacuum extraction vaginal delivery: 17/104 (16.3%) Fetal/neonatal complications: 11/17 (64.7%) Subgaleal /cephalic 10/17 (58.9%) Intracranial 1/17 (5.9%) Umbilical 0/17 (0.0%) Retro-orbital 0/17 (0.0%) Oral 0/17 (0.0%) Haematuria 0/17 (0.0%) Caesarean sections: 13/117 (11.1%) Primary PPH: 1/13 (7.7%) Fetal/neonatal complications: 3/13 (23%) Subgaleal /cephalic 1/13 (7.7%) Intracranial 1/13 (7.7%) Umbilical 1/13 (7.7%) Retro-orbital 0/13 (0.0%) Oral 0/13 (0.0%) Haematuria 0/13 (0.0%)

FFP = frozen fresh plasma, PPH = post-partum haemorrhage

von Willebrand disease

For women with von Willebrand disease (vWD), particularly severe vWD, the delivery of a child may result in severe bleeding unless treated appropriately. All four studies that met the inclusion criteria were low-level evidence (Level IV).

Three poor–average quality studies reported on safety outcomes associated with the pregnancy and delivery of infants in women affected by vWD (Chediak et al. 1986; Greer et al. 1991) (Table 50).

All three studies noted that the levels of factor VIII, von Willebrand antigen and von Willebrand factor activity increased significantly during gestation (Ljung et al. 1994, p=0.0001), peaking in the third trimester (no data given).

Vaginal bleeding resulted in the miscarriage or elective termination of a relatively high proportion of pregnancies in the study by Kadir et al. 1998, with 36% continuing to full term. Complications of pregnancy loss included excessive bleeding (10%) and secondary

haemorrhage (10%), which required blood transfusion and/or cryoprecipitate or factor concentrate. The majority of births in all three studies were normal vaginal delivery.

All studies reported that postpartum haemorrhage was a common outcome for women with vWD. Primary postpartum haemorrhage was reported in all three studies, with rates ranging from 19–27% of deliveries, resulting in severe bleeding which required treatment either with cryoprecipitate, whole blood or fresh plasma. Secondary postpartum haemorrhage was reported by two of the three studies and occurred in 20–36% of deliveries. Chediak et al. 1986 reported that postpartum haemorrhage tended to occur in women with more severe type of vWD. However, the number of women enrolled in this study was too small to make any firm conclusions. The larger retrospective case series by Kadir et al. 1998 did not confirm the von Willebrand status of women affected by postpartum haemorrhage. Greer et al. 1991 noted that the high rate of postpartum haemorrhage was likely to be associated with the increase in factor VIII during pregnancy, combined with the rapid fall during delivery, especially in women with Type 2 and Type 3 vWD. In patients with Type 1 vWD, a rise in factor VIII to >50 IU/dl appears to be sufficient to allow an uncomplicated vaginal delivery. Greer et al. 1991 recommended that all women with Type 2 or 3 vWD, and those Type 1 women who fail to reach optimal factor VIII:C levels (50 IU/dl), be treated immediately postpartum with blood products containing von Willebrand factor. In addition, women who deliver by caesarean should be administered blood products.

The study by Kadir et al. 1998 reported 4% of infants, born to women with vWD, experienced bleeding episodes immediately after delivery and recommended that invasive fetal monitoring techniques such as scalp electrodes or fetal blood sampling should be avoided.

Chediak et al. 1986 recommended that the delivery of infants by women affected by vWD should be assessed on an individual basis.

In addition, all the women enrolled in the case series reported by Greer et al. 1991 had been referred to the clinic for menorrhagia and reported prolonged menses, ranging in duration from five to 14 days. Although vWD is not a common disorder, it is the most common inherited bleeding disorder and Greer et al. recommend that it should be considered in the assessment of women referred for menorrhagia and for their future management during pregnancy.

Table 50. Infant delivery and von Willebrand disease

Study	Level and quality of evidence	Population	Outcomes
(Schulman et al. 1991)	Level IV: case series Quality score: 3/3 Measurement bias minimised Selection bias minimised Follow-up adequate	370 patients with disorders of primary haemostasis. 133 vWD, 237 platelet function defects, aged 3–80 years	DDAVP (0.2–0.3 µg/kg, route of administration not specified) When given before labour in one patient, labour ceased and had to be induced.
(Greer et al. 1991)	Level IV: retrospective case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Patients representative	8 women with von Willebrand, 14 pregnancies	Vaginal deliveries: 12/14 Primary PPH: 1/12 Treatment: blood transfusion Secondary PPH: 4/12 Treatment: Cryoprecipitate, blood transfusion Maternal complications: 1/12 Threatened miscarriage Forceps deliveries: 1/14 Primary PPH: 1/1 Treatment: cryoprecipitate, blood transfusion Secondary PPH: 1/1 Treatment: cryoprecipitate, blood transfusion Caesarean sections: 1/14 Treatment: cryoprecipitate
(Kadir et al. 1998)	Level IV: retrospective case series Quality score: 2/3 Selection bias uncertain Follow-up adequate Patients representative	31 women, 84 pregnancies, 85 foetuses 27 Type 1; 2 Type 2; 2 Type 3 Mean gestation 40 weeks (range 34–42 weeks)	Live birth 55/85 (64.7%) Miscarriage or termination: 30/84 (35.7%) Fetal or neonatal complications: 2/55 (3.6%) Vaginal deliveries: 43/54 (79.6%) Forceps deliveries: 6/54 (11.1%) Caesarean sections: 5/54 (9.3%) Blood loss: 750->2000 mls Treatment: pdFVIII/vWF; FFP; blood transfusion
(Chediak et al. 1986)	Level IV: case series Quality score: 1/3 Selection bias likely Follow-up adequate Patients representative	Six women, eight deliveries, 11 pregnancies (3 spontaneous abortions)	Fetal or neonatal complications: Data for only 7/8 (87.5%) deliveries 5/7 (71.4%) affected Vaginal deliveries: 3/8 Primary PPH: 2/3 Severe vaginal bleeding, massive lumbar bleeding Treatment: Whole blood, fresh plasma, cryoprecipitate Caesarean sections: 5/8 Primary PPH: 1/5 Vaginal bleeding Treatment: Cryoprecipitate Maternal complications: 2/5 placenta praevia, membrane rupture, water intoxification after desmopressin Treatment: cryoprecipitate before delivery, curettage, postpartum desmopressin

DDAVP = 1-D-deamino-8D-arginine vasopressin; FFP = fresh frozen plasma; pdFVIII/vWF = von Willebrand factor rich concentrate; PPH = postpartum haemorrhage

No available studies concerning the delivery of infants in other rare bleeding disorders met the inclusion criteria for an evaluation of effectiveness or safety.

A range of other issues that may impact on the care of newborns with haemophilia A or B was reported in the literature. The recommendations relating to these issues were based on case reports and expert opinion, a lower level of evidence than that included for evaluation in this systematic review.

The early neonatal period is a time of high risk for the newborn with haemophilia. The pattern of bleeding in neonates differs markedly from that seen in older children with haemophilia (Kulkarni & Lusher 2001). From a narrative review of histories of 349 newborns with haemophilia, the most frequent bleeding events occurred following circumcision (30%—most of which occurred prior to 1970), intracranial haemorrhage (27%), puncture bleeds (16%)—such as heel sticks, venipuncture, and vitamin K injections—and subgaleal or cephalohaematoma (13%) (Kulkarni & Lusher 2001). Joint bleeds, the main bleeding event in older children, represent one per cent of bleeding episodes in neonates. Since these data were gathered from published case reports, they are prone to publication bias. However, they provide an indication of the difference in the patterns of bleeding presented in newborns and older children or adults.

Expert opinion suggests that pregnancy in women with rare coagulation disorders should be managed by an obstetrician in collaboration with a specialist haematologist (Chalmers 2004; Giangrande 1998; Kulkarni & Lusher 2001). Recommendations include: immunisation against hepatitis B, as a safeguard should blood products be required at delivery; if the use of forceps is necessary to avoid prolonged labour, they should be applied with great care, by avoiding rotation of the head in midcavity and limiting their use to low forceps delivery when the head is deeply engaged in the pelvis. Recombinant coagulation factor may be required after forceps delivery in haemophilia newborns; newborns with mild haemophilia and a normal screening test (prothrombin time or activated partial thromboplastin time)[bb], may still be at risk of a bleed, such as intracranial haemorrhage in the first few days after birth. Therefore, factor assays should be performed on cord or peripheral samples and repeated at six months; since factor IX levels in mild haemophilia B may overlap with normal low FIX at birth, repeat testing should be performed at six months; all infants with intracranial haemorrhages should be evaluated for a bleeding disorder, as >30 per cent of all newborns with haemophilia have no family history of haemophilia; in cases of haemorrhage, rFVIII or rFIX should be administered to provide immediate haemostasis. If diagnosis of haemophilia is unconfirmed, 15–20 ml/kg fresh frozen plasma may be considered for acute haemorrhage; and any necessary injections for the newborn should be performed with extra care and followed by local application of pressure applied for five minutes with close observation of the site for 24 hours. If umbilical stump bleeding occurs, infants should be tested for factor II, X or factor XIII deficiency (Kasper 2004).

[bb] Prothrombin time (PT) measures the time required for blood to clot and may be used to measure the presence and activity of factors I, II, V, VII and X. PT is lengthened by quantitative or functional reduction in clotting factors

Partial thromboplastin time (PTT) measures the time needed for blood to clot and may be used to screen for factor deficiencies. PTT is increased above normal (25–41 seconds) with heparin, warfarin, thrombolytics, clotting factor deficiency, liver disease, vitamin K deficiency and disseminated intravascular coagulation

Evidence-based clinical practice guidelines

On the basis of available evidence, pregnancy and infant delivery in haemophilia carriers and women with von Willebrand disease should be managed as follows (Level IV evidence).

Antenatal care

- Genetic counselling should be accessible to all haemophilia carriers and women with von Willebrand disease covering the potential risks (to the foetus and mother) of both antenatal testing and complications during pregnancy and delivery.
- Antenatal testing options depend on the stage of pregnancy. All procedures carry risks—chorionic villus sampling is the preferred method. Factor replacement may be required for invasive procedures (expert opinion).
- Haemostatic support is rarely necessary for haemophilia A carriers, but may be required for invasive tests. However, since levels of FVIII rise during normal pregnancy, from the second trimester, and drop immediately after delivery, the risk of haemorrhage is higher during the first trimester and 3–5 days after delivery. Therefore, FVIII:C levels should be monitored.
- Since levels of FIX remain unchanged throughout pregnancy, women with low baseline FIX may require rFIX to control haemorrhage. FIX:C should be measured soon after pregnancy is confirmed and monitored in the third trimester and postpartum.

Delivery of infants

- Vaginal delivery is preferred for all infants with haemophilia or suspected haemophilia unless obstetric factors indicate caesarean section. If necessary, early recourse to caesarean is the preferred alternative, with monitoring of factor levels and an available supply of appropriate recombinant factor concentrate.
- The use of invasive fetal monitoring, such as scalp electrodes, instrument deliveries and long labours should be avoided in affected male foetuses, or if fetal sex or coagulation status is unknown. Vacuum (Ventouse) extraction is contraindicated due to the higher risk of fetal complications.

Postpartum and postnatal period–Newborn

- Cord or peripheral blood samples should be taken from male infants with suspected bleeding disorders to ascertain coagulation factor status.
- Heel sticks and venipuncture should be avoided if possible and vitamin K injections should be delayed until diagnosis of haemophilia is excluded. Oral vitamin K may be used as the preferred route for prophylaxis in confirmed haemophilia infants.

(cont.)

(cont.)

Postpartum and postnatal period—Mother

- Women may develop inhibitors to FVIII or FIX postpartum. See Acquired haemophilia.
- Although prophylactic use of DDAVP should be avoided during labour, women with a mild form of von Willebrand disease (Type 1) may require DDAVP to increase and maintain factor levels in the first 3–4 days after delivery. See section on DDAVP.
- Patients with Type 2 or 3 von Willebrand disease and those with Type 1 who fail to reach optimal FVIII:C levels may be treated with pdFVIII/vWF concentrates postpartum.

Other Aspects of Management

There is a range of management issues that should be considered in the treatment of patients with coagulation disorders. However, there is very little published evidence on which to base recommendations. The following section on comprehensive care and management of bleeding episodes is largely informed by low-level evidence and expert opinion.

Comprehensive care

The optimal management of patients includes more than treating or preventing acute bleeding episodes. It should include the management of disease-related joint and muscle damage and address psychosocial needs such as education, employment, psychology and psychiatry services. The aim of disease management is to optimise quality of life by minimising disease and treatment-associated morbidity and mortality. These goals can be attained through comprehensive care, including home therapy, and access to safer products (Association of Hemophilia Clinic Directors of Canada 1995a).

Specialist haemophilia centres are best equipped to provide comprehensive interdisciplinary care for patients with blood coagulation disorders. Therefore, all aspects of disease management, including rheumatology, orthopaedic surgery, dentistry, clinical genetics, infectious diseases, physiotherapy and gynaecology should be managed in consultation with a haemophilia specialist. One good quality retrospective cohort study of 2950 patients with haemophilia (Level III-2 evidence) found that those patients whose treatment was managed through a haemophilia treatment centre had a significantly decreased risk of death than those treated elsewhere, even after adjustment for other associations through multivariate analysis [RR=0.6, 95% CI 0.5, 0.8; p=0.002] (Soucie et. al 2000).

Haemophilia and von Willebrand disease have a large impact on families in many ways, and parents, spouses and siblings can participate actively in patient care. It is essential that families be well informed about the diseases and their implications, including treatment strategies. Parents and persons with haemophilia are often very medically sophisticated and knowledgeable about the disease, so should be involved in decision-making processes about treatment strategies.

The extended family may require genetic counselling and, when appropriate, be offered carrier testing and antenatal diagnosis (Association of Hemophilia Clinic Directors of Canada 1995a). Mutation testing of affected individuals is crucial to provide accurate diagnosis of carrier status (expert opinion, AHCDO Executive Committee 2005).

As a result of the transmission of viral infections, such as HIV, hepatitis B and C, the need for counselling of both the patient and the family has increased, prompting greater need for education about safe sexual practices for those who are infected (Association of Hemophilia Clinic Directors of Canada 1995a).

Home therapy allows patients with severe or moderate haemophilia to have immediate access to treatment in the event of a haemorrhage. This may result in decreased medical costs, improved quality of life, and decreased amount of time spent in hospital and away from school and employment (Valentino et alr 2004). Soucie et al. 2001 studied the

relationship between home therapy (receiving factor infusions outside a medical setting) and haemorrhagic bleeding complications over a four year period in a good quality retrospective cohort study (Level III-2 evidence). Patients receiving home therapy were 20% less likely to have a haemorrhagic bleeding complication than those who did not use home therapy (RR= 0.8, 95% CI 0.7, 0.9; $p \leq 0.05$). After adjusting for all other determinants—such as disease severity, ethnicity, employment status and health insurance—patients using home therapy and consulting a haemophilia treatment centre had the highest probability of avoiding a haemorrhagic bleeding complication during follow-up. Those patients using neither had the lowest probability of avoiding a haemorrhagic bleeding complication during follow-up, whereas patients using either home therapy or a haemophilia treatment centre had intermediate probability of avoiding bleeding complications.

Central venous access devices may facilitate the use of home treatment in those less than four years of age, and detailed education pertaining to the essential procedures required to avoid infections and other complications should be provided to patients and their families (Valentino et al. 2004).

Management of bleeding episodes

When a patient with haemophilia presents with a bleeding episode, the administration of factor replacement should be the first course of action, particularly when the bleeding occurs in the head, neck, chest or abdomen and may be life threatening. Once infused, diagnostics and examinations may begin. For most acute bleeds, once factor concentrates have been administered, discharge instructions should follow the rule of RICE (rest, ice, compression, elevation), taking weight off through use of crutches etc. and, in the event of a joint bleed, supporting the joint through the use of splints and other mobility aids.

Issues in treating young patients

The feasibility of prophylaxis or tolerisation treatments for patients with haemophilia depends on the availability of adequate venous access for use in home therapy. In young children, repeated access to peripheral veins may be difficult. To overcome this problem, two main methods have been developed: 1) central venous access devices—either fully implanted or external; or 2) arteriovenous fistulae, an alternative internal vascular access device for factor infusion. The decision to introduce a central venous catheter should take into account the combined social and medical indications (access to a peripheral vein, feasibility of home treatment) while balancing the potential risks (infections, thrombosis or other rare complications). It has been suggested that implantation of central venous catheters on psychological grounds alone should be discouraged and children who are afraid of venipuncture should be assisted by other means (Ljung 2004).

Safety of central venous access in haemophilia

The best available information on the safety of central venous access devices (CVADs) was obtained from a systematic review of 48 studies (Level IV evidence) and 2704 patients covering the benefits and risks of both fully implanted and external devices in haemophilia patients. The results were pooled where possible, and a total of 1190 infections were reported (40% of CVADs and 44% of patients), giving a pooled

incidence of 0.66 per 1000 CVAD days. The most common types of infection were due to *Staphylococcus epidermidis* or *Staphylococcus aureus*, which showed that the predominant source of catheter-related infections were from the flora of the patient's skin. The three independent risk factors for infection were age, inhibitors and type of CVAD. Children over six years of age were 46% more likely to develop infections compared to those aged 2–6 years. Those with inhibitors were 67% more likely to develop infection than those without. Meanwhile, the incidence of infections in those with fully implanted CVADs was only 31% of the rate of those with external CVADs. The pooled incidence of thrombotic complications from CVADs was 0.06 per 1000 CVAD days (1.8% of CVADs and 2.0% of patients) and when a multivariate analysis was performed, neither age nor presence of inhibitors was found to affect the incidence of thrombosis (Level IV evidence) (Valentino et al. 2004). More serious complications included pinch-off syndrome (which occurs when the catheter becomes blocked, due to compression between the first rib and the clavicle), port erosion (where the skin overlying the septum deteriorates), or when the child outgrew the catheter and the tip became separated from the optimal vessel.

In order to reduce infections associated with CVAD use, strict adherence to hand washing and aseptic technique remains vital. Adequate initial training and frequent review and reinforcement of procedures may reduce infection rates (Valentino et al. 2004).

In young patients where the peripheral vein is not accessible CVADs are a valuable tool for assisting in the administration of factor concentrates, which may avert life-threatening haemorrhages or prevent development of arthropathy. However, the risk of infections and other rare complications means that health professionals should periodically review the need for a CVAD and peripheral veins should be used where possible (Valentino et al. 2004).

Safety of internal arteriovenous fistulae

One prospective case series examined the use of internal arteriovenous fistulae as an alternative to central venous access devices. From a series of 27 patients and 31 devices, no infectious complications were noted. However, the authors found that five out of 31 arteriovenous fistulae did not develop or maintain sufficient blood flow for long-term factor concentrate infusion. Five patients had complications, such as bleeding, thrombosis, and symptoms of distal ischaemia. Overall, 84% of devices with successful access were deemed suitable for long-term use (Level IV evidence) (Santagostino et al. 2003). Currently, there is insufficient evidence to make recommendations on the use of internal arteriovenous fistulae.

Evidence-based clinical practice guidelines

- On the basis of the evidence, central venous access devices assist in administering factor concentrates in children. However, adequate aseptic technique should be taught and frequently reviewed in order to avoid infection (Level IV evidence).
- The evidence suggests that external devices should be avoided due to much higher rates of infection than fully implanted devices (Level IV evidence).

Summary and Conclusions

The previous Australian clinical practice guidelines for the treatment of haemophilia A, B, von Willebrand disease and other rare bleeding disorders are based on the consensus of experts in the field of coagulation disorders (See Appendix G). These guidelines were modified by the Haemophilia Foundation Australia Medical Advisory Panel in March 2000 from existing guidelines developed by the United Kingdom Haemophilia Centre Directors Organisation Executive Committee (Haemophilia Foundation Australia Medical Advisory Panel 2000).

The consensus guidelines were limited to:

- Selection of products
- Safety data
- Recommendations about informing patients and consent, vaccination against hepatitis A and B, risk reduction, use of DDAVP, tranexamic acid and aminocaproic acid
- Specific recommendations about products most suitable for haemophilia A, B, von Willebrand disease, deficiencies in factors II, V, VII, X, XI, XIII, or fibrinogen, and future treatment of hereditary coagulation disorders.

Areas that consensus guidelines did not address included:

- Recommendations for the use of recombinant products for all patients with haemophilia A and B
- Tolerisation
- Treatment of patients with inhibitors
- Prophylaxis
- Infant delivery
- Acquired haemophilia
- Surgical and dental procedures
- Other management issues.

The new evidence-based guidelines have attempted to address these areas and provide recommendations based on the highest level of available evidence. Where empirical evidence was not available, recommendations follow those in the previous guidelines and/or consensus-based expert opinion. The evaluation of studies for this review was performed in the context of the newly introduced policy to provide access to recombinant products for all people with haemophilia A or B.

In the absence of good quality comparative studies in several sections of this review, the recommendations for the treatment and management of haemophilia A, B, vWD and other rare coagulation disorders have been based on a large body of low level evidence that is heterogeneous in nature and of relatively poor quality.

Research question 1

What is best practice for the treatment of acute bleeding episodes in patients with haemophilia A, B, vWD and other rare coagulation disorders?

Haemophilia A, without inhibitors

The best available evidence indicates that recombinant FVIII is the treatment of choice for patients without inhibitors to FVIII (Level II evidence for effectiveness; Level III-2 for safety). Inhibitor testing, particularly in young children and/or those with severe haemophilia, should be performed no earlier than three days after initial factor concentrate administration, or when the expected response is absent, with re-testing at regular intervals (Level IV evidence).

Patients with mild–moderate haemophilia A may be treated using DDAVP, at a dose of 0.3 μg/kg diluted in 50ml of 0.9% saline and infused over ≥30 minutes. DDAVP may be administered intravenously or subcutaneously with comparable results (Level IV evidence). DDAVP may be administered once every 24 hours, becoming less effective after repeated doses (Level IV evidence). Predose monitoring of electrolyte concentrations is recommended if DDAVP is administered more than once in 24 hours (expert opinion). A test dose of DDAVP and FVIII/vWF assay should be performed to demonstrate efficacy (Level IV evidence). Caution should be taken to restrict fluid intake during DDAVP treatment to prevent fluid overload (Level IV evidence). If DDAVP is given more than once in a 24 hour period, predose monitoring of electrolyte concentrations is recommended (expert opinion). DDAVP should be used with caution in the elderly; and it is not recommended in those with arteriovascular disease and in young children (<2 years) (expert opinion).

Haemophilia B, without inhibitors

The best available evidence indicates that recombinant FIX is safe and effective for the treatment of bleeding episodes in haemophilia B patients without inhibitors (Level IV evidence for safety and effectiveness). Due to large inter-patient variability, individual dosing regimens should be monitored by FIX recovery assays (Level II evidence). Compared to plasma-derived FIX, recombinant FIX dosage should be increased 1.6 times for patients aged ≤15 years and 1.2 times for patients aged 16 years and over (Level III-2 evidence). Since there is a risk of anaphylaxis occurring within the first 50 FIX exposure days, patients should be closely monitored (expert opinion).

Von Willebrand disease

Patients with mild vWD may be treated using DDAVP in the manner described above for patients with mild–moderate haemophilia A. DDAVP should be used only as an adjunct to factor replacement therapy in patients with severe vWD and not as the primary treatment (Level II evidence). Patients unresponsive to (or contraindicated for) DDAVP should receive pdFVIII/vWF concentrate, which may be administered every 8–12 hours (Level IV evidence).

Research question 2

What is best practice for the prophylactic treatment of patients with haemophilia A, B or von Willebrand disease?

Based on Level II evidence, prophylaxis is recommended for haemophilia patients without inhibitors. Prophylaxis with factor concentrates should be initiated *after* bleeding episodes have commenced, rather than at diagnosis, due to the possible increased risk of inhibitor development associated with administration of factor concentrates in very young children (Level IV evidence).

Central venous access devices may assist in the regular infusion of factor concentrates in children. However, adequate aseptic technique should be taught and frequently reviewed to avoid infection (Level IV evidence). External venous access devices should be avoided due to the higher rates of infection compared to fully implanted devices (Level IV evidence).

Haemophilia A, without inhibitors

Recombinant FVIII is the treatment of choice for prophylaxis in patients without inhibitors to FVIII (Level IV evidence for safety and effectiveness).

Haemophilia B, without inhibitors

Recombinant FIX is safe and effective for prophylaxis in haemophilia B patients without inhibitors (Level II evidence for effectiveness; Level IV evidence for safety). As discussed in Research question 1, dosing regimens should take into account the lower rFIX recovery compared to pdFIX and inter-patient variability (Level II evidence).

Von Willebrand disease

There was insufficient evidence to determine the effectiveness of intranasal DDAVP as prophylaxis for the prevention of menorrhagia in women with von Willebrand disease (Level II evidence).

Research question 3

What is the best method for treating bleeding episodes in patients with inhibitors to factor VIII or IX?

Haemophilia A, with inhibitors to FVIII

Recombinant FVIIa is the treatment of choice for acute bleeding episodes in patients with high titre and/or high responding inhibitors to FVIII (Level II evidence for effectiveness; Level IV evidence for safety). Recombinant FVIIa may be infused as a bolus dose of 90 μg/kg for adults (Level IV evidence). Doses up to 200–250 μg/kg may be required for children (expert opinion). Activated prothrombin complex concentrates (aPCCs) may be considered for controlling mild–severe bleeding in patients with high titre inhibitors. However, patients should be closely monitored for adverse reactions, which, though rare, may be serious. The maximum daily dose of FEIBA should not exceed 200 IU/kg (Level II evidence). Plasmapheresis (with or without immunoadsorption) may be used to reduce inhibitors in high titre/high responders before infusion with FVIII to control bleeding. However, patients should be monitored for potential anaphylactic reactions (Level IV evidence). There is insufficient evidence to

recommend the use of high dose FVIII concentrates for the treatment of acute bleeding episodes in patients with inhibitors to FVIII. Immunosuppression therapy with cyclophosphamide to reduce inhibitors is not recommended for treating acute bleeding episodes (Level IV evidence).

Haemophilia B, with inhibitors to FIX

Recombinant FVIIa is the preferred treatment for acute bleeding episodes in patients with high titre and/or high responding inhibitors to FIX (Level II evidence for effectiveness; Level IV evidence for safety). APCCs also control mild–severe bleeding in patients with high titre inhibitors. However, patients should be closely monitored for adverse reactions (Level IV evidence).

Acquired haemophilia

Bleeding episodes in patients with acquired haemophilia require prompt treatment (Level IV evidence).

Inhibitors <5 BU: DDAVP should be used at the dose recommended for von Willebrand disease (Research question 1). Plasma-derived factor VIII concentrate may be used at a dose of 20 IU/kg for each BU of inhibitor plus an additional 40 IU and tested after 15 minutes. If response is poor, another bolus injection may be given (Level IV evidence).

Inhibitors >5 BU: Activated prothrombin complex concentrates (aPCCs) may be administered at a dose of 50–200 IU/kg/day in divided doses (Level IV evidence). Activated recombinant FVII (rFVIIa) may be administered at a dose of 90 μg/kg every 2–6 hours until the bleeding stops (Level IV evidence). Due to the risk of thrombotic events, patients should be closely monitored after treatment (Level IV evidence).

Research question 4

What is best practice for the implementation of tolerisation procedures for patients with inhibitors to factor VIII or IX?

Haemophilia A, with inhibitors to FVIII

There is no consensus on tolerisation protocols in Australia. Protocols used range from 25 IU/kg three times per week, to 100 IU/kg/day (JBC FVIII/FIX working party & National Blood Authority 2004). When factor concentrates are used, recombinant factors are preferred rather than plasma-derived factors due to their higher safety profile regarding transmission of blood-borne agents (Level IV evidence). The Bonn protocol may be considered for young patients (Level IV evidence). Treatment is more likely to be successful in patients with low pre-treatment inhibitor titres; and when there is less time between the development and treatment of inhibitors (Level IV evidence). The Malmö protocol may be considered when patients have long-standing inhibitors (Level IV evidence).

Haemophilia B, with inhibitors to FIX

Recombinant FIX is the preferred treatment for tolerisation protocols in patients with inhibitors to FIX (Level IV evidence). Close monitoring is recommended to prevent anaphylactic reactions (expert opinion).

Acquired haemophilia

Patients with acquired haemophilia should be treated for the underlying disorder before deciding on strategies to eliminate inhibitors (Level IV evidence).

Postpartum: Patients may be monitored, without treatment, as inhibitors most frequently disappear spontaneously. Alternatively, immunosuppressive therapy may be considered (Level IV evidence).

Drug-related: The drug should be withdrawn to allow spontaneous disappearance of inhibitors. Alternatively, immunosuppressive therapy may be considered (Level IV evidence).

Autoimmune disease: Immunosuppressive therapy should be given, as inhibitors are unlikely to disappear spontaneously (Level IV evidence).

Malignant neoplasm: Patients should be treated for the primary malignancy. Immunosuppressive therapy should then be given (Level IV evidence).

Idiopathic: Patients should be given immunosuppressive therapy (Level IV evidence).

Research question 5

What is the best method of managing patients with haemophilia A, B, von Willebrand disease and other rare coagulation disorders undergoing surgical and dental procedures?

Consensus-based recommendations for the management of patients undergoing surgery (Association of Hemophilia Clinic Directors of Canada 1995a) or dental procedures (Stubbs & Lloyd 2001) have been outlined in detail (Table 37 and Appendix G). The available evidence base that was evaluated in this review is consistent with the recommendations in these existing guidelines.

Based on the evidence evaluated in the current review, the following management approaches are recommended:

Haemophilia A or B, without inhibitors

Recombinant factor VIII is safe (Level III-2 evidence) and effective (Level IV evidence) for haemophilia A patients and recombinant factor IX is safe and effective (Level IV evidence) for haemophilia B patients, before or after surgery as required. Tranexamic acid may be used as secondary prophylaxis for surgical or dental procedures (Level IV evidence).

Haemophilia A or B, with inhibitors

Recombinant FVIIa may be considered the first line of treatment for dental and other surgical procedures in patients with high titre and/or high responder inhibitors. Evidence for the use of recombinant FVIII/FIX concentrates during surgery or dental procedures is currently awaited. Factor VIII concentrate may be considered for use during surgery in patients with low titre, low-responding inhibitors to FVIII, but should be avoided in patients with high-responding inhibitors (Level IV evidence).

Von Willebrand disease

DDAVP, which may be used in conjunction with topical therapies such as fibrin glue and tranexamic acid, may be considered for use prior to dental extractions or surgery in patients who respond to DDAVP. A test dose is recommended to determine responsiveness (Level IV evidence). Plasma-derived FVIII/vWF concentrates may be used to control bleeding in patients who do not respond to DDAVP (Level IV evidence).

Research question 6

What is best practice in the delivery of infants with haemophilia A or B and the management of infant delivery in women with von Willebrand disease and other rare coagulation disorders? Unless stated, all recommendations are based on Level IV evidence.

Antenatal care

Counselling pertaining to the potential risks of antenatal testing and the potential complications during pregnancy and delivery should be accessible to all haemophilia carriers and women with von Willebrand disease. If antenatal testing is accepted, chorionic villus sampling is the preferred method. Factor concentrates may be required for invasive procedures. FIX levels in haemophilia B carriers and FVIII levels in haemophilia A carriers should be monitored, particularly in the third trimester and postpartum.

Delivery of infants

Vaginal delivery is the recommended mode of delivery, unless obstetric factors indicate caesarean section. Invasive fetal monitoring, such as scalp electrodes, instrument deliveries and long labours should be avoided for affected male infants. Vacuum extraction delivery is contraindicated. Use of DDAVP in women with von Willebrand disease is not recommended during labour.

Postpartum and postnatal care

Cord or peripheral blood samples, to ascertain coagulation factor status, should be taken from male infants of haemophilia carriers and infants with suspected bleeding disorders. All infants with intracranial haemorrhage should be evaluated for the presence of a bleeding disorder, even where there is no family history of haemophilia. DDAVP is contraindicated in neonates. Heel sticks and venipuncture should be avoided if possible, other than to assess coagulation factor status. Intramuscular vitamin K is associated with bleeding in infacts with haemophilia. Oral vitamin K is available as an alternative. Fibrin glue may be used in conjunction with factor concentrates to achieve haemostasis if circumcision is performed (Level IV evidence). DDAVP may be used for prophylaxis during the first 3–4 days after delivery in women with mild Type 1 von Willebrand disease to increase and maintain factor levels. All Type 2 and 3 von Willebrand disease and Type 1 patients who fail to reach optimal FVIII:C levels may be treated with pdFVIII/vWF concentrates postpartum (Level IV evidence).

Areas for further research

Participation in international and national research projects

Although the published literature pertaining to haemophilia and von Willebrand disease comprises a large quantity of lower level research (uncontrolled before-and-after studies, case series and case reports), there is a dearth of good quality comparative studies that minimise bias and confounding. With regard to the other rare bleeding disorders described in this review, the evidence base is particularly sparse. If future treatments are to be based on reliable evidence, better-designed higher-level studies are required to investigate the safety and effectiveness not only of haemostatic products, but also the optimal dose regimens for treatment (acute bleeding episodes, prophylaxis, immune tolerance induction, infant delivery, surgery and dental procedures) and a range of management issues. To ensure the recruitment of adequate sample sizes to provide statistical power, multi-centred controlled trials (both national and international studies) are encouraged where possible to provide higher-level evidence to support clinical practice guidelines.

National Registry

It would also be advantageous to Australians with bleeding disorders and for generating research that is relevant to the Australian setting if an Australian Registry of patients with bleeding disorders was established. This registry, which should include data from all the states and territories of Australia, would be a valuable mechanism for reporting viral transmission, adverse events and other complications of treatment, and could act as an early warning system for detecting the presence of unknown immunogenic agents or other possible contaminants in products. It could also provide useful data on long-term outcomes of treatment options.

Immunosuppressive therapy

The evidence emerging from this systematic review indicates that immunosuppressive therapy with cyclophosphamide is not recommended for patients with inhibitors, due to poor haemostatic control and a high incidence of adverse events. In contrast, several small case series have found that the immunosuppressant, rituximab, has a better short term safety profile than those used previously, such as cyclophosphamide or prednisolone. However, the body of evidence is insufficient to make recommendations for its use. Further good quality well-designed research is needed to determine its safety and effectiveness in both the short- and long-term for eliminating inhibitors.

Recombinant von Willebrand factor concentrates

There remains a theoretical risk of viral and prion transmission from the use of factor concentrates that are derived from plasma. The development of a recombinant von Willebrand factor concentrate should put patients at less risk of infectious diseases than those containing plasma-derived products and support should be given to research this potential therapeutic product.

Prophylaxis for von Willebrand disease patients

There have been several studies that reported beneficial effects of a DDAVP nasal spray or a high dose of tranexamic acid as prophylaxis for menorrhagia in patients with von Willebrand disease. However, sample sizes were generally too small to provide conclusive evidence. Well-designed and controlled studies should be conducted to determine the safety and effectiveness of different prophylaxis strategies, particularly with the less invasive treatments, such as nasal sprays or mouthwashes that may be easily self-administered by patients with menorrhagia. Similarly, further studies using a combination of treatments, such as tranexamic acid and DDAVP are necessary to determine whether they effectively reduce excessive menstrual bleeding in these patients.

Tolerisation

There is currently no consensus on the best method for tolerisation. Participation in ongoing multi-centre studies on tolerisation for both haemophilia A and B patients (with inhibitors) should be encouraged so that this expensive treatment option is used most effectively. Moreover, comparative studies on the effectiveness and safety of high-dose versus low-dose protocols for tolerisation are essential (e.g. the International Immune Tolerance Study). More research is needed on treatment of long standing high titre inhibitors or relapsed inhibitors. Controlled comparative studies are needed to confirm findings from lower level evidence that the Malmö protocol is more effective in patients with long standing inhibitors.

Surgery and dental procedures

Further study is required to assess the optimal duration of treatment after a surgical or dental procedure. The current knowledge base regarding surgical procedures in patients with blood clotting disorders consists solely of case series or case reports. Randomised controlled trails are required to establish what protocol is safest and most effective.

Ascertaining response to rFVIIa

Activated rFVII has been found to be useful in patients with inhibitors, but futher research is needed to ascertain the mechanisms of response from this treatment. No evidence of a dose response relationship has been found (Dejgaard 2003).

Currently the response to treatment with rFVIIa is not able to be adequately measured.

New approaches to treatment

Although gene therapy for haemophilia A is still in its infancy, experimental studies appear to show some promise and approximately five different trials, using vector transgene expression, are in Phase I (Rick et al. 2003). The ultimate goal of gene therapy is the long-term, sustained, therapeutic production of appropriate coagulant factors without an immune response to the transgene product or vector. Alternative approaches include: 1) the use of pre-messenger RNA repair, which use endogenous splicing mechanisms to correct the defective RNA; 2) Gene-modified circulating endothelial progenitor cells, which are capable of synthesising FVIII, may be isolated from

peripheral blood, expanded in culture, and modified to carry the normal FVIII gene; and 3) gene-modified stem cell therapy, which involves the use of multipotent adult progenitor cells derived from marrow stroma. These stem cells may be genetically modified to synthesise coagulation factors prior to retransplantation. However, it may take several months before sufficient cells are generated for transplantation.

Determination of phenotype-genotype relationship

Further research should be done in determining the relationship between phenotypes and genotypes in haemophilia and, in particular, in von Willebrand disease. While the genomic sequence of von Willebrand factor gene is available, better techniques in describing the phenotypes are needed for both clinical and research purposes. Through collecting data on correlations between phenotypes and genotypes, it is hoped that better classification of the disease may occur, which will allow more appropriate management of the disorder.

Acquired Haemophilia

Research is needed to determine the safest and most effective immunosuppressant therapy for use in acquired haemophilia.

Glossary and Abbreviations

ABDR	Australian Bleeding Disorders Registry
AHCDO	Australian Haemophilia Centre Directors' Organisation
aPCCs	Activated prothrombin complex concentrates
AP-FVIII	Affinity-purified factor VIII
aPTT	Activated partial thromboplastin time
AHF-HP	Antihaemophilic factor—high purity
AHMAC	Australian Health Ministers' Advisory Committee
AP-FVIII	Affinity-purified factor VIII
BDDrFVIII	B-domain deleted recombinant factor VIII
BT	Bleeding time—time for bleeding to stop from a superficial incision
BU	Bethesda Units—a measure of inhibitor activity; the amount of inhibitor that will inactivate 50% or 0.5 unit of a coagulation factor during the incubation period
CI	Confidence interval
CJD	Creutzfeld-Jakob disease
CVAD	Central venous access device
Cytopaenia	Decrease in the number of blood cells
DDAVP	1-deamino-8-D-arginine vasopressin (desmopressin)
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
ED	Days of exposure prior to inhibitor development
ELISA	Enzyme linked immunosorbent assay
Epistaxis	Nosebleed
Erythema	Redness of the skin
FEIBA	Factor Eight Inhibitor Bypassing Agent
FFP	Clinical fresh frozen plasma

FL-FVIII	Full-length FVIII
Fractionation	A process that uses heat to separate blood into its components
FII	Factor II, fibrinogen
FV	Factor V
FVII	Factor VII
FVIII:C	Factor VIII coagulant activity
FIX	Factor IX
FX	Factor X
FXI	Factor XI
FXIII	Factor XIII
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Haemarthrosis	Bleeding into joint spaces
Haematoma	Bleeding into an organ or tissue
High responders	Exhibit high levels of inhibitors (>5 BU/ml) following factor concentration administration
High titre	More than five Bethesda Units per millilitre (BU/ml)
HIV	Human immunodeficiency virus
Hyponatraemia	Abnormal decrease in blood sodium concentration
IgG	Immunoglobulin G
Inhibitor	An antibody that neutralises the function of factor concentrates
IQR	Inter quartile range
ITI	Immune Tolerance Induction
IU	International Units—internationally accepted unit of measurement for amount of clotting factor
IVR	In vivo recovery
JBC	Jurisdictional Blood Committee
Low responders	Show minimal or no increase in inhibitor titres following factor concentrate administration

Low titre	Less than or equal to five Bethesda Units per millilitre
Lymphopaenia	Decrease in lymphocytes in the blood
MASAC	Medical and Scientific Advisory Council (USA)
MI	Myocardial infarction
MTPs	Minimally treated patients—who received ≤ prior infusions
NBDR	National Bleeding Disorder Registry
Neutropaenia	Decrease in neutrophils in the blood
NHMRC	National Health and Medical Research Council
Pancytopaenia	Deficiency of all cell elements in the blood
Paraesthesia	Abnormal burning, prickling sensation
PBAC	Pictorial Blood Assessment Chart
PCCs	Prothrombin Complex Concentrates
PCR	Polymerase chain reaction
pdFIX	Plasma-derived factor IX
pdFVIII	Plasma-derived factor VIII
PFA-100	Platelet function analyser
PPH	Postpartum haemorrhage
PPT	Partial prothrombin time
Prophylaxis	An attempt to prevent bleeding episodes by administering amounts of blood clotting factors
Pruritis	Itching of the skin
PT	Prothrombin time
PTPs	Previously treated patients
PUPs	Previously untreated patients
Rco	Ristocetin-cofactor activity
rFIX	Recombinant factor IX
rFVIIa	Activated recombinant factor VII
rFVIII	Recombinant factor VIII

RR	Relative risk/rate ratio
SD	Standard deviation
Tachyphylaxis	Rapidly decreasing response to a drug after administration of a few doses
Tolerisation	Induction of immune tolerance (desensitisation to blood clotting factors)
Teichopsia	Jagged visual sensation resembling the walls of a medieval town
Thrombophlebitis	Inflammation of a vein associated with thrombus formation
Urticaria	Transient allergic reaction of the skin—severe itching
vCJD	variant Creutzfeldt-Jakob disease
vWD	von Willebrand disease
vWF	von Willebrand factor
vWF:Ag	von Willebrand factor antigen
vWF:CB	von Willebrand factor-collagen binding
vWF:FVIIIB	von Willebrand factor-factor VIII binding
vWF:Rco	von Willebrand factor-ristocetin cofactor binding

References

AHMAC 2003, *Report of the Working Party on the supply and use of factor VIII and factor IX in Australia*, Department of Health and Ageing, Canberra.

AIHW 2004, *National Hospital Morbidity Database*, viewed 25 June 2004, www.aihw.gov.au

Ananyeva, N, Khrenov, A et al. 2004, 'Treating haemophilia A with recombinant blood factors: a comparison', *Expert Opin Pharmacother,* 5 (5), pp. 1061–1070.

Arkin, S, Rose, E et al. 1991, 'Clinical efficacy of recombinant factor VIII', *Semin Hematol,* 28 (2 Suppl. 1), pp. 47–51.

Association of Hemophilia Clinic Directors of Canada 1995a, 'Hemophilia and von Willebrand's disease: 1. Diagnosis, comprehensive care and assessment. Association of Hemophilia Clinic Directors of Canada. Updated 1999', *Can Med Assoc J,* 153 (1), pp. 19–25.

Association of Hemophilia Clinic Directors of Canada 1995b, 'Hemophilia and von Willebrand's disease: 2. Management. Association of Hemophilia Clinic Directors of Canada', *Can Med Assoc J,* 153 (2), pp. 147–157.

Auerswald, G, Eberspacher, B et al. 2002, 'Successful treatment of patients with von Willebrand disease using a high-purity double-virus inactivated factor VIII/von Willebrand factor concentrate (Immunate (registered trademark))', *Semin Thromb Hemost,* 28 (2), pp. 203–213.

Australian Bleeding Disorder Registry 2004, *ABDR Report,* National Blood Authority, Canberra.

Australian Haemophilia Centre Directors' Organisation 2004, *Guidelines for the treatment of inhibitors in Haemophilia A*, Canberra.

Avanoglu, A, Celik, A et al. 1999, 'Safer circumcision in patients with haemophilia: The use of fibrin glue for local haemostasis', *BJU International,* 83 (1), pp. 91–94.

Aygoren-Pursun, E, Scharrer, I et al. 1997, 'A multicenter pharmacosurveillance study for the evaluation of the efficacy and safety of recombinant factor VIII in the treatment of patients with hemophilia A', *Thromb Haemost,* 78 (5), pp. 1352–1356.

Bastounis, E, Pikoulis, E et al. 2000, 'General surgery in haemophiliac patients', *Postgrad Med J,* 76 (898), pp. 494–495.

Baudo, F, De Cataldo, F & Gaidano, G 2004, 'Treatment of acquired factor VIII inhibitor with recombinant activated factor VIIa: data from the Italian registry of acquired hemophilia', *Haematologica,* 89 (6), pp. 759–761.

Berntorp, E 1994, 'Plasma product treatment in various types of von Willebrand's disease', *Haemostasis,* 24 (5), pp. 289–297.

Berntorp, E 1997, 'Second generation, B-domain deleted recombinant factor VIII', *Thromb Haemost,* 78 (1), pp. 256–260.

Berntorp, E 1999, 'von Willebrand factor containing factor VIII concentrates', *Haemophilia,* 5 (Suppl. 2), pp. 60–63.

Berntorp, E, Astermark, J et al. 2003. 'Consensus perspective on prophylactic therapy for haemophilia: Summary statement', *Haemophilia,* 9 (Suppl. 1), pp. 1–4.

Bjorkman, S, Shapiro, AD & Berntorp, E 2001, 'Pharmacokinetics of recombinant factor IX in relation to age of the patient: implications for dosing in prophylaxis', *Haemophilia,* 7 (2), pp. 133–139.

Bolton-Maggs, PH 2000, 'Factor XI deficiency and its management', *Haemophilia,* 6 (Suppl 1), pp. 100–109.

Bolton-Maggs, PH & Pasi, KJ 2003, 'Haemophilias A and B', *Lancet,* 361 (9371), pp. 1801–1809.

Bolton-Maggs, PH, Perry, DJ et al. 2004, 'The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation', *Haemophilia,* 10 (5), pp. 593–628.

Braunwald, E, Fauci, AS et al. 2001, *Harrison's (15th Edition) principles of internal medicine,* Vol. 1 .15 McGraw-Hill Medical Publishing Division, New York.

Bray, GL, Gomperts, ED et al. 1994, 'A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. The Recombinate Study Group', *Blood,* 83 (9), pp. 2428–2435.

Canadian Hemophilia Society 2004, *Factor II deficiency (Prothrombin deficiency)*, viewed 7 January 2005, www.hemophilia.ca/en/2.3.2.php.

Carcao, MD & Aledort, L 2004, 'Prophylactic factor replacement in hemophilia', *Blood Rev,* 18 (2), pp. 101-113.

Cattaneo, M, Moia, M et al. 1989, 'DDAVP shortens the prolonged bleeding times of patients with severe von Willebrand disease treated with cryoprecipitate. Evidence for a mechanism of action independent of released von Willebrand factor', *Blood,* 74 (6), pp. 1972–1975.

Chalmers, EA. 2004, 'Haemophilia and the newborn', *Blood Rev,* 18 (2), pp. 85–92.

Chediak, JR, Alban, GM & Maxey, B 1986, 'von Willebrand's disease and pregnancy: management during delivery and outcome of offspring', *Am J Obstet Gynecol,* 155 (3), pp. 618–624.

Chuansumrit, A, Hathirat, P et al. 1993, 'Response of patients with bleeding disorder to DDAVP administration', *Southeast Asian J Trop Med Public Health,* 24 (Suppl 1), pp. 174–179.

Clarke, M & Oxman, AD 2000, *Cochrane reviewers' handbook 4.0* , 'The Cochrane Collaboration', viewed 26 July 2004, www.cochrane.org/cochrane/hbook.htm.

Collins, P, Macartney, N et al. 2004, 'A population based, unselected, consecutive cohort of patients with acquired haemophilia A', *Br J Haematol,* 124 (1), pp. 86–90.

Cooper, H & Hedges, LV (eds.) 1994), *The handbook of research synthesis,* Russel Sage Foundation, New York.

Daffos, F, Forestier, F et al. 1988, 'Prenatal diagnosis and management of bleeding disorders with fetal blood sampling', *Am J Obstet Gynecol,* 158 (4), pp. 939–946.

de la Fuente, B, Kasper, CK et al. 1985, 'Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin', *Ann Intern Med,* 103 (1), pp. 6–14.

De Sio, L, Mariani, G & Muzzucconi, G 1985, 'Comparison between subcutaneous and intravenous DDAVP in mild and moderate Hemophilia A', *Thromb Haemost,* 54 (2), pp. 387–389.

Dejgaard, A 2003, 'Update on Novo Nordisk's clinical trial programme on NovoSeven®', *Blood Coag Fibrinolysis*, 14 (Suppl 1), S39–S41.

Delgado, J, Jimenez-Yuste, V et al. 2003, 'Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors', *Br J Haematol,* 121 (1), pp. 21–35.

Delgado, J, Villar, A et al. 2002, 'Acquired hemophilia: a single-center survey with emphasis on immunotherapy and treatment-related side-effects', *Eur J Haematol,* 69 (3), pp. 158–164.

Department of Health and Ageing 2004, *Access to recombinant factor VIII and IX*, viewed 14 September 2004, www.nba.gov.au/current.htm.

Department of Health and Ageing 2003, *Report of the Expert Advisory Group on Hepatitis C and Plasma in 1990,* Canberra.

Dewald, DL, Briggs, B & Smith, RE 1980, 'Intranasal administration of desmopressin acetate (DDAVP) to hemophiliacs', *Thromb Res,* 18 (5), pp. 617–622.

Di Paola, J, Nugent, D & Young, G 2001, 'Current therapy for rare factor deficiencies', *Haemophilia,* 7 (Suppl 1), pp. 16–22.

DiMichele, DM 1998, 'Immune tolerance: A synopsis of the international experience', *Haemophilia,* 4 (4), pp. 568–573.

Djulbegovic, B, Marasa, M et al. 1996, 'Safety and efficacy of purified factor IX concentrate and antifibrinolytic agents for dental extractions in hemophilia B', *Am J Hematol,* 51 (2), pp. 168–170.

Dobrkovska, A, Krzensk, U & Chediak, JR 1998, 'Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease', *Haemophilia,* 4 (Suppl 3), pp. 33–39.

Downs, SH & Black, N 1998, 'The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions', *J Epidemiol Community Health,* 52 (6), pp. 377–384.

Dunn, AL, Powers, JR et al. 2000, 'Adverse events during use of intranasal desmopressin acetate for haemophilia A and von Willebrand disease: a case report and review of 40 patients', *Haemophilia,* 6 (1), pp. 11–14.

Economides, DL, Kadir, RA & Lee, CA 1999, 'Inherited bleeding disorders in obstetrics and gynaecology', *Br J Obstet Gynaecol,* 106 (1), pp. 5–13.

Ewenstein, BM, Gomperts, ED et al. 2004, 'Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclate): a prospective pharmacovigilance study', *Haemophilia,* 10 (5), pp. 491–498.

Ewenstein, BM, Joist, JH et al. 2002, 'Pharmacokinetic analysis of plasma-derived and recombinant F IX concentrates in previously treated patients with moderate or severe hemophilia B', *Transfusion,* 42 (2), pp. 190–197.

Favaloro, E, Lloyd, J et al. 2005, 'A cross-over, multi-centre study to compare the pharmacokinetics of two factor concentrates (Biostate and AHF (High Purity)) in people with von Willebrand disorder (Draft).' *Manuscript in preparation.*

Federici, AB, Baudo, F et al. 2002, 'Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study', *Haemophilia,* 8 (6), pp. 761–767.

Federici, AB, Mazurier, C et al. 2004, 'Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study', *Blood,* 103 (6), pp. 2032–2038.

Federici, AB, Sacco, R et al. 2000, 'Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases', *Haemophilia,* 6 (2), pp. 71–77.

Fijnvandraat, K, Berntorp, E et al. 1997, 'Recombinant, B-domain deleted factor VIII (r-VIII SQ): pharmacokinetics and initial safety aspects in hemophilia A patients', *Thromb Haemost,* 77 (2), pp. 298–302.

Franchini, M, Gandini, G et al. 2002, 'Evaluation of the PFA-100 system for monitoring desmopressin therapy in patients with type 1 von Willebrand's disease', *Haematologica,* 87 (6), p. 670.

Franchini, M, Rossetti, G et al. 2003, 'Efficacy and safety of factor VIII/von Willebrand's factor concentrate (Haemate-P) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand disease', *Haematologica,* 88 (11), pp. 1279–1283.

Ghirardini, A, Chistolini, A et al. 1988,'Clinical evaluation of subcutaneously administered DDAVP', *Thromb Res,* 49 (3), pp. 363–372.

Ghirardini, A, Mariani, G et al. 1987, 'Concentrated DDAVP: further improvement in the management of mild factor VIII deficiencies', *Thromb Haemost,* 58 (3), pp. 896–898.

Giangrande, DP 1996, *Inhibitory antibodies*, UK Haemophilia Centre Directors' Organisation, viewed 6 July 2004, ww.medicine.ox.ac.uk/ohc/Inhibi.htm.

Giangrande, PL 2002, 'Safety and efficacy of KOGENATEI Bayer in previously untreated patients (PUPs) and minimally treated patients (MTPs)', *Haemophilia,* 8 (Suppl 2), pp. 19–22.

Giangrande, PLF 1998, 'Management of pregnancy in carriers of haemophilia', *Haemophilia,* 4 (6), 779–784.

Giles, AR, Rivard, GE et al. 1998, 'Surveillance for factor VIII inhibitor development in the Canadian Hemophilia A population following the widespread introduction of recombinant factor VIII replacement therapy', *Transfus Sci,* 19 (2), pp. 139–148.

Gill, JC, Ewenstein, BM et al. 2003, 'Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy', *Haemophilia,* 9 (6), pp. 688–695.

Gill, JC, Ottum, M & Schwartz, B 2002, 'Evaluation of high concentration intranasal and intravenous desmopressin in pediatric patients with mild hemophilia A or mild-to-moderate type 1 von Willebrand disease', *J Pediatr,* 140 (5), pp. 595–599.

Greer, IA, Lowe, GDO et al. 1991, 'Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies', *Br J Obstet Gynaecol,* 98 (9), pp. 909–918.

Gringeri, A 1998, 'Evaluation study on prophylaxis: a randomised Italian trial (ESPRIT). One year report [abstract]', *Haemophilia,* 4 (3), p. 171.

Gringeri, A 2003, 'Prospective controlled studies on prophylaxis: an Italian approach', *Haemophilia,* 9 (Suppl 1), pp. 38–42; discussion p. 43.

Gringeri, A, Tagliaferri, A et al. 2004, 'Efficacy and inhibitor development in previously treated patients with haemophilia A switched to a B domain-deleted recombinant factor VIII', *Br J Haematol,* 126 (3), pp. 398–404.

Gruppo, R, Brown, D et al. 2004, 'Increased breakthrough bleeding during prophylaxis with B-domain deleted factor VIII - a robust meta-analytic finding', *Haemophilia,* 10, pp. 1–3.

Gruppo, R, Brown, D et al. 2003, 'Comparative effectiveness of full-length and B-domain deleted factor VIII for prophylaxis - a meta-analysis', *Haemophilia,* 9 (3), pp. 251–260.

Haemophilia Foundation Australia 2004a, *Do we have to wait for another disaster like Hepatitis C before governments will act?*, viewed 7 July 2004, www.haemophilia.org.au/knowledge/files/143/june172004final.pdf.

Haemophilia Foundation Australia 2004b, *Haemophilia Foundation Australia*, viewed 4 August 2004, www.haemophilia.org.au.

Haemophilia Foundation Australia Medical Advisory Panel 2000, *Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders in Australia*, viewed 26 July 2004, www.ahcdo.org.au/sitebuilder/guidelines/files/3/guidelinesmarch00.pdf.

Hay, C, Mauser-Bunschoten, E et al. 2000a, *Protocol: An International randomised controlled trial of immune-tolerance induction*, Manchester.

Hay, CR, Baglin, TP et al. 2000b, 'The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO)', *Br J Haematol,* 111 (1), pp. 78–90.

Hitchens, K 2004, 'Special Report: Helping Hemophiliacs', *Drug Topics,* 148 (HSE17).

Hoyer, LW, Carta, CA et al. 1985, 'Prenatal diagnosis of classic hemophilia (hemophilia A) by immunoradiometric assays', *Blood,* 65 (6), pp. 1312–1317.

Israels, S 2004a, *Factor VII deficiency*, eMedicine, viewed 16 December 2004, www.emedicine.com/ped/topic3041.htm.

Israels, S 2004b, *Factor XIII deficiency*, eMedicine, viewed 16 December 2004, www.emedicine.com/ped/topic3040.htm.

JBC FVIII/FIX working party & National Blood Authority 2004, *Development of evidence-based clinical practice guidelines for the use of recombinant and plasma-derived factor VIII and IX (meeting)*, Melbourne, 15 December 2004.

Kadir, RA, Economides, DL et al. 1997, 'The obstetric experience of carriers of haemophilia', *Br J Obstet Gynaecol,* 104 (7), pp. 803–810.

Kadir, RA., Lee, CA et al. 1998, 'Pregnancy in women with von Willebrand's disease or factor XI deficiency', *Br J Obstet Gynaecol,* 105 (3), pp. 314–321.

Kadir, RA., Lee, CA et al. 2002, 'DDAVP nasal spray for treatment of menorrhagia in women with inherited bleeding disorders: a randomized placebo-controlled crossover study', *Haemophilia,* 8 (6), pp. 787–793.

Kasper, CK 2004, *Hereditary plasma clotting factor disorders and their management. Treatment of Hemophilia Monograph Series, No. 4,* World Federation of Hemophilia, Montreal, Canada.

Kelly, KM, Butler, RB et al. 1997, 'Superior in vivo response of recombinant factor VIII concentrate in children with hemophilia A', *J Pediatr,* 130 (4), pp. 537–540.

Khan, KS, Ter Riet, G et al. 2001, *Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews,* NHS Centre for Reviews and Dissemination, University of York, York.

Kingdon, HS & Lundblad, RL 2002, 'An adventure in biotechnology: the development of haemophilia A therapeutics - from whole-blood transfusion to recombinant DNA to gene therapy', *Biotechnol Appl Biochem,* 35 (Pt 2), pp. 141–148.

Kisker, CT, Eisberg, A & Schwartz, B 2003, 'Prophylaxis in factor IX deficiency product and patient variation', *Haemophilia,* 9 (3), pp. 279–284.

Kreuz, W, Ettingshausen, CE et al. 2002, 'Inhibitor development in previously untreated patients with hemophilia A: a prospective long-term follow-up comparing plasma-derived and recombinant products', *Semin Thromb Hemost,* 28 (3), pp. 285–290.

Kulkarni, R, Aledort, LM et al. 2001, 'Therapeutic choices for patients with hemophilia and high-titer inhibitors', *Am J Hematol,* 67 (4), pp. 240–246.

Kulkarni, R & Lusher, J 2001, 'Perinatal management of newborns with haemophilia', *Br J Haematol,* 112 (2), pp. 264–274.

Laffan, M, Brown, SA et al. 2004, 'The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization', *Haemophilia,* 10 (3), pp. 199–217.

Leissinger, C, Becton, D et al. 2001, 'High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A', *Haemophilia,* 7 (3), pp. 258–266.

Lillicrap, D, Poon, MC et al. 2002, 'Efficacy and safety of the factor VIII/von Willebrand factor concentrate, haemate-P/humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease', *Thromb Haemost,* 87 (2), pp. 224–230.

Ljung, R 2004, 'Central venous catheters in children with haemophilia', *Blood Rev,* 18 (2), pp. 93–100.

Ljung, R, Lindgren, AC et al. 1994, 'Normal vaginal delivery is to be recommended for haemophilia carrier gravidae', *Acta Paediatr,* 83 (6), pp. 609–611.

Lloyd Jones, M, Wight, J et al. 2003, 'Control of bleeding in patients with haemophilia A with inhibitors: a systematic review', *Haemophilia,* 9 (4), pp. 464–520.

Lorenzo, JI, Lopez, A et al. 2001, 'Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age', *Br J Haematol,* 113 (3), pp. 600–603.

Lusher, J, Abildgaard, C et al. 2004, 'Human recombinant DNA-derived antihemophilic factor in the treatment of previously untreated patients with hemophilia A: final report on a hallmark clinical investigation', *J Thromb Haemost,* 2 (4), pp. 574–583.

Lusher, JM, Arkin, S et al. 1993, 'Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A—Safety, efficacy, and development of inhibitors', *N Engl J Med,* 328 (7), pp. 453–459.

Manco-Johnson, MJ, Nuss, R et al. 2000, 'Joint evaluation instruments for children and adults with haemophilia', *Haemophilia,* 6 (6), pp. 649–657.

Manco-Johnson, MJ & Blanchette, VS 2003, 'North American prophylaxis studies for persons with severe haemophilia: Background, rationale and design', *Haemophilia,* 9 (SUPPL. 1), pp. 44–49.

Manno, CS 1999, 'Treatment options for bleeding episodes in patients undergoing immune tolerance therapy', *Haemophilia,* 5 (Suppl 3), pp. 33–41.

Mannucci, PM 2001, 'How I treat patients with von Willebrand disease', *Blood,* 97 (7), pp. 1915–1919.

Mannucci, PM, Bettega, D & Cattaneo, M 1992, 'Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP)', *Br J Haematol,* 82 (1), pp. 87–93.

Mannucci, PM, Brettler, DB et al. 1994, 'Immune status of human immunodeficiency virus seropositive and seronegative hemophiliacs infused for 3.5 years with recombinant factor VIII. The Kogenate Study Group', *Blood,* 83 (7), pp. 1958–1962.

Mannucci, PM, Chediak, J et al. 2002, 'Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study', *Blood,* 99 (2), pp. 450–456.

Mannucci, PM, Vicente, V et al. 1987, 'Intravenous and subcutaneous administration of desmopressin (DDAVP) to hemophiliacs: pharmacokinetics and factor VIII responses', *Thromb Haemost,* 58 (4), pp. 1037–1039.

Mariana, G, Ciavarella, N & Mazzucconi, MG 1984, 'Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients', *Clin Lab Haematol,* 6 (3), pp. 229–238.

Medical and Scientific Advisory Council (MASAC) 2001, *Recommendation concerning prophylaxis (Prophylactic administration of clotting factor concentration to prevent bleeding),* National Hemophilia Foundation, New York.

Mohri, H 2002, 'High dose of tranexamic acid for treatment of severe menorrhagia in patients with von Willebrand disease', *J Thromb Thrombolysis,* 14 (3), pp. 255–257.

Morfini, M, Longo, G et al. 1992, 'Pharmacokinetic properties of recombinant factor VIII compared with a monoclonally purified concentrate (Hemofil M). The Recombinate Study Group', *Thromb Haemost,* 68 (4), pp. 433–435.

Morrison, AE, Ludlam, CA & Kessler, C 1993, 'Use of porcine factor VIII in the treatment of patients with acquired hemophilia', *Blood,* 81 (6), pp. 1513–1520.

Mulrow, CD, Cook, DJ & Davidoff, F 1997, 'Systematic reviews: Critical links in the great chain of evidence', *Ann Intern Med,* (126), pp. 389–391.

NHMRC 2000a, *How to review the evidence: systematic identification and review of the scientific literature,* National Health and Medical Research Council, Canberra.

NHMRC 2000b, *How to use the evidence: assessment and application of scientific evidence,* National Health and Medical Research Council, Canberra.

NHMRC Guidelines Assessment Register Consultants Working Party 2004, *Minimum requirements for evidence tables,* Guideline Assessment Register, National Health and Medical Research Council, Canberra.

Nilsson, IM., Berntorp, E et al. 1992, 'Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B', *J Intern Med,* 232 (1), pp. 25–32.

Nilsson, IM & Hedner, U 1976, 'Immunosuppressive treatment in haemophiliacs with inhibitors to factor VIII and factor IX', *Scand J Haematol,* 16 (5), pp. 369–382.

Nitu-Whalley, IC, Griffioen, A et al. 2001, 'Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease', *Am J Hematol,* 66 (4), pp. 280–284.

Nolan, B, White, B et al. 2000, 'Desmopressin: therapeutic limitations in children and adults with inherited coagulation disorders', *Br J Haematol,* 109 (4), pp. 865–869.

Ong, YL., Hull, DR & Mayne, EE 1998, 'Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid', *Haemophilia,* 4 (1), pp. 63–65.

Paisley, S, Wight, J et al. 2003, 'The management of inhibitors in haemophilia A: introduction and systematic review of current practice', *Haemophilia,* 9 (4), pp. 405–417.

Pall Corporation 2004, *Pall Corp prion removal technology featured at International Transmissible Spongiform Encephalopathy conference (press release)*, viewed 6 January 2005, www.pall.com/news_articles_34853.asp.

Palmer, BF, Gates, JR & Lader, M 2003, 'Causes and management of hyponatremia', *Ann Pharmacother,* 37 (11), pp. 1694–1702.

Panicker, J, Warrier, I et al. 2003, 'The overall effectiveness of prophylaxis in severe haemophilia', *Haemophilia,* 9 (3), pp. 272–278.

Petrini, P 2001, 'What factors should influence the dosage and interval of prophylactic treatment in patients with severe haemophilia A and B?' *Haemophilia,* 7 (1), pp. 99–102.

Pettersson, H, Nilsson, IM et al. 1981, 'Radiologic evaluation of prophylaxis in severe haemophilia', *Acta Paediatr Scand,* 70 (4), pp. 565–570.

Pollmann, H, Richter, H et al. 1999, 'When are children diagnosed as having severe haemophilia and when do they start to bleed? A 10-year single-centre PUP study', *Eur J Pediatr,* 158 (Suppl 3), S166–170.

Poon, MC, Lillicrap, D et al. 2002, 'Recombinant factor IX recovery and inhibitor safety: A Canadian post-licensure surveillance study', *Thromb Haemost,* 87 (3), pp. 431–435.

Powell, JS, Ragni, MV et al. 2003, 'Phase 1 trial of FVIII gene transfer for severe hemophilia A using a retroviral construct administered by peripheral intravenous infusion', *Blood,* 102 (6), pp. 2038–2045.

Ragni, MV, Pasi, KJ et al. 2002, 'Use of recombinant factor IX in subjects with haemophilia B undergoing surgery', *Haemophilia,* 8 (2), pp. 91–97.

Rakocz, M, Mazar, A et al. 1993, 'Dental extractions in patients with bleeding disorders. The use of fibrin glue', *Oral Surg Oral Med Oral Pathol,* 75 (3), pp. 280–282.

Rick, ME, Walsh, CE & Key, NS 2003, 'Congenital bleeding disorders', *Hematology (Am Soc Hematol Educ Program)*, pp. 559–574.

Rodeghiero, F, Castaman, G & Mannucci, PM 1996, 'Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A', *Thromb Haemost,* 76 (5), pp. 692–696.

Rodriguez-Merchan, EC, Wiedel, JD et al. 2003, 'Elective orthopaedic surgery for inhibitor patients', *Haemophilia,* 9 (5), pp. 625–631.

Rose, EH & Aledort, LM 1991, 'Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease', *Ann Intern Med,* 114 (7), pp. 563–568.

Roth, DA, Kessler, CM et al. 2001a, 'Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates', *Blood,* 98 (13), pp. 3600–3606.

Roth, DA, Tawa, NE et al. 2001b, 'Nonviral transfer of the gene encoding coagulation factor VIII in patients with severe hemophilia A', *N Engl J Med,* 344 (23), pp. 1735–1742.

Rothschild, C, Laurian, Y et al. 1998, 'French previously untreated patients with severe hemophilia A after exposure to recombinant factor VIII: incidence of inhibitor and evaluation of immune tolerance', *Thromb Haemost,* 80 (5), pp. 779–783.

Sallah, S 2004, 'Treatment of acquired haemophilia with factor eight inhibitor bypassing activity', *Haemophilia,* 10 (2), pp. 169–173.

Sallah, S & Wan, JY 2003, 'Efficacy of 2-chlorodeoxyadenosine in refractory factor VIII inhibitors in persons without hemophilia', *Blood,* 101 (3), pp. 943–945.

Santagostino, E, Gringeri, A et al. 2003, 'Long-term safety and feasibility of arteriovenous fistulae as vascular accesses in children with haemophilia: a prospective study', *Br J Haematol,* 123 (3), pp. 502–506.

Saulnier, J, Marey, A et al. 1994, 'Evaluation of desmopressin for dental extractions in patients with hemostatic disorders.' *Oral Surg Oral Med Oral Pathol,* 77 (1), pp. 6–12.

Scharrer, I 1995, 'The need for highly purified products to treat hemophilia B', *Acta Haematol,* 94 (Suppl 1), pp. 2–7.

Scharrer, I 2002, 'Experience with KOGENATEI Bayer in surgical procedures', *Haemophilia,* 8 (Suppl 2), pp. 15–18.

Scharrer, I, Brackmann, HH et al. 2000, 'Efficacy of a sucrose-formulated recombinant factor VIII used for 22 surgical procedures in patients with severe haemophilia A', *Haemophilia,* 6 (6), pp. 614–618.

Schiavoni, M, Ettore, C et al. 1983, 'Tranexamic acid as prophylaxis in haemophilia. A randomized double-blind study [abstract]', *Thromb Haemost,* pp. 50, 444.

Schulman, S, Johnsson, H & Lindstedt, M 1991, 'Desmopressin as a haemostatic agent in patients with disorders of primary haemostasis', *Acta Chir Eur J Surg,* 157 (11-12), pp. 647–652.

Schwartz, RS, Abildgaard, CF et al. 1990, 'Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A', *N Engl J Med,* 323 (26), pp. 1800–1805.

Senate Community Affairs References Committee 2004, *Hepatitis C and the blood supply in Australia,* Senate Printing Unit, Parliament House, Canberra.

Seremetis, S, Lusher, JM et al. 1999, 'Human recombinant DNA-derived antihaemophilic factor (factor VIII) in the treatment of haemophilia A: conclusions of a 5-year study of home therapy. The KOGENATE Study Group', *Haemophilia,* 5 (1), pp. 9–16.

Siegel, J 2004, *Factor XI deficiency*, eMedicine, viewed 16 December 2004, www.emedicine.com/med/topic3515.htm.

Sindet-Pedersen, S, Stenbjerg, S & Ingerslev, J 1988, 'Control of gingival hemorrhage in hemophilic patients by inhibition of fibrinolysis with tranexamic acid', *J Periodontal Res,* 23 (1), pp. 72–74.

Soucie, JM, Nuss, R et al. 2000, 'Mortality among males with hemophilia: relations with source of medical care', *Blood*, 96 (2), pp. 437–442.

Soucie, JM, Symons, J et al. 2001, 'Home-based factor infusion therapy and hospitalization for bleeding complications among males with haemophilia', *Haemophilia*, 7 (2), pp. 198–206.

Soucie, JM, Siwak, EB et al. 2004, 'Human parvovirus B19 in young male patients with hemophilia A: associations with treatment product exposure and joint range-of-motion limitation', *Transfusion,* 44 (8), pp. 1179–1185.

Stajcic, Z, Baklaja, R et al. 1989, 'Primary wound closure in haemophiliacs undergoing dental extractions', *Int J Oral Maxillofac Surg,* 18 (1), pp. 14–16.

Stasi, R, Brunetti, M et al. 2004, 'Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia', *Blood,* 103 (12), 4424–4428.

Stata Corporation 2004, *Intercooled Stata 8.2 for Windows* [computer program], Stata Corporation, College City, Texas.

Steen, CJ & Schwartz, RA 2004, *Factor X*, eMedicine, viewed 16 December 2004, www.emedicine.com/med/topic3495.htm.

Stieltjes, N, Altisent, C et al. 2004, 'Continuous infusion of B-domain deleted recombinant factor VIII (ReFacto) in patients with haemophilia A undergoing surgery: clinical experience', *Haemophilia,* 10 (5), pp. 452–458.

Street, AM & Ekert, H 1996, 'Haemophilia—darkest hours before the dawn', *Med J Aust,* 164 (8), pp. 453–455.

Stubbs, M & Lloyd, J 2001, 'A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B', *Aust Dent J,* 46 (1), pp. 37–40.

Tarantino, MD, Collins, PW et al. 2004, 'Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A', *Haemophilia,* 10 (5), pp. 428–437.

Thompson, AR, Gill, JC et al. 2004, 'Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P)', *Haemophilia,* 10 (1), pp. 42–51.

United Kingdom Haemophilia Centre Doctors' Organisation 2003, 'Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders', *Haemophilia,* 9 (1), pp. 1–23.

Valentino, LA, Ewenstein, B et al. 2004, 'Central venous access devices in haemophilia', *Haemophilia,* 10 (2), pp. 134–146.

van der Bom, JG, Mauser-Bunschoten, EP et al. 2003, 'Age at first treatment and immune tolerance to factor VIII in severe hemophilia', *Thromb Haemost,* 89 (3), pp. 475–479.

Verbruggen, B, Novakova, I et al. 1995, 'The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability', *Thromb Haemost,* 73 (2), pp. 247–251.

Warrier, AI & Lusher, JM 1983, 'DDAVP: a useful alternative to blood components in moderate hemophilia A and von Willebrand disease', *J Pediatr,* 102 (2), pp. 228–233.

Waymouth Resources Limited 2003, *NSX Announcement: Proposed transaction with Living Cell Technologies Ltd*, viewed 12 July 2004, www.newsx.com.au/ftp/news/WAY15102003175752.pdf.

White, G, Shapiro, A et al. 1998, 'Clinical evaluation of recombinant factor IX', *Semin Hematol,* 35 (2 Suppl 2), pp. 33–38.

White, GC2nd, Courter, S et al. 1997, 'A multicenter study of recombinant factor VIII (Recombinate) in previously treated patients with hemophilia A. The Recombinate Previously Treated Patient Study Group', *Thromb Haemost,* 77 (4), pp. 660–667.

Wiestner, A, Cho, HJ et al. 2002, 'Rituximab in the treatment of acquired factor VIII inhibitors', *Blood,* 100 (9), pp. 3426–3428.

Wight, J, Paisley, S & Knight, C 2003, 'Immune tolerance induction in patients with haemophilia A with inhibitors: a systematic review', *Haemophilia,* 9 (4), pp. 436–463.

World Health Organization 2002, *Delivery of Treatment of Haemophilia, Report of a Joint WHO/WFH/ISTH Meeting*, London, UK.

Yoshioka, A, Fukutake, K et al. 2003, 'Clinical evaluation of a recombinant factor VIII preparation (Kogenate) in previously untreated patients with hemophilia A', *Int J Hematol,* 78 (5), pp. 467–474.

Yoshioka, A, Shima, M et al. 2001, 'Safety and efficacy of a new recombinant FVIII formulated with sucrose (rFVIII-FS) in patients with haemophilia A: a long-term, multicentre clinical study in Japan', *Haemophilia,* 7 (3), pp. 242–249.

Young, J, Hyde, C et al. 1999, 'Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema.' *Thorax,* 54 (9), pp. 779–789.

Zanon, E, Martinelli, F et al. 2000, 'Proposal of a standard approach to dental extraction in haemophilia patients. A case-control study with good results', *Haemophilia,* 6 (5), pp. 533–536.

Ziv, O & Ragni, MV 2004, 'Bleeding manifestations in males with von Willebrand disease', *Haemophilia,* 10 (2), pp. 162–168.

Appendix A Terms of Reference for Undertaking Guidelines

A. Services

1. Develop national clinical guidelines for the use of recombinant factors VIII and IX for patients with haemophilia A and B

2. Develop national clinical guidelines for the use of plasma-derived factors VIII and IX for patients with haemophilia A, B and von Willebrand disease

3. Develop national tolerisation protocols for tasks 1 and 2 above

4. Collect and consolidate information on product usage for patients with other rare bleeding disorders, including an analysis on tolerisation within this group

5. Attend and participate in education and implementation workshop(s)

B. Required contract material

The contractor shall produce both clinical practice guidelines and a final report to the National Blood Authority.

1. The guidelines shall include:

    a. Management of haemophilia A, B and von Willebrand disease
    b. Adjunctive haemostatic agents
    c. Treatment of bleeding episodes, including surgery, dental and prophylaxis
    d. Delivery of infants
    e. Complications of treatment, including:
        (i) Inhibitor development
        (ii) Infectious diseases and other safety and quality issues
    f. Validation—data requirements for refined data analysis (clinical audit and outcomes)
    g. Other aspects of management
    h. Selection of products

2. In addition to a reconciliation of costs, the final report to the NBA shall identify strategies and approaches for education of healthcare professionals and recipients and identify potential research directions.

Appendix B Working Party Membership

Contractors

Researchers:	Dr Petra Bywood, Research Officer Ms Skye Newton, Research Officer Ms Linda Mundy, Research Officer Ms Tracy Merlin, Manager
Consultant Methodologist:	Professor Janet Hiller, Director Adelaide Health Technology Assessment Department of Public Health, University of Adelaide
Consultant Clinician:	Dr Ben Saxon, Transfusion Medicine Specialist Australian Red Cross Blood Service-Discovery

National Blood Authority

John Haines	National Blood Authority
Julianne Brettargh	National Blood Authority
Ray Carty	Scientific Officer, Corporate Services and Quality, National Blood Authority
Ms Tamsen Marriott	Corporate Services and Quality, National Blood Authority
Ms Stephanie Gunn	Branch Manager Policy, Planning and Corporate Services, National Blood Authority

Recombinant FVIII and FIX Working Party Members

Dr Chris Brook	Director, Rural and Regional Health and Aged Care Services Victorian Department of Human Services
Ms Sharon Caris	Executive Director, Haemophilia Foundation Australia
Prof Brendon Kearney (Chair)	Executive Director Clinical Systems, SA Department of Human Services
Dr Ahti Lammi	Director of Haematology, New Childrens Hospital, Westmead
Dr John Rowell	Director, Queensland Haemophilia Centre
Prof Alison Street	Director and Associate Professor of Medicine, Haematology Department, Alfred Hospital, Melbourne

Appendix C Australian haemophilia treatment centres

Director	Address	
A/Prof Ross Baker	Thrombosis and Haemophilia Service, Kirkman House, Royal Perth Hospital, Wellington Street, Perth, WA, 6000	Ph: 08 9224 2897/2667, Fax: 08 9224 8022, ross.baker@rph.health.wa.gov.au
Dr Chris Barnes	Department of Haematology/Oncology, Royal Children's Hospital, Flemington Road, Parkville, VIC, 3052	Ph: 03 9345 5522, Fax: 03 9345 5099, chris.barnes@rch.org.au
Dr David Jupe	Haematology Department, Royal Hobart Hospital, GPO Box 1061L, Hobart, TAS, 7001	Ph: 03 6238 8418, Fax: 03 6263 7463, david.jupe@dchs.tas.gov.au
Dr Ahti Lammi	Haematology Department, New Children's Hospital, Hawkesbury Road, Westmead, NSW, 2145	Ph: 02 9845 0000, Fax: 02 9845 3332, artl@chw.edu.au
Dr Michael Leahy	Haematology Department, Fremantle Hospital, PO Box 480, Fremantle, WA, 6959	Ph: 08 9431 2886, Fax: 08 9431 2881, tabili.leahy@health.wa.gov.au
A/Prof John Lloyd	Division of Haematology, IMVS, PO Box 14, Rundle Mall, Adelaide, SA, 5000	Ph: 08 8222 5410, Fax: 8222 5963, john.lloyd@imvs.sa.gov.au
Dr Liane Lockwood	Haemophilia Centre, Royal Children's Hospital, Herston Road, Herston, QLD, 4029	Ph: 07 3636 9030, Fax: 07 3636 1552, Liane_Lockwood@health.qld.gov.au
Dr Michael Pidcock	Department of Haematology, The Canberra Hospital, Yamba Drive, Garran, ACT, 2606	Ph: 02 6244 2929/2894, Fax: 02 6244 2892, michael.pidcock@act.gov.au
Dr Jamie Price	Haematology Department, Princess Margaret Hospital, GPO Box D184, West Perth, WA, 6005	Ph: 08 9340 8231, Fax: 08 9340 8384, james.price@health.wa.gov.au
Dr Scott Dunkley	Haemophilia Treatment Centre, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW, 2050	Ph: 02 9515 7013, Fax: 02 9515 8946 fiona.rennison@email.cs.nsw.gov.au stephen.matthews@email.cs.nsw.gov.au
Dr John Rowell	Haematology Department, Royal Brisbane Hospital, Herston Road, Herston, QLD, 4029	Ph: 07 3636 8067, Fax: 07 3252 1342, john_rowell@health.qld.gov.au
Dr Susan Russell	Centre for Children's Cancer & Blood Disorders, Sydney Children's Hospital, High Street, Randwick, NSW, 2031	Ph: 02 9382 1690, Fax: 02 9382 1789, Susan.Russell@unsw.edu.au
Dr Ben Saxon	Department of Haematology, Women's and Children's Hospital, 71 King William Road, North Adelaide, SA, 5006	Ph: 08 8161 7327, Fax: 08 8161 6567, saxonb@wch.sa.gov.au
Dr Michael Seldon	Haematology Department, Newcatle Mater Misericordiae Hospital, Locked Bag 7, Hunter Region Mail Centre, NSW, 2310	Ph: 02 4921 1216, Fax: 02 4960 2136, mseldon@mater.health.nsw.gov.au
Dr Sid Selva	Darwin Private Hospital, PO Box 42571, Casuarina, NT, 0810	Ph: 08 8920 6176, Fax: 08 8920 6183, S.Selva@physicians-nt.com
Prof Alison Street	Department of Haematology, The Alfred Hospital, Commercial Road, Prahran, VIC, 3181	Ph: 03 9276 3120, Fax: 03 9276 3781, a.street@alfred.org.au

Appendix D Currently available product information

Haemophilia A (without inhibitors)

Shaded boxes represent evidence-based information from either current systematic review or from evidence cited in previous consensus-based guidelines (Australian Haemophilia Centre Directors' Organisation 2004), unshaded boxes represent data from product information sheets, current as at January 2005.

Table 51. A matrix of treatment recommendations for patients with haemophilia A (without inhibitors to FVIII)

Indication	Product	Mild	Moderate	Severe	Precautions
Acute bleeding	DDAVP	*Mild to moderate haemophilia:* 0.3 µg/kg in 50 ml 0.9% saline infused intravenously or subcutaneously over ≥ 30 minutes One dose in 24 hours (≤3 consecutive days). Restrict fluid intake			Test dose for efficacy Use with caution in the elderly Contraindicated in patients with arteriovascular disease and in children < 2 years
	rFVIII	*Minor haemorrhage:* Require peak post-infusion FVIII activity in the blood: 20–40 IU/dL Infuse every 12 to 24 hours for 1–3 days until bleeding has stopped, pain resolved or healing achieved	*Moderate haemorrhage:* Require peak post-infusion FVIII activity in the blood: 30–60 IU/dL Infuse every 12 to 24 hours for 3 days or more until pain and disability resolved	*Severe haemorrhage:* Require peak post-infusion FVIII activity in the blood: 60–100 IU/dL Repeat infusions every 8–24 hours until resolved	Appropriate laboratory tests should be performed to ensure appropriate levels of FVIII in patient plasma are achieved and maintained If FVIII levels fail to reach expected levels or bleeding continues, the presence of inhibitors should be suspected Inhibitor testing may be performed within 20 exposure days after initial dose
	pdFVIII	*Minor haemorrhage:* Require peak post-infusion FVIII activity in the blood: 20–30 IU/dL Dose: 10–15 IU/kg Infused 1–2 times a day, for 1–2 days	*Moderate-severe haemorrhage:* Require peak post-infusion FVIII activity in the blood: 30–80 IU/dL Dose: 15–40 IU/kg Infused 1–3 times a day, for 1–2 days or 7–10 days for intracranial haemorrhage		When factor concentrates are used, recombinant factors are preferred rather than plasma-derived, due to their higher safety profile regarding transmission of blood-borne agents (cont.)

Table 51 (cont.)	Tranexamic acid	*Standard dose:* 2–3 tablets of 0.5 g taken 2–3 times daily *Epistaxis* 1.5 g orally 3 times daily for 4–10 days Solution may be applied topically to the nasal mucosa by soaking gauze strip in solution and packing nasal cavity	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates
Prophylaxis	rFVIII	Recommended dose range for FVIII prophylaxis is 25–40 IU/kg, 3 times per week or more frequently as required	Prophylaxis in patients with severe haemophilia should only be started after bleeding episodes have commenced, due to possible increased risk of inhibitor development with administration in very young children
Infant delivery	Genetic counselling	Should be accessible to all carriers of haemophilia, including potential risks of antenatal testing and potential complications during pregnancy and delivery for both the foetus and mother	
	Antenatal care	Antenatal testing options depend on stage of pregnancy Chorionic villus sampling is the preferred method Factor replacement may be required for invasive procedures	*Mother* Although haemostatic support is rarely necessary, there is a slight risk of bleeding in first trimester and 3–5 days after delivery. Therefore, FVIII:C levels should be monitored
	Delivery of infants	Vaginal delivery should be considered for all infants with or suspected of haemophilia unless obstetric factors indicate caesarean section	Instrument delivery should be avoided (forceps and vacuum extraction), as should fetal scalp electrodes Early recourse to caesarean is recommended when there is a failure of labour to progress
		Cord blood samples or peripheral blood samples may be taken from male infants of haemophilia carriers	*Infant* Heel sticks and venipuncture should be avoided Vitamin K injections should be avoided in affected male infants; oral vitamin K may be used as an alternative

(cont.)

Table 51 (cont.) Surgery	rFVIII	*Minor surgery:* Require peak post-infusion FVIII activity in the blood: 60–80 IU/dL Single infusion plus oral antifibrinolytic therapy for 1 hour, repeat if required	*Major surgery:* Require post-infusion FVIII activity in the blood (pre- and post-operative): 80–100 IU/dL Repeat infusions every 8–24 hours according to the rate of healing	Appropriate laboratory tests should be performed to ensure appropriate levels of FVIII in patient plasma is achieved and maintained If FVIII levels fail to reach expected levels or bleeding continues, the presence of inhibitors should be suspected
	pdFVIII	*Minor surgery:* Loading: Require peak post-infusion FVIII activity in the blood: 50–60 IU/dL Dose: 20–30 IU/kg Maintenance: Require peak post-infusion FVIII activity in the blood: 20–50 IU/dL Dose: 15–30 IU/kg	*Major surgery* Loading: Require peak post-infusion FVIII activity in the blood: 80–100 IU/dL Dose: 40–50 IU/kg Maintenance: Require peak post-infusion FVIII activity in the blood: 20–100 IU/dL Dose: 10–40 IU/kg	When factor concentrates are used, recombinant factors are preferred rather than plasma-derived, due to their higher safety profile regarding transmission of blood-borne agents
	Tranexamic acid	Intravenous dose: 10 mg/kg 2–3 times per day (intravenous preparation available in Australia through Special Access Scheme) Oral dose: 25 mg/kg 2–3 times per day Total doses: 80–100 mg/kg/day given orally Paediatric dose 35 mg/kg/8hours		*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates

(cont.)

Table 51 (cont.)	Fibrin glue	Fibrin sealant should only be used topically Dose depends on size to be treated 4 cm^2= 0.5 mL 8 cm^2= 1.0 mL 16 cm^2= 2.0 mL 40 cm^2= 5.0 mL	Fibrin glue is derived from human plasma, which may contain infectious agents such as viruses Risk has been minimised through donor screening and inactivating known viruses, but there is still a potential risk of unknown infectious agents Contraindicated in patients hypersensitive to bovine proteins
Dental	Tranexamic acid	10 mg/kg given intravenously (available through SAS in Australia) prior to dental surgery 25 mg/kg given orally 3–4 times per day for 6–8 days	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates

DDAVP = desmopressin; FEIBA = Factor eight inhibitor bypassing agent; SAS= Special Access Scheme

Haemophilia A (with inhibitors)

Shaded boxes represent evidence-based information from either current systematic review or from evidence cited in previous consensus-based guidelines (Australian Haemophilia Centre Directors' Organisation 2004), unshaded boxes represent data from product information sheets, current as at January 2005.

Table 52. A matrix of treatment recommendations for patients with haemophilia A (with inhibitors to FVIII)

	Product	Mild-Moderate	Severe	Precautions
Acute bleeding	rFVIIa Higher doses required for young children	Early intervention doses of 90 µg/kg have been found effective in treating mild–moderate joint, muscle and mucocutaneous bleeds 1–3 doses repeated at 3 hourly intervals to achieve haemostasis, and 1 additional dose to maintain haemostasis *Mild bleed in low-titre, high-responder or high titre* 90 µg/kg every 2 hours for a minimum 2 doses, followed by further dose If response is not observed, treatment with aPCCs should be considered	*Major bleed in low-titre, high responder* 90 µg/kg every 2 hours for 12 hours or until clinical response is observed Dose interval may be increased to 3–4 hours If response is not observed, treatment with aPCCs should be considered *High titre* 90 µg/kg every 2 hours for 12 hours, increase to every 3 hours depending on clinical response Dose interval may be extended to every 4 hours Therapy may be continued to 14 days Alternative schedule is 320 µg/kg every 6 hours	
	rFVIII	*Mild bleed in low-titre, low-responder* 50–100 IU/kg repeated every 8–12 hours	*Major bleed in a low-titre, low-responder* 50–150 IU/kg repeated every 8–12 hours Levels maintained and monitored at >50% until healing completed	
	aPCCs FEIBA	*Joint haemorrhage* 50–100 IU/kg 2 times per day until clear signs of clinical improvement, reduction of swelling or mobilisation of joint *Mucous membrane bleeding* 50–100 IU/kg at 6 hourly intervals, not exceeding 200 IU/kg/day *Soft tissue haemorrhage* 100 IU/kg at 12 hourly intervals, not exceeding 200 IU/kg/day *Other severe haemorrhages* 100 IU/kg at 12 hourly intervals		Monitor for side effects which, while rare, are serious Patients should be monitored for thrombotic complications
		Mild bleed in low-titre, high-responder or high titre 60–80 units/kg FEIBA as a single dose	*Major bleed in a low-titre, high-responder or high titre* 60–100 units/kg FEIBA two times per day (maximum 200 units/kg/day)	

(cont.)

Table 52 (cont.)	Plasmapheresis		Monitor for possible anaphylactic reactions
	Immuno-suppression	Cyclophosphamide immunosuppressants not recommended (future guidelines may include other new immunosuppressants (e.g. Rituximab), but currently not enough evidence is available)	
	Tranexamic acid	*Standard dose:* 2–3 tablets of 0.5 g taken 2–3 times daily *Epistaxis* 1.5 g orally 3 times daily for 4–10 days Solution may be applied topically to the nasal mucosa by soaking gauze strip in solution and packing nasal cavity	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates
Surgery/ Dental	rFVIIa	An initial dose of 90 µg/kg immediately prior to surgery Repeat dose after 2 hours, then 2–3 hour intervals for 24–48 hours In major surgery dosage should continue every 2–4 hours for 6–7 days, dosage interval may then increase to every 6–8 hours for another 2 weeks *Major bleed in low-titre, high responder* 90 µg/kg every 2 hours for 12 hours or until clinical response is observed Dose interval may be increased to 3–4 hours If response is not observed, treatment with aPCCs should be considered *High titre* 90 µg/kg every 2 hours for 12 hours, increase to every 3 hours depending on clinical response Dose interval may be extended to every 4 hours Therapy may be continued to 14 days Alternative schedule is 320 µg/kg every 6 hours	(cont.)

Table 52 (cont.)	rFVIII	*Surgery in a low-titre, low-responder* 50–150 IU/kg repeated every 8–12 hours Monitor and maintain levels at >50% until healing completed	FVIII may be used for patients with low- titre, low-responding inhibitors but should be avoided in high-responding inhibitors
	FEIBA	*Surgery in a low-titre, high-responder or high titre* 60–100 units/kg FEIBA two times per day (maximum 200 units/kg/day)	Monitor for side effects; rare, but potentially serious Patients should be monitored for thrombotic complications
	Tranexamic acid	10 mg/kg given intravenously (available through SAS in Australia) prior to dental surgery 25 mg/kg given orally 3–4 times per day for 6–8 days after dental surgery Intravenous dose: 10 mg/kg 2–3 times per day (available through SAS in Australia) Oral dose: 25 mg/kg 2–3 times per day Paediatric dose 35 mg/kg/8hours	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates
	Fibrin glue	Fibrin sealant should only be used topically Dose depends on size to be treated 4 cm^2= 0.5 mL 8 cm^2= 1.0 mL 16 cm^2= 2.0 mL 40 cm^2= 5.0 mL	Fibrin glue is derived from human plasma, which may contain infectious agents such as viruses Risk has been minimised through donor screening and inactivating known viruses, but there is still a potential risk of unknown infectious agents Contraindicated in patients hypersensitive to bovine proteins
Tolerisation	rFVIII	Patients eligible for an international randomised controlled trial comparing high and low dose protocols should participate Doses range from 25 IU/kg 2–3 times per week to 100 IU/kg/day Tolerisation should continue until FVIII recovery > 60%, and normal FVIII half life	

aPCCs = activated prothrombin complex concentrates; FEIBA = Factor eight inhibitor bypassing agent; SAS= Special Access Scheme

Haemophilia B (without inhibitors)

Shaded boxes represent evidence-based information from either current systematic review or from evidence cited in previous consensus-based guidelines (Australian Haemophilia Centre Directors' Organisation 2004), unshaded boxes represent data from product information sheets, current as at January 2005.

Table 53. A matrix of treatment recommendations for patients with haemophilia B (without inhibitors to FIX)

	Product	Mild	Moderate	Severe	Precautions
Acute bleeding	rFIX	*Uncomplicated haemarthroses, superficial muscular or soft tissue:* Circulating FIX activity required: 20–30 IU/dL Infuse every 12–24 hours for 1–2 days	*Intramuscle or soft tissue with dissection, mucous membranes, dental extractions, haematuria:* Circulating FIX activity required: 25–50 IU/dL Infuse every 12–24 hours for 2–7 days or until bleeding stops and healing begins	*Pharynx, retropharynx, retroperitoneum:* Circulating FIX activity required: 50-100 IU/dL Infuse every 12–24 hours for 7–10 days	Patients transferred from pdFIX may need higher dose of rFIX: Ratio of pdFIX:rFIX: ≤15 years = 1:1.6 >15 years = 1:1.2 An assay should be used to monitor factor levels
	pdFIX	Desired plasma concentration of factor IX: 20–30 IU/dL Dose: 20–30 IU/kg Infuse 1 time per day for 1–2 days	Desired plasma concentration of factor IX: 30–50 IU/dL Dose: 30–50 IU/kg Infuse 1–2 times per day for 1-5 days		When factor concentrates are used, recombinant factors are preferred rather than plasma-derived, due to their higher safety profile regarding transmission of blood-borne agents
	Tranexamic acid	*Standard dose:* 2–3 tablets of 0.5 g taken 2–3 times daily *Epistaxis* 1.5 g orally 3 times daily for 4–10 days Solution may be applied topically to the nasal mucosa by soaking gauze strip in solution and packing nasal cavity			*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates

(cont.)

Table 53 (cont.) Prophylaxis	rFIX	64–96 IU/kg three times per week for patients ≤15 years, more frequently if required 48–72 IU/kg three times per week for patients >15 years, more frequently if required	Prophylaxis should only be started after bleeding episodes have commenced, due to current debate that there is an increased risk of inhibitor development with administration in very young children
Infant delivery	Genetic counselling	Should be accessible to all carriers of haemophilia, including potential risks of antenatal testing and potential complications during pregnancy and delivery for both the foetus and mother	
	Antenatal care	Antenatal testing options depend on stage of pregnancy Chorionic villus sampling is the preferred method Factor replacement may be required for invasive procedures	
		Women with low FIX may require rFIX to control haemorrhage FIX:C should be measured soon after pregnancy is confirmed and monitored in third trimester and postpartum	
	Delivery of infants	Vaginal delivery should be considered for all infants with or suspected of haemophilia unless obstetric factors indicate caesarean section	*Mother* Instrument delivery should be avoided (forceps and vacuum extraction) as should fetal scalp electrodes Early recourse to caesarean is recommended when there is a failure of labour to progress
		Cord blood samples or peripheral blood samples may be taken from male infants of haemophilia carriers	*Infant* Heel sticks and venipuncture should be avoided Vitamin K injections should be avoided in affected male infants; oral vitamin K may be used as an alternative
Surgery/ Dental	rFIX	Circulating FIX activity required: 50–100 IU/dL Infuse every 12–24 hours for 7–10 days	When factor concentrates are used, recombinant factors are preferred rather than plasma-derived, due to their higher safety profile regarding transmission of blood-borne agents
	pdFIX		
	Tranexamic acid	10 mg/kg given intravenously (available through SAS in Australia) prior to dental surgery 25 mg/kg given orally 3–4 times per day for 6–8 days after dental surgery Intravenous dose: 10 mg/kg 2–3 times per day (available through SAS in Australia) Oral dose: 25 mg/kg 2–3 times per day Paediatric dose: 35 mg/kg/8hours	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates (cont.)

Table 53 (cont.)	Fibrin glue	Fibrin sealant should only be used topically Dose depends on size to be treated 4 cm^2= 0.5 mL 8 cm^2= 1.0 mL 16 cm^2= 2.0 mL 40 cm^2= 5.0 mL	Fibrin glue is derived from human plasma, which may contain infectious agents such as viruses Risk has been minimised through donor screening and inactivating known viruses, but there is still a potential risk of unknown infectious agents Contraindicated in patients hypersensitive to bovine proteins

FEIBA = Factor eight inhibitor bypassing agent; SAS= Special Access Scheme

Haemophilia B (with inhibitors)

Shaded boxes represent evidence-based information from either current systematic review or from evidence cited in previous consensus-based guidelines (Australian Haemophilia Centre Directors' Organisation 2004), unshaded boxes represent data from product information sheets, current as at January 2005.

Table 54. A matrix of treatment recommendations for patients with haemophilia B (with inhibitors to FIX)

	Product	Mild-moderate	Severe	Precautions
Acute bleeding	rFVIIa	Early intervention doses of 90 µg/kg have been found effective in treating mild–moderate joint, muscle and mucocutaneous bleeds 1–3 doses repeated at 3 hourly intervals achieve haemostasis, and 1 additional dose maintains haemostasis	Initial dose of 90 µg/kg, dosing every 2 hours until clinical improvement observed If further treatment is needed, dosing interval may be extended to every 3 hours for 1–2 days, and increased to every 4, 6, 8, or 12 hours as judged appropriate	
	aPCCs			Patients should be closely monitored for adverse events, which though rare, may be serious
	Tranexamic acid	*Standard dose:* 2–3 tablets of 0.5 g taken 2–3 times daily *Epistaxis* 1.5 g orally 3 times daily for 4–10 days Solution may be applied topically to the nasal mucosa by soaking gauze strip in solution and package nasal cavity		*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates (cont.)

Table 54 (cont.)			
Tolerisation	rFIX	There is no information available on tolerisation protocols for haemophilia B patients	
Surgery/Dental	rFVIIa	An initial dose of 90 µg/kg immediately prior to surgery Repeat dose after 2 hours, then at 2–3 hourly intervals for 24–48 hours In major surgery dosage should continue every 2–4 hours for 6–7 days, then increase dosage interval to every 6–8 hours for another 2 weeks	
	Fibrin glue	Fibrin sealant should only be used topically Dose depends on size to be treated 4 cm^2= 0.5 mL 8 cm^2= 1.0 mL 16 cm^2= 2.0 mL 40 cm^2= 5.0 mL	Fibrin glue is derived from human plasma, which may contain infectious agents such as viruses Risk has been minimised through donor screening and inactivating known viruses, but there is still a potential risk of unknown infectious agents Contraindicated in patients hypersensitive to bovine proteins
	Tranexamic acid	10 mg/kg given intravenously (available through SAS in Australia) prior to dental surgery 25 mg/kg given orally 3–4 times per day for 6–8 days after dental surgery Intravenous dose: 10 mg/kg 2–3 times per day (available through SAS in Australia) Oral dose: 25 mg/kg 2–3 times per day Paediatric dose: 35 mg/kg/8hours	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history) should be closely monitored Should not be used with FEIBA or other prothrombin complex concentrates

aPCCs = activated prothrombin complex concentrates; FEIBA = Factor eight inhibitor bypassing agent; SAS= Special Access Scheme

von Willebrand disease

Shaded boxes represent evidence-based information from either current systematic review or from evidence cited in previous consensus-based guidelines (Australian Haemophilia Centre Directors' Organisation 2004), unshaded boxes represent data from product information sheets, current as at January 2005.

Table 55. A matrix of treatment recommendations for patients with von Willebrand disease

Indication	Product	Recommendations	Precautions
Acute bleeding	DDAVP	0.3 µg/kg in 50ml 0.9% saline infused intravenously or subcutaneously over ≥ 30 minutes One dose in 24 hours (≤3 consecutive days). Restrict fluid intake	Test dose for efficacy Use with caution in the elderly Contraindicated in patients with arteriovascular disease and in children < 2 years
	pdFVIII/vWF concentrate	Patients unresponsive to (or contraindicated for) DDAVP should receive pdFVIII/vWF concentrate	
	Tranexamic acid	2–3 tablets 0.5 g, 2–3 times a day, taken with water	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored
Menorrhagia	Tranexamic acid	Start treatment when bleeding is first noticed Take 2–3 tablets 4 times a day for 4 days Swallow with water If menstrual bleeding is not reduced by tranexamic acid, alternative therapy should be considered	If menstrual bleeding is irregular, the cause of irregularity should be established prior to use of tranexamic acid *Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored

(cont.)

Table 55 (cont.)	DDAVP	0.3 µg/kg in 50 ml 0.9% saline infused intravenously or subcutaneously over ≥ 30 minutes One dose in 24 hours (≤3 consecutive days). Restrict fluid intake	Test dose for efficacy Use with caution in the elderly Contraindicated in patients with arteriovascular disease and in children < 2 years
	Oestrogens		
Infant delivery	DDAVP	Women with Type 1 vWD may require DDAVP in the first 3–4 days after delivery	Instrument delivery should be avoided (forceps and vacuum extraction) as should fetal scalp electrodes Early recourse to caesarean is recommended when there is a failure of labour to progress Heel sticks and venipuncture should be avoided Vitamin K injections should be avoided in affected infants; oral vitamin K may be used as an alternative
	Genetic counselling	Should be accessible to all women with vWD, including potential risks of antenatal testing and potential complications during pregnancy and delivery for both the foetus and mother	
	Antenatal care	Antenatal testing options depend on stage of pregnancy Chorionic villus sampling is the preferred method Factor concentrates may be required for invasive procedures	
Surgery/Dental	DDAVP	0.3 µg/kg in 50 ml 0.9% saline infused intravenously or subcutaneously over ≥ 30 minutes One dose in 24 hours (≤3 consecutive days). Restrict fluid intake	Test dose for efficacy Use with caution in the elderly Contraindicated in patients with arteriovascular disease and in children < 2 years
	pdFVIII/vWF concentrate		
	Tranexamic acid	To be used in conjunction with DDAVP or FVIII/vWF 10 mg/kg given intravenously (available through SAS in Australia) prior to dental surgery 25 mg/kg given orally 3-4 times per day for 6–8 days after dental surgery Intravenous dose: 10 mg/kg 2–3 times per day (available through SAS in Australia) Oral dose: 25 mg/kg 2–3 times per day Paediatric dose: 35 mg/kg/8hours	*Contraindications:* Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis Subarachnoid haemorrhage Hypersensitivity to tranexamic acid or any of the ingredients *Precautions:* Patients with a high risk of thrombosis (family history or previous thrombotic event) should be closely monitored
	Fibrin glue	To be used in conjunction with DDAVP or pdFVIII/vWF Fibrin sealant should only be used topically Dose depends on size to be treated 4 cm^2= 0.5 mL 8 cm^2= 1.0 mL 16 cm^2= 2.0 mL 40 cm^2= 5.0 mL	Fibrin glue is derived from human plasma, which may contain infectious agents such as viruses Risk has been minimised through donor screening and inactivating known viruses, but there is still a potential risk of unknown infectious agents Contraindicated in patients hypersensitive to bovine proteins

DDAVP = desmopressin; FEIBA = Factor eight inhibitor bypassing agent; pdFVIII/vWF concentrate = plasma-derived factor concentrate enriched with von Willebrand factor; SAS= Special Access Scheme

Appendix E Methodology

Inclusion criteria

Studies were included for each area of the guidelines (e.g. management of the disease, delivery of infants), if they addressed the population, therapy, comparator, outcomes, study design, search period and language delineated in Box 1.

Box 1. Study selection criteria

Selection criteria	Inclusion criteria
Population	*Management of the diseases*
	All patients with clinically diagnosed haemophilia A, haemophilia B, von Willebrand disease, or other rare bleeding disorders.
	Treatment of bleeding episodes/Prophylaxis and treatment/Adjunctive haemostatic agents
	All patients with clinically diagnosed haemophilia A, haemophilia B, von Willebrand disease, or other rare bleeding disorders (including those undergoing surgery or dental care).
	Delivery of infants
	Pregnant women who are carriers of haemophilia A or haemophilia B or with von Willebrand Disease. Infants with haemophilia A, B or von Willebrand Disease.
	Tolerisation procedures
	Patients with haemophilia A or B with inhibitors to factor VIII or IX.
Therapy	*Management of the diseases*
	Haemophilia A or B: Management of patients using recombinant factor VIII or IX.
	Von Willebrand disease: Management of patients using plasma-derived factor VIII.
	Treatment of bleeding episodes
	Haemophilia A or B: On-demand treatment of patients with recombinant factor VIII or IX.
	Von Willebrand disease: On-demand treatment of patients using plasma-derived factor VIII with von Willebrand factor.
	Prophylaxis and treatment of the diseases
	Haemophilia A or B: Prophylaxis and treatment of patients using recombinant factor VIII or IX (including before, during and after surgery, dental care and other situations where there is a risk of bleeding).
	Von Willebrand disease: Prophylaxis and treatment of patients using plasma-derived factor VIII (including before, during and after surgery, dental care and other situations where there is a risk of bleeding).
	Adjunctive haemostatic agents
	Treatment of patients with adjunctive haemostatic agents, such as antifibrinolytic agents (e.g. aminocaproic acid, tranexamic acid), desmopressin, and topical applications (e.g. thrombin and fibrin sealant).
	Delivery of infants
	Haemophilia A or B: Prophylactic or on-demand treatment with recombinant factor VIII or IX ante-, peri- and postnatally.
	Von Willebrand disease: Prophylactic or on-demand treatment with plasma-derived factor VIII ante-, peri- and postnatally.
	Tolerisation procedures
	Treatment with regular administration of recombinant factor VIII or IX. (cont.)

(cont.)	
Comparator	*Haemophilia A or B*: 'Usual' or standard care of patients using appropriate plasma-derived factors[a].
	Von Willebrand disease: Standard care of patients using desmopressin (mild) or concentrated von Willebrand factor (severe)
Outcomes[b]	*Primary*: mortality (survival), morbidity (including transmission of viral infections, thrombosis, myocardial infarction), number and severity of bleeding episodes (including clotting activity, recovery/response to factor), level of factor, development/level of inhibitors
	Secondary: Quality of life, hospitalisation, length of treatment (including number of infusions required, number of exposure days), dose required for haemostasis control
Study design	*Effectiveness:* Systematic reviews, randomised controlled trials, non-randomised controlled trials, cohort studies, before-and-after controlled studies, case-control studies. When high quality evidence was not available, large case series of consecutive patients, analysed on an intention-to-treat basis, were included.
	Safety: Systematic reviews, randomised controlled trials, non-randomised controlled trials, cohort studies, before-and-after controlled studies, case-control studies, case-series
Search Period	1966 to September 2004
Language	Studies in languages other than English were translated and included if they represented a higher level of evidence than that available in the English literature evidence-base.
Limitations	Human

[a] All children <18 years old and adults who have not been infected with a virus have been using recombinant factors only. From 1 October 2004, all haemophilia patients were given access to recombinant products (Department of Health and Ageing 2004); [b] Objective outcome measures are preferred to subjective outcome measures

Search strategies

The electronic sources listed in Table 56 were searched for potentially relevant literature. Other sources of literature (Table 57) were also searched.

Table 56. Bibliographic databases

Electronic database	Time period
AustHealth	1997 to September 2004
Cinahl	1977 to September 2004
Cochrane Library—including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1966 to September 2004
Current Contents	1993 to September 2004
Embase.com (includes Medline and Embase)	1966 to September 2004
Pre-Medline	1966 to September 2004
ProceedingsFirst	1993 to September 2004
PsycInfo	1983 to September 2004
Web of Science—Science Citation Index Expanded	1995 to September 2004

Table 57. Other sources of evidence (1966 to September 2004)

Electronic database	Time period
Australian Department of Health and Ageing	http://www.health.gov.au/
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment International	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
NHMRC— National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
National Library of Medicine Health Services / Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
Trip database	http://www.tripdatabase.com
UK National Research Register	http://www.update-software.com/national/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
Websites of Haemophilia/Haematology Associations	See Appendix F
Other medical and health websites	See Appendix F
Hand searching (Journals from 2003–2004)	
Blood reviews	Library or electronic access
Journal of thrombosis and haemostasis	Library or electronic access
Thrombosis and haemostasis	Library or electronic access
Clinical and laboratory haematology	Library or electronic access
Haematology	Library or electronic access
Blood	Library or electronic access
Haemophilia	Library or electronic access
Annals of haematology	Library or electronic access
British journal of haematology	Library or electronic access
Transfusion	Library or electronic access
Vox sanguinis	Library or electronic access
Expert clinicians	
Any information provided by expert clinicians associated with this review was assessed as to whether it met the inclusion criteria.	Clinical consultants
Pearling	
All included articles had their reference lists searched for additional relevant source material.	

The search terms used—including text words and indexing (e.g. Emtree) headings—when searching the electronic databases (Table 56) are given in Table 58.

Table 58. Search terms utilised

Area of inquiry	Search terms
All searches	EMTREE Hemophilia A; Hemophilia B; von Willebrand disease; blood clotting factor 8; blood clotting factor 9 Text words H*emophilia*; factor VIII; factor IX; factor 8; factor 9; von Willebrand disease; von Willebrands disease; von Willebrand syndrome; von Willebrands syndrome
Management	EMTREE Disease management; patient care; therapy Text words Disease management
Adjunctive haemostatic agents	EMTREE Aminocaproic acid; tranexamic acid; antifibrinolytic agent Text words Aminocaproic acid; tranexamic acid; thrombin; fibrin; desmopressin; antifibrinolytic agent
Inhibitor development	EMTREE Blood clotting inhibitor; activated prothrombin complex Text words Inhibitor*; tabiliz*; toleri?ation; toleri?ed; tolerance induction; immune tolerance; FEIBA
Treatment of bleeding episodes	EMTREE Dental care; surgery; prophylaxis; bleeding Text words Dental; surgery; surgical; prophyla*; bleeding
Infant delivery	EMTREE Labor; obstetric care; delivery Text words Labo*r; obstetric; delivery
Infectious diseases and other safety issues	EMTREE Hepatitis; acquired immune deficiency syndrome; life expectancy; complication; infection; side effect; risk assessment; safety; bleeding; human immunodeficiency virus infection; adverse drug reaction; mortality; morbidity Text words Safety; mortality; morbidity; AIDS; HIV; human immunodeficiency virus; haemorrhage; hepatitis; bleeding; complication*; adverse event*

The process for selecting studies for this review and clinical guidelines document is shown in Figure 2.

Figure 2. Study selection process

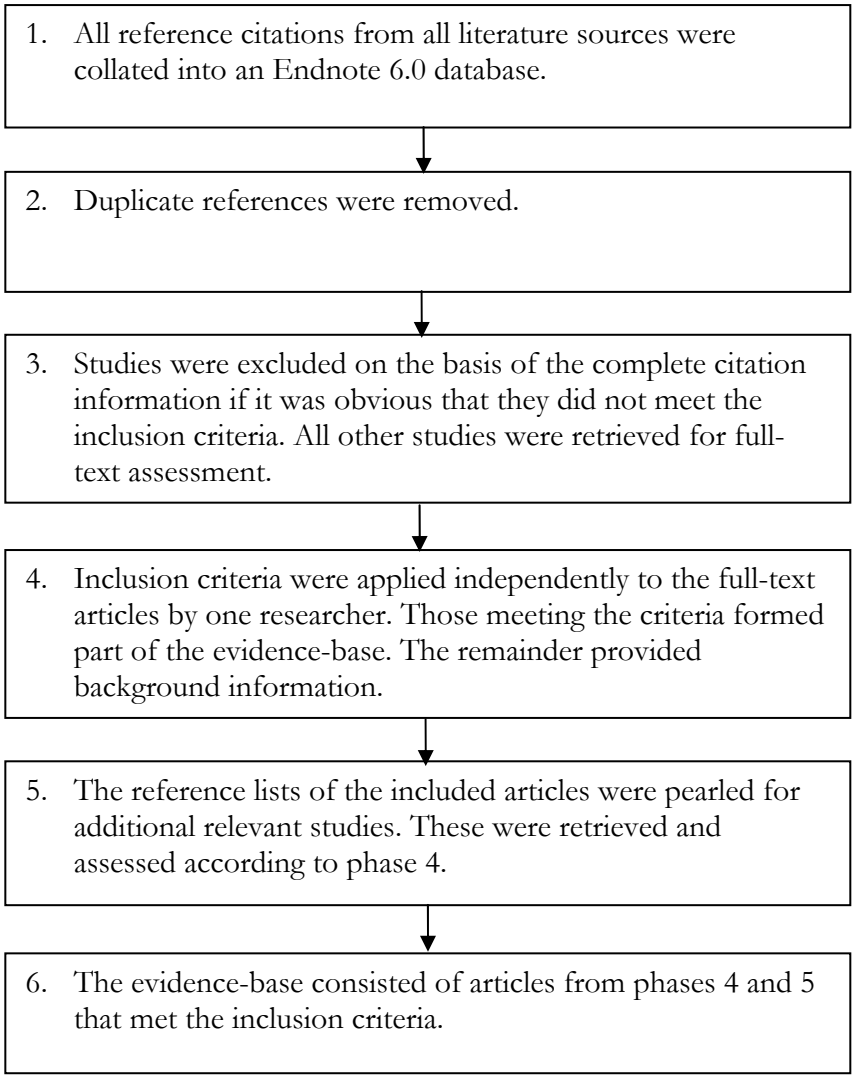

Table 59 provides a breakdown of the study selection process in terms of the number of literature citations or articles retrieved and retained from each phase of the process. Any doubt concerning inclusions at Phase 4 was resolved by group consensus.

Table 59. Number of citations initially retrieved and then retained at each phase

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6 (Total Included)
29 945	12 087	1220	439	14	96

Database searches generated 29,945 citations published between 1966 and September 2004. After duplicates were removed, 12,087 citations were screened initially by two reviewers who excluded articles that were clearly not relevant to this report. Articles excluded immediately by title and abstract included narrative reviews, letters, comments and opinions, editorials and individual case reports.

Four hundred and thirty-nine full-text articles were retrieved and provided data for this review. Of these, 82 were included to assess effectiveness and safety issues. A further 14 studies were included after the reference lists of the included articles were pearled. The total evidence base comprised 96 original studies and systematic reviews.

Appendix F Specialty Websites

Haemophilia websites

- Abstracts from Haemophilia—*the Journal of WFH*
  http://www.blackwell-synergy.com
- American Society of Hematology
  http://www.hematology.org/
- Association of Hemophilia Clinic Directors of Canada
  www.ahcdc.ca/
- Australasian Society of Thrombosis and Haemostasis
  http://www.asth.org.au/
- Australia and New Zealand Society of Blood Transfusion
  http://www.anzsbt.org.au/
- Australian Bleeding Disorders Registry
  http://www.ahcdo.org.au/abdr
- Australian Haemophilia Centre Directors' Organisation
  http://www.ahcdo.org.au/
- British Society of Haematology
  http://www.b-s-h.org.uk/
- Haematology Society of Australia and New Zealand
  http://www.hsanz.org.au/
- Haemophilia Directors for Scotland and Northern Ireland
  www.rcpe.ac.uk/esd/clinical_standards/hdsni/hdsni_index.html
- Haemophilia Foundation ACT (HFACT)
  http://www.hfact.org.au
- Haemophilia Foundation Australia
  http://www.haemophilia.org.au
- Haemophilia Foundation Queensland (HFQ)
  http://www.hfq.org.au
- Haemophilia Foundation Victoria (HFV)
  http://www.haemophiliavic.org.au
- Haemophilia Society (UK)
  http://www.haemophilia.org.uk

- Hemophilia Galaxy
  http://www.hemophiliagalaxy.com

- Hemophilia Village
  http://www.hemophilia-village.net

- National Hemophilia Foundation (US)
  http://www.hemophilia.org

- New Zealand Haemophilia Foundation
  http://www.haemophilia.org.nz

- Oxford Haemophilia Centre
  http://www.medicine.ox.ac.uk

- Shemophilia (US)
  http://www.shemophilia.org

- South African Haemophilia Foundation
  http://www.haemophilia.org.za

- The British Committee for Standards in Haematology
  http://www.bcshguidelines.com/

- The Canadian Hemophilia Society
  http://www.hemophilia.ca

- The Haemophilia Alliance (UK)
  http://www.haemophiliaalliance.org.uk

- The International Society of Haemostasis and Thrombosis
  http://www.med.unc.edu/isth/welcome

- United Kingdom Haemophilia Centre Directors Organisation
  www.medicine.ox.ac.uk/ohc/ukhcdo.htm

- World Federation of Hemophilia
  http://www.wfh.org

Other relevant medical and health websites

- Australian Red Cross Blood Service
  http://www.donateblood.com.au

- Medicines Australia
  http://www.medicinesaustralia.com.au/

- National Blood Authority
  http://www.nba.gov.au

- Novo Seven
  http://www.novoseven.com

- World Health Organization
  http://www.who.int/en/

Appendix G Consensus Clinical Practice Guidelines

Previous Australian clinical guidelines on treatment and prophylaxis

6.1. General recommendations (Haemophilia Foundation Australia Medical Advisory Panel 2000)

6.1.1. Patient information and consent. Good practice dictates that the necessity for treatment is appropriately explained to the patient and/or parent. This should include the advantages and risks of different therapies to allow an informed decision to be made. When consent has been obtained this should be recorded in the case notes.

6.1.2. Vaccination against hepatitis A and B. All patients who are not immune to hepatitis A or B and who currently receive, or may require, blood products should be vaccinated. At present revaccination with hepatitis A vaccine is not recommended and the vaccine is not currently licensed for use in children under the age of one year. Immunity to hepatitis B requires periodic reassessment and revaccination when appropriate.

6.1.3. Risk reduction. The use of fractionated, virucidally treated, concentrates when available has been the treatment of choice in achieving haemostasis in congenital coagulation factor deficiency since these products carry a lower risk of transmitting serious viral infection than cryoprecipitate or FFP[cc] (Grade B recommendation based on Level III evidence). It is acknowledged that despite new viral inactivation techniques it is possible that coagulation factor concentrates still transmit virus infection. For this reason recombinant factor VIII is now preferred to treatment with plasma-derived concentrates.

6.1.4. Use of DDAVP (desamino-8-D-arginine vasopressin, desmopressin). DDAVP should be considered for all patients with mild/moderate haemophilia A or mild vWD, as this avoids the risk of viral transmission and is less expensive (Grade B recommendation based on Level IIa evidence). DDAVP is generally administered intravenously at a dose of 0.3 mcg/kg diluted in 50 mL of 0.9% saline and infused over at least 30 minutes. An unlicensed intranasal spray preparation of DDAVP (Octim Nasal Spray, Ferring) is available[dd] at a dose of 300 mcg for adults and 150 mcg for children. An unlicensed* concentrated subcutaneous preparation (Octim injection, Ferring) is also available and should be given at the usual dose of 0.3 mcg/kg. Efficacy should be demonstrated irrespective of the route employed, by measuring FVIII/vWF. Intranasal DDAVP has been shown to be comparable to the effect of an intravenous dose of 0.2

[cc] FFP—fresh frozen plasma

[dd] Nasal spray is not routinely available for use (personal communication, Dr John Rowell)

*not registered under the Therapeutic Goods Act

mcg/kg DDAVP. DDAVP should be used with caution in elderly individuals, pregnant women and avoided in those with evidence of arteriovascular disease. Precautions to prevent fluid overload leading to hyponatraemia must be taken particularly in young children and DDAVP is probably best avoided in those younger than two years of age.

6.1.5. Tranexamic acid. Tranexamic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin and is available in an intravenous or oral preparation (both in suspension and tablet form). The intravenous preparation is not currently licensed* in Australia. Tranexamic acid is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP (Grade A recommendation based on Level Ia evidence). The recommended intravenous dose is 10 mg/kg 2–3 times daily and the oral dose 25 mg/kg 2–3 times daily (Grade B recommendation based on Level IIa evidence). Tranexamic acid is contra-indicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with FEIBA[ee] or other prothrombin complex concentrates (Grade C recommendation based on Level IV evidence). Tranexamic acid can be used in combination with NovoSeven[ff].

6.1.6 Aminocaproic acid[gg]. Aminocaproic acid is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin and is available as an intravenous preparation. It is particularly useful for bleeding from the gastrointestinal tract, menorrhagia, open wounds, dental surgery and in conjunction with DDAVP (Grade A recommendation based on Level Ia evidence). The recommended intravenous dose is 1 g hourly by continuous infusion. Aminocaproic acid is contraindicated in patients with thromboembolic disease and should be avoided in patients with haematuria. It should not be used with FEIBA or other prothrombin complex concentrates (Grade C recommendation based on Level IV evidence). Aminocaproic acid can be used in combination with rFVIIa.

6.2. Specific recommendations

Licensed* coagulation factor concentrates should be used in preference to unlicensed* products. Each patient should be considered individually taking into account the following recommendations.

6.2.1. Haemophilia A—factor VIII deficiency. For patients for whom coagulation factor concentrate is the treatment of choice the following therapeutic strategies are recommended. Recombinant factor VIII is the treatment of choice for all patients. As

---

[ee] Factor Eight Inhibitor Bypassing Agent

[ff] Recombinant human coagulation factor VIIa (rFVIIa)

[gg] Aminocaproic acid may become unavailable as the company, AMICAR, has ceased production (personal communication, Dr Ben Saxon, Red Cross Blood Service)

* Registered under the Therapeutic Goods Act

† These recommendations have changed according to the 2004 government announcement to fund access to recombinant clotting factors for all haemophilia patients. Access to recombinant factors is no longer prioritised according to patient group.

the introduction of recombinant factor VIII has to be prioritised then those who may benefit most should receive it first†.

6.2.2. von Willebrand disease. DDAVP should be used for DDAVP-responsive vWD patients in preference to plasma-derived products. Where DDAVP is not likely to be effective, or is contraindicated, FVIII concentrate or purified von Willebrand factor is the treatment of choice. Cryoprecipitate is not virally inactivated and carries a risk of virus transmission. It is, however, recognised that there are some circumstances in which its use may be justified (Grade B recommendation based on Level IIb evidence).

6.2.3. Haemophilia B—factor IX deficiency. Patients with factor IX deficiency should be treated with high-purity FIX concentrates because they cause less haemostatic activation than PCCs[hh] (Grade A recommendation based on Level Ib evidence)†.

6.2.4. Factor XI deficiency. The majority of patients with FXI:C levels < 15 u/dL will suffer excessive bleeding following trauma or surgery and should be managed with infusions of factor XI concentrate. In those with partial deficiency of factor XI (15–70 u/dL) bleeding is more difficult to predict. Where there is a clear history of abnormal bleeding and haemostatic support is required, the use of FXI concentrate is justified. The dose of FXI should be sufficient to raise the level of factor XI: C to 70 u/dL and the level should not exceed 100 u/dL because of the risk of thrombosis (maximum dose 30 u/kg) (Grade C recommendation based on Level IV evidence). Where there is no history of bleeding, tranexamic acid may be used alone, but in the event of subsequent excessive bleeding must be replaced by FXI concentrate. Patients should be assessed for preexisting risk of thrombosis and the concentrate should be used with great caution in those with a history of cardiovascular disease (Grade C recommendation based on Level IV evidence). FFP might be a suitable alternative when FXI concentrate is contraindicated.

6.2.5. Factor VII deficiency. A purified, heat-treated FVII concentrate is available. This should replace PCCs and FFP as the treatment of choice in situations in which haemostatic support is necessary. The dose of FVII required depends on the severity of the deficiency and on clinical circumstances. The level of FVII required for haemostasis may be as low as 10–20 u/dL and this can be achieved by administering 5–10 i.u. FVII/kg (Grade C recommendation based on Level IV evidence). Recombinant factor VIIa can also be used in factor VII deficiency.

6.2.6. Factor II or X deficiency. There is currently no specific factor II or X concentrate available and PCCs remain the treatment of choice (Grade C recommendation based on Level IV evidence).

6.2.7. Factor V deficiency. There are no specific concentrates available for use in FV deficiency and therefore FFP is the only available treatment (Grade C recommendation based on Level IV evidence).

[hh] Prothrombin complex concentrates

† These recommendations have changed according to the 2004 government announcement to fund access to recombinant clotting factors for all haemophilia patients. Access to recombinant factors is no longer prioritised according to patient group.

6.2.8. Factor XIII deficiency. FXIII concentrate prepared from human plasma is now available and is the treatment of choice (Grade C recommendation based on Level IV evidence).

6.2.9. Fibrinogen deficiency. Unlicensed* concentrates of fibrinogen have recently become available and since these products are virally inactivated it is anticipated that they may replace cryoprecipitate in the near future (Grade C recommendation based on Level IV evidence).

6.2.10. Future treatment of hereditary coagulation disorders. Recombinant factor VIII and IX will be used widely because of continuing concerns about the safety of plasma-derived concentrates. It is anticipated that recombinant factor VIII, which is formulated without addition of human albumin as a stabiliser, will become licensed. Furthermore it is known that recombinant factor VIII being manufactured without using any bovine or human proteins will eventually replace current products. Recombinant factor IX[ii] is currently licensed in the USA. It should be introduced for routine haemophilia B care using criteria similar to those for recombinant factor VIII.

Clinical guidelines on prophylactic treatment using factors VIII and IX

(Revised by the Clinical Advisory Sub Committee—Haemophilia, September 2000) (AHMAC 2003)

1. The goal of prophylaxis is to improve quality of life for patients with severe–moderate haemophilia A and B by maintaining sufficient factor VIII and IX levels to prevent spontaneous joint bleeding and the morbidity associated with complications of joint bleeds.

2. Factor VIII and factor IX prophylaxis is recommended for all children with severe haemophilia A and B up the age of 18 years. If the supplies of factors VIII and IX permit, consideration should be given to extending prophylaxis treatment to severe haemophilia A and B patients older than 18 years.

3. For the purposes of these guidelines, children have severe haemophilia when they have major spontaneous bleeds into joints and their factor VIII and IX levels are less than 5%.

4. The recommended dosage range for factor VIII prophylaxis is 25–40 IU per kilo, three times a week or more frequently as required. The recommended dosage for factor IX prophylaxis is 40–60 IU per kilo, twice a week or more frequently as required. The amount of factors VIII and IX used for prophylaxis will vary from

[ii] Recombinant factor IX has been registered for use in Australia since 2000 and funding to supply commenced in 2001 (personal communication, Sharon Caris, Haemophilia Foundation Australia)

* not registered under the Therapeutic Goods Act

patient to patient but for each patient will be the minimum amount of factor VIII or IX required to prevent spontaneous joint bleeding. Please note that the guidelines for factor IX dosage are based on plasma concentrates[ii].

5. The age at which prophylaxis therapy is introduced will vary from one to two years to around five years depending on the number and severity of bleeds and whether the patient and his family are willing to comply with the prophylactic treatment regime.

6. The recommended priority groups* for receiving recombinant factor VIII and factor IX for treatment/prophylaxis, are in the following order of priority:

    a. Previously untreated patients (PUPs)

    b. Patients who have been previously treated with plasma-derived factor VIII and factor IX but who have no evidence of hepatitis B, hepatitis C or HIV infection

7. The recommended priority groups* for receiving recombinant factors VIII and IX for treatment/prophylaxis (as supplies become available) in addition to the above groups are, in order of priority:

    a. virally infected children (up to 18 years); and

    b. virally infected adults

Guidelines for the treatment of inhibitors in haemophilia A

Developed by AHCDO (Australian Haemophilia Centre Directors' Organisation 2004).

General comments

The diagnosis of an inhibitor, irrespective of titre, requires active monitoring and treatment to determine whether the inhibitor progresses to a high titre inhibitor or is transient. The diagnosis of an inhibitor should be conducted using Bethesda criteria. After initial diagnosis of a low titre inhibitor in a patient with haemophilia A, routine doses of factor VIII may be as much as doubled and the clinical response and inhibitor titre monitored. Subsequent poor clinical response or rising titre levels indicate a non-transient inhibitor. The diagnosis of a high titre inhibitor, which does not respond to factor VIII, should be treated with an alternative product.

[ii] The dosage for prophylaxis with recombinant factors are: factor VIII—1:1 (plasma-derived:recombinant) factor IX—1:1.25 (plasma-derived:recombinant)

* Access to recombinant factors is no longer prioritised according to patient group.

There is an incidence of inhibitors in those with mild haemophilia A following treatment with factor VIII concentrates and the guidelines will also apply to those patients. DDAVP is occasionally used in mild to moderate haemophilia but is often ineffective.

Minor bleeds include muscle and joint haemarthrosis but are not trauma related. Major bleeds include trauma related muscle or joint injury, severe spontaneous muscle bleeds e.g. psoas or iliacus, and haemorrhages affecting an organ.

Surgery, which affects inhibitor patients, includes dental procedures, insertion of intravenous access devices and emergency and major elective procedures. Both dental surgery and insertion of intravenous access devices require shorter durations of replacement therapy.

Products available

3.1.1. Factor VIII: In the case of life threatening haemorrhage, infusion of factor VIII in large doses can be used to swamp the inhibitor. This therapy is mostly used in patients with low responding inhibitors (inhibitor titre is <5 BU/mL after infusion of factor VIII). In patients who are high responders, this treatment may be effective provided the inhibitor level is less than 5 BU/mL. Factor VIII levels should be observed to assess and monitor response. Anamnesis can occur 5–7 days after therapy and make factor VIII ineffective. Recombinant and plasma-derived factor VIII are available.

3.1.2. Recombinant Factor VII: This product has been widely used in Australia and has proved to be highly effective in the management of spontaneous bleeding episodes, which are life or limb threatening. Evidence in the literature suggests that it is effective in 79–92% of such episodes. In addition, there is evidence that it is effective in over 90% of cases of surgery. Recombinant factor VIIa is infused as a bolus. Continuous infusion of recombinant factor VIIa may reduce the quantity and cost of treatment but evidence is conflicting. A recent study suggests continuous infusion of 50 μg/kg/hr is effective in surgery. Antifibrinolytics are administered concurrently. The standard adult dose of recombinant factor VIIa is 90 μg/kg. However, in children the mean half-life is substantially reduced to 1.32 hours and thus higher doses of up to 200–250 μg/kg may be required. Present indications for funding of recombinant factor VIIa by the National Blood Authority (NBA) are for limb and life threatening haemorrhages. There is widespread evidence that recombinant factor VIIa is effective for treatment of all haemorrhage in patients with high responding factor VIII inhibitors. The appropriate treatment for all haemorrhages should be extended to all children and adults regardless of their state of residency.

3.1.3. Activated Prothrombin Complex Concentrates (APCCs) eg FEIBA VH: Activated prothrombin complex concentrate, such as FEIBA VH, is effective in the treatment of 90% of bleeding episodes, and has been effective in the management of bleeding during major surgery. An effective dose is 60–100 units/kg twice per day. The maximum daily dose of FEIBA is 200 units/kg/day. Antifibrinolytic agents, such as tranexamic acid, should not be administered concurrently with FEIBA. It should be noted that FEIBA contains small amounts of factor VIII and therefore may cause elevation of inhibitor titres in some patients. The 1997 Working Party Report did not recommend the use of these agents as first choice because they are plasma-derived rather than recombinant products, there is a reported high incidence of thrombosis associated with their use, and it is not possible to measure their activity in a standardised way.

Nevertheless, AHCDO recommends that these products remain an option for treatment for complex cases in which alternative methods have proved ineffective. In patients who are having frequent bleeds, a trial of FEIBA as prophylaxis should be considered. The suggested dose is 75–100 units/kg three times a week.

3.1.4. Prothrombinex-HT: Despite general scepticism about the effectiveness of prothrombinex-HT in the management of joint haemorrhage, some patients report benefit and continue to be treated with this product. There are concerns about the incidence of thrombosis when using repeated high doses, particularly in the presence of liver disease and when used in combination with antifibrinolytics. There is no evidence of efficacy in serious haemorrhages in surgery. AHCDO recommends that recombinant factor VIIa is used in future for these patients.

3.1.5. Antifibrinolytic therapy: The recommended dose of tranexamic acid is 80–100 mg/kg/day, with a standard dose being 1 g qid given orally (recommended paediatric dose is 35 mg/kg/8hr). An intravenous preparation is available in Australia through the SAS. Intravenous epsilon aminocaproic acid (EACA) is no longer produced and not available.

3.1.6. Plasmapheresis/Immunoadsorption: Plasmapheresis can be used to reduce inhibitor titres to allow effective therapy with factor VIII. Specific immunoadsorption using the Malmö protocol is not available in Australia. There is as yet little information on the use of immunosuppression in patients with factor VIII inhibitors but some experimental protocols are being proposed. Immunosuppression has been associated with side effects including delayed wound healing and increased susceptibility to infection. Rituximab (anti CD 20 monoclonal antibody) therapy may be considered as an adjunct therapy to reduce inhibitor titres.

Treatment regimens

3.2.1. Low titre inhibitor (<5 BU/ml), low responder

Minor bleeding: The recommended dose of factor VIII is 50–100 IU/kg repeated every 8–12 hours. The response should be assessed clinically and factor VIII levels monitored.
Major bleeding: The recommended dose of factor VIII is 50–150 IU/kg repeated every 8–12 hours. The response should be assessed clinically and factor VIII levels monitored and maintained at > 50% until healing has completed.

3.2.2. Low titre inhibitor (<5 BU/ml) but history of high responder

Minor bleeding: Infusions of factor VIII will cause an anamnestic rise of the levels of factor VIII inhibitor within 3–5 days rendering further therapy with factor VIII ineffective. The recommended adult dose of recombinant factor VIIa is 90 μg/kg (recommended paediatric dose may be up to 200–250 μg/kg) at 2 hourly intervals for a minimum of 2 doses or until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

Major bleeding: The recommended adult dose of recombinant factor VIIa is 90 μg/kg (recommended paediatric dose may be up to 200–250 μg/kg) at 2 hourly intervals for 12 hours or until an objective clinical response is observed. Dose intervals can be increased

to 3 or 4 hours. The duration of therapy depends on the extent of the initial haemorrhage. If no response is observed, treatment with APCC should be considered.

3.2.3. High titre inhibitor (>5 BU/ml)

Minor bleeding: The recommended adult dose of recombinant factor VIIa is 90 μg/kg (recommended paediatric dose may be up to 200–250 μg/kg) at 2 hourly intervals for a minimum of 2 doses or until an objective clinical response is observed. This should be followed up with a further single dose. If no response is observed treatment with APCC should be considered.

Major bleeding: The recommended adult dose of recombinant factor VIIa is 90 μg/kg (recommended paediatric dose may be up to 200–250 μg/kg) at 2 hourly intervals for 12 hours; then increased to 3 hourly intervals depending on the observed clinical response. If appropriate, the dose interval can be further increased to 4 hours as a maintenance dosage. The duration of therapy is dependent on the severity of the haemorrhage. If major surgery has been performed, the duration of therapy may extend to 14 days. An alternative dosing scheme is 320 μg/kg every 6 hours. If no response is observed, treatment with APCC should be considered.

3.2.4. Elective Major Surgery

Major surgery in patients with inhibitors carries a high degree of risk and should only be carried out in recognised HTCs after careful consultation and agreement with at least one other Australian haemophilia specialist. All such discussions should be documented. It is recommended that a pharmacokinetic study be undertaken before surgery. The dosage regimen is based on the regimen for major bleeds (Sections 3.2.1, 3.2.2 and 3.2.3 above).

Dental surgery and the insertion of IV access devices require 3–5 days of therapy and antifibrinolytics.

3.2.5. Emergency Major Surgery

The dosage regimen is based on the regimen for major bleeds (Sections 3.2.1, 3.2.2 and 3.2.3 above). If time allows, there should be consultation and agreement with one other haemophilia specialist as in Elective Major Surgery. Any such discussion should be documented. The patient should be transferred to a recognised HTC as soon as practicable.

3.2.6. Home Therapy

AHCDO recommends that home therapy only be considered with close monitoring and regular medical supervision.

Tolerisation

Tolerisation should be considered in all those patients with recent persisting inhibitors. Written informed consent should be obtained before starting. Intensive replacement therapy for immune tolerance usually requires central venous access.

Haemophilia A

The International Registry on Tolerisation identifies better results in those patients with lower age at the start of Immune Tolerance Induction (ITI); shorter elapsed time of inhibitor presence before ITI; lower maximum pre-treatment inhibitor titres and treatment with higher doses of FVIII.

AHCDO strongly recommends participation in an international randomised trial of high dose versus low dose factor VIII tolerisation protocols. All patients considered eligible for the trial should be involved

For patients who do not enter an international trial, there are a number of published tolerisation protocols that describe a variety of doses of factor VIII (e.g 50 IU/kg three times a week up to 200 IU/kg daily) as well as the use of immune suppression. Tolerisation should continue until eradication of the inhibitor demonstrated by a greater than 60% recovery and normal half-life of factor VIII. Tolerisation should only be attempted in consultation with a physician experienced in the management of patients with haemophilia and inhibitors.

Acquired Haemophilia A

Immunosuppression is recommended for eradication of inhibitors in acquired haemophilia A.

It is recommended that adults with severe haemophilia A who have had an inhibitor for many years, and in some instances decades, should be managed with treatment of haemorrhage by infusion of recombinant factor VIIa. Adult patients with mild or moderate haemophilia A who develop inhibitors often have mild inhibitors, which may decline with time. These patients should be treated with desmopressin (DDAVP) for minor bleeds and recombinant factor VIIa for more serious haemorrhages. Tolerisation may be considered if haemorrhages cannot be controlled by recombinant factor VIIa.

Protocols for dental procedures in patients with haemophilia A, B or von Willebrand disease *

	Local anaesthetic infiltration	Local anaesthetic inferior alveolar nerve block	Supragingival scale only	Subgingival scale or a restorative procedure requiring a matrix band	Minor soft tissue abscess/ swelling
Haemophilia A					
Mild (>5 IU/dl)	No pre-treatment required	No pre-treatment required	No pre-treatment required	A pre-treatment dose of 1 g, oral tranexamic acid capsules followed by 1 g qid for 24 h post-treatment	FVIII at 10 IU/kg pre-treatment
Moderate (5–2 IU/dl)	No pre-treatment required	FVIII at 10 IU/kg pre-treatment	No pre-treatment required	FVIII at 7 IU/kg and a pre-treatment dose of 1 g, oral tranexamic acid capsules followed by 1 g qid for 3 days post-treatment	FVIII at 10 IU/kg pre-treatment
Severe (<2 IU/dl)	No pre-treatment required	FVIII at 10 IU/kg pre-treatment	A pre-treatment dose of 1g only, oral tranexamic acid capsules	FVIII at 7 IU/kg and a pre-treatment dose of 1g, oral tranexamic acid capsules followed by 1 g qid for 3 days post-treatment	FVIII at 10 IU/kg pre-treatment
Haemophilia B					
Mild	No pre-treatment required	No pre-treatment required	No pre-treatment required	A pre-treatment dose of 1g oral tranexamic acid capsules followed by a dose of 1 g quid for 24 hours post-treatment	Prothrombinex-HT at 20 IU/kg pre-treatment
Moderate	No pre-treatment required	Prothrombinex-HT at 20 IU/kg pre-treatment	No pre-treatment required	Prothrombinex-HT at 14 IU/kg pre-treatment and a pre-treatment dose of 1g oral tranexamic acid capsules followed by a dose of 1g qid for 3 days post-treatment	Prothrombinex-HT at 20 IU/kg pre-treatment
Severe	No pre-treatment required	Prothrombinex-HT at 20 IU/kg pre-treatment	A pre-treatment dose of 1g only oral tranexamic acid capsules	Prothrombinex-HT at 14 IU/kg pre-treatment and a pre-treatment dose of 1g oral tranexamic acid capsules followed by a dose of 1g qid for 3 days post-treatment	Prothrombinex-HT at 20 IU/kg pre-treatment
Von Willebrand disease (Type 1)					
Mild§ (>30 IU/dl)	No pre-treatment required	No pre-treatment required	No pre-treatment required	A pre-treatment dose of 1 g oral tranexamic acid capsules followed by a dose of 1 g qid for 24 hours post-treatment	Desmopressin pre-treatment
Moderate§ (10–30 IU/dl)	No pre-treatment required	No pre-treatment required	No pre-treatment required	A pre-treatment dose of 1 g oral tranexamic acid capsules followed by a dose of 1g qid for 24 hours post-treatment	FVIII at 10 IU/kg or desmopressin pre-treatment
Severe§ (<10 IU/dl)	No pre-treatment required	FVIII at 10 IU/kg pre-treatment	A pre-treatment dose of 1g only tranexamic acid capsules	FVIII at 7 IU/kg and a pre-treatment dose of 1g oral tranexamic acid capsules followed by a dose of 1g qid for 3 days post-treatment	FVIII at 10 IU/kg pre-treatment

*modified from Stubbs and Lloyd 2001; § arbitrary distinctions in disease severity devised by authors; qid = once per day; bd = twice per day; tds = three times per day

Appendix H Critical Appraisal Checklists

Systematic review critical appraisal checklist

Source: Khan et al. 2001

Title of assessment:
Title of systematic review:
Author(s):
Year:
Comparators:
Score : **/6**

1. **What is the review's objective?**

   What were the population/participants, interventions, outcomes and study designs?

2. **What sources were searched to identify primary studies?**

   What sources (e.g. databases) were searched and were any restrictions by date, language and type of publication used? Were other strategies used to identify research?

3. **What were the inclusion criteria and how were they applied?**

4. **What criteria were used to assess the quality of primary studies and how were they applied?**

5. **How were the data extracted from the primary studies?**

6. **How were the data synthesised?**

   How were differences between studies investigated?

   How were the data combined? Was it reasonable to combine the studies?

   What were the summary results of the review?

   Do the conclusions flow from the evidence reviewed?

Checklist for appraising the quality of intervention studies

THE UNIVERSITY OF ADELAIDE AUSTRALIA

STUDY QUALITY ASSESSMENT CHECKLIST

Suitable for trials, cohorts and case-control studies assessing interventions

(Downs and Black (1998)–adapted for this NBA assessment)

Clinical practice guidelines for factor VIII and factor IX

Author(s):
Institution(s):
Year:
Study Design:
Comparators:

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

Yes	
no	

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
   If the main outcomes are first mentioned in the Results section, the question should be answered 'no'.

yes	1
no	0

3. *Are the characteristics of the patients included in the study clearly described?*
   In cohort studies and trials, inclusion and/or exclusion criteria should be given.

Yes	1
no	0

4. *Are the interventions of interest clearly described?*
   Interventions that are to be compared should be clearly described.

Yes	1
no	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
   Possible confounders = age, gender, severity of the disease, inhibitors, HIV, HAV, HBV, HCV, previous exposure to factors

yes	2
partially	1
no	0

6. *Are the main findings of the study clearly described?*
   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions (This question does not cover statistical tests which are considered below).

Yes	1
no	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
   In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

Yes	1
no	0

8. *Have all important adverse events that may be a consequence of the intervention been reported?*

This should be answered 'yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events.
Adverse events = infections, infectious diseases, development of inhibitors, thrombosis, myocardial infarction.

Yes	1
no	0

9. *Have the characteristics of patients lost to follow-up been described?*
This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.

Yes	1
no	0

10. *Have the actual probability values been reported (eg 0.035 rather than <0.05) for the main outcomes, except where the probability value is less than 0.001?*

yes	1
no	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as 'unable to determine'.

Yes	1
no	0
unable to determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1
no	0
unable to determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
For the question to be answered 'yes' the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered 'no' if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1
no	0
unable to determine	0

Internal validity – Bias

14. *Was an attempt made to blind study subjects to the intervention they have received?*
For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'.

Yes	1
no	0
unable to determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

Yes	1
no	0
unable to determine	0

16. *If any of the results of the study were based on 'data dredging', was this made clear?*
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes'.

Yes	1
no	0
unable to determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?*
Where follow-up was the same for all study patients the answer should be 'yes'. If different

lengths of follow-up were adjusted for by, for example, survival analysis the answer should be 'yes'. Studies where differences in follow-up are ignored should be answered 'no'.

yes	1
no	0
unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
    The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes'. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

Yes	1
no	0
unable to determine	0

19. *Was compliance with the intervention/s reliable?*
    Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered 'no'. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered 'yes'.

Yes	1
no	0
unable to determine	0

20. *Were the main outcome measures used accurate (valid and reliable)?*
    For studies where the outcome measures are clearly described, the question should be answered 'yes'. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes'.

Yes	1
no	0
unable to determine	0

Internal validity – Confounding (selection bias)

21. *Were the patients in different intervention groups (trials and cohort studies) recruited from the same population?*
    For example, patients for all comparison groups should be selected from the same hospital. The question should be answered 'unable to determine' where there is no information concerning the source of patients included in the study.

Yes	1
no	0
unable to determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) recruited over the same period of time?*
    For a study which does not specify the time period over which the patients were recruited, the question should be answered as 'unable to determine'.

Yes	1
no	0
unable to determine	0

23. *Were study subjects randomised to intervention groups?*
    Studies which state that subjects were randomised should be answered 'yes' except where method of randomisation is unknown or would not ensure random allocation. For example, alternate allocation would score 'no' because it is predictable.

Yes	1
no	0
unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
    All non-randomised studies should be answered 'no'. If assignment was concealed from patients but not from staff, it should be answered 'no'.

yes	1
no	0
unable to determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
    This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention-to-treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the

treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as 'no'.

yes	1
no	0
unable to determine	0

26. *Were losses of patients to follow-up taken into account?*
    If the number of patients lost to follow-up are not reported, the question should be answered as 'unable to determine'. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes'.

Yes	1
no	0
unable to determine	0

Subscale Scores

Reporting = /11
External validity = /3
Bias = /7
Confounding = /6

Total Quality Index Score = /27

Power

27. *Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?*

    a. Was there enough power to detect a difference of ..%, in the outcome '….'?

    Sample sizes – n_1 = n_2 =
    power =

Checklist for the critical appraisal of case series

Source: Young et al. 1999, *Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema.* A West Midlands Development and Evaluation Committee Report, University of Birmingham, pp. 51–53.

Title of review:
Title of study:
Author(s):
Year:
Comparators:
Score: **/3**

1. **Was the study conducted prospectively?**
   Were the key outcomes measured before and after the intervention, using clear criteria defined *a priori*?

2. **Was the method of selection of cases identified and appropriate?**
   Were patients selected consecutively or in an unbiased manner?

   Was there evidence that the characteristics of the included cases were not significantly different from those of the treated population?

3. **Was the duration and completeness of follow-up reported and was it adequate?**
   Are the number and characteristics of losses to follow-up presented? #

   Are losses to follow-up managed by performing sensitivity analysis and/or including them in the final analysis?

Losses to follow-up >20% are unacceptable, particularly if unaccounted for.

Checklist for assessing the clinical importance of benefit or harm

Rank scoring for appraising the clinical importance of benefit / harm

Source: NHMRC 2000b

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Clinically important effect:

Rank Score : /4

Ranking	Clinical importance of benefit/harm
1	A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention.
2	The point estimate of effect is clinically important but the confidence interval includes clinically unimportant effects.
3	The confidence interval does not include any clinically important effects.
4	The range of estimates defined by the confidence interval includes clinically important effects but the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect.

Checklist for assessing the relevance of outcomes

Rank scoring for classifying the relevance of evidence

Source: NHMRC 2000b

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Rank Score : **/5**

Ranking	Relevance of the evidence
1	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival.
2	Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

Appendix I Evidence Tables

Summary tables for intervention studies

(NHMRC Guidelines Assessment Register Consultants Working Party 2004)

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Arkin et al 1991)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] rFVIII Clinical Trial Group, partially funded by Cutter Biological, Miles Inc.</td></tr>
<tr><td colspan="2">Study design [3] historical control study</td><td colspan="2">Level of evidence [4] III-3</td><td colspan="2">Location/setting [5] Home care setting, worldwide centres</td></tr>
<tr><td colspan="3">Intervention [6] rFVIII prophylaxis therapy
(20-40 IU/kg, 3 x week)
Sample size [7]14 (Stage I)</td><td colspan="3">Comparator(s) [8] pdFVIII (Koate HS) treatment

Sample size [9] Not stated</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – moderate-severe haemophilia A patients aged 4-72 without inhibitors, PTPs
Comparator group(s) – no info provided on historical control group</td></tr>
<tr><td colspan="3">Length of follow-up [11] Not reported</td><td colspan="3">Outcome(s) measured [12] In vivo recovery FVIII, adverse events</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Historical control</td><td>Comparison of study groups [14] Unable to ascertain</td><td>Blinding [15] No</td><td>Treatment/ measurement bias [16] Possible</td><td colspan="2">Follow-up (ITT) [17] Unable to ascertain</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Quality score: 5/27
Selection bias likely
Confounding likely
Follow-up uncertain
External validity unclear</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Incremental FVIII recovery</td><td>Intervention group [20]
2.7±0.6</td><td>Control group [21]
2.5±0.33</td><td colspan="2">Measure of effect/effect size [22]
8.0% difference in recovery
p=0.29
95% CI [25]</td><td>Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="3"></td><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27] 2</td></tr>
<tr><td colspan="6">Any other adverse effects [28] ‘uncommon and mild’- erythema, cold hands/feet, burning at infusion site, dry mouth. More severe= dizziness, hypotension, rash, shortness of breath. Frequency of adverse reactions= 1%</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] Unclear</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS				
Reference [1] (Cattaneo et al 1989)				
Affiliation/source of funds [2] National Institute of Health grant				
Study design [3] Randomised controlled crossover trial	Level of evidence [4] II	Location/setting [5] 1 treatment centre, Milan, Italy		
Intervention [6] Cryoprecipitate + DDAVP (0.3µg/kg) Sample size [7] 10	Comparator(s) [8] Cryoprecipitate + saline Sample size [9] 10			
Patient characteristics [10] 10 PTPs with severe vWD, (type not specified) with prolonged bleeding time (>30 minutes) with need for cryoprecipitate for joint or muscle haemorrhage				
Length of follow-up [11] Crossover at day 15, follow-up not stated	Outcome(s) measured [12] BT, vWF:Ag, vWF:RiCof			
INTERNAL VALIDITY				
Allocation [13] random (method not specified)	Comparison of study groups [14] same patients – crossover	Blinding [15] Double- both patient and operator	Treatment/ measurement bias [16] same patients – crossover	Follow-up (ITT) [17] ITT used complete
Overall quality assessment (descriptive) [18] Unable to assess external validity Bias minimised Confounding avoided				
RESULTS				
Outcome [19] No significant difference between cryo and saline, but significant between cryo and DDAVP.	Intervention group [20] BT After cryo=12±2 minutes BT After DDAVP=9±2 minutes	Control group [21] BT after cryo= 15±3 minutes BT after saline= 15±3	Measure of effect/effect size [22] P<0.01 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1/4 Clinically important difference in BT		Relevance (1-5) [27] 1/5	
Any other adverse effects [28] Not reported				
EXTERNAL VALIDITY				
Generalisability [29] Only severe patients (type not specified)				
Applicability [30]				
Comments [31]				

STUDY DETAILS				
Reference [1] (De Sio et al 1985)				
Affiliation/source of funds [2] Not stated				
Study design [3] non randomised controlled trial	Level of evidence [4] III-2	Location/setting [5] 1 treatment centre, Rome, Italy		
Intervention [6] Intravenous DDAVP (0.3µg/kg) Sample size [7] 18 8 people received both	Comparator(s) [8] Subcutaneous DDAVP (0.3µg/kg) Sample size [9] 16			
Patient characteristics [10] 26 patients, 21 mild haemophilia A, 5 moderate haemophilia A Intervention group –13 mild haemophilia A, 5 moderate haemophilia A Comparator group(s) –13 mild haemophilia A, 3 moderate haemophilia A				
Length of follow-up [11] 2 hours	Outcome(s) measured [12] FVIII:C ratio post/pre			
INTERNAL VALIDITY				
Allocation [13] Not stated	Comparison of study groups [14] Not stated	Blinding [15] No	Treatment/ measurement bias [16] Unclear	Follow-up (ITT) [17] Adequate
Overall quality assessment (descriptive) [18] Bias possible Confounding possible				
RESULTS				
Outcome [19] No statistically significant differences between treatments in FVIII:C activity at 60 minutes post DDAVP	Intervention group [20] I hour post FVIII:C Mean=24.9 SD=12.4	Control group [21] I hour post FVIII:C Mean=25.4 SD=12.4	Measure of effect/effect size [22] t=.288, p>0.5 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 3/4			Relevance (1-5) [27] None
Any other adverse effects [28] Moderate increase of pulse rate and/or blood pressure, frequently associated with mild facial flushing.				
EXTERNAL VALIDITY				
Generalisability [29] Unable to assess external validity				
Applicability [30]				
Comments [31]				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Ewenstein et al 2002)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Mononine Comparison Study Group. (Funded in part by MonoFIX (Aventis Behring, King of Prussia, PA)</td></tr>
<tr><td colspan="2">Study design [3] Randomised crossover study</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5]
15 haemophilia centres in United States</td></tr>
<tr><td colspan="3">Intervention [6] Single bolus infusion (50 IU/kg) – non bleeding
rFIX- 7 day washout

Sample size [7] 38 (crossover design)</td><td colspan="3">Comparator(s) [8] Single bolus infusion (50 IU/kg) – non bleeding
pdFIX- 7 day washout

Sample size [9] 38 (crossover design)</td></tr>
<tr><td colspan="6">Patient characteristics [10] Clinically diagnosed with moderate-severe haemophilia B, aged > 5 years, prior treatment with FIX. No patients had inhibitors, acquired haemophilia, abnormal prothrombin time

Intervention group and Comparator group – median age 18.5 (range 7-75)
FIX:C <1%= 14
FIX:C 1-5%=21
FIX:C >5%=3</td></tr>
<tr><td colspan="3">Length of follow-up [11] 48 hours</td><td colspan="3">Outcome(s) measured [12] recovery of pd/rFIX -> plasma level FIX:C (IU/dL)</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
randomisation protocol not stated</td><td>Comparison of study groups [14] same participants</td><td>Blinding [15]
double-blind</td><td>Treatment/ measurement bias [16] none</td><td colspan="2">Follow-up (ITT) [17]
Done</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias minimised; confounding avoided; patients representative; follow-up adequate</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
recovery FIX (IU d/L rise per IU/kg infused)</td><td>Intervention group [20]
0.86±0.31 IU/dL/kg</td><td>Control group [21]
1.71±0.73 IU/dL/kg</td><td>Measure of effect/effect size [22]
0.85 IU/dL/IU/Kg

95% CI [25] [0.66-1.04]
p<0.0001</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="3"></td><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 1/4</td><td colspan="2">Relevance (1-5) [27] 2/5</td></tr>
<tr><td colspan="6">Any other adverse effects [28] Not reported</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] PTPs in non-bleeding state</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Fijnvandraat et al 1997; Berntorp 1997)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]Pharmacia AB</td></tr>
<tr><td colspan="2">Study design [3] Randomised single-blinded crossover trial</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] Multicentre, Sweden and the Netherlands</td></tr>
<tr><td colspan="3">Intervention [6] rFVIII SQ
(50 IU/kg)

Sample size [7] 12</td><td colspan="3">Comparator(s) [8] pdFVIII
(50 IU/kg, Octonativ)

Sample size [9] 12</td></tr>
<tr><td colspan="6">Patient characteristics [10] 12 PTPs with severe haemophilia A, aged 17-64 years, without inhibitors

Intervention group – as above
Comparator group(s) –as above</td></tr>
<tr><td colspan="3">Length of follow-up [11] 50 hours</td><td colspan="3">Outcome(s) measured [12] Incremental FVIII recovery (IU/kg^{-1}) % change</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
randomised</td><td>Comparison of study groups [14] same patients</td><td>Blinding [15]
single blinded (patient)</td><td>Treatment/ measurement bias [16] possible</td><td colspan="2">Follow-up (ITT) [17]
complete</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias minimised; confounding avoided; follow-up adequate; patients representative</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Incremental FVIII recovery (IU/kg^{-1})</td><td>Intervention group [20]
2.4±0.21</td><td>Control group [21]
2.4±0.26</td><td>Measure of effect/effect size [22] percentage change=0

95% CI [25]</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]

Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] None reported</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29]</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS		
Reference [1] (Giles et al 1998)		
Affiliation/source of funds [2] Association of Hemophilia Centre Directors of Canada (AHCDC)- partial funding/products provided by Bayer Corp- not clear		
Study design [3] non randomised controlled trail	Level of evidence [4] III-2	Location/setting [5] Haemophilia Centres in Canada
Intervention [6] PTPs transferred to rFVIII Sample size [7] 814	Comparator(s) [8] PTPs transferred to affinity-purified FVIII Sample size [9] 58	
Patient characteristics [10] Intervention group – haemophilia A participants switched to rFVIII Comparator group(s) –haemophilia A participants switched to affinity purified FVIII		
Length of follow-up [11] 2 years	Outcome(s) measured [12] level of FVIII inhibitors (Bethesda assay)	

INTERNAL VALIDITY				
Allocation [13] patient preference	Comparison of study groups [14] similar inhibitors at baseline	Blinding [15] Not done	Treatment/ measurement bias [16] random variation in follow-up across participants	Follow-up (ITT) [17] <60%
Overall quality assessment (descriptive) [18] relevant to real situation but high loss to follow-up Selection bias not minimised (patient self-selection) Confounding unclear Follow-up adequate External validity uncertain				

RESULTS					
Outcome [19]	Intervention group [20]		Control group [21]		Measure of effect/effect size [22] 95% CI [25]	Benefits (NNT) [23] 95% CI [25]
Bethesda assay	Year 1	Year 2	Year 1	Year 2		
0	74.3%	79.7%	75.4%	78.1%		
<0.5	22.0%	15.3%	17.5%	15.6%		Harms (NNH) [24] 95% CI [25]
>0.5	3.8%	5%	7.0%	6.3%		
	Clinical importance (1-4) [26]					Relevance (1-5) [27]
Any other adverse effects [28] None reported						

EXTERNAL VALIDITY
Generalisability [29] Participants are good representation
Applicability [30]
Comments [31]

STUDY DETAILS				
Reference [1] (Kadir et al 2002)				
Affiliation/source of funds [2] Ferring Pharmaceuticals, Katherine Dormandy Trust				
Study design [3] randomised controlled crossover trial	Level of evidence [4] II		Location/setting [5] Home treatment, United Kingdom	
Intervention [6] DDAVP (300µg) intranasal Sample size [7]	Comparator(s) [8] Placebo nasal spray Sample size [9]			
Patient characteristics [10] 39 women with menorrhagia. Mild-moderate vWD, heterozygote FXI-deficiency, and carriers of haemophilia (DDAVP/placebo)- mean age= 32.2 years Baseline Mean PBAC score =292.1 (placebo/DDAVP)- mean age=31.6 years Baseline Mean PBAC score=262.1				
Length of follow-up [11] 2 months	Outcome(s) measured [12] Mean difference in PBAC (Pictorial Blood Assessment Chart) scores Side effects			
INTERNAL VALIDITY				
Allocation [13] randomised (method not specified)	Comparison of study groups [14] No significant differences between	Blinding [15] double-blinded	Treatment/ measurement bias [16] Treated and measured the same	Follow-up (ITT) [17] Did use ITT, except those who did not return diaries.
Overall quality assessment (descriptive) [18] Quality score: 24/27 Unable to assess external validity Bias minimised Confounding avoided				
RESULTS				
Outcome [19] Both placebo and DDAVP resulted in significant decrease in PBAC score from baseline. Insignificant different between placebo and DDAVP	Intervention group [20] PBAC score- 140	Control group [21] PBAC score- 148	Measure of effect/effect size [22] No significant differences 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26]			Relevance (1-5) [27]
Any other adverse effects [28] 83 % experienced one or more adverse events. 69% on DDAVP, 52% on placebo (p=0.3) Headache, weight gain				
EXTERNAL VALIDITY				
Generalisability [29] Patients representative				
Applicability [30] More benefit than harm				
Comments [31]				

STUDY DETAILS				
Reference [1] (Kelly et al 1997)				
Affiliation/source of funds [2] Products supplied by Baxter-Hyland corporation Division of Haematology, Children's hospital of Philadelphia, University of Pennsylvania, Philadelphia				
Study design [3] quasi- randomised controlled trial	Level of evidence [4] III-1	Location/setting [5] Children's hospital- United States		
Intervention [6] Recovery study in non-bleeders Hemofil M (50 IU/kg) -> 72 hours-> Recombinate (50 IU/kg) Sample size [7] 10	Comparator(s) [8] Hemofil M (50 IU/kg) -> 72 hours-> Hemofil M Sample size [9] 10			
Patient characteristics [10] 10 haemophilia A patients aged 7-12 years without inhibitors, PTPs Intervention group – 2nd 5 participants Comparator group(s) –1st 5 participants				
Length of follow-up [11] 72 hours	Outcome(s) measured [12] Recovery/response rate, inhibitor (Bethesda assay)			
INTERNAL VALIDITY				
Allocation [13] sequential 5 participants	Comparison of study groups [14] same participants	Blinding [15] double-blind	Treatment/ measurement bias [16] same participants	Follow-up (ITT) [17] complete
Overall quality assessment (descriptive) [18] Selection bias minimised Confounding avoided Follow-up adequate Patients representative				
RESULTS				
Outcome [19]	Intervention group [20] Recombinate	Control group [21] Hemofil	Measure of effect/effect size [22]	Benefits (NNT) [23]
Response	1.91±0.14%	1.5±0.15% (p=0.007)	95% CI [25]	95% CI [25]
Recovery	100.5±4.5%	78.7±6.2% (p=0.007)		Harms (NNH) [24]
Ratio actual: predicted recovery	>0.66 in 100% patients	<0.66 in 30% patients		95% CI [25]
	Clinical importance (1-4) [26] 2/4		Relevance (1-5) [27] 2/5	
Any other adverse effects [28] none reported				
EXTERNAL VALIDITY				
Generalisability [29] Participants are representative of paediatric patients (PTPs)				
Applicability [30] Potential benefits of rFVIII outweigh potential harms				
Comments [31] Significantly better response and recovery with rFVIII compared to pdFVIII				

STUDY DETAILS				
Reference [1] (Kisker et al 2003)				
Affiliation/source of funds [2] The Mononine Study group, financially supported by Aventis Behring				
Study design [3] randomised crossover trial	Level of evidence [4] II	Location/setting [5] University of Iowa, USA		
Intervention [6] rFIX (50 IU/kg, BeneFIX®) Sample size [7] 15	Comparator(s) [8] pdFIX (50 IU/kg, MonoFIX®) Sample size [9] 15			
Patient characteristics [10] 15 non-bleeding severe haemophilia B patients, aged >12 years, without inhibitors Intervention group – as above Comparator group(s) –as above				
Length of follow-up [11] 7-30 days	Outcome(s) measured [12] Incremental factor recovery, IU/kg^{-1}, % change			
INTERNAL VALIDITY				
Allocation [13] random – not stated how	Comparison of study groups [14] same patients	Blinding [15] double blinded	Treatment/ measurement bias [16] minimised	Follow-up (ITT) [17] complete
Overall quality assessment (descriptive) [18] Selection bias minimised Confounding avoided Follow-up adequate Good external validity				
RESULTS				
Outcome [19] Incremental factor recovery, IU/kg^{-1}	Intervention group [20] 0.86 (0.39-1.48)	Control group [21] 1.67 (0.86-4.66)	Measure of effect/effect size [22] 48.5%, p=0.002 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1/4		Relevance (1-5) [27] 2/5	
Any other adverse effects [28] Not reported. Follow-up probably too short for development of inhibitors				
EXTERNAL VALIDITY				
Generalisability [29] Representative				
Applicability [30]				
Comments [31]				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Kreuz et al 2002)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]</td></tr>
<tr><td colspan="2">Study design [3] Historical control group</td><td colspan="2">Level of evidence [4] III-3</td><td colspan="2">Location/setting [5] Haemophilia centre, University Hospital, Frankfurt am Main, Germany</td></tr>
<tr><td colspan="3">Intervention [6]
rFVIII treatment: on-demand, prophylaxis, surgery

Sample size [7] 21</td><td colspan="3">Comparator(s) [8]
pdFVIII treatment: on-demand, prophylaxis, surgery

Sample size [9] 51</td></tr>
<tr><td colspan="6">Patient characteristics [10] PUPs with moderate-severe haemophilia A, no detectable inhibitors

Intervention group – participants after 1989 treated with rFVIII

Comparator group(s) –participants up to 1989 treated with pdFVIII</td></tr>
<tr><td colspan="3">Length of follow-up [11] 23 years</td><td colspan="3">Outcome(s) measured [12] inhibitor development</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Historical</td><td>Comparison of study groups [14] Unsure</td><td>Blinding [15] None</td><td>Treatment/ measurement bias [16] Possible</td><td colspan="2">Follow-up (ITT) [17] complete</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias likely
Confounding possible
Follow-up unclear
Patients representative</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Inhibitor development

Exposure days prior to inhibitor development</td><td>Intervention group [20]
4 (19.0%) high titre
0 low titre

22 (31%)</td><td>Control group [21]
13 (25.5%) high titre
5 (9.8%) low titre

15 (4-195)</td><td rowspan="2">Measure of effect/effect size [22]

95% CI [25]</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] None</td><td colspan="3">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] none reported</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] Representative population- long term follow-up, despite this- small sample size</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS				
Reference (Mannucci et al 1987)				
Affiliation/source of funds [2] Supported by grants from Ferring AB and Valeas				
Study design [3] randomised crossover study	Level of evidence [4] II	Location/setting [5] Malmö, Sweden		
Intervention [6] Intravenous DDAVP (0.3µg/kg) Sample size [7] 14	Comparator(s) [8] Subcutaneous DDAVP (0.3µg/kg) Sample size [9] 14			
Patient characteristics [10] mild and moderate haemophilia A patients (median FVIII:C level 7 U/dL, range 2-31) Intervention group –as above Comparator group(s) –as above				
Length of follow-up [11] 24 hours- recovery study	Outcome(s) measured [12] pharmacokinetics – peak and half-life FVIII:C			
INTERNAL VALIDITY				
Allocation [13] randomised crossover	Comparison of study groups [14] same participants	Blinding [15]	Treatment/ measurement bias [16] same participants, bias minimised	Follow-up (ITT) [17] ITT done
Overall quality assessment (descriptive) [18] Unable to assess external validity Bias minimised Confounding avoided				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Peak FVIII:C mean±/sd	2363±2368	582±158	p<0.02	95% CI [25]
Half-life FVIII:C	4.4±1.1	4.7±1.6	NS 95% CI [25]	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26]			Relevance (1-5) [27]
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisability [29] unclear				
Applicability [30]				
Comments [31]				

STUDY DETAILS				
Reference [1] (Mannucci et al 2002)				
Affiliation/source of funds [2] Grant from Alpha therapeutics				
Study design [3] Randomised crossover trial	Level of evidence [4] II		Location/setting [5] Multicentre study	
Intervention [6] Alphanate® Solvent Detergent (A-SD) 60 vWF:Rcof IU/kg Sample size [7] 6 then crossover with 6	Comparator(s) [8] Alphanate® Solvent Detergent/Heat Treated (A-SD/HT) 60 vWF:Rcof IU/kg Sample size [9] 6 then crossover with 6			
Patient characteristics: 12 patients with type 3 von Willebrand disease				
Length of follow-up [11] 186 days	Outcome(s) measured [12] Bleeding time, in vivo half lives of FVIII:C, vWF:Ag, vWF:Rcof, number of bleeding episodes			
INTERNAL VALIDITY Quality score: 22/27				
Allocation [13] Randomised (not specified how)	Comparison of study groups [14] No sig diffs	Blinding [15] Not stated	Treatment/ measurement bias [16] Minimised	Follow-up (ITT) [17] Follow-up adequate. Not ITT as one Pp was found to have inhibitors and was excluded from analysis. Data given.
Overall quality assessment (descriptive) [18] Selection bias minimised Confounding minimised Follow-up adequate External validity unclear				

RESULTS				
Outcome [19] Median bleeding time at baseline over 30 minutes. At 1 hour post infusion was 10.5 minutes.	A-SD [20] In vivo half life FVIII:C= 20.9 vWF:Ag=12.4 vWF:Rcof=7.1	A-SD/HT [21] In vivo half life FVIII:C= 23.8 vWF=12.9 vWF:Rcof=6.5	Measure of effect/effect size [22] No sig diff between treatments 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 3/4			Relevance (1-5) [27]
Any other adverse effects [28] none				
EXTERNAL VALIDITY				
Generalisability [29] Unable to determine				
Applicability [30] The benefits outweigh any harms				
Comments [31] Not available in Australia. Lower purity than recombinant, so not for HA. For use in vWD patients.				

STUDY DETAILS				
Reference [1] (Morfini et al 1992)				
Affiliation/source of funds [2] Baxter Healthcare Corporation				
Study design [3] non randomised crossover trial	Level of evidence [4] III-2	Location/setting [5] Multicentre, Europe and United States		
Intervention [6] All had rFVIII (50 IU/kg, Recombinate™) one week after Hemofil Sample size [7] 47	Comparator(s) [8] All patients had pdFVIII (50 IU/kg, Hemofil®) Sample size [9] 47			
Patient characteristics [10] 47 PTPs with severe haemophilia A, without inhibitors, same for both intervention and comparators				
Length of follow-up [11] 24 hours	Outcome(s) measured [12] Incremental FVIII recovery (IU/kg^{-1}) % change, In vivo recovery (%)			
INTERNAL VALIDITY				
Allocation [13] All had pdfVIII followed by rFVIII one week later	Comparison of study groups [14] Same	Blinding [15] Not stated	Treatment/ measurement bias [16] Unlikely	Follow-up (ITT) [17] Complete
Overall quality assessment (descriptive) [18] Quality score: 16/27 Selection bias possible Confounding avoided Follow-up adequate Patients representative				
RESULTS				
Outcome [19]	Intervention group [20]	Control group [21]	Measure of effect/effect size [22]	Benefits (NNT) [23]
Incremental FVIII recovery	2.31	1.99	16.1% difference in recovery	95% CI [25]
In vivo recovery (%)	107.1±45.6	92.2±32.0	14.9% difference in in vivo recovery p<0.019 95% CI [25]	Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 3/4		Relevance (1-5) [27] 2/5	
Any other adverse effects [28] None reported				
EXTERNAL VALIDITY				
Generalisability [29] Representative				
Applicability [30] More benefits than harms				
Comments [31]				

STUDY DETAILS				
Reference [1] (Poon et al 2002)				
Affiliation/source of funds [2] Association of Hemophilia Clinic Directors of Canada (AHCDC) &* Canadian Association of Nurses in Hemophilia Care				
Study design [3] historical control study	Level of evidence [4] III-3	Location/setting [5] Hemophilia Clinics (16) in Canada		
Intervention [6] rFIX 50 IU/kg Sample size [7] 126	Comparator(s) [8] pdFIX (prior infusions) Sample size [9] 78			
Patient characteristics [10] haemophilia B patients aged 1-74				
	Severe	Moderate	Mild	
Intervention group –	61 (48.4%)	24 (19%)	41 (32.5%)	
Comparator group(s) –	44 (59.5%)	12 (16.2%)	18 (24.3%)	
Length of follow-up [11] up to 5 years	Outcome(s) measured [12] recovery of FIX -> (expected rise in FIX levels of 50 U/dL)			
INTERNAL VALIDITY				
Allocation [13] N/A	Comparison of study groups [14] N/A	Blinding [15] N/A	Treatment/ measurement bias [16] N/A	Follow-up (ITT) [17]
Overall quality assessment (descriptive) [18] Good Selection bias uncertain Confounding possible Follow-up adequate Patients representative				
RESULTS				
Outcome [19] Incremental FIX recovery, % IU/kg^{-1} (50 IU/kg)	Intervention group [20] 0.77±0.19	Control group [21] 1.05±0.26	Measure of effect/effect size [22] % change= 26.7% p-value <0.0001 95% CI [25]	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1/4		Relevance (1-5) [27] 2/5	
Any other adverse effects [28] Anaphylactic reaction From Canadian registry data: 2 patients (of 244) exposed to rFIX for 1-5 years developed anaphylactic reactions				
EXTERNAL VALIDITY				
Generalisability [29] Representative population				
Applicability [30] Potential benefits outweigh potential harms				
Comments [31] Lower recovery rate is based on 1:1 ratio. Current recommendations are 1:1.25 – This study suggests using 1.29x more recombinant than plasma-derived FIX				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Schiavoni et al 1983)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]
Not stated</td></tr>
<tr><td colspan="2">Study design [3]
Randomised controlled trail, double blinded</td><td colspan="2">Level of evidence [4]
II</td><td colspan="2">Location/setting [5]
Haemophilia summer camp, Sweden</td></tr>
<tr><td colspan="3">Intervention [6]
Tranexamic acid 25mg/kg 3x daily as prophylaxis</td><td colspan="3">Comparator(s) [8]
Placebo</td></tr>
<tr><td colspan="6">Sample size [7] 26 in total. Not stated how many in each group.</td></tr>
<tr><td colspan="6">Patient characteristics [10]
26 patients: 17 severe haemophilia A, 2 mild haemophilia A, 7 severe haemophilia B- Not stated what characteristics of treatment groups were.</td></tr>
<tr><td colspan="3">Length of follow-up [11] 2 weeks</td><td colspan="3">Outcome(s) measured [12] Number of spontaneous and traumatic bleeding episodes, amount of FVIII used.</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
Randomised- method unknown</td><td>Comparison of study groups [14] Unknown</td><td>Blinding [15] double (unclear who)</td><td>Treatment/ measurement bias [16] unlikely</td><td colspan="2">Follow-up (ITT) [17]
Adequate</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
External validity low
Bias minimised
Confounding avoided
Reporting poor</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="2">Outcome [19]</td><td>Intervention group [20] 11 traumatic bleeds
6 spontaneous bleeds
589 units FVIII used per bleeding episode
533 units FIX used per bleeding episode</td><td>Control group [21] 14 traumatic bleeds
4 spontaneous bleeds
825 units FVIII used per bleeding episode
637 units FIX used per bleeding episode</td><td>Measure of effect/effect size [22]
No statistically significant differences between groups due to small sample sizes
95% CI [25]</td><td colspan="2">Benefits (NNT) [23]
95% CI [25]
Harms (NNH) [24]
95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 3/4</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] none reported</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] Unable to determine external validity.</td></tr>
<tr><td colspan="6">Applicability [30] Not clear</td></tr>
<tr><td colspan="6">Comments [31] Prophylaxis with rFVIII or rFIX should now be used in most of this population, therefore benefit of tranexamic acid for prophylaxis is questionable.</td></tr>
</table>

<table>
<tr><td colspan="5">STUDY DETAILS</td></tr>
<tr><td colspan="5">Reference [1] (Seremetis et al 1999) (Schwartz et al 1990)</td></tr>
<tr><td colspan="5">Affiliation/source of funds [2] The Recombinant FVIII Study Group</td></tr>
<tr><td colspan="2">Study design [3] non randomised crossover study</td><td colspan="2">Level of evidence [4] III-2</td><td>Location/setting [5] Multicentre-worldwide</td></tr>
<tr><td colspan="2">Intervention [6]
rFVIII (Cutter Biological)
1 x IV single bolus- non bleeding Stage 1.

Sample size [7] 17</td><td colspan="3">Comparator(s) [8]
PdFVIII (Koate-HS)
1 x IV single bolus

Sample size [9] 17</td></tr>
<tr><td colspan="5">Patient characteristics [10] 16 severe, 1 moderate haemophilia A, PTPs, without inhibitors

Intervention group – as above

Comparator group(s) –as above</td></tr>
<tr><td colspan="2">Length of follow-up [11] 48 hours- recover study</td><td colspan="3">Outcome(s) measured [12] Recovery, aPTT, length of treatment</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] no randomised crossover</td><td>Comparison of study groups [14] same participants</td><td>Blinding [15] none</td><td>Treatment/ measurement bias [16] same participants</td><td>Follow-up (ITT) [17] done</td></tr>
<tr><td colspan="5">Overall quality assessment (descriptive) [18]
Selection bias unclear
Confounding avoided
Follow-up adequate
Patients representative</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Mean incremental recovery</td><td>Intervention group [20]
Week 1= 2.68±0.52 (p=0.026)
Week 13= 2.7±0.61 (p=0.20)
Week 25= 2.92±0.99 (p=0.017)</td><td>Control group [21] pd-FVIII
2.42±0.33% per IU/kg</td><td>Measure of effect/effect size [22]

95% CI [25]</td><td>Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="3"></td><td>Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26] 3/4</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="5">Any other adverse effects [28] mild-moderate adverse events associated with Kogenate®:
Burning/erythema at infusion site, nausea, pruritis, dizziness, rash, dyspnea, chest tightness, dry mouth; no inhibitors detected</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisability [29]</td></tr>
<tr><td colspan="5">Applicability [30]</td></tr>
<tr><td colspan="5">Comments [31]</td></tr>
</table>

STUDY DETAILS				
Reference [1] (Soucie et al 2000)				
Affiliation/source of funds [2] Hemophilia Surveillance System				
Study design [3] Retrospective cohort study	Level of evidence [4] III-2	Location/setting [5] information from physicians, clinical laboratories, hospitals, and haemophilia treatment centres in Colorado, Georgia, Louisiana, Massachusetts, New York and Oklahoma, United States		
Intervention [6] treatment by haemophilia treatment centre (HTC) Sample size [7] 1979		Comparator(s) [8] treatment without contact with HTC private physicians or haematologists= 13%, hospital and nonhospital based clinics= 4% hospitals or emergency rooms only= 8% Sample size [9] 971		
Patient characteristics [10] males with haemophilia A or B (not acquired)				
Length of follow-up [11] 3 years		Outcome(s) measured [12] mortality		
INTERNAL VALIDITY				
Allocation [13] Non randomised	Comparison of study groups [14] Unclear	Blinding [15] none	Treatment/ measurement bias [16] likely to be treated and measured the same	Follow-up (ITT) [17] Not stated
Overall quality assessment (descriptive) [18] Selection bias unlikely Confounding uncertain – adjusted for Follow-up unclear Patients representative				
RESULTS				
Outcome [19] Mortality	Intervention group [20] 149 (28.1%)	Control group [21] 86 (38.3%)	Measure of effect/effect size [22] RR= 0.7 95% CI= 0.6, 0.9 After multivariate analysis RR=0.6 95% CI= 0.5, 0.9	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1		Relevance (1-5) [27] 1	
Any other adverse effects [28]				
EXTERNAL VALIDITY				
Generalisability [29] Good				
Applicability [30] Good				
Comments [31]				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Soucie et al 2001)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Hemophilia Surveillance System</td></tr>
<tr><td colspan="2">Study design [3] Retrospective cohort study</td><td colspan="2">Level of evidence [4] III-2</td><td colspan="2">Location/setting [5] treatment centres in 6 states, United States</td></tr>
<tr><td colspan="3">Intervention [6] home therapy

Sample size [7] 1257</td><td colspan="3">Comparator(s) [8] No home therapy

Sample size [9] 1393</td></tr>
<tr><td colspan="6">Patient characteristics [10]
males with haemophilia A or B (not acquired) for whom home therapy status was able to be ascertained
median age= 19.9 years (range= 0.5 months to 95 years)
5.3% had inhibitors at baseline
80% haemophilia A
50% severe disease</td></tr>
<tr><td colspan="3">Length of follow-up [11] 4 years</td><td colspan="3">Outcome(s) measured [12] hospitalised bleeding complications</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Non randomised</td><td>Comparison of study groups [14] those on home therapy more likely to be white, employed, have commercial or government insurance, higher levels of factor usage, receiving HTC care, on continuous prophylaxis and inhibitors at baseline</td><td>Blinding [15] none</td><td>Treatment/ measurement bias [16] likely to be treated and measured the same</td><td colspan="2">Follow-up (ITT) [17] Good- (loss to follow-up only 3.3%)</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18] Good, 23/27
Selection bias unlikely
Confounding uncertain – adjusted for
Follow-up adequate
Patients representative</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
No. of bleeding complications</td><td>Intervention group [20]
360 (28.6%)</td><td>Control group [21]
448 (32.2%)</td><td>Measure of effect/effect size [22]
RR= 0.8
95% CI [25]
0.7, 0.9
p≤0.05</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="2"></td><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26] 1</td><td colspan="2">Relevance (1-5) [27] 1</td></tr>
<tr><td colspan="6">Any other adverse effects [28]</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] Good</td></tr>
<tr><td colspan="6">Applicability [30] Good</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS				
Reference [1] (Soucie et al 2004)				
Affiliation/source of funds [2] Not stated				
Study design [3] Retrospective cohort study	Level of evidence [4] III-2	Location/setting [5] 130 haemophilia treatment centres, United States		
Intervention [6] Sample size [7]	No factor concentrates 77	rFVIII 484	rFVIII + pdFVIII 178	pdFVIII 59
Patient characteristics [10] males with haemophilia, born on or after February 1, 1993	60 mild haemophilia, 13 moderate haemophilia, 4 severe haemophilia No inhibitors	61 mild haemophilia, 124 moderate haemophilia, 299 severe haemophilia 31 with inhibitors	10 mild haemophilia, 28 moderate haemophilia, 140 severe haemophilia 49 with inhibitors	15 mild haemophilia, 10 moderate haemophilia, 34 severe haemophilia 11 with inhibitors
Length of follow-up [11] 2-7 years		Outcome(s) measured [12] B19 antibodies		
INTERNAL VALIDITY				
Allocation [13] unclear	Comparison of study groups [14] No. sig diffs	Blinding [15] none	Treatment/ measurement bias [16] possible	Follow-up (ITT) [17] Adequate
Overall quality assessment (descriptive) [18] Selection bias unlikely Confounding uncertain Follow-up adequate Patients representative				
RESULTS				
Outcome [19] Odds ratio compared with no exposure groups (95% CI)	rFVIII alone 0.8 (0.4-1.5) p=0.5	rFVIII + pdFVIII 1.9 (1.0-3.6) p=0.05	pdFVIII 7.6 (3.6-15.9) p<0.001	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26] 1		Relevance (1-5) [27]2	
Any other adverse effects [28] B19 virus associated with loss of range of movement				
EXTERNAL VALIDITY				
Generalisability [29] Good				
Applicability [30] Good				
Comments [31] Shows clearly rFVIII is safer than pdFVIII				

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Stajcic et al 1989)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] Not stated</td></tr>
<tr><td colspan="2">Study design [3] Randomised controlled trial</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] Out-patient hospital, Yugoslavia</td></tr>
<tr><td colspan="3">Intervention [6] Primary wound closure: EACA+ silk suture + FVIII

Sample size [7] 25
12 had one side each done both ways</td><td colspan="3">Comparator(s) [8] Open wound group: EACA + FVIII

Sample size [9] 25</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Intervention group – primary wound closure
15 severe, 2 moderate, 8 mild haemophilia
Comparator group(s) – Open wound
11 severe, 10 moderate, 4 mild haemophilia
Both at once-
9 severe, 1 moderate, 2 mild haemophilia</td></tr>
<tr><td colspan="3">Length of follow-up [11] 5-7 days</td><td colspan="3">Outcome(s) measured [12] Clot size, post operative bleeding, amount FVIII required post-operatively</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] randomised</td><td>Comparison of study groups [14] No sig. Differences at inception</td><td>Blinding [15] No</td><td>Treatment/ measurement bias [16] Possible</td><td colspan="2">Follow-up (ITT) [17] Complete</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias minimised
Confounding uncertain
Follow-up adequate
Patients representative</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Clot size significantly smaller in closed wound group, less bleeding.</td><td rowspan="2">Intervention group [20]
Clot size large=15/25
Post op. bleeding=2/25
Post op FVIII=2.7 IU/kg</td><td rowspan="2">Control group [21]
Clot size large=1/22
Post op bleeding=0/25
Post op FVIII=0</td><td rowspan="2">Measure of effect/effect size [22]
Size of clot= chi^2 test for difference: p<0.001
Post op. bleeding=Fisher exact test: p=0.72
95% CI [25]</td><td>Benefits (NNT) [23]

95% CI [25]</td><td></td></tr>
<tr><td>Harms (NNH) [24]

95% CI [25]</td><td></td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="3">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28]</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] Predominantly severe haemophilia. Not much information on participants so hard to assess external validity</td></tr>
<tr><td colspan="6">Applicability [30] While using unvalidated measure, it does find clear patterns of benefit from primary wound closure</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (Tarantino et al 2004)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2] several authors employed by Baxter Healthcare-product manufacturer,
rAHF-PFM Clinical study group</td></tr>
<tr><td colspan="2">Study design [3] Randomised crossover trial</td><td colspan="2">Level of evidence [4] II</td><td colspan="2">Location/setting [5] 2 treatment centres-Austria and Switzerland</td></tr>
<tr><td colspan="3">Intervention [6] rAHF-PFM (no human or animal plasma)

Sample size [7] 56-Part 1, 55 Part 3</td><td colspan="3">Comparator(s) [8] rFVIII (Recombinate rAHF)

Sample size [9] 56 Part 1, 55 Part 3</td></tr>
<tr><td colspan="6">Patient characteristics [10]
PTPs≥ 150 ED, moderate-severe haemophilia
Exclude hypersensitivity to Recombinate rAHF, inhibitors >1.0 BU
Intervention group –

Comparator group(s) – same participants</td></tr>
<tr><td colspan="3">Length of follow-up [11] 0.25-48 hours</td><td colspan="3">Outcome(s) measured [12] PK-potency aPTT assay</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13]
randomised</td><td>Comparison of study groups [14] same participants</td><td>Blinding [15]
double-blinded</td><td>Treatment/ measurement bias [16] same participants</td><td colspan="2">Follow-up (ITT) [17]
30/55 (54.5%)</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias minimised
Confounding avoided
Follow-up adequate
Patients representative</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Recovery (IU/kg)</td><td>Intervention group [20]
2.4±0.5</td><td>Control group [21]
2.6±0.5</td><td>Measure of effect/effect size [22]
Not significant
95% CI [25]</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="3"></td><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="3">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] 19 mild-moderate adverse events related to AHF-PFM:
Taste perversion, headache, fever, diarrhoea, dizziness, hot flushes, pain (upper abdomen, lower chest), shortness of breath, sweating, nausea, itching</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29] see exclusions</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

<table>
<tr><td colspan="6">STUDY DETAILS</td></tr>
<tr><td colspan="6">Reference [1] (White et al 1998)</td></tr>
<tr><td colspan="6">Affiliation/source of funds [2]
The Recombinate PTP Study Group</td></tr>
<tr><td colspan="2">Study design [3] Non-randomised crossover study</td><td colspan="2">Level of evidence [4] III-2</td><td colspan="2">Location/setting [5] Multicentre</td></tr>
<tr><td colspan="3">Intervention [6] Phase 2 Trial
50 IU/kg rFVIII (Recombinate)

Sample size [7] 69- 67 severe, 2 moderate</td><td colspan="3">Comparator(s) [8]
50 IU/kg pdFVIII (Hemofil M)- solvent detergent treated

Sample size [9]</td></tr>
<tr><td colspan="6">Patient characteristics [10]
Severe-moderate haemophilia A, without inhibitors, PTPs
• prophylaxis for surgery- Case series 13 participants
Intervention group – same group

Comparator group(s) –</td></tr>
<tr><td colspan="3">Length of follow-up [11] 1) 24 hours, 2) prophylaxis 18 months, 30 months</td><td colspan="3">Outcome(s) measured [12] ½ life, FVIII recovery, patient rated response, blood loss (surgery)</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation [13] Non-randomised</td><td>Comparison of study groups [14]</td><td>Blinding [15] No</td><td>Treatment/ measurement bias [16]</td><td colspan="2">Follow-up (ITT) [17] Yes</td></tr>
<tr><td colspan="6">Overall quality assessment (descriptive) [18]
Selection bias minimised
Confounding avoided
Follow-up adequate
External validity uncertain</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td rowspan="3">Outcome [19]
Minimal blood loss (surgery), as expected (0-200 ml)</td><td>Intervention group [20]
2.4± 0.97%</td><td>Control group [21]
2.47± 0.33%
2.42± 0.85</td><td rowspan="2">Measure of effect/effect size [22]

95% CI [25]
p=0.59</td><td colspan="2">Benefits (NNT) [23]

95% CI [25]</td></tr>
<tr><td colspan="2">Harms (NNH) [24]

95% CI [25]</td></tr>
<tr><td colspan="2">Clinical importance (1-4) [26]</td><td colspan="2">Relevance (1-5) [27]</td></tr>
<tr><td colspan="6">Any other adverse effects [28] No. of adverse events= 13, (number of infusions= 13, 591)
Slight flushing, nausea, epistaxis, brief dizziness</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability [29]</td></tr>
<tr><td colspan="6">Applicability [30]</td></tr>
<tr><td colspan="6">Comments [31]</td></tr>
</table>

STUDY DETAILS				
Reference [1] (Zanon et al 2000)				
Affiliation/source of funds [2] Not stated				
Study design [3] Prospective cohort study	Level of evidence [4] III-2	Location/setting [5] 1 treatment centre, Italy		
Intervention [6] For haemophilia FVIII or FIX to 30% of normal. 20 mg/kg tranexamic acid, anaesthesia, fibrin sponge, silk suture Sample size [7] 77	Comparator(s) [8] For non-haemophilia patients Silk sutures Sample size [9] 184			
Patient characteristics [10] Intervention group – 32 severe haemophilia A, 39 moderate haemophilia A, 3 severe haemophilia B, 3 moderate haemophilia B Comparator group(s) –184 subjects with bleeding disorders, liver disease or use of anticoagulant drugs				
Length of follow-up [11] 7 days- 5 years	Outcome(s) measured [12] No. of bleeding complications			
INTERNAL VALIDITY				
Allocation [13]- non random	Comparison of study groups [14]	Blinding [15] No	Treatment/ measurement bias [16] Unclear	Follow-up (ITT) [17] Yes- complete
Overall quality assessment (descriptive) [18] Selection bias uncertain Confounding uncertain Follow-up adequate Patients representative				
RESULTS				
Outcome [19] Number of bleeding complications not statistically different between groups	Intervention group [20] 2 bleeding complications	Control group [21] 1 bleeding complication	Measure of effect/effect size [22] OR=0.2 P=0.2 95% CI [25] 0.01-2.22	Benefits (NNT) [23] 95% CI [25] Harms (NNH) [24] 95% CI [25]
	Clinical importance (1-4) [26]		Relevance (1-5) [27]	
Any other adverse effects [28] 2 bleeding complications- late bleeding post extraction, and haematoma at site of anaesthesia injection				
EXTERNAL VALIDITY				
Generalisability [29] only moderate-severe haemophilia				
Applicability [30]				
Comments [31] More a dental surgery protocol than focusing on individual treatments				

Explanatory Notes

STUDY DETAILS

[1] Full reference citation details

[2] Details of how the study was funded or other relevant affiliations of the authors (designed to expose potential conflicts of interest, such as drug company funding for the drug being trialled)

[3] The study type (eg RCT, case-control study, cohort study), with additional detail where relevant

[4] As per the NHMRC levels of evidence, provided at pg-8 of the NHMRC Toolkit publication: *How to use the evidence: assessment and application of scientific evidence*

[5] Country/setting (eg hospital, primary care, hospice)

[6] Provide detail on the intervention. This will generally be a therapeutic procedure such as treatment with a pharmaceutical agent, surgery, a dietary supplement, a dietary change or psychotherapy. Some other interventions are less obviously categorised as interventions, such as early detection (screening) and patient educational materials. The key characteristic is that a person or their environment is manipulated in the hope of benefiting that person or reducing harm

[7] Number of participants enrolled in the intervention/treatment group

[8] The intervention (eg drug, therapy, placebo) used as a comparison in the study. There may be more than one comparator

[9] Number of participants enrolled in the comparison/control group(s)

[10] Any factors that may confound/influence the results and/or the external validity (see below) of the results (eg age, sex, comorbidities, obesity, existing medications, previous surgery)

[11] Length of follow-up of the participants

[12] The outcomes studied (list all outcomes in terms of primary and secondary outcomes). Indicate which outcomes are relevant to the review/guidelines inclusion criteria

INTERNAL VALIDITY (QUALITY ASSESSMENT)

[13] The method used to assign patients to treatment or control groups (eg coin toss, random number table, computer-generated random numbers, sealed envelopes). Also indicate whether the allocation list was concealed (eg computerised random number generation, administered from a central trial office, assigned locally)

[14] The results of the group analysis, noting any clinically or statistically significant differences between the groups at study inception

[15] Whether the participants, outcome assessors and (if different) investigators were blinded to the group allocation

[16] Indicate whether, aside from the experimental treatment, the groups were treated and measured the same

[17] The proportion of participants that were followed up and whether all participants were analysed according to the group to which they were initially allocated, regardless of whether or not they dropped out, fully complied with the treatment, or crossed over and received the other treatment ('intention to treat analysis' – ITT)

[18] Describe your assessment (in words) of the overall quality of the study. Is the study quality good enough that you have confidence in the results?

RESULTS

[19] The outcome relevant for this entry in the database (Note: more than one table may be required if there are several outcomes relevant to different clinical questions/guidelines)

[20] For binary outcomes, show numbers of patients with the outcome. For continuous outcomes, show means ± standard deviations; or medians and interquartile ranges

[21] For binary outcomes, show numbers of patients with the outcome. For continuous outcomes, show means ± standard deviations; or medians and interquartile ranges. Add number of columns as needed (eg 3-arm trials)

[22] Absolute and relative measures of effect eg risk differences (absolute risk reduction or absolute risk increase), mean differences, relative risk, odds ratio

[23] A measure of benefit, when the treatment increases the probability of a good event. The number needed to treat to benefit (NNT) = the number of participants who must receive the treatment to create one additional improved outcome in comparison with the control treatment; calculated as 1/absolute benefit increase, rounded up to the next highest whole number

[24] A measure of harm, when the treatment increases the risk of specified adverse outcomes of a condition or reduces the probability of a good event. The number needed to treat to harm (NNH) = the number of patients who, if they receive the treatment, would lead to one additional person being harmed compared with patients who receive the control treatment; calculated as 1/absolute risk increase, rounded up to the next highest whole number

[25] 95% confidence interval (CI) for all measures, if available, otherwise use P-value

[26] Insert the words corresponding to the appropriate rating from the scale provided at pg-23 of the NHMRC Toolkit publication: *How to use the evidence: assessment and application of scientific evidence*

[27] Insert the words corresponding to the appropriate rating from the scale provided at pg-28 of the NHMRC Toolkit publication: *How to use the evidence: assessment and application of scientific evidence*

[28] Information on any adverse events mentioned in the study

EXTERNAL VALIDITY

[29] Are the patients in the study so different from those being considered for the guideline that the results may not be applicable to them?

[30] Will the potential benefits outweigh any potential harms of treatment in the guideline population?

[31] Add your overall comments regarding the interpretation or implications of this study

Study profiles of included studies

Level of evidence	Quality score	Study Design	Study	Setting	Population	Treatment	Comparator	Outcome(s) assessed	Length of follow-up
III-3	5/27	Historically controlled study	(Arkin et al. 1991)	Home-care setting, worldwide centres	14 non-bleeding PTPs with moderate-severe haemophilia A, aged 4–72, without inhibitors Historical controls: no description provided	rFVIII (20–40 IU/kg, 3 x week)	pdFVIII	Incremental FVIII recovery (IU/kg^{-1}) % change Adverse events	Not reported
IV	3/3	Prospective case series	(Auerswald et al. 2002)	Multicentre, Germany, Austria	14 patients with vWD	Bolus doses of 43.5 IU FVIII/kg and continuous infusion of 3.4-9.6 IU FVIII/kg pdFVIII	N/A	Clinician judged haemostasis, bleeding complications Adverse events	55 hours
IV	2/3	Prospective case series	(Avanoglu et al. 1999)	1 treatment centre, Turkey	22 patients: 21 haemophilia A, 1 haemophilia B, aged 6–17 years	Fibrin glue + pdFVIII or pdFIX + tranexamic mouth wash	FVIII alone	Bleeding episodes Adverse events	12 days
IV	2/3	Uncontrolled before-and-after study Case series	(Aygoren-Pursun et al. 1997)	Multicentre, Germany	39 PTPs with mild–severe haemophilia A, aged 2–62 years, treated for bleeding episodes, prophylaxis and surgery	rFVIII (50 IU/kg, Kogenate®)	N/A	Incremental FVIII recovery (IU/kg^{-1}) Number of infusions per bleeding episode Adverse events	12 months
II	21/27	Randomised single blinded controlled trial	(Berntorp 1997)	Multicentre, Sweden and the Netherlands	12 PTPs with severe haemophilia A, aged 17–64 years, without inhibitors	rFVIII SQ[b] (50 IU/kg)	pdFVIII (50 IU/kg, Octonativ)	Incremental FVIII recovery (IU/kg^{-1}) % change	50 hours
IV	2/3	Uncontrolled before-and-after study	(Bjorkman et al. 2001)	Not stated	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors	rFIX	N/A	Incremental FIX recovery, % IU/kg^{-1}	72 hours
IV	2/3	Prospective case series	(Bray et al. 1994)	Multicentre, United States	73 PUPs with moderate–severe haemophilia A, aged 2 days–50 months, without inhibitors	rFVIII	N/A	Development of inhibitors, no. of exposure days prior to inhibitor development Adverse events	3-22 months

II	20/27	Randomised crossover trial	(Cattaneo et al. 1989)	I treatment centre, Milan, Italy	10 PTPs with severe vWD, (type not specified) with prolonged bleeding time (>30 minutes)	Cryoprecipitate + DDAVP (0.3 µg/kg)	Cryoprecipitate + saline	BT, vWF:Ag, vWF:RiCof	Not stated Cross-over at day 15
IV	1/3	Retrospective case series	(Chediak et al. 1986)	1 treatment centre, Chicago, United States	6 women, 8 deliveries, 11 pregnancies	Whole blood, fresh plasma, cryoprecipitate, curettage, desmopressin postpartum	N/A	Adverse events	Not stated
IV	2/3	Prospective case series	(Chuansumrit et al. 1993)	1 hospital, Bangkok, Thailand	22 patients: 13 haemophilia A, 1 type 1 vWD, 8 with inherited or acquired platelet dysfunction, aged 2–26 years	DDAVP (0.3–0.4 µg/kg) intravenous	N/A	Adverse events	48 hours
IV	3/3	Prospective case series	(Collins et al. 2004)	Multicentre, United Kingdom	18 acquired haemophilia: 14 no underlying disorder, 1 gastric carcinoma, 1 polymyalgia rheumatica, 1 Castlemanns disease, 1 Depoxil, aged 38–87, median 70 years	Prednisolone + cyclophosphamide	N/A	Adverse events	12 months
IV	1/3	Retrospective case series	(Daffos et al. 1988)	1 treatment centre, Paris, France	93 pregnant women with haemorrhagic disorders: Haemophilia A: 35 obligate and 44 putative carriers, Haemophilia B: 8 women obligate and 4 putative carriers, vWD: 1 x Type 1; 1 x Type 2A	Antenatal diagnosis: fetal blood sampling Treatment as required: cryoprecipitate	N/A	Effectiveness of antenatal diagnosis, Adverse events	Not stated
IV	2/3	Prospective case series	(de la Fuente et al. 1985)	2 treatment centres, United States	68 patients: 32 mild and 8 moderate–severe haemophilia A, 13 type 1 vWD, 7 type 2A vWD, 1 type 2B vWD, aged 2–66 years	DDAVP (0.3 µg/kg) intravenous	N/A	Clinician judged haemostasis, need for alternative therapies Adverse events	7 days
III-2	17/27	Non randomised controlled trial	(De Sio et al. 1985)	1 treatment centre, Rome, Italy	26 patients, 21 mild haemophilia A, 5 moderate haemophilia A	Intravenous DDAVP (0.3 µg/kg)	Subcutaneous DDAVP (0.3 µg/kg)	FVIII:C levels, post/pre FVIII:C ratio Side effects	2 hours

IV	4/6	Systematic review	(Delgado et al. 2003)	Mixed	20 retrospective or prospective case series of 249 patients with acquired haemophilia, median age 64 years (8–93 years)	DDAVP, human FVIII, porcine FVIII, aPCCs, rFVIIa, intravenous immunoglobulin, plasmapheresis and immunoadsorption, FVIII immune tolerance	N/A	Response rates to treatment of bleeding episodes and to eradication therapy	Not stated
IV	2/3	Prospective case series	(Dewald et al. 1980)	1 clinical research centre, Ohio, United States	5 patients: 4 haemophilia A, 1 vWD	DDAVP (0.4 µg/kg) intranasal	N/A	Side effects	24 hours
IV	2/3	Prospective case series	(Djulbegovic et al. 1996)	Unclear—1 treatment centre? United States	8 patients with haemophilia B	EACA or tranexamic acid ± FIX	N/A	Adverse events	30 days
IV	2/3	Prospective case series	(Dobrkovska et al. 1998)	1 treatment centre, Chicago, United States	6 patients with vWD: 2 x Type 1B, 2 x Type 2A, 2 x Type 3	80 IU vWF:RcoF kg^{-1} and 32 IU FVIII:C kg^{-1} pdFVIII	N/A	In vivo recovery and half lives of vWF:Ag, vWF:Rcof and FVIII:C, BT Adverse events	60 hours
IV	2/3	Retrospective case series	(Dobrkovska et al. 1998)	18 treatment centres, Canada	97 patients with vWD: 32 x Type 1, 5 x Type 2A, 18 x Type 2B, 28 x Type 3, 14 x Other	11.9–222.8 IU vWF:Rcof/kg pdFVIII for surgery, prophylaxis or bleeding episodes	N/A	Clinician judged haemostasis, Median in vivo recovery FVIII:C, vWF:RcoF Adverse events	21 days
IV	2/3	Retrospective case series	(Dunn et al. 2000)	1 treatment centre, Washington DC, United States	40 patients: 24 types 1 and 2 vWD, 16 mild–moderate haemophilia A and symptomatic haemophilia A carriers aged 5–58 years	DDAVP intranasally, 150 µg if under 50 kg, 300 µg if over 50 kg	N/A	Adverse events	Not stated
II	22/27	Randomised crossover trial	(Ewenstein et al. 2002)	15 treatment centres, United States	38 non-bleeding PTPs with severe haemophilia B, aged 7–75 years, without inhibitors	rFIX	pdFIX	Incremental FIX recovery, % IU/kg^{-1} % change	48 hours
IV	2/3	Retrospective case series	(Federici et al. 2000)	1 haemophilia centre, Milan, Italy	63 patients with vWD: 31 x Type 1, 22 x Type 2, 10 x Type 3	Tranexamic acid± fibrin glue,± DDAVP or pdFVIII	N/A	Number of bleeding complications	8 days

IV	1/3	Retrospective case series	(Federici et al. 2002)	Multicentre, Italy	22 patients with vWD: 9 x Type 1, 7 x Type 2B, 6 x Type 3	17–92 IU FVIII:C/kg/day pdFVIII	N/A	Clinician judged haemostasis No. of bleeding episodes controlled with 1 infusion Adverse events	26 days
IV	3/3	Before-and-after study	(Federici et al. 2004)	5 treatment centres, Europe	66 patients with type severe type 1 or 2 vWD, BT more than 15 minutes, aged 12–65 years	DDAVP (0.3 µg/kg) intravenous infusion	N/A	No. responsive to DDAVP Responsive= 3-fold increase post/pre treatment in FVIII:C and vWF:Rco + BT ≤12 minutes	4 hours
II	21/27	Randomised single blinded controlled trial	(Fijnvandraat et al. 1997)	Multicentre, Sweden and the Netherlands	12 PTPs with severe haemophilia A, aged 17–64 years, without inhibitors	rFVIII SQ[b] (50 IU/kg)	pdFVIII (50 IU/kg, Octonativ)	Incremental FVIII recovery (IU/kg^{-1}) % change	50 hours
IV	1/3	Retrospective case series	(Franchini et al. 2003)	3 treatment centres, Italy	26 patients with vWD: 19 x Type 1, 7 x Type 2B	125.0-976.4 IU vWF:Rcof/kg pdFVIII for major surgery, 42.9–173.3 IU vWF:Rcof/kg pdFVIII for minor surgery, 27.2-160.0 IU vWF:Rcof/kg pdFVIII for dental extractions	N/A	vWF:Ag, vWF:Ag, FVIII:C levels pre/post, in vivo recovery of vWF:Ag, amount of pdFVIII used Adverse events	23 days
IV	2/3	Prospective case series	(Ghirardini et al. 1987)	Unclear	25 patients: 23 mild haemophilia A, 2 moderate haemophilia A	DDAVP (0.3 µg/kg) subcutaneous	N/A	Adverse events	60 minutes
IV	2/3	Prospective case series	(Ghirardini et al. 1988)	Unclear	24 patients: 16 mild haemophilia A, 2 moderate haemophilia A, 6 type 1 vWD patients	DDAVP subcutaneous (0.3 µg/kg) + tranexamic acid + fibrin glue for dental	N/A	No. of bleeding complications Adverse events	7 days

IV	1/3	Retrospective case series	(Giangrande 2002)	19 treatment centres, Europe and Israel	31 PUPs and MTPs with severe haemophilia A, aged ≤ 4 years, without inhibitors	rFVIII	N/A	Number of infusions per bleeding episode Development of inhibitors No. of exposure days prior to inhibitors	2 years
III-2	15/27	Non randomised controlled trial	(Giles et al. 1998)	Multicentre, Canada	872 PTPs with mild–severe haemophilia	rFVIII	Affinity purified-FVIII	Inhibitor development associated with factor replacement therapy	2 years
IV	2/3	Prospective case series	(Gill et al. 2002)	1 treatment centre,	25 patients: 9 haemophilia A, 16 vWD	DDAVP intranasal (150 µg for under 50 kg)	N/A	Adverse events	24 hours
IV	3/3	Prospective case series	(Gill et al. 2003)	19 treatment centres, United States	33 patients with vWD: 9 x Type 1, 4 x Type 2A, 7 x Type 2B, 27 x Type 3, 6 x Other	Loading dose 25.7–143.2 IU/kg plus 16/4–182.9 UK/kg maintenance dose pdFVIII	N/A	Clinician judged haemostasis Adverse events	>7 days
IV	2/3	Retrospective case series	(Greer et al. 1991)	1 treatment centre, Glasgow, United Kingdom	18 obligate carriers of haemophilia A, 34 pregnancies, 5 obligate carriers of haemophilia B, 11 pregnancies	Treatment as required: cryoprecipitate, tranexamic acid, fresh frozen plasma, whole blood transfusions	N/A	Adverse events	30 year period
IV	3/3	Prospective case series	(Gringeri et al. 2004)	Multicentre, Italy	25 PTPs with severe haemophilia A, aged 6–60 years, without inhibitors	rFVIII	N/A	Number of infusions per bleeding episode Inhibitor development No. of exposure days prior to inhibitors	6 months
IV	2/3	Retrospective case series	(Gringeri et al. 2004)	Multicentre, Italy	94 PTPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes or prophylaxis	rFVIII	N/A	Inhibitor development No. of exposure days prior to inhibitors	2 years
IV	3/6	Systematic review	(Gruppo et al. 2003)	Mixed	13 observational studies	B-domain deleted rFVIII for prophylaxis	Full length FVIII for prophylaxis (pdFVIII or rFVIII)	No. of breakthrough bleeding episodes, half life of FVIII	12 year period

IV	3/3	Prospective case series	(Hoyer et al. 1985)	Multicentre, United States and Canada	92 pregnancies at risk of haemophilia A	Antenatal diagnosis Treatment as required	N/A	Effectiveness of antenatal diagnosis Adverse events	6 year period
IV	2/3	Retrospective case series	(Kadir et al. 1997)	1 treatment centre, London, United Kingdom	24 haemophilia A and 8 haemophilia B obligate carriers, 82 pregnancies	Antenatal diagnosis Treatment as required: DDAVP, vWF rich concentrates, rFVIII, oral contraceptive pill, fresh frozen plasma	N/A	Uptake and results of antenatal diagnosis Adverse events	10 year period
IV	2/3	Retrospective case series	(Kadir et al. 1998)	1 treatment centre, London, United Kingdom	31 women with vWD (27 Type 1; 2 Type 2; 2 Type 3), 11 with XI deficiency, 84 pregnancies, 85 foetuses	Treatment as required: DDAVP, vWF rich concentrate, fresh frozen plasma, tranexamic acid, oral contraceptive pill, blood transfusions	N/A	Mode of delivery Adverse events	17 year period
II	24/37	Randomised controlled trial	(Kadir et al. 2002)	Home treatment, United Kingdom	39 women with menorrhagia. Mild-moderate vWD, heterozygote FXI-deficiency, and carriers of haemophilia	DDAVP (300 µg) intranasal	Placebo nasal spray	Mean difference in Pictorial Blood Assessment Chart scores Side effects	2 months
III-1	21/27	Quasi-randomised single-blinded (investigator) controlled trial	(Kelly et al. 1997)	1 treatment centre, Philadelphia, United States	10 non-bleeding PTPs with severe haemophilia A, aged 6–12, without inhibitors	rFVIII (50 IU/kg, Recombinate™)	pdFVIII (50 IU/kg, Hemofil®M)	Incremental FVIII recovery (IU/kg^{-1})% change	72 hours
II	21/27	Randomised double-blinded crossover trial	(Kisker et al. 2003)	1 treatment centre, Iowa City, United States	15 non-bleeding severe haemophilia B patients, aged >12 years, without inhibitors	rFIX (50 IU/kg, BeneFIX®)	pdFIX (50 IU/kg, Mononine®)	Incremental factor recovery, IU/kg^{-1} , % change	7-30 days
III-3	11/27	Historical control study	(Kreuz et al. 2002)	1 treatment centre, Frankfurt, Germany	72 PUPs with moderate–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis, or surgery	rFVIII	pdFVIII	Development of inhibitors No. of exposure days prior to inhibitors	23 year period

IV	1/3	Before and after study Prospective case series	(Leissinger et al. 2001)	Multicentre, United States	333 patients enrolled. 124 mild haemophilia A, 135 mild type 1 vWD, 37 moderate type 1 vWD, 23 haemophilia carriers, 14 other bleeding disorders, aged 5–64 years	DDAVP (150 µg) intranasal	N/A	Clinical judged haemostasis Adverse events	48 hours
IV	2/3	Retrospective case series	(Lillicrap et al. 2002)	18 treatment centres, Canada	97 patients with vWD: 32 x Type 1, 5 x Type 2A, 18 x Type 2B, 28 x Type 3, 14 x Other	11.9–222.8 IU vWF:Rcof/kg dFVII for surgery, prophylaxis or bleeding episodes	N/A	Clinician judged haemostasis, Median in vivo recovery FVIII:C, vWF:RcoF Adverse events	21 days
IV	2/3	Retrospective case series	(Ljung et al. 1994)	Multicentre, Sweden	117 pregnant women, 117 deliveries of haemophilic children 101 haemophilia A (77 severe, 24 moderate) 16 haemophilia B (12 severe, 4 moderate)	Blood sampling, vitamin K injections Treatment as required: Whole blood transfusion	N/A	Adverse events	20 year period
IV	6/6	Systematic review	(Lloyd Jones et al. 2003)	Mixed	52 relevant papers: 8 randomised controlled trials, 2 non randomised controlled trials, 1 survey, 39 case series/uncontrolled prospective studies	Human FVIII, porcine FVIII, PCCs, aPCCs, rFVIIa, plasmapheresis, extracorporeal protein A adsorption, cimetidine or immunosuppression	N/A	No. patients with haemostatic control Adverse events	Not stated
IV	2/3	Retrospective case series	(Lorenzo et al. 2001)	2 treatment centres, Spain	62 consecutive severe haemophilia A patients	FVIII prophylaxis	N/A	Cumulative incidence of inhibitors at 3 years from first FVIII exposure	≤75 days
IV	2/3	Prospective case series	(Lusher et al. 1993)	Multicentre, United States, Canada, Europe, United Kingdom	95 PUPs with mild-severe haemophilia A, aged 0–658 months, treated for bleeding episodes or prophylaxis	rFVIII	N/A	Development of inhibitors Adverse events	3.5 years

IV	2/3	Prospective case series	(Lusher et al. 2004)	28 treatment centres, Europe and United States	102 PUPs with mild–severe haemophilia A, without inhibitors, treated for bleeding episodes, prophylaxis or surgery	rFVIII	N/A	Number of infusions per bleeding episode Development of inhibitors No. of exposure days prior to inhibitors Adverse events	2–5 years or 100 exposure days
II	23/27	Randomised crossover trial	(Mannucci et al. 1987)	Multicentre, Europe	14 mild and moderate haemophilia A (median FVIII:C level 7 U/dL, range 2–31)	Intravenous DDAVP (0.3 µg/kg)	Subcutaneous DDAVP (0.3 µg/kg)	Peak FVIII:C, half life of FVIII:C	24 hours
IV	2/3	Before and after study Prospective case series	(Mannucci et al. 1992)	1 treatment centre, Milan, Italy	37 patients, 22 with mild haemophilia A, 15 with mild type 1 vWD, aged 16–63 years	DDAVP (0.3 µg/kg) intravenous	N/A	FVIII:C, vWF:Ag, RiCof, BT post/pre treatment ratios	4 days
III-3	16/27	Historically controlled study	(Mannucci et al. 1994)	13 treatment centres in Europe and United States	PTPs with moderate-severe haemophilia A, 30 HIV seropositive, 31 HIV seronegative	rFVIII	pdFVIII	Change in immune status	Median 3.5 years
II	22/27	Randomised crossover trial	(Mannucci et al. 2002)	Multicentre, United States, Europe	12 patients with type 3 vWD	60 vWF:Rcof IU/kg pdFVIII-SD	60 vWF:Rcof IU/kg pdFVIII-SD/HT	Bleeding time, in vivo half lives of FVIII:C, vWF:Ag, vWF:Rcof	Crossover 7–186 days later 24 hours
IV	3/3	Before and after study Prospective case series	(Mannucci et al. 2002)	Multicentre, United States, Europe	81 patients with vWD: 15 x Type 1, 29 x Type 2A, 5 x Type 2B, 32 x Type 3	pdFVIII-SD	pdFVIII-SD/HT	Clinical judged haemostasis, need for alternative therapy, BT Adverse events	50 hours
IV	1/3	Before and after study Retrospective case series	(Mariana et al. 1984)	Multicentre, Bari and Rome, Italy	43 patients, 21 mild haemophilia A, 2 moderate haemophilia A, 20 vWD (types 1 and 2)	DDAVP (0.3 µg/kg) intravenous	DDAVP (0.4 µg/kg) intravenous	Cessation/prevention of bleeding Adverse events	11 days
IV	1/3	Retrospective case series	(Mohri 2002)	? Japan	3 patients with menorrhagia, 1 type 1 vWD, 2 type 2A vWD, aged 23–43 years	Single dose tranexamic acid (3 g for 1–5 days)	N/A	Control of menorrhagia after treatment Adverse events	5 years

III-2	16/27	Non-randomised crossover trial	(Morfini et al. 1992)	Multicentre, Europe and United States	47 PTPs with severe haemophilia A, without inhibitors	rFVIII (50 IU/kg, Recombinate™)	pdFVIII (50 IU/kg, Hemofil®)	Incremental FVIII recovery (IU/kg^{-1}) % change, In vivo recovery (%)	24 hours
IV	2/3	Retrospective case series	(Morrison et al. 1993)	47 treatment centres in Europe and North America	65 patients with acquired haemophilia, associations: unknown= 55%, pregnancy=11%, malignancy=12%, connective tissue or autoimmune disease=17%, skin disease=2%, drug treatment =3%	Porcine FVIII	N/A	Clinical judged haemostasis	Not stated
IV	3/3	Before and after study Prospective case series	(Nolan et al. 2000)	1 treatment centre, Ireland	133 patients with bleeding disorders. 91 type 1 vWD, 20 mild haemophilia A, 22 platelet function disorders	DDAVP (0.3 µg/kg) continuous infusion	N/A	No. responsive to DDAVP Response= increase of FVIII:C into normal range for haemophilia, increase of vWF:Ag, vWF:FVIIIB and FVIII:C into normal range for vWD. Normal range for all = 0.5-1.5 IU/dl Side effects	Not stated 90 minutes?
IV	2/3	Retrospective case series	(Nitu-Whalley et al. 2001)	1 treatment centre, London, United Kingdom	27 patients with types 1 (93%) and 2 (7%) vWD most of whom had responded to DDAVP, aged 14–57 years	Intravenous DDAVP (0.3 µg/kg) + tranexamic acid for mucosal surgery	N/A	Clinician judged haemostasis	16 days
IV	1/3	Retrospective case series	(Ong et al. 1998)	1 hospital, Belfast, United Kingdom	4 patients with menorrhagia, 1 type 1 vWD, 2 type 2A vWD, 1 type 2B vWD, aged 17–42 years.	Single dose tranexamic acid (4 g for 3–5 days)	N/A	Control of menorrhagia after treatment Adverse events	4 years
IV	2/3	Uncontrolled before-and-after study	(Panicker et al. 2003)	1 treatment centre, Detroit, United States	22 patients with severe haemophilia A and 3 children with severe haemophilia B, aged 1.7–20.4	Prophylaxis with rFIX	N/A	Incremental FIX recovery, IU/kg^{-1}	13 year period

III-3 IV	15/27 2/3	Historical control study Prospective case series	(Poon et al. 2002)	16 treatment centres, Canada	PTPs with mild–severe haemophilia B, aged 1–74 years	rFIX	pdFIX	Incremental FIX recovery, % IU/kg^{-1} % change Adverse events	≤5 years
IV	2/3	Uncontrolled before-and-after study	(Ragni et al. 2002)	12 treatment centres, Europe and United States	26 PTPs with mild–severe haemophilia B and 2 female haemophilia B carriers	rFIX for surgery	N/A	Adverse events	30 days
IV	2/3	Prospective case series	(Rakocz et al. 1993)	1 treatment centre, Israel	80 patients with bleeding disorders, 37 severe haemophilia A/B, 4 mild haemophilia A/B, 10 mild/moderate vWD, 29 other	Fibrin glue used with aprotinin concentration 1,000 or 10,000 KIU/ml ± ranexamic acid mouthwash	N/A	Adverse events	10 days
IV	2/3	Prospective case series	(Rodeghiero et al. 1996)	17 treatment centres, Italy	79/169 patients, 43 vWD, 36 haemophilia A	DDAVP (20 µg for >70 kg or 40 µg for <70 kg) subcutaneous in home treatment	N/A	Side effects	12 months
IV	2/3	Prospective case series	(Rose & Aledort 1991)	1 treatment centre? United States	22 patients, 11 vWD, 8 mild haemophilia A, 3 symptomatic carriers of haemophilia A	DDAVP (300 µg for adults, 150 µg for children—unspecified age) intranasally	N/A	Adverse events	2–4 days
IV	2/3	Uncontrolled before-and-after study Case series	(Roth et al. 2001a)	20 treatment centres, Europe and United States	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors	rFIX	N/A	Incremental FIX recovery, % IU/kg^{-1} Number of infusions per bleeding episode Development of inhibitors No. of exposure days prior to inhibitors Adverse events	2 years

IV	2/3	Prospective case series	(Rothschild et al. 1998)	21 treatment centres, France	50 PUPs with severe haemophilia A, aged 1–43	rFVIII	N/A	Development of inhibitors No. of exposure days prior to inhibitors	12 months
IV	1/3	Retrospective case series	(Sallah 2004)	3 treatment centres, United States	34 patients with acquired haemophilia, associations: 10 x none, 3 x post partum, 1 x drug reaction, 6 x cancer, 3 x lupus, 10 x other	75 IU/kg of FEIBA	N/A	% with complete or partial response (control of bleeding) Side effects	48 hours
IV	3/3	Prospective case series	(Santagostino et al. 2003)	1 treatment centre, Milan, Italy	27 patients with severe haemophilia who had difficulties in venipuncture	Arteriovenous fistulae as vascular access	N/A	No. of bleeding complications, failure of permanent vascular access, thrombotic complications, shunt-related complications	5–44 months
IV	2/3	Uncontrolled before-and-after study	(Saulnier et al. 1994)	3 hospitals, France	14 vWD patients, mean age 24 years	DDAVP (0.3 µg/kg) + tranexamic acid + fibrin glue	N/A	Number without bleeding complication, Post/pre ratio of FVIII:C, vWF:Ag, RiCof	15 days
IV	2/3	Uncontrolled before-and-after study	(Scharrer 2002; Scharrer et al. 2000)	5 treatment centres, Europe	15 PTPs and 7 PUPs with severe haemophilia A, without inhibitors	rFVIII	N/A	Adverse events	24 months
II	13/27	Randomised double blind controlled trial	(Schiavoni et al. 1983)	Haemophilia Summer camp, Sweden	26 patients, 17 severe haemophilia A, 2 mild haemophilia A, 7 severe haemophilia B	Tranexamic acid 25 mg/kg 3x daily as prophylaxis	Placebo	Number of bleeding episodes, amount of FVIII used	2 weeks
IV	3/3	Before-and-after study Case series	(Schulman et al. 1991)	1 treatment centre, Stockholm, Sweden	370 patients with disorders of primary haemostasis. 133 vWD, 237 platelet function defects, aged 3–80 years	DDAVP (0.2–0.3 µg/kg) route of administration not specified	N/A	No. responsive to DDAVP Responsive= return to normal or reduction by more than 20% of BT, or greater than 2-fold increase in vWF. 'Normal' not stated Side effects	24 hours

III-2 IV	19/37 3/3	Non-randomised crossover trial Prospective case series	(Schwartz et al. 1990)	Multicentre, Worldwide	17 non-bleeding PTPs with moderate-severe haemophilia A, without inhibitors 58 PTPs with moderate–severe haemophilia A, without inhibitors, treated	rFVIII (50 IU/kg) rFVIII (50 IU/kg)	pdFVII (50 IU/kg, Koate HS)	Incremental FVIII recovery (IU/kg^{-1}) % change, number of infusions per bleeding episode Development of inhibitors Adverse events	48 hours
III-2 IV	19/37 3/3	Non-randomised crossover trial Prospective case series	(Seremetis et al. 1999)	Multicentre- home treatment program	17 non-bleeding PTPs with moderate-severe haemophilia A, without inhibitors 58 PTPs with moderate–severe haemophilia A, without inhibitors, treated	rFVIII (50 IU/kg)	pdFVII (50 IU/kg, Koate HS)	Incremental FVIII recovery (IU/kg^{-1}) % change, number of infusions per bleeding episode Development of inhibitors Adverse events	3 years
IV	1.5/3	Retrospective/ Prospective case series	(Sindet-Pedersen et al. 1988)	1 hospital, Denmark	15 patients: 13 haemophilia A, 2 haemophilia B	Tranexamic acid orally (25 mg/kg 4x daily) or as mouthwash (10 ml of 5% tranexamic acid solution, 4x daily for 2 minutes) ± FVIII	N/A	Adverse events	Not stated
III-2	21/27	Retrospective cohort study	(Soucie et al. 2004)	130 treatment centres, United States	818 males with haemophilia A, born after 1 February 1993	rFVIII, rFVIII + pdFVIII, pdFVIII	No FVIII	B19 parvovirus antibodies	2–7 years
III-2	22/27	Retrospective cohort study	(Soucie et al. 2000)	Both haemophilia and non-haemophilia treatment centres, 6 states in United States	2950 males with haemophilia A or B, identified over 3 year period	Haemophilia treatment centre	Non-haemophilia treatment centre	Mortality	3 years
III-2	23/27	Retrospective cohort study	(Soucie et al. 2001)	Medical treatment centres, 6 states of United States	2650 males with haemophilia A or B	Home treatment	No home treatment	Haemorrhagic bleeding complications	4 years

II	14/27	Randomised controlled trial	(Stajcic et al. 1989)	1 treatment centre, Yugoslavia	62 patients with mild–severe haemophilia A, undergoing dental extractions	Open wound: EACA + FVIII	Closed wound: EACA + silk suture + FVIII	Clot size, post operative bleeding, amount FVIII required post-operatively	5–7 days
IV	2/3	Retrospective case series	(Stasi et al. 2004).	1 treatment centre,	10 acquired haemophilia: 6 with no underlying disorder, 1 x rheumatoid arthritis, 1 x prostate carcinoma, 1 x low-grade non-Hodgkin lymphoma, and 1 after pregnancy, aged 27–78 years, median 61 years	Rituximab immunosuppressant 375 mg/m^2	N/A	No. achieved partial or complete remission of inhibitors Side effects	12–41 months
IV	1/3	Retrospective case series	(Stieltjes et al. 2004)	9 treatment centres, Europe	16 PTPs with mild–severe haemophilia A, without inhibitors	Recombinant B-domain deleted FVIII	N/A	Adverse events	3 year period
II IV	25/27 3/3	Double blinded randomised controlled trial Case series	(Tarantino et al. 2004)	2 treatment centres, Austria and Switzerland	56 PTPs with moderate–severe haemophilia A, aged 10–65 years, without inhibitors, with ≥150 exposure days	R-FVIII (50 IU/kg)	rAHF-PFM[a] (50 IU/kg)	Incremental FVIII recovery (IU/kg^{-1}), % change Development of inhibitors Adverse events	0.25–48 hours
IV	2/3	Prospective case series	(Thompson et al. 2004)	28 treatment centres, United States	39 patients with vWD: 16 x Type 1, 4 x Type 2A, 5 x Type 2B, 8 x Type 3, 6 x Other	32.5–216.8 IU vWF:Rco/ kg pdFVIII	N/A	No. and dose of infusions needed, clinician judged haemostasis Adverse events	>21 days
IV	6/6	Systematic review	(Valentino et al. 2004)	Mixed	2074 patients with haemophilia A, B von Willebrand or other congenital coagulation disorders from 48 studies	Central venous access devices (CVAD), fully implanted	Central venous access devices, external	Infections, thrombotic complications and other adverse events	Mean 578 days per CVAD
IV	2/3	Retrospective case series	(van der Bom et al. 2003)	1 treatment centre, Utrecht, The Netherlands	81 consecutive severe haemophilia A patients	FVIII prophylaxis	N/A	Cumulative incidence of inhibitors at 100 days from first FVIII exposure Mean number of infusions before antibodies	3–26 years (mean= 16 years)

IV	2/3	Before-and-after study Prospective case series	(Warrier & Lusher 1983)	1 hospital, Michigan, United States	38 patients, 31 vWD, 7 mild–moderate haemophilia A and 3 normal subjects	DDAVP via intranasal drip (2–4 µg/kg) or intravenous (0.2–0.3 µg/kg)	N/A	% Rise in FVIII:C, FVIII:RAg, FVIII:RCof, BT Side effects	270 minutes 24 hours
IV	2/3	Retrospective case series	(Wiestner et al. 2002)	2 treatment centres, United States	4 patients with acquired haemophilia, associations: 1 x chronic renal failure, 1 x ascites and lymphadenopathy, 1 x lupus, 1 x mild haemophilia	Rituximab immunosuppressant 375 mg/m^2	N/A	Adverse events	7–12 months
IV	2/3	Prospective case series	(White et al. 1997)	Multicentre	69 PTPs with moderate–severe haemophilia A, without inhibitors	rFVIII	N/A	Development of inhibitors Adverse events	24 hours–30 months
II	17/27	Randomised crossover trial	(White et al. 1998)	20 treatment centres, Europe and United States	11 PTPs with haemophilia B	rFIX	pdFIX	Incremental FIX recovery, % IU/kg^{-1}, % change	72 hours
IV	2/3	Case series	(White et al. 1998)	20 treatment centres, Europe and United States	56 PTPs with moderate–severe haemophilia B, aged 4–56 years, without inhibitors	rFIX	N/A	Number of infusions per bleeding episode Development of inhibitors	2 years
IV	6/6	Systematic review	(Wight et al. 2003)	Mixed	1 semi-structured review, 29 case series, 8 case reports, 4 registries (probably overlap)	Any form of immune tolerance induction: Bonn, Malmo, Low-dose, Porcine FVIII	N/A	Success rates (undetectable inhibitors)	≤103 months
IV	2/3	Prospective case series	(Yoshioka et al. 2001)	Multicentre, Japan	20 PTPs with moderate–severe haemophilia A, aged 12–55 years, without inhibitors, treated for bleeding episodes	rFVIII-FS[d] (10-50 IU/kg, Kogenate®)	N/A	Incremental FVIII recovery (IU/kg^{-1}) Number of infusions per bleeding episode	12–24 weeks

IV	2/3	Prospective case series	(Yoshioka et al. 2003)	33 treatment centres in Japan	43 PUPs and MTPs with mild–severe haemophilia A, aged 3–386 months, treated with rFVIII (Kogenate®) for bleeding episodes	rFVIII	N/A	Number of infusions per bleeding episode Development of inhibitors No. of exposure days prior to inhibitors	3 months– 2 years
III-2	16/27	Cohort study	(Zanon et al. 2000)	1 treatment centre, Padova, Italy	71 haemophilia A and 6 haemophilia B patients undergoing dental extractions Controls: 184 non-haemophilic patients undergoing dental extractions	rFVIII /rFIX + tranexamic acid + fibrin sponge + silk suture	Silk suture	No. of bleeding complications	7 days 5 year period

vWD= von Willebrand disease SD= solvent detergent; HT= heat treated, BT= bleeding time, FVIII:RAg= factor VIII antigen, FVIII:RCof= factor VIII ristocetin cofactor , FVIII:C= factor VIII coagulant activity, vWF= von Willebrand factor, FVIII= factor VIII , vWD= , pdFVIII= plasma derived factor VIII , PTP= previously treated patients, N/A= not applicable