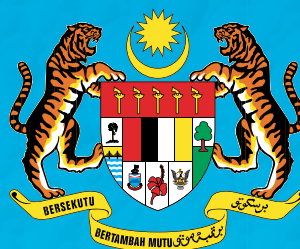


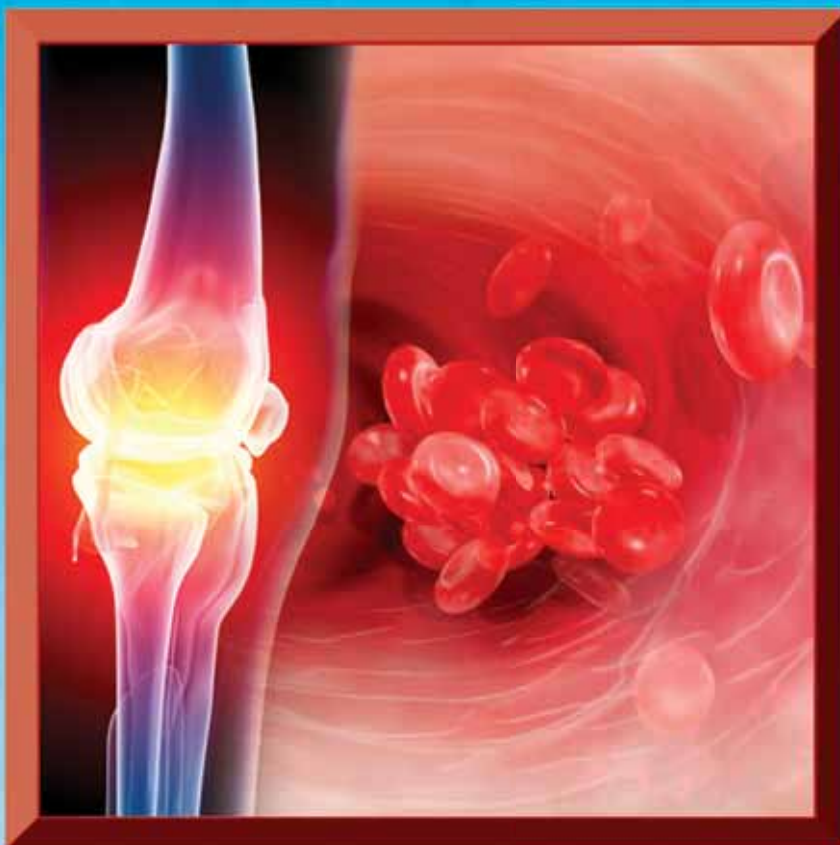
2012

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HEALTH TECHNOLOGY ASSESSMENT REPORT



MINISTRY OF HEALTH MALAYSIA



MANAGEMENT OF HAEMOPHILIA

MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

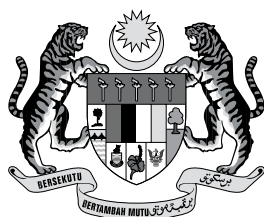
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MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

MANAGEMENT OF HAEMOPHILIA

DISCLAIMER

This Health Technology Assessment report has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organisations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health Malaysia.

EXECUTIVE SUMMARY

Background

Haemophilia is an inherited bleeding disorder that results from a low level of proteins needed for normal blood clotting. There are two main types of haemophilia, haemophilia A, which is caused by a lack or decrease of clotting factor VIII (FVIII); and haemophilia B, which is caused by a lack or decrease of clotting factor IX (FIX). The occurrence of haemophilia A and B is approximately one per 5000 and one per 50,000 male births respectively, with no racial predilection. The mean prevalence of haemophilia A for high income countries was $12.8 \pm (\text{SD } 6.0)$ per 100,000 males whereas it was 6.6 ± 4.8 per 100,000 males for the rest of the world. The mean prevalence of haemophilia A in Malaysia has increased from 5.6 per 100,000 males in 1998 to 6.6 per 100,000 males in 2006, the mean was 5.9 ± 0.4 per 100,000 males. As for haemophilia B, for the highest income country, the prevalence was 2.69 ± 1.61 per 100,000 males whereas the prevalence for the rest of the world was 1.20 ± 1.33 per 100,000 males. The reported prevalence for Malaysia was 1.00 ± 0.11 per 100,000 males.

Haemophilia arthropathy due to repeated joint bleeds is the major cause of morbidity in persons with haemophilia. In patients with severe form of the disease, bleeding episodes may occur as frequently as 20-30 times per year, and life-threatening bleedings such as intracranial haemorrhage may occur. The basic treatment to stop or prevent bleeding in haemophilia patients is by giving clotting factor replacement therapy. The optimal approach is by giving factor replacement in such a way that bleeds and chronic joint damage are prevented, short and long-term complications avoided and there is full integration of the patient into society.

Replacement therapy for haemophilia is usually given either prophylactically or on-demand approach. Prophylaxis is the regular continuous treatment started after the first joint bleed and before the age of two years, or before the age of two years without previous joint bleed whereas on-demand factor infusion, also known as episodic therapy is defined as therapy to abrogate an acute haemorrhage.

Unfortunately, some patients developed neutralising antibodies (inhibitors) to replacement factors (factor VIII (FVIII) or factor IX (FIX)) rendering such treatment ineffective. The development of inhibitors is one of the challenging complications of treatment in haemophilia patients resulting in increased morbidity and significant economic burden. Although several factors are known to influence the risk of inhibitor development, the source of factor concentrate for replacement therapy, namely recombinant or plasma-derived factor concentrates may also have an effect on inhibitor development.

Inhibitor eradication by immune tolerance induction (ITI) is generally accepted as the most preferred treatment option. However, in about 30% of haemophilia A patients and a larger proportion of patients with haemophilia B, who undergo ITI, failure to eradicate the inhibitor is observed. In these patients, in those waiting for ITI to start, as well as in those undergoing ITI, acute bleeding episodes are generally managed by preparations containing activated coagulation factors. These products known as bypassing agents are able to bypass factor VIII and factor IX dependent steps in the coagulation cascade and promote haemostasis by enhancing thrombin generation. Currently there are two bypassing agents available namely activated recombinant factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC).

The history of comprehensive care of haemophilia, embracing diagnosis, treatment and multidisciplinary support has evolved over the past 60 years. It is defined as a continuing supervision of all medical and psychosocial factors affecting the haemophilia patients and their family. In many developed countries, comprehensive care were made possible because of the advanced economic condition of these countries, provide comprehensive services including haemophilia care, orthopaedic and dental services and education, as well as psychosocial support.

Policy Question

Should a national haemophilia program be introduced in Malaysia?

Objective

1. To assess the efficacy and resource implications of prophylaxis treatment when compared to on-demand treatment for patients with haemophilia
2. To assess the safety, effectiveness and cost-effectiveness of recombinant factors compared to plasma-derived
3. To assess the efficacy and resource implications of rFVIIa when compared to Activated Prothrombin Complex Concentrates (aPCC) and the resource implications
4. To assess the effectiveness of comprehensive care including non-pharmacological management for haemophilia and other rare bleeding disorders patients

Methods

Major electronic databases such as MEDLINE, EMBASE, and Cochrane Database of Systematic Review were searched up to August 2012. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised and data were extracted and narratively presented.

Results and conclusion

Fifty one studies met the inclusion and exclusion criteria.

Prophylaxis compared to on-demand approach

This review included 26 studies which met the inclusion and exclusion criteria including two systematic reviews. There were only two randomised controlled trials (RCT) identified and these studies have been combined in one of the systematic review and meta-analysis. The other studies were non-RCT, retrospective cohort studies and cross-sectional studies. Most of these studies were conducted in European countries and United States of America but there were two studies conducted in Asian countries namely in Iran and Taiwan. These studies were heterogeneous, thus the results were not pooled.

There was good level of evidence from systematic reviews of RCT supported by numerous observational studies that the used of prophylaxis approach in haemophilia treatment was effective in decreasing the frequency of joint bleeds and preventing or slowing down the development of haemophilic arthropathy. However, the evidence showed that the cost of treatment was high and mainly contributed by the cost of factor concentrates. Prophylaxis approach was shown not to increase the risk of inhibitor development and there was no increase risk of infection.

Recombinant compared to plasma-derived factors

Nine studies met the inclusion and exclusion criteria. There were two systematic reviews identified which summarised non-randomised and observational studies. One randomised controlled trial, three prospective non-randomised studies and two retrospective cohort studies were also included. No study on cost-effectiveness was retrieved. However, the studies included have high risk of bias, thus the results were not pooled.

There was insufficient evidence to answer the research question on the efficacy and safety of recombinant factor compared to plasma-derived factor concentrates. Only fair level of evidence with high risk of bias was available for haemophilia A. The evidence showed inconsistent results for recovery of rFIX and pd-FIX. Limited good level of evidence showed that recovery of rFIX was lower compared to pd-FIX. As for safety, it cannot be concluded that plasma-derived factors has lower risk of inhibitor development due to inconsistency of the results.

There was no retrievable evidence on cost-effectiveness from the available scientific databases. Only the costs of the factors were available from Pharmacy Department of Hospital Ampang and Hospital Kuala Lumpur. There were other factors that may affect the cost such as the risk of inhibitors, infection rate, efficacy, hospitalisation and other adverse events which should be calculated into the cost.

Treatment of patient with inhibitors

Twelve studies were included to address research question 3 on the effectiveness and cost-effectiveness of rFVIIa when compared to aPCC for haemophilia patients with inhibitors. One meta-analysis, four systematic reviews, two RCTs, three cost-minimisation analyses and two costing studies were selected which met the inclusion criteria.

Two RCTs compared head to head the rFVIIa and aPCC. These two RCTs however were included in three of the systematic reviews included in this review. Eight of the primary studies and reviews included were sponsored by industries.

Good level of evidence showed that rFVIIa and aPCC had similar efficacy and both can be administered as single intravenous bolus (270 µg/kg of rFVIIa, 75-100 IU/kg of aPCC). There was no higher risk of adverse events reported in rFVIIa compared to aPCC. Fair level of evidence suggested that rFVIIa is more cost-effective compared to aPCC.

Comprehensive care

There were three observational studies and one guidelines retrieved that reported the benefits of comprehensive care. All the studies were from United States.

Fair level of evidence showed that comprehensive care reduced the mortality rate in haemophilia patients, reduced the hospitalisation days and reduced the number of days lost from school or work. There was insufficient evidence on cost-effectiveness, however the fair level of evidence suggested that comprehensive care leads to cost saving.

Recommendation

Based on the good level of evidence retrieved, prophylaxis therapy is recommended in haemophilia patients to improve their quality of life and prevent complications. Since the cost of factor concentrates is high, a low or intermediate dose prophylaxis may be considered.

No specific recommendation can be made with regards to recombinant and plasma-derived factors. There was insufficient evidence to address this decision problem. More primary research in the form of well designed and adequately powered RCTs is required.

The use of bypassing agents either rFVIIa or aPCC is recommended for treatment of any kind of bleeds in haemophilia patients with inhibitors since the limited good level of evidence showed that both the bypassing agents had similar efficacy. Further well designed, high quality research is needed to study the relative effectiveness of rFVIIa compared to plasma-derived aPCC. A study among our population is strongly encouraged to provide better insight on the response to these bypassing agents.

Based on the available evidence and the current practice of haemophilia management worldwide, comprehensive care for haemophilia patients is recommended and seemed to be the way forward to improve the quality of care and prevent complications.

A national haemophilia program should be introduced in Malaysia to address several issues pertaining to management of haemophilia patients such as care delivery, medical expertise and treatment products. World Federation of Haemophilia steps to set up a national haemophilia program may be used as a guide. A registry which is an important component of comprehensive care should be incorporated in the national program. A registry enables centres to monitor their performance and the use of resources both at a local and national level.

A local economic evaluation should be conducted to assess the best model of treatment for haemophilia patients in Malaysia that will not only improve the outcome of the patients but also be cost-effective.

TABLE OF CONTENTS

DISCLAIMER	i
AUTHORS	ii
EXPERT COMMITTEE	ii
REVIEWERS	iii
ACKNOWLEDGEMENT	iii
DISCLOSURE	iii
EXECUTIVE SUMMARY	iv
TABLE OF CONTENTS	vii
GLOSSARY AND LIST OF ABBREVIATIONS	ix
Chapter 1 Background	1
Description of health problem	1
Current service provision	2
Chapter 2 Definition of Policy Question and Objectives	3
Policy Question	3
Overall aims and objectives of the assessment	3
Chapter 3 Methods	4
Search Strategy	4
Inclusion and exclusion criteria	4
Quality assessment strategy, grading of evidence and conclusion	6
Data extraction strategy	6
Data synthesis	6
Chapter 4 Overall Search Results	7
Chapter 5 Prophylaxis approach compared to on-demand approach in managing haemophilia	8
Introduction	8
Characteristics of included studies	9
Efficacy	12
Safety	15
Cost-effectiveness	16
Discussion	19
Conclusion	22
Recommendation	22

Chapter 6 Recombinant versus plasma derived factors	23
Introduction	23
Characteristics of included studies	24
Efficacy	25
Safety	26
Cost-effectiveness	28
Discussion	28
Conclusion	29
Recommendation	29
Chapter 7 Treatment of patients with inhibitors	30
Introduction	30
Characteristics of included studies	31
Efficacy	32
Safety	33
Cost-effectiveness	33
Discussion	36
Conclusion	37
Recommendation	37
Chapter 8 Comprehensive Haemophilia Care	38
Introduction	38
Characteristics of included studies	40
Efficacy	40
Cost-effectiveness	41
Discussion	41
Conclusion	43
Recommendation	43
REFERENCES	49
Appendix 1	49
Appendix 2	54
Appendix 3	55
Appendix 4	56
Appendix 5	57
Appendix 6	58
Appendix 7	59
Appendix 8	60
Appendix 9	111

GLOSSARY AND LIST OF ABBREVIATIONS

GLOSSARY	
Primary prophylaxis Factor infusions given to prevent bleeding and its consequences, usually starting in the first or second year of life, before the third but usually after a first bleed	Secondary prophylaxis Factor infusions in order to prevent recurrent bleeding, beginning after target joint bleeding has developed or after three joint or significant soft tissue bleeds have occurred and given regularly prior to activities
Target Joint 3 or more bleeds into the same joint in a consecutive 3-month period	Bypassing agent Agent that is able to bypass factor VIII-dependent step in the coagulation cascade and promote haemostasis by enhancing thrombin generation.
Joint bleed An episode characterized by pain, thought to represent intra-articular bleeding	Comprehensive care The continuing supervision of all medical and psychosocial factors affecting haemophilia patients and their family

LIST OF ABBREVIATIONS	
ADR	Adverse Drug Reaction
AEs	Adverse events
ANOVA	Analysis of Variance
aPCC	Activated Prothrombin Complex Concentrates
BA	Bypassing Agent
BU	Bethesda Unit
CANAL	Concerted Action on Neutralising Antibodies in severe haemophilia A
CCC	Comprehensive Care Centre
CDSR	Cochrane Database of Systematic Review
CEAC	Cost-effectiveness acceptability curve
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Database of Controlled Trials
CI	Confidence interval
CVAD	Central venous access device
DALY	Disability Adjusted Life Years
EHA	Established haemophilic arthropathy
EM	Expectation-maximisation
ESPRIT	Evaluation Study on Prophylaxis: a Randomized Italian Trial
European PedNet	European Paediatric Network for Haemophilia Management
FEIBA	Factor Eight Inhibitor Bypass Activity
FFP	Fresh Frozen Plasma
FIX	Factor IX
FVIII	Factor VIII

HIV	Human immunodeficiency virus
HSS	Haemophilia Surveillance System
HTA	Health Technology Assessment
HTC	Haemophilia Treatment Centre
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
IQR	Interquartile range
ITI	Immune tolerance induction
ITT	Intention to Treat
IU	International Unit
JOS	Joint Outcome Study
MD	Mean difference
N	number
NHS	National Health Service UK
NNT	Number Needed to Treat
OHE	Office of Health Economics
PCC	Prothrombin complex concentrates
pd-FVIII	Plasma-derived FVIII
PP	Primary Prophylaxis
PROSPERA	International Prospective Register for Systematic Reviews
PUPS	Previously untreated patients
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
rFVIIa	Recombinant Activated Factor VII
rFVIII	Recombinant FVIII
SAEs	Serious adverse events
SD	Standard Deviation
SMD	Standardised Mean Difference
SP	Secondary Prophylaxis
UK	United Kingdom
US FDA	US Food and Drug Administration
vWD	Von Willebrand Disease
vWF	Von Willebrand Factor
WFH	World Federation of Haemophilia
WTP	Willingness to pay
YLD	Years Live with Disability

CHAPTER 1 : BACKGROUND

Description of health problem

Haemophilia is an inherited bleeding disorder that results from a low level of proteins needed for normal blood clotting. There are two main types of haemophilia, haemophilia A, which is caused by a lack or decrease of clotting factor VIII (FVIII); and haemophilia B, which is caused by a lack or decrease of clotting factor IX (FIX). These X-linked disorders represent the large majority of inherited deficiencies of clotting factors, occurring in approximately one per 5000 and one per 50,000 male births, with no racial predilection. According to their residual endogenous FVIII/FIX concentrations, individuals with a factor level <1 IU/dL are classified as severe haemophilia and represent about half of diagnosed cases. Subjects with factor levels between 1-5 IU/dL and >5 IU/dL have moderate and mild haemophilia, respectively.¹ Together with von Willebrand disease, a defect of primary haemostasis associated with a secondary defect in coagulation factor VIII (FVIII), these X-linked disorders include 95% to 97% of all the inherited deficiencies of coagulation factors.

According to World Federation of Haemophilia, the reported haemophilia A and haemophilia B prevalence varied considerably among countries. The prevalence of haemophilia A for high income countries was 12.8 ± 6.0 (mean \pm SD) per 100,000 males whereas it was 6.6 ± 4.8 per 100,000 males for the rest of the world. The prevalence of Haemophilia A in Malaysia has increased from 5.6 per 100,000 males in 1998 to 6.6 per 100,000 males in 2006, the mean was 5.9 ± 0.4 per 100,000 males.² As for haemophilia B for the highest income country was 2.69 ± 1.61 per 100,000 males whereas the prevalence for the rest of the world was 1.20 ± 1.33 . The reported prevalence in Malaysia was 1.00 ± 0.11 per 100,000 males.³

Haemophilia has been recognised since antiquity as a distinct clinical entity. Egyptian papyri and Hebrew Talmudic documents contain descriptions of this disorder. The first accurate account in the modern medical literature dates back to the early 19th century. The delineation of its genetic transmission and its characterization as haemophilia followed soon thereafter. The discovery in 1937 that administration of normal plasma corrects the prolonged clotting time of haemophilic blood inaugurated the modern era of treatment and prophylaxis.⁴ However, blood or plasma transfusion alone cannot completely normalise blood coagulation in an adult male with haemophilia since 5 litre of blood or 2 to 3 litre of plasma must be given. The treatment was ineffective and did not prevent the onset of joint disorders. Mortality was high, and in 1960 the average length of life was 23 years. Treatment improved during the 1960s with access to products that concentrated the coagulation factors two to three times and the concept of factor concentrate was introduced.⁵

Since then, replacement of haemostatic concentrations of the deficient factor has been the mainstay of treatment of bleeding episodes, according to the type and severity of bleeds and until complete resolution of symptoms.⁶ Recurrent joint bleeds, inevitably leading to crippling arthropathy were the hallmark of these diseases before 1970s, when plasma fractions containing FVIII or FIX were still not available. At that time the mortality of bleeding was very high and the life expectancy of persons with haemophilia was much lower than that of the general population.¹

Haemophilia care does not consist only of replacement therapy and haematologic follow up. The haematologist's clinical and laboratory expertise should be conjugated to other diagnostic and therapeutic facilities for the management of bleeding at various sites, surgery and chronic complications. The need for a multidisciplinary integrated approach at specialised centres for this rare congenital disease requiring complex management has been recognised since 1960s.¹

In the western world today, it is possible for a child with haemophilia receiving adequate treatment to live a near normal life. An accurate diagnosis is quickly established, the family is educated on the management and the child is put either on prophylactic factor replacement or on-demand replacement given at home.⁶ But, this level of treatment is expensive. In Sweden for example, it costs US\$100,000 per year to provide prophylactic factor replacement for one child with haemophilia.⁶

Current service provision

In Malaysia, currently there is no national standard or holistic approach in the management of patients with haemophilia to ensure high quality multidisciplinary approach to improve patient outcomes and optimise resource utilisation.

The haematology service started in the blood bank in 1980s and hence for historical reasons, haemophilia care is provided by the blood bank. Haemophilia patients receive their treatment from the blood bank and referred to the haematology or paediatric wards when required.⁷

In the past two decades many advances have been made in understanding bleeding disorders (haemophilia, haemophilia with inhibitors and other rare bleeding disorders), in terms of the level of expertise required to treat the patients, how the patients should be treated, and where they should go to receive treatment. The need for the provision of adequate treatment is also important to prevent disability and the social costs linked to it such as incomplete education and unemployment.

Currently there are two haemophilia treatment centres in Malaysia; one attached to the National Blood Bank, Hospital Kuala Lumpur and the other at Hospital Ampang. At Hospital Ampang, care is comprehensive and provided by specialists (haematologists) conducting the assessment and acute treatment of the patient's haemophilia condition with integrated clinics offering services such as physiotherapy and dental care. At the National Blood Bank, patients receive their treatment via the haemophilia expert nurse and blood bank doctors but expert medical assessment is limited and access to dental care and physiotherapy means a trip to the nearby Hospital Kuala Lumpur.⁷

Home-treatment is currently being practised in Hospital Ampang and National Blood Bank while patients from outside Klang Valley receive on-demand treatment (which may be suboptimal) from the respective state hospitals.⁷

The National Blood Bank procures haemophilia factor replacements (prothrombin complex concentrate (PCC), Factor IX (FIX), factor VIII (FVIII)) and allocates them upon request to the 13 state hospitals. Ampang Centre of Excellence for Haematology purchases their own factors as the National Blood Bank has inadequate supply.⁷

Bypassing agents for the treatment of haemophilia with inhibitors are only prescribed at the National Blood Bank haemophilia treatment centre but not all patients have access to these. Of the 81 estimated haemophilia patients with inhibitors in Malaysia, very few of those received treatment with bypassing agents. The remaining inhibitor patients receive only PCC. For bleeding episodes in the brain, intracranial haemorrhage (ICH); iliopsoas bleeds and surgery, the patients receive activated recombinant FVII (rFVIIa). For bleeding into joints, patients do not get a bypassing agent; they only receive PCC. The National Blood Bank only has budget sufficient for use in its own haemophilia treatment centre. At Hospital Ampang, all acquired haemophilias with life or limb-threatening haemorrhage is treated with rFVIIa or Factor Eight Inhibitor Bypass Activity (FEIBA).⁷

Based on the current service provision in Malaysia, the review was requested by a Senior Consultant Paediatric Haemato-oncologist in order to improve the quality of care of haemophilia patients in the country.

CHAPTER 2 : DEFINITION OF POLICY QUESTION AND OBJECTIVES

Policy question

Should a national haemophilia program be introduced in Malaysia?

Overall aims and objectives of the assessment

This project aims to provide evidence based guidance on management of haemophilia patients and ultimately identify the best model of care for haemophilia patients to be adopted or adapted in Malaysia. In order to do so, certain critical areas of care were identified to be assessed and these objectives were outlined:

1. To assess the efficacy and resource implications of prophylaxis treatment when compared to on-demand treatment for patients with haemophilia
2. To assess the safety, effectiveness and cost-effectiveness of recombinant factors compared to plasma-derived
3. To assess the efficacy and resource implications of recombinant activated FVII (rFVIIa) when compared to activated prothrombin complex concentrate (aPCC) the resource implications
4. To assess the effectiveness of comprehensive care including non-pharmacological management of haemophilia

One of the objectives to assess the effectiveness of the screening program and diagnostic strategies for haemophilia and rare bleeding disorders which was initially outlined in the protocol was dropped due to scarcity of evidence.

These objectives were developed into a series of questions, which were addressed in a phased review:

1. Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and other rare bleeding disorders and what are the resource implications?
2. Is recombinant factor VIII and factor IX more cost-effective compared to plasma-derived?
3. In patient with inhibitors, is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?
4. Is comprehensive care effective and what is the role of non-pharmacological in a (dental, physiotherapy, orthopaedics, genetic counselling, psychologist, rehabilitation, nutrition, nursing) for haemophilia?

CHAPTER 3 : METHODS

Methods of the review, analysis and inclusion criteria has been specified in advance and documented in a protocol. The protocol was registered with International Prospective Register of Systematic Reviews (PROSPERO), Centres for Reviews and Dissemination, University of York, United Kingdom on 25 May 2012 with registration number CRD42012002450.

Search strategy

The search aimed to systematically identify all literature related to the questions in this review. The last search was conducted in August 2012.

Sources searched

Eight electronic databases were searched from inception: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); Pubmed; EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases.

In addition to the database searches, articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals.

Search terms

A combination of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords free text were used. Copies of the search strategies used in MEDLINE are included in Appendix 4 (these were adapted for use in other databases). The search was limited by including search filters for 'human studies'

Inclusion and exclusion criteria

Eligibility assessment was conducted by two reviewers in an unblinded standardised manner independently using these prespecified inclusion and exclusion criteria.

Inclusion criteria

Articles were selected for inclusion in this systematic review on the basis of the following criteria:

Study design

For systematic review of clinical effectiveness, systematic reviews, meta-analysis, RCT and non-randomised comparative studies will be included.

For systematic review on cost-effectiveness of haemophilia program, which will include prophylaxis versus on-demand treatment, all cost-effectiveness studies of satisfactory quality will be included.

For systematic review on comprehensive care or non-pharmacological care, systematic reviews, review papers and primary studies will be discussed.

Population

Patients with all types of haemophilia and clotting factor deficiency/coagulation bleeding disorders.

Intervention

- i. treatment – prophylaxis
- ii. recombinant factor
- iii. comprehensive care

Comparators

- i. on-demand treatment
- ii. plasma-derived factors
- iii. non-comprehensive care

Outcome

One or more of the following outcome measures were assessed

- i. Effectiveness of the haemophilia programme as measured by detection rate, mortality rate, survival rate, quality of life, and quality adjusted life years (QALY) gained
- ii. Effectiveness and adverse events of the prophylaxis and on-demand treatment as well as recombinant and plasma-derived factors as measured by joint bleeds, quality of life, clinical scale on joint functions, arthropathy
- iii. Cost, cost-benefit, cost-effectiveness, and cost-utility of the haemophilia programme and treatment strategies

Publication

Full text articles published in English

Exclusion criteria

- i. Animal study
- ii. Narrative review
- iii. Laboratory study
- iv. Non-English full text articles
- v. Platelet disorders
- vi. Connective tissue diseases
- vii. Articles published before year 2000 on economic evaluations were excluded

Quality assessment strategy, grading of evidence and conclusion

The validity of the eligible studies was assessed by two reviewers independently using prespecified criteria. For systematic reviews and meta-analysis, the criteria assessed include an unbiased selection of articles, heterogeneity of the included studies and publication bias. For RCTs, the criteria assessed were sequence generation, allocation concealment, blinding, explanation on loss to follow up, intention to treat analysis and other potential sources of bias such as funding. For non-randomised studies with comparison, the criteria assessed were random selection of participants, prospective or retrospective study, blinding, explanation on loss to follow up, control of confounding factors and other potential sources of bias. For economic evaluation, we used two steps to evaluate the risk of bias. First we used the same criteria as RCTs and non-RCTs, then we appraised following Critical Appraisal Skill Programs checklist for economic evaluation. The risk assessment checklists which were developed a priori were presented in Appendix 5. Summaries on risk assessment for studies included in each chapter were presented in the relevant chapter.

The quality of the evidence was later graded according to US/Canadian Preventive Services Task Force grading system (see Appendix 6).⁸ To be caution in interpretation, the grades chosen to indicate the strength of evidence cannot be interpreted as the ultimate truth. It is also important to note that when scientific evidence is concluded as being insufficient, this does not necessarily mean that the given method has no effect.

Data extraction strategy

Data from included studies were extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements were resolved through discussion. A third person, whose decision is final were consulted when disagreements persist after discussion.

Information was extracted from each included trial on (1) characteristics of trial participants (2) the trials inclusion and exclusion criteria (3) type of intervention (4) type of control used (5) outcome measures (including joint bleeds, quality of life, clinical scale on joint functions, arthropathy, incremental cost-effectiveness ratio (ICER) and other cost measures.

Data synthesis

All the data extracted were summarised in evidence table. The evidence was presented to a multidisciplinary expert committee member. Data were assessed for suitability for pooling with regards to the intervention, study design, populations, comparators and outcome. Due to methodological and clinical heterogeneity of the studies, a narrative synthesis was used.

The overall search results were presented in Chapter 4. The detailed results were presented in chapters according to the research questions, namely

Chapter 5: Prophylaxis approach compared to on-demand approach in managing haemophilia

Chapter 6: Recombinant versus plasma-derived factors

Chapter 7: Treatment of patients with inhibitors

Chapter 8: Comprehensive Haemophilia Care

CHAPTER 4 : OVERALL SEARCH RESULTS

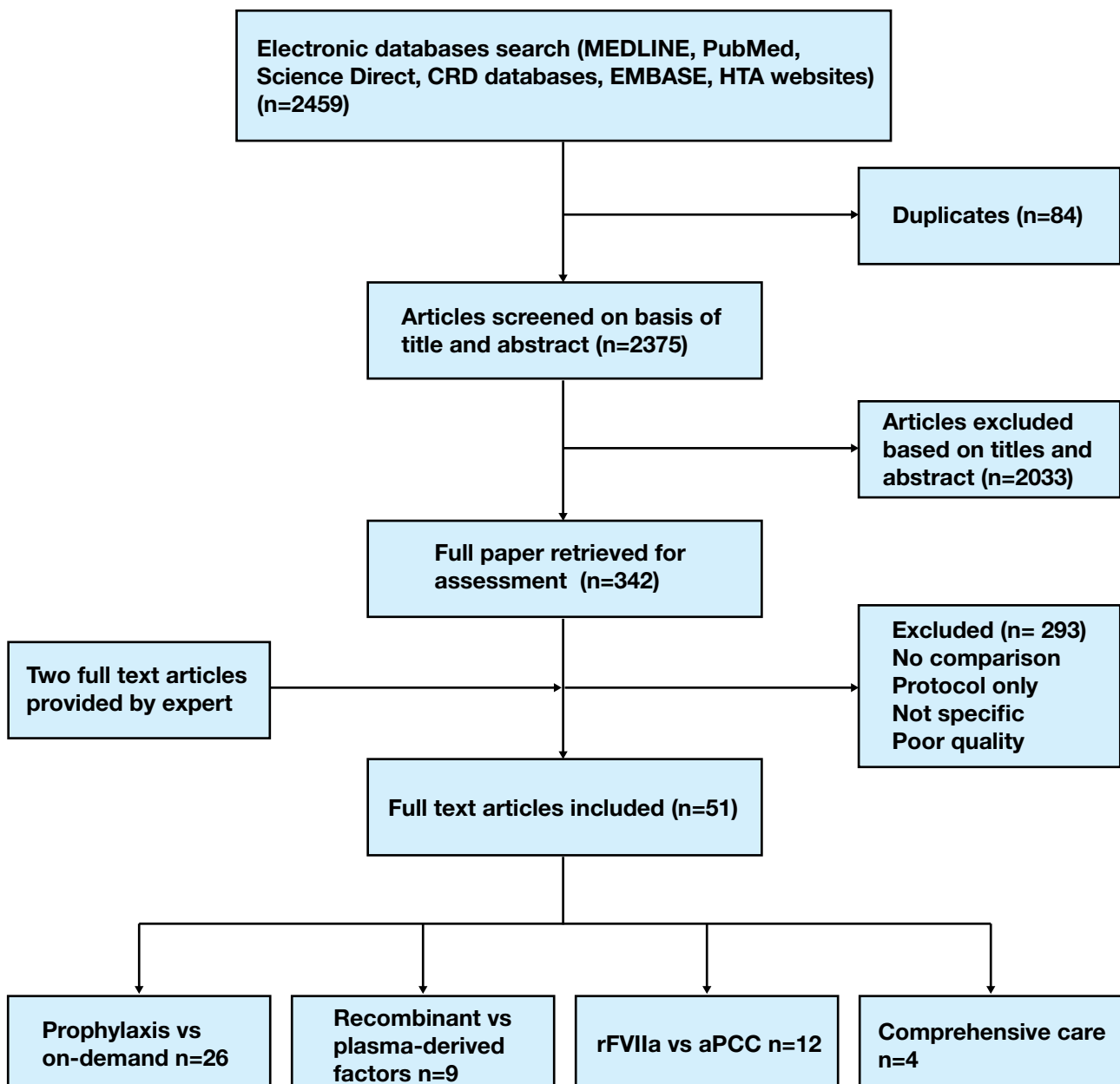
The electronic searches identified 2459 articles. Out of these, 84 were duplicates. Two reviewers screened 2375 titles and abstracts. A total of 342 full text articles were ordered. Forty nine articles met our inclusion and exclusion criteria. Two articles on haemophilia B were provided by an expert in this field and included in the evidence as they fulfilled the inclusion and exclusion criteria.

A flow diagram showing the number of articles identified, retrieved and included in the review is presented in Figure 1.

The evidence tables of these studies were presented in Appendix 8. The excluded studies were listed in Appendix 9.

The characteristics of included studies are discussed in the relevant chapters.

Figure 1. Flow chart of study selection



CHAPTER 5 : **PROPHYLAXIS APPROACH COMPARED TO ON-DEMAND APPROACH IN MANAGING HAEMOPHILIA**

Introduction

Haemophilia arthropathy due to repeated joint bleeds is the major cause of morbidity in persons with haemophilia. In patients with severe form of the disease, i.e. factor VIII (FVIII) or factor IX (FIX) levels < 0.01 IU/mL or 1% of normal, bleeding episodes may occur as frequently as 20-30 times per year, and furthermore, life-threatening bleedings such as ICH may occur.^{9, 10}

The optimal approach to haemophilia treatment is the use of clotting factor preparations in such a way that bleeds and chronic joint damage are prevented, short and long-term complications avoided and there is full integration of the patient into society.¹¹

On-demand factor infusion, also known as episodic therapy is defined as therapy to abrogate an acute haemorrhage. Cessation of bleeding does not reverse the deleterious effects of synovial tissues by the blood already accumulated in the affected joint.⁴

The concept of regular infusion of factor concentrates to prevent bleeding in haemophilia was first introduced in Sweden, the Malmö Centre in 1958 by Nilsson et al.¹² At that time, FVIII was not always available in sufficient amounts and the doses given were small compared with the norms in Sweden today. Moreover many patients who received prophylaxis had already developed arthropathy prior to prophylaxis initiation. Despite these limitations, Nilsson et al reported the most comprehensive experience of prophylaxis up to the date comprising 60 patients in 1992, demonstrating that prophylactic treatment protects patients from the development of haemophilic arthropathy.⁹

However, the evidence on prophylaxis was obtained mainly from observational studies and without comparisons. In many countries, haemophilia patients are still treated as on-demand. A survey published in 2006 included 147 haemophilia treatment centre (HTC) that monitored 16115 haemophilia patients in the United States, Canada, Australia, Sweden, Belgium, Brazil, Finland, Hungary, Iceland, Israel, Japan, Malaysia, Mexico, Holland, New Zealand, South Africa, Spain and Taiwan. Overall 37% of patients with severe haemophilia A were receiving prophylaxis while 54% received on-demand therapy (inhibitor patients were classed separately and accounted for the remaining 9%). Primary prophylaxis was prescribed for 19% of severe haemophilia A patients, secondary prophylaxis for 12% and secondary intermittent prophylaxis for 6% of patients.¹³

There is no universal agreement on the definition of “prophylactic therapy” for haemophilia as shown in Table 1. The European PedNet group (the European Paediatric Network for Haemophilia Management) has suggested definitions of prophylaxis in 1998 and later updated in 2006 to reflect the variety of prophylaxis regimens implemented in many countries today.¹⁴ Berntorp et al in 2002 reported the Consensus Perspectives on Prophylactic Therapy for haemophilia which defined primary prophylaxis either based on age or onset of bleeding.¹⁵ Another set of definitions, Canadian Consensus definition has been reported by Ota et al in 2007.¹⁶

Table 1. Definition of prophylaxis treatment

Source	Primary Prophylaxis	Secondary Prophylaxis
The Canadian Consensus Study¹⁶	Factor infusions given to prevent bleeding and its consequences, usually starting in the first or second year of life, before the third but usually after a first bleed	Factor infusions in order to prevent recurrent bleeding, beginning after target joint bleeding has developed or after three joints or significant soft tissue bleeds have occurred and given regularly or prior to activities
Berntop et al¹⁵	<p>Determined by age: long-term continuous (with the intent of treating 52 weeks/year up to adulthood and receiving treatment a minimum of 46 weeks/year) treatment started before the age of 2 years and prior to any clinically evident joint bleeding</p> <p>Determined by first bleed: long-term continuous (with the intent of treating 52 weeks/year up to adulthood and receiving treatment a minimum of 46 weeks/year) started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed) irrespective of age</p>	Long-term continuous (with the intent of treating 52 weeks/year up to adulthood and receiving treatment a minimum of 46 weeks/year) treatment not fulfilling the criteria for primary prophylaxis
PedNet¹⁴	<p>Primary prophylaxis A</p> <p>Regular continuous treatment started after the first joint bleed and before the age of two years</p> <p>Primary prophylaxis B</p> <p>Regular continuous treatment started before the age of two years without previous joint bleed</p>	<p>Secondary prophylaxis A</p> <p>Regular continuous (long-term) treatment started after two or more joint bleeds or after the age of two years</p> <p>Secondary prophylaxis B</p> <p>Intermittent regular (short term) treatment, because of frequent bleeds</p>

The aim of this chapter is to compare the efficacy, safety and resource implications of the different treatment strategies for patients with haemophilia.

Characteristics of included studies

Study design

Twenty six studies were included in this review, where one of the studies is a systematic review and meta-analysis, one HTA report, two RCTs, two non-RCT, eight retrospective cohort, three cross-sectional studies and a postmarketing surveillance study. As for economic evaluation, three of the studies were cost-utility analysis, four cost-effectiveness analyses, four costing studies and a willingness to pay study.

Participants

Most of the studies included patients with haemophilia A and haemophilia B without inhibitors. A few studies did not indicate whether they included patients with inhibitors.

Intervention

Studies using prophylaxis approach in managing haemophilia patients which include primary prophylaxis and secondary prophylaxis either using high dosage or intermediate dosage of concentrates were included in this review.

Comparators

The prophylaxis approach was compared with on-demand, episodic or enhanced episodic approach. In one study, primary prophylaxis were compared with secondary prophylaxis and in another study high dosage of prophylaxis concentrates was compared with intermediate dosage.

Outcome measures

The outcome measures assessed in the studies included short term outcome such as bleeding episodes and joint haemorrhages, and long-term outcome on preservation of joints and target joint development.

Joint arthropathy is frequently measured by Pettersson radiologic score. Pettersson score evaluates x-rays of the six main joints. Each joint is scored from 0 to 13 points, 0 points signifying no signs of arthropathy. The maximum total score is 78 points.¹⁷ See Appendix 7

Other outcome measured in the studies were clotting factor concentrate usage, days of hospitalisation, days away from school or work, quality of life, cost, ICER and incremental cost-utility ratio (ICUR).













Country




The HTA report was conducted in Sweden; the RCTs were from Italy and United States. One of the non-randomised controlled studies was conducted in Poland and UK and another study was conducted in the United States and Europe. Four of the retrospective cohort studies used cohort from different countries such as Sweden, France, the Netherlands and Norway, other studies were conducted in Spain, Taiwan, United Kingdom, Italy and New Zealand. Two of the cross-sectional studies were conducted in multiple countries in Europe, and one in Spain. The economic evaluation studies were conducted in the United Kingdom, Canada, Sweden, Norway, Germany, the Netherlands and Iran.

Risk of bias

Two reviewers assessed the risk of bias of the included studies. The results were summarised in Figure 2 and Figure 3.

Figure 2. Summary risk of bias of RCTs that compared prophylaxis with on-demand approach

CRITERIA ASSESSED	GRINGERI 2011	MANCO-JOHNSON 2007
Sequence generation		
Allocation sequence concealment		
Blinding		
Explanation on loss to follow up		
Intention to treat analysis		
"Other" potential sources of bias		

LEGEND	 YES	 NO	 CAN'T TELL
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The two RCTs included in this review were not double blinded probably due to the nature of the intervention. However, the assessors were blinded. The Manco-Johnson et al study has low risk of bias but Gringeri et al study has unclear risk of bias. Gringeri study was supported by an unrestricted grant from industry. Manco-Johnson study was supported by grants from the Centers for Disease Control and Prevention and the National Institutes of Health, United States of America.

Figure 3. Summary risk of bias of non-randomised studies that compared prophylaxis and on-demand approach

CRITERIA ASSESSED	RANDOM SELECTION OF PARTICIPANTS	PROSPECTIVE STUDY	BLINDING	EXPLANATION ON LOSS TO FOLLOW UP	ANALYSIS TAKES INTO ACCOUNT CONFOUNDING FACTORS	"OTHER" POTENTIAL SOURCES OF BIAS
Fischer 2002	−	−	−	+	+	+
Royal 2002	−	−	−	+	+	+
Schram 2003	−	−	?	+	+	+
Carlsson 2003	−	−	−	+	+	+
Van den Berg 2003	?	−	−	+	−	?
Morado 2005	+	−	−	−	−	?
Fischer 2003	−	−	−	+	+	+
Miners 1998	+	−	−	+	+	?
Collins 2010	−	+	−	−	−	+
Dmozynska 2011	−	+	−	+	−	+
Smith 2005	−	+	−	+	−	+
Van Dijk 2005	−	+	−	+	−	−
Fischer 2011	−	−	−	+	+	+
Tagliaferri 2008	−	−	−	+	−	−
Schobess 2008	+	−	−	+	+	−
Liou 2011	?	−	−	+	+	+

LEGEND	YES	NO	CAN'T TELL
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The observational or non-randomised studies were mostly retrospective except three studies. There was no element of blinding in any of the studies. Nine of the studies were fully or partially industry funded. These studies were at high risk of bias.

Efficacy

lorio et al in a systematic review evaluated the effect of preventive use of clotting factor concentrates in haemophilia A and haemophilia B patients. They compared primary prophylaxis approach with either on-demand approach, placebo (used in earlier studies) or other types of prophylaxis. Six studies with a total of 142 participants were identified and included in the review. Two studies were randomised controlled open trials (Gringeri 2011 (ESPRIT study) and Manco-Johnson 2007 (Joint Outcome study, JOS)) and four were cross-over in design (Aronstam 1976, Aronstam 1977, Carlsson 1997, Morfini 1976). The studies were clinically and methodologically heterogeneous and meta-analyses could only be performed for two studies (Gringeri 2011 and Manco-Johnson 2007). The pooled result showed statistically significant reduction of total bleeding in patients treated on prophylaxis when compared to those treated on-demand where the rate ratio was 0.30 (95% CI 0.12 to 0.76), however there was significant statistical heterogeneity where I^2 was 99%.^{18 Level I}

For radiologic joint score outcome, the review reported that patients on primary prophylaxis in the ESPRIT study showed statistically significant protection from joint damage when compared to standard on-demand treatment where the risk difference was 0.70 (95% CI 0.39 to 1.01). The difference in JOS study was borderline with risk difference (RD) 0.15 (95% CI -0.01 to 0.31).^{18 Level I} The number needed to treat (NNT) for joint damage from the primary papers, in ESPRIT study, was two (based on radiological findings) which means that two patients need to be treated to prevent one joint damage. As for JOS study (based on MRI findings) the NNT was three which means that three patients need to be treated to prevent a joint damage.^{19, 20 Level I}

In terms of quality of life outcome, it was only reported in ESPRIT study, where Haemo-QoL questionnaire showed that overall QoL was 22.2 (SD 8.2), in a scale from 0 to 100 where 100 indicates completely deteriorated QoL. A significant difference was found in children receiving on-demand treatment versus those receiving prophylaxis in the subscale exploring the dimension “family”, which was more impaired in the on-demand treatment group where the mean difference (MD) was 32.73 (95% CI 22.30 to 43.16).^{18 Level I}

As for clotting factor concentrate usage, there was a significant increase in consumption of factor VIII in patients treated with prophylaxis when compared to those treated on-demand, MD 5270 IU/month per patient (95% CI 4230 to 6320), I^2 0%.^{18 Level I}

Berntop et al conducted a HTA on treatment of haemophilia. They included nine studies to answer question on the differences in outcome with prophylaxis and on-demand treatment. They also included four studies with prophylaxis or on-demand treatment reporting orthopaedic, school outcome or resource utilisation. The studies were described narratively and no statistical pooling was done. They concluded that the scientific evidence is insufficient to determine if there are any differences in the long-term effects (>6 years of follow up) of different treatment regimens in haemophilia A and B. Clinical experience and the results from retrospective, observational studies suggested that early prophylaxis treatment yields better results than on-demand treatment but this should be confirmed by prospective longitudinal studies.^{5 Level I}

Collins et al conducted an open label prospective cross-over trial in the United States and Europe among male patients aged 30-45 years with severe haemophilia. The patients were treated on-demand with sucrose-formulated recombinant factor VIII (rFVIII-FS, Kogenate FS) for six months followed by seven months treatment with prophylaxis at a stable dose of 20 – 40 IU/kg three times per week administered at home by slow intravenous infusion at a maximum rate of 2 mL/min. The median for all bleeds was 20.5 (IQR 14-37) during on-demand treatment and 0 (IQR 0-3) $p < 0.001$ during prophylactic treatment. For joint bleeds, the median was 15.0 (IQR 11-26) during on-demand treatment and 0 (IQR 0-3), $p < 0.001$ during prophylactic treatment. The Gilbert score was significantly reduced after the prophylaxis treatment where the score was 24.8 ± 15.1 , 25.3 ± 11.7 and 19.8 ± 11.7 at baseline, month 6 and month 13 respectively, $p < 0.001$. The consumption of rFVIII-FS concentrates were 581 infusions during on-demand and 1650 infusions during prophylaxis. 89.8% of infusions were administered for treatment of spontaneous or trauma bleeds during the on-demand period (and 7.7% for preventive prophylaxis), only 3.2% of infusions were for spontaneous or trauma bleeds during prophylaxis period (94.4% were for regular or preventive prophylaxis). Total consumption per patient was 70421 ± 43057 and 211933 ± 54725 IU respectively.^{21 Level II-1}

Dmoszynska et al reported a multicentre open label, non-randomised prospective study conducted in Poland and United Kingdom. Seventy patients with moderate to severe haemophilia A were included where 11 of them was treated prophylactically with Optivate and another 59 patients was treated on-demand with the same product. Optivate is an intermediate-purity FVIII/von Willebrand factor (VWF) concentrate manufactured using a dry heat-treatment at 80°C for 72 h. The mean number of bleeds per patient was 23.5 for prophylaxis group (mean 0.24 (95% CI 0.08 – 0.40) new bleeds per week per patient) compared to 70.4 for on-demand patients (mean 0.75 (95% CI 0.65 – 0.86) new bleeds per week per patient). The total number of bleeds in the prophylaxis was 258 and on-demand was 4151. The mean dose per infusion/patient IU/kg was 41.5 (95% CI 4.90, 14.12) in the prophylaxis group, and 26.0 (95% CI 22.15, 29.90) in the on-demand group.²² Level II-2

Fischer et al compared two cohorts comprising 49 severe haemophilia patients on intermediate dosage prophylaxis from the Netherlands receiving 15 – 25 IU/kg two or three times weekly for haemophilia A and 30-50 IU/kg once or twice weekly for haemophilia B with 106 patients receiving on-demand treatment from France. Patients primarily treated with prophylaxis had fewer joint bleeds per year (median 2.8 versus 11.5), a higher proportion of patients without joint bleeds (29% versus 9%), lower clinical scores (median 2.0 versus 8.0), and less arthropathy as measured by Pettersson score (median 7 points versus 16 points). The mean annual clotting factor consumption was 1488 ± 783 IU/kg/year in the prophylaxis group and 1612 ± 1442 IU/kg/year in the on-demand group.²³ Level II-2

Fischer et al reported another study comparing three cohorts of patients with severe haemophilia. The first cohort comprised of 24 patients from Sweden who received high dose prophylaxis with 25 – 40 IU/kg three times a week for haemophilia A and 30-50 IU/kg twice a week for haemophilia B. The second cohort was 49 patients from the Netherlands who received intermediate dose prophylaxis of 15-25 IU/kg two to three times per week for haemophilia A and 30-50 IU/kg once or twice weekly for haemophilia B. The median annual number of joint bleeds was 0.5 (IQR 0.2 – 1.8), 2.8 (IQR 0 – 7.8) and 11.5 (IQR 3.8 – 24.0) in the high dose, intermediate dose and on-demand group respectively. The median Pettersson score was 4 (IQR 0 – 15), 7 (IQR 3 – 15) and 16 (IQR 8 – 28) respectively. The median clinical score was 0 (IQR 0 – 1.0), 2.0 (0.3 – 5.0) and 8.0 (IQR 3.3 – 14.0) respectively. The clotting factor consumption was 4301 IU/kg/year (IQR 3034 – 4726), 1550 IU/kg/year (IQR 824 – 1968) and 1260 IU/kg/year (IQR 630 – 2130) respectively.¹⁷ Level II-2

Carlsson et al reported a retrospective cohort study conducted from 1989-1999 among 156 patients with severe haemophilia A and B in Norway and Sweden. The patients were born between 1949 and 1989 (for prophylaxis group) and between 1939 and 1981 (for the on-demand group). Ninety five patients received primary prophylaxis and 61 patients were on-demand. Median annual factor concentrates consumption in the prophylaxis population was about three times as large as for the on-demand patients. For adults the median total IU/kg per annum for prophylaxis was 3024 IU (IQR 2328 – 3864) and for on-demand 780 IU (IQR 400 – 1303). For outcome on hospitalisation, patients on on-demand treatment had more total number of hospital days (320 versus 246) and undergone more invasive procedures (121 versus 48). As for employment, on-demand patients were more on 100% sick leave/early retirement in the year 1999 (33%) compared to patients on prophylaxis (9%). Panel data analysis conducted showed that patients on prophylactic treatment had 50 percentage units lower probability of undergoing a major surgical procedure. A person who had been on prophylactic treatment all the time between 2 and 18 years old had a 74 percentage unit lower risk of having a longer period of loss of working days due to haemophilia compared with a person who did not have any prophylaxis between 2 and 18 years ($p < 0.01$). The factors associated with variations in annual factor concentrate use of on-demand patients were being adults (18 years old and above), the prescribed dose per kg when haemorrhaging and the number of weeks of secondary prophylaxis during the year. Among children on prophylaxis, the factors identified were having haemophilia A and weighed relatively more than other children in the same age. Among adults on prophylaxis, increasing the dose per kg body weight by 1 IU increased annual consumption of factor concentrate by 2580 IU.²⁴ Level II-2

Van den Berg reported a retrospective cohort study conducted among 156 patients with severe haemophilia born between 1970 and 1980. Three cohorts were compared; Swedish cohort who received high dose prophylaxis regime (19 patients), Dutch cohort who received intermediate dose prophylaxis (21 patients) and French cohort who received on-demand treatment (116 patients). The mean annual number of joint bleeds was three in Swedish cohort, 5.3 in Dutch cohort and 16.3 in French cohort. The mean Pettersson score was 6.5, 6.0 and 18.8 respectively. The mean orthopaedic joint score was 2.4, 2.0 and 7.7 respectively. The mean clotting factor consumption was highest in the Swedish cohort (3713 IU/kg/year) followed by Dutch cohort (1828 IU/kg/year) and French cohort (1634 IU/kg/year). The mean age at start of prophylaxis was 2.6 years in Swedish cohort and 4.6 years in Dutch cohort. The mean age at the start of home-treatment was 9.1 years in Dutch cohort and 8.9 years in French cohort. The data was not available for Swedish cohort.²⁵ Level II-2

Liou et al compared 13 patients with severe haemophilia who received secondary prophylaxis with 37 patients who received on-demand treatment in Taiwan. The median number of bleeding episodes (min-max value) was 7.76 (1.18-18.22) in prophylaxis group and 31.91 (16.36-78.21) in on-demand, $p<0.0001$. The median number of joint bleeding episodes was 5.18 (0.94 – 17.33) in prophylaxis group and 27.12 (3.47 – 73.24) in the on-demand group, $p<0.001$. Regression analysis after adjusting for age, weight, month followed up and age squared showed patient treated on-demand would be expected to have 24.6 more bleeding episodes per year than a patient on prophylaxis treatment. The median annual FVIII utilisation (IU/kg/year) was 1824 in the prophylaxis group and 1324 in the on-demand group, $p<0.01$.²⁶

Level II-2

Miners et al conducted a retrospective study in the United Kingdom in two parts. The first part was to evaluate the annual median number of bleeds between 1980 and 1995 where 179 patients with severe (<1 IU/dL) haemophilia A, B and vWD were included. A subgroup of these patients 25 adults and 22 children who had previously received treatment on-demand and who had switched to treatment with prophylaxis were included in the second part of the study in order to examine the effects of change. Between 1980 and 1995, a total of 38104 bleeds occurred where 63% were joint bleeds. The overall median number of bleeds per patient for the 16-year period was 162 (range 1-1096). In 1980, patients had a median of 23.5 bleeds (range 1-107) but by 1995 this has dropped to 14 (range 0-52). In 1980, there was a median of 20 (range 1-67) joint bleeds per patient, but in 1995 this had fallen to 8 (0-45), both decreases were significant ($p<0.0001$). As for the effect of switching from treatment on-demand to prophylaxis, in adults, prior to prophylaxis, the median of bleeds was 37 (range 11-132) per year and used a median of 560 (range 196-3120) IU/kg/year of clotting factor. In year 0, there was 13 bleeds (range 0-92), 65% reduction compared to prior to prophylaxis. However, the clotting factor usage increased 350%, 1935 (range 592-3376) IU/kg/year. For children, the median of bleeds prior to prophylaxis was 21 (range 3 – 64) bleeds per year and used a median of 1974 (range 700-3750) IU/kg/year of clotting factor. In year 0, there was 11 bleeds (range 0 – 49) but the clotting factor usage increased to 2967 (range 1742-5472) IU/kg/year.²⁷ Level II-2

Tagliaferri conducted a retrospective observational cohort study using each patient as its own control in Italy. Eighty four severely affected haemophilia patients, who had switched from on-demand to prophylaxis during adolescent or adulthood because they bleed frequently and/or had developed target joints, were included. Switching to prophylaxis reduced the mean annual number of total and joint bleeds (35.8 versus 4.2 and 32.4 versus 3.3, $p<0.01$, respectively) and days lost from work/school (34.6 versus 3.0, $p<0.01$). Secondary prophylaxis reduced the mean orthopaedic score (18.1 versus 13.8, $p=0.13$) in the whole cohort but the difference was not statistically significant. The mean Pettersson score remained unchanged in the whole cohort and either subgroup (13.9 on-demand versus 13.7 on secondary prophylaxis). Prophylaxis significantly reduced the mean annual number of days of hospitalisation, of medical visits at haemophilia centres, of orthopaedic consultations and of instrumental exams. Haemophilia patients on secondary prophylaxis consumed annually more factor concentrates than on-demand (mean 3987 (876) IU/kg versus 2871 (2049) IU/kg, $p<0.01$). There was improvement of patients in all the five domains of Health Related Quality of Life (HRQoL) when put on secondary prophylaxis irrespective of age and orthopaedic score at the start of prophylaxis.²⁸ Level II-2

Smith et al reported an open label multicentre postmarketing surveillance study in Europe and New Zealand among 60 previously treated and untreated patients with moderate to severe haemophilia A (FVIII < 5%) without inhibitor. Thirty two patients received prophylaxis treatment with ReFacto and 28 patients received on-demand treatment. ReFacto is a recombinant β -domain deleted FVIII and does not contain human serum albumin in the final formulation. Mean Spontaneous bleed (SD) per year in prophylaxis group was 10.33 (SD 10.63). ReFacto resolved 81.7% of breakthrough bleeds with one or two infusions. In the on-demand group, 542 bleeding episodes occurred, 95.2% of bleeds were resolved with one or two infusions.^{29 Level II-2}

Schramm et al published a multicentre, cross-sectional study of 1042 haemophilia subjects across Europe to compare various health outcomes associated with on-demand versus prophylactic factor substitution therapy. There were 335 patients who received prophylaxis therapy and 670 who received on-demand treatment. After multivariate analysis controlling for age, haemophilia type, severity, inhibitor status, HIV status and type of employment, people treated on-demand were 3.4 times more likely to suffer a joint bleed during the 6-month reporting period than those treated prophylactically, OR 3.4 (95% CI 2.43 to 4.76). After stratifying for age, subjects who were 30 years old and younger, and who were treated on-demand, had an average 7.55 more joint bleeds than subjects treated prophylactically, after adjusting for each of the other independent variables, OR 7.55 (95% CI 5.02, 10.08). Subjects who were over 30 years old and who were treated on-demand had 3.33 more joint bleeds, on average, than subjects treated prophylactically after adjusting for each of the other independent variables, OR 3.33 (95% CI 1.94, 4.72).^{30 Level II-3}

Royal et al reported on the outcomes of quality of life measured by SF-36 of the same study as Schramm et al. The final population for multivariate analysis was 903. The adjusted overall multivariate model showed significant differences in the two treatment groups when all eight dimensions were tested simultaneously ($p < 0.001$). The significant dimensions were less bodily pain, better general health and physical functioning. Subjects were also stratified by HIV status. HIV-negative subjects differed significantly by treatment group and reported significantly lower bodily pain, better general health and scored higher in physical functioning, mental health and social functioning. HIV-positive subjects who were treated on-demand scored higher than subjects treated prophylactically in vitality dimension.^{31 Level II-3}

Lucia et al reported the Spanish Epidemiological Study in Haemophilia carried out in 2006. The study enrolled 2400 patients where 2081 (86.7%) had haemophilia A and 319 (13.3%) had haemophilia B. In terms of severity, 32.8% of the patients were severe, 13.9% were moderate and 53.3% were mild cases. Among the patients, 399 (19.2%) were on prophylaxis where 81 (20.3%) were on primary prophylaxis (PP) and 303 (75.9%) were secondary (SP) and 15 (3.7%) were undetermined. Half of the 682 patients with severe haemophilia A, 313 (45.9%) were on prophylactic treatment. Established haemophilic arthropathy (EHA) was proved for 555/1228 (45.2%) patients. Among the patients, 142/313 (45.4%) with severe haemophilia A who were on prophylaxis were detected to have EHA but only in 2.9% of patients under PP versus 59% of patients receiving SP. No EHA reported in adult severe haemophilia A (HA) patient on the PP, whereas 70.4% on SP had joint damage ($p < 0.00001$). Recombinant FVIII administered for prophylaxis to 71.4% of HA patients and plasma-derived products were used in 28.6%.^{32 Level II-3}

Safety

Iorio et al reported that there was no significant difference against prophylaxis in the rate of infections per treatment group observed, RD 0.14 (95% CI -0.14 to 0.42), I^2 75% (Chi² 4.04, $p = 0.04$). The inhibitor rate was not significantly higher in patients on prophylaxis RD 0.06 (95% CI -0.03 to 0.15), I^2 0% (Chi² 0.06, $p = 0.81$). Sensitivity analysis conducted on adverse events in patients with central venous catheter showed no significant difference, RD 0.03 (95% CI -0.26 to 0.19).^{18 Level I}

Berntop et al in their review concluded that the scientific evidence is insufficient to determine whether the risk of developing inhibitors against coagulation factors is more, or possibly less, for the prophylactic treatment compared with that seen in the treatment only when necessary on-demand.^{5 Level I}

Hacker et al analysed data from JOS study to compare the rate of central venous access device infections in haemophilia patients who received prophylaxis treatment compared with patients on on-demand. The number of participants with a central venous access device (CVAD) who developed a CVAD-related infection while on study was six (21%) in the prophylaxis arm and six (24%) in the episodic arm. Seven of these children developed more than one infection, resulting in a total of 22 incident infections. The mean years CVAD was indwelling before the first infection occurred in the study was 1.6 (95% CI 0.2 to 2.9) in the prophylaxis group and 0.7 (95% CI, 0.2 to 1.2) in episodic therapy group. The crude and adjusted rate ratios for first CVAD-related infection per 1000 CVAD days associated with episodic therapy versus prophylaxis were 1.42 (95%CI 0.46 to 4.40) and 1.23 (95%CI 0.33 to 4.56), respectively. Among 12 children with a CVAD-related infection, three of them had an inhibitor ≥ 0.5 Bethesda Units (BU).^{33 Level I}

Collins et al reported 51 adverse events occurred in 13 patients (65%). Twenty-six of the adverse events (AEs) occurred during the on-demand period and 25 during prophylaxis. About 94% of AEs were mild to moderate and none lead to withdrawal of study. Six SAEs occurred in two patients during the study (one patient during each treatment period) and not considered to be treatment-related and no inhibitor formation was detected during either treatment period.^{21 Level II-1}

Dmoszynska et al reported 22 treatment-related AEs occurred in seven patients (one on prophylaxis) (10%) which include headaches (4%) and dizziness (3%). All patients had negative screens for inhibitors to FVIII throughout the studies, no virus transmission occurred and there was no significant change in laboratory values.^{22 Level II-2}

Morado et al reported a retrospective cohort study among 50 patients with severe haemophilia A who were born between years 1993 to 2003 in Spain. Fifteen patients (30%) developed inhibitors where 12 of them were high responders and three were low responders. The mean age at time of inhibitor appearance was two years (21 months) and ranged from 10 days to 6 years. The response to immunotolerance treatment ranges from 50% to 75%. All the patients with inhibitors were on-demand treatment at the time of inhibitor development. 78% of on-demand patients showed an inhibitor as opposed to none of the 31 patients receiving prophylaxis treatment.^{34 Level II-2}

Smith et al reported five treatment-related, non-SAEs in three patients (one patient had dizziness and phlebitis, one had drug effect decreased and another had drug effect decreased and back pain). A total of seven SAEs were reported. Four SAEs were considered not related to ReFacto which include gastroenteritis, haemorrhage, myocardial ischaemia and suspected ICH. The remaining three SAEs were inhibitor cases; two had to be withdrawn from the study.^{29 Level II-2}

Cost-effectiveness

Iorio et al reported cost analysis with societal perspective conducted in ESPRIT study. ICER per bleeding events avoided in patients on prophylaxis was EUR 7537 whereas for maintaining all joints unaffected over the whole treatment period was EUR 201,601.12.^{18 Level I}

Berntop et al included eight studies in their review on cost-effectiveness of strategy of intervention namely on-demand versus prophylaxis. The studies included were divided into empirical studies and model studies. The empirical studies were included for statements regarding scientific support but model studies only for discussion of economical consequences. Although all the studies included had a health care perspective, but the outcomes for comparison of costs were different. The review concluded that due to few studies of different aims and different study designs, evidence of cost-effective strategies of intervention of patients with haemophilia cannot be stated and although there were few studies published, it was evident that the patient's weight was an important cost driver for the utilisation of factor concentrate and thus for costs of health care intervention of haemophilia.^{5 Level I}

Liao et al evaluated the economic outcomes of both secondary prophylaxis and on-demand therapy for severe haemophilia A. There was significant between-group difference ($p < 0.05$) in median total annual medical cost between prophylaxis therapy (1615.78, range 1042.49 – 4022.12) USD/kg and on-demand therapy (1210.25, range 167.63 – 6217.84) USD/kg. The median annual total factor VIII cost was also significantly different between prophylaxis therapy (1598.27, range 1034.28 – 4007.38) USD/kg and on-demand therapy (1139.6, range 160.43 – 5724.63) USD/kg. The total non-FVIII drug cost and percentage of the outpatient cost attributable to FVIII concentrate usage were also significantly different (99.4% in the prophylaxis group versus 98.76% in the on-demand group). Predictive modelling of scenarios was developed where Scenario 1 – all patients with severe haemophilia A receive on-demand therapy, Scenario 2 – all patients with severe haemophilia A receive secondary prophylaxis therapy, Scenario 3 – 26% of patients receive secondary prophylaxis, 74% receive on-demand therapy, Scenario 4 – 30% of patients who are on secondary prophylaxis will switch to on-demand therapy during adulthood (after 18 years old), Scenario 5 – 30% of the 26% of patients receiving secondary prophylaxis switch to on-demand after 18 years old. 74% stay on on-demand. It was estimated that Scenario 1 would cost USD14 815 692 per patient per year in Taiwan. Scenario 2, 3, 4 and 5 would cost USD16 894 513, USD15 357 816, USD14 904 077 and USD14 889 478 respectively.²⁶ Level II-2

A cost-effectiveness study was conducted by Daliri et al in Iran. It was based on third party payers' perspective and obtained data from retrospective chart review. Twenty-five patients with severe haemophilia (factor level $< 1\%$), without inhibitor or HIV infection were included. Eleven of them were on prophylaxis and 14 were on on-demand treatment. The total factor consumption was 250,500 IU (59.75%) in the prophylaxis group and 168,750 IU (40.25%) in the on-demand group. The mean (\pm SD) of factor consumption was 22,772.73 ($\pm 11,203.48$) and 12,053.57 ($\pm 6,776.78$) respectively. The total bleeding episodes was 17 (6.88%) in the prophylaxis group and 230 (93.12%) in the on-demand group. The mean bleeding per patient per month was 0.25 in the prophylaxis group and 2.73 in the on-demand group. The incremental cost per avoided bleed was 3,201,656 Rials (€213.45) over 6 months in Iran. The results were insensitive to changes in price of clotting factor.³⁵ Level II-2

Lippert et al conducted a cost-effectiveness analysis based on data from multicentre cross-sectional survey involving Germany, Sweden, United Kingdom and The Netherlands. The analysis was conducted based on third party payer's perspective. A total of 506 patients with severe haemophilia A and B (factor level $< 1\%$) without inhibitor were included in the study. The results showed that with prophylactic treatment the incremental cost per avoided bleeding was €6,650 for patients 30 years and younger, €11,731 for patients aged more than 30 years old in Germany. In Sweden the incremental costs per avoided bleed for patients aged more than 30 years was €14,138. In the Netherlands, the incremental costs per avoided bleed for patients aged 30 years and older was €10,833. In United Kingdom the incremental cost per avoided bleeding was €9,315 for patients 30 years and younger and €14,001 for patients aged more than 30 years. ICER for prophylaxis versus on-demand treatment in 1 year HIV-infected patients aged 30 years or less, ranged from €1.24 million per QALY in Germany to €1.73 million per QALY in the United Kingdom. The ICER for HIV-negative patients aged 30 years or younger ranged from €2.21 million per QALY in Germany to €3.10 million per QALY in the United Kingdom. For HIV-negative patients aged over 30 years, the ICER ranged from €4.77 million per QALY in Germany to €5.7 million per QALY in Sweden and the United Kingdom.³⁶ Level II-2

Miners et al evaluated the cost-effectiveness of prophylaxis compared with treatment on-demand. The primary outcome measure used was the number of bleeds experienced by patients. The ICER for prophylaxis compared with treatment on-demand was £547 per bleed avoided ($\{£76683 - £27751\} / 192.5 - 103$).²⁷ Level II-2

Tagliaferri et al calculated the overall cost of concentrate based on retrospective study they conducted, the cost of prophylaxis was higher than that of on-demand treatment (mean, 2990 (SD 657) versus 2153 (SD 1537), $p = 0.01$).²⁸ Level II-2

Schramm et al reported in countries where there were relatively similar numbers of subjects treated on-demand and those treated prophylactically (Germany, Sweden, United Kingdom), the cost for factor replacement therapy was significantly higher for subjects treated prophylactically.³⁰ Level II-3

Carlsson et al conducted a cost evaluation study together with a retrospective cohort study. The study was based on societal perspective. They included 156 patients with severe haemophilia A and B (factor VIII/IX activity <1%) in Norway and Sweden who were born between 1949 and 1989 (for prophylaxis group) and between 1939 and 1981 (on-demand group). The mean cost for an adult (18+) patient-year for on-demand was EUR 51,518 ± 36,035 (mean ± SD) and for prophylaxis EUR 147,939 ± 65,963 (590 and 504 patient-years for on-demand and prophylaxis respectively). Factor concentrate was identified as the major source of costs in both strategies (74% and 94%, respectively). Both other health care cost and costs in other sectors were greater for on-demand (EUR 1807 and 11,358, respectively) than for prophylaxis (EUR 1126 and 7530, respectively). Panel data analysis showed that the average predicted annual cost for a 30 year old on-demand patient was EUR 51,832 (95% CI 44,324-59,341) and for prophylaxis EUR 146,118 (95% CI 129,965-162,271) where the expected annual costs were nearly three times higher for prophylaxis than for on-demand treatment.^{37 Level II-2}

Carlsson et al also reported a willingness to pay study among 609 Swedish households. The mean estimated WTP (year 2002) was EUR 39 (95% CI 31-47) for on-demand and EUR 65 (95% CI 55- 73) for prophylaxis. The WTP for on-demand and prophylaxis exceeded the calculated cost of treatment per taxpayer of providing on-demand and prophylactic treatment. The estimated WTP varied in different subsamples of individual characteristics but confidence intervals always overlapped that of the main results. Sensitivity analysis showed that the ranking of the two treatment alternatives was robust in that the WTP was greater for prophylaxis in all possible subsets.^{38 Level III}

Miners et al conducted a cost-utility analysis with Markov modelling based on United Kingdom National Health Service (UK NHS) perspective in 2002 and updated the report in 2009. They used 100 hypothetical cohort with severe haemophilia A (<1 IU/dL) to model the effect of prophylaxis and on-demand therapy for 70 years time horizon or lifetime. The mean expected costs of treating on-demand and with PP over a 70-years time horizon were approximately £644,000 and £858,000 respectively. The associated QALY is 13.95 and 19.58 respectively. The ICER is £38,000 per QALY. Based on CEAC, the probability of PP being cost-effective at £30,000 per additional QALY is 13%, rising to over 90% at a willingness to pay per additional QALY of £100,000. The CEAC moves sharply to the left (indicating more favourable cost-effectiveness for prophylaxis) following reductions in the clotting factor price, the discount rate for future QALYs and the time between prophylactic infusions of FVIII.^{39, 40 Level III}

Risebrough et al conducted a cost-utility analysis based on Canada societal perspective. They used Markov modelling with 3-month cycles. The model was built based on hypothetical cohort of males with severe haemophilia A (FVIII < 2 %) who began treatment at age 1 and continued for 5 years. The efficacy data was derived from two retrospective case-control studies and one prospective study. They compared three types of therapy; Standard Prophylaxis (SP) who received 25 FVIII units/kg on alternate days, tailored (escalating dose) prophylaxis (EscDose) who began prophylaxis with 50 FVIII units/kg once a week and increased to a higher dosage if they met the escalation criteria and on-demand group who received 40 U/kg upon presentation of bleeding and 20 U/kg on days 1 and 3 postbleed. The expected cost of 5 years of SP was \$569,835 per child compared to \$443,185 for EscDose and \$277,209 for on-demand. The cost for FVIII accounted for 82% and 86% of EscDose and SP respectively. When compared with on-demand, EscDose decreased bleeding episodes by 52 joints-bleeds at an additional cost of \$165,976 (\$33,195 per year). Compared to Demand SP decreased bleeding by 65 joint bleeds at an additional cost of \$292,626. ICER to prevent a joint bleed with EscDose compared to demand was \$3,192. Each additional joint bleed avoided with SP compared to EscDose, cost \$9046. The cost for avoiding a target joint (TJ) was \$244,082 for EscDose compared with on-demand and \$361,857 for SP compared with EscDose. Comparing Demand to EscDose the ICUR was \$542,938 per QALY gained. The incremental cost per QALY gained for EscDose compared with SP was >\$1,000,000/QALY gained. Sensitivity analysis showed that cost of FVIII was a cost driver in the model.^{41 Level III}

There was no local economics study available. The price of recombinant factor VIII concentrate (Kogenate) is ██████████ per 250 IU and the price of plasma-derived factor VIII ranged from ██████████ per 250 IU. (Source: Pharmacy Department, Hospital Ampang and Hospital Kuala Lumpur)

Discussion

This systematic review included 26 studies which met the inclusion and exclusion criteria including two systematic reviews. There were only two RCT identified and these studies have been combined in Iorio et al systematic review and meta-analysis. The other studies were non-RCT, retrospective cohort studies and cross-sectional studies. Most of these studies were conducted in European countries and United States of America but there were two studies conducted in Asian countries namely in Iran and Taiwan. These studies were heterogeneous, thus the results were not pooled.

Overall the results showed that prophylactic therapy, either primary or secondary prophylaxis lead to better short term as well as long-term outcome.^{18, 20, 26, 27} Based on ESPRIT and JOS studies outcome, two or three patients need to be treated to prevent a joint damage which indicated that the prophylaxis therapy is effective.^{19, 20} The evidence also showed that prophylaxis did not reverse established joint damage; it decreases frequency of bleeding and may slow progression of joint disease and improve quality of life. This evidence was supported by all the other comparative observational studies included in this review, though the studies were at high risk of bias and sponsored by industries.^{17, 30}

Social outcomes were measured in Carlsson et al study, patients who were on prophylaxis treatment had shorter hospital days and 50% less probability of undergoing a major surgical procedure. In terms of employment, patients on prophylaxis, had a 74% less risk of having longer period of loss of working days due to haemophilia.²⁴ Studies also showed that patients on prophylaxis have better quality of life.^{20, 31}

Another aspect of early treatment being discussed is whether the mode of treatment has an impact on inhibitor development. The meta-analysis and all the prospective studies showed that there was not significantly higher rate of inhibitors development in haemophilia patients on prophylaxis treatment.^{18-20, 22} Only one study of low quality showed that more patients on on-demand developed inhibitors.³⁴

Other important aspect of safety is the risk of infections. The systematic review showed that there was no significant difference in the infection rate in prophylaxis compared to on-demand treatment.¹⁸ The Universal Database of the Centre for Disease Control in the USA studied viral seroconversions in people with haemophilia between 1988 and 2002. While no patients had seroconverted to HIV and only one patient had seroconverted to hepatitis C, all other seroconversions registered were due to vaccination against hepatitis A and B. Similarly lack of product-related infectious disease was found in 81 Austrian patients followed in a mixture of a retrospective and a 2 years prospective trial covering 772 patient-years.⁴²

There were 11 economics studies included in this review; three of the studies were cost-utility study, three cost-effectiveness analysis, four costing studies and a willingness to pay study. Three of the studies were based on societal perspectives. The rest were either based on health care perspectives or third party payer perspectives. Two studies showed that factor concentrates contributed to more than 90% of the treatment cost^{26, 37} where in certain studies only the cost of factor concentrates were taken into consideration.^{20, 35} Majority of the studies were conducted in European countries, but there were two studies from Asian countries.

All the studies showed that the cost of prophylaxis approach was higher when compared to on-demand approach, two to three times more in most studies. The economic impact was evaluated for short term as well as long-term outcome. If only the cost of the concentrates were taken into account, the ICER per bleeding events avoided ranged from €213.45 over 6 months in Iran to €14,138 in patients aged more than 30 years in Sweden.^{35, 36} The cost increased in patients with HIV infections.³⁶ Tailored escalating dose has also been studied in order to find innovative and potentially less costly alternative compared to SP regime, it was more expensive than on-demand but provided a considerable reduction in the incidence of joint haemorrhage and related morbidity.⁴¹ Cost of FVIII has been shown as the cost driver in most of the studies.^{40, 41}

Other than the cost implications, there are still many issues not answered such as at what age should prophylaxis starts, is there any difference in outcome if the treatment stops after the child reach certain age and what is the dosage to be used.

In terms of dosing, the Malmö protocol and Utrecht protocol has long-term data (more than 20 years).^{23, 25} The Malmö protocol used 25 – 40 IU/kg three times a week for haemophilia A and 30-50 IU/kg twice a week for haemophilia B, whereas the Utrecht protocol used 15-25 IU/kg two to three times per week for haemophilia A and 30 – 50 IU/kg once or twice weekly for haemophilia B.²⁵ However many different protocols are followed for prophylaxis, even within the same country, and optimal regimen remains to be defined.⁴³

Two retrospective cohort studies probably conducted among the same cohort in Sweden, the Netherlands and France showed that the annual number of joint bleeds was markedly reduced in patients receiving high dose prophylaxis and intermediate dose prophylaxis when compared with on-demand treatment. However, the clotting factor consumption was only 12% more in the intermediate dose prophylaxis when compared with on-demand treatment whereas patients on high dose prophylaxis consumed 127% more.^{17, 25} Another study by Fischer et al, comparing high dose prophylaxis and intermediate dose prophylaxis, the age-adjusted clotting factor consumption was two times higher in the high dose regimen and there was no statistically significant difference in the age-adjusted Pettersson score and SF-36 score.²³ However, the median annual number of joint bleeds was lower in patients treated with high dose regimen. After adjustment for age, the annual number of joint bleeds was 77% lower for high dose prophylaxis.²³

A cohort study was conducted in Denmark and the Netherlands showed patients who discontinued therapy had slightly higher risk of joint bleeds but there was no significant changes in clinical score and Pettersson score.⁴⁴

A multicentre cohort study in Germany compared primary and secondary prophylaxis. Patients receiving PP had slightly lower annual bleeding frequency, but there was no significant difference in development of synovitis and Pettersson score between the two groups.⁴⁵

Prophylaxis is currently practiced in countries where there are no significant resource constraints. In United Kingdom, the guideline from United Kingdom Haemophilia Centre Doctors' Organisation which was approved by the British Committee for Standards in Haematology recommended that children with severe haemophilia receive prophylactic infusions of factor VIII with the aim of preventing haemarthroses and other bleeding episodes. The prophylaxis should be commenced by the second joint bleed or significant soft tissue bleed and should consist of a factor VIII concentrate dose (25 – 50 IU/kg) administered ideally every 48 hour unless circumstances dictate otherwise.⁴⁶

In Sweden, prophylactic treatment of haemophilia A and B usually started at 1 -1 1/2 years of age before the onset of joint bleeds, i.e PP. In haemophilia A, FVIII, 20- 40 IU/kg/day is administered every second day or three times weekly and in haemophilia B, FIX, 20 – 40 IU/kg/day were given every third day or twice weekly. Home-treatment either through peripheral vein or a central venous line (Port-A-Cath) is practiced and the dose and dose interval was optimised by means of pharmacokinetic studies.⁴⁷

In Hong Kong, a survey conducted among 222 patients with mild to severe haemophilia (all male) under the care of the Hospital Authority showed that 57 (34%) of all severe to moderate cases aged 2 to 36 years received prophylactic treatment. In Hong Kong, FVIII and FIX (plasma-derived) are available as specialist item under public health system without additional cost while recombinant factor only available as patient-paid item.⁴⁸

A cross-sectional multicentre study in 2006 in Spain involving 2400 patients where 2081 were haemophilia A patients (32.8% severe, 13.9% moderate, 53.3% mild cases) and 319 (13.3%) haemophilia B patients showed that 399 (19.2%) patients were on prophylaxis where 81 (20.3%) were on PP, 303 (75.9%) were on secondary prophylaxis and 15 (3.7%) were undetermined.⁴⁹

A survey in Japan in 2001 showed that there was only one centre providing prophylaxis treatment. In 2006, another survey among 1540 haemophilia A and B patients showed that 23% of haemophilia A and 17% of haemophilia B received prophylaxis where 24% started prophylaxis under 2 years of age, 31% between 2 to 5 years old, 26% between age 6 to 14 years and 19% age more than 15 years.⁵⁰

The result of this review is in line with the World Federation of Haemophilia and World Health Organization recommendation that prophylaxis be considered optimum therapy.⁴³ Although, prophylaxis is the recommended treatment for haemophilia but in many countries it is still not implemented.

There are barriers to early and long-term prophylaxis in children with haemophilia.²⁰ The main barriers to the use of prophylaxis are supply of coagulation factor concentrates, the costs, perceived need of prophylaxis and fear of complications. Historical background and earlier experience of haemophilia treatment in the country influence the acceptance of prophylactic treatment among caregivers and caretakers.⁵¹

A survey in 2006 showed that 80% of nurses ranked infrequent bleeds as one of the top five reasons against administering prophylaxis, and 60% considered this as top five concerns for their patients. Venous access was ranked as a top five concern according to 61% of nurses and 59% cited this as a reason against prophylaxis for patients. Cost was a major issue for nurses in the USA, and compliance was of high concern for UK nurses.¹³

Prophylaxis as currently practiced in countries where there are no significant resource constraints is an expensive treatment and is only possible if significant resources are allocated to haemophilia care. However it is postulated to be cost-effective in the long-term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life.⁴³ However, long-term research taken into accounts all the resource utilised is lacking to prove this hypothesis.

This issue has been address by World Federation of Haemophilia (WFH) and suggested that in countries with significant resource constraints, lower doses of prophylaxis given more frequently may be an effective option.⁴³

This review has some limitations which should be considered. The focuses of the review was to compare prophylaxis approach with on-demand approach, thus we did not specifically assessed the effects of PP compared to secondary prophylaxis. We noticed that there were differences in the dosages used for prophylaxis as well as the on-demand treatment, however we did not analyse in depth the effect of the different dosages used. We conducted extensive search from the electronic databases, we went through all the abstract of the relevant titles but finally we only included full text articles in English. Given the time and resource available, we critically appraised the included systematic reviews and meta-analysis, however we were unable to critically appraise all the primary papers where the reviews were based.

Conclusion

There was good level of evidence from systematic reviews of RCT supported by numerous observational studies that the used of prophylaxis approach in haemophilia treatment was effective in decreasing the frequency of joint bleeds and preventing or slowing down the development of haemophilic arthropathy. However, the evidence showed that the cost of treatment was high and mainly contributed by the cost of factor concentrates. Prophylaxis approach was shown not to increase the risk of inhibitor development and there was no increase risk of infection.

Recommendation

Based on the available evidence, prophylaxis therapy is recommended in haemophilia patients to improve their quality of life and prevent complications. Since the cost of factor concentrates is high, a low or intermediate dose prophylaxis may be considered.

A local economic evaluation should be conducted to assess the best model of treatment for haemophilia patients in Malaysia that will not only improve the outcome of the patients but also be cost-effective.

CHAPTER 6 : RECOMBINANT VERSUS PLASMA-DERIVED FACTORS

Introduction

Haemophilia is a rare inherited bleeding disorder due to mutation of the gene which is almost exclusively found in males as the gene is located on the X chromosome. Prior to the availability of treatment with factor VIII and IX preparations, most of haemophilia patients died from uncontrolled bleeding before reaching 20 years of age.⁵²

Prophylaxis treatment was pioneered for haemophilia A in late 1950s and in haemophilia B in early 70s in Sweden by Nilsson and colleagues. At that time factor VIII was not always available and the doses given were small compared with today's norm.⁹ By the late 1960s, scientists and manufacturers developed methods for separating factor VIII and factor IX from pooled plasma, resulting in neatly packaged bottles of freeze dried (lyophilised) factor VIII or factor IX concentrates. Each bottle had a label indicating the amount of factor VIII or factor IX it contained, allowing more accurate dosing. By the early 1970s, the availability of these concentrates led to home-treatment, greatly changing the lives of people with haemophilia.⁵³

Then in early 1980s, the epidemic of HIV devastated the haemophilia community. Manufacturers of plasma-derived clotting factor concentrates attempted to kill these viruses with dry heat, solvent-detergent treatment, and pasteurization, with varying degrees of success.⁵³ In 1985 nearly 75% of the severe haemophilia patients in US had acquired HIV through the infected plasma-derived factors. More than half of these infected individuals died from HIV by 1995, when effective treatment for HIV infection first became widely available. As the community dealt with the horrors of HIV, a second epidemic gradually became apparent where over 95% of severe haemophilia A patients had also acquired hepatitis C infection through plasma-derived preparations of factor VIII.⁵²

Fortunately several developments occurred over the past 20 years. Amongst others, preparations of the plasma-derived products have been improved, steps have been added to test donor populations that provide plasma for purification of factor VIII, steps have been added to inactivate any viruses present, and additional steps of factor VIII purification have been included. The success of these effort is demonstrated by the fact that no transmission of HIV, hepatitis C, or other virus has been documented to be associated with any of these modern plasma-derived factor VIII preparations since 1990.⁵²

The first recombinant FVIII concentrate produced in cell cultures was approved in 1992. Manufacturers were then no longer dependent on blood plasma apart from the human albumin in the production process. In 1993 and 1999, two more recombinant factor VIII concentrates were approved.⁵

The rFVIII products are divided into four generations. First, second, and third generations are defined by the amount of human plasma-derived protein and the fourth generation is defined by its lacking of the β -domain of the FVIII molecule.

According to Powel JS, no matter how good the therapy is, two major concerns continue to trouble the treatment approaches especially for severe haemophilia A (HA).⁵² First is development of inhibitory antibodies that neutralise infused factor VIII and the second concern is risk of infection and thrombosis due to placement of a CVAD. According to the Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products, the inhibitor formation occur in up to about 30% of previously untreated patients (PUP) with severe HA, usually within the first 100 exposure days.⁵⁴

The guideline also stated that in cases in which the inhibitor occurs in the PUP, patient related factors such as FVIII mutations, family history, and ethnicity are important determinants of the inhibitor development. Besides that, proper monitoring including clinical observations and laboratory test should be conducted in such patients.⁵⁴

The development of inhibitors is one of the challenging complications of treatment in haemophilia patients resulting in increased morbidity and significant economic burden. Although several factors are known to influence the risk of inhibitor development, the source of factor concentrate for replacement therapy, may also have an effect on inhibitor development.⁵⁵

Other factor that determines the choice of coagulation factor concentrates is the cost of the concentrates. Due to all these issue, this review was carried out to determine the safety, efficacy and resource implications of recombinant factors when compared with plasma-derived factors.

Characteristics of included studies

Study design

Nine studies were included in this review. Two of the studies (Berntorp 2011, Iorio 2010) were systematic reviews. Schwartz 1990, Kelly 1997, Kreuz 2002 and Ewenstein 2002 were controlled trials. A post-licensure surveillance study was also included. Two retrospective cohort studies, Goudemand 2006 and Gouw 2007 (CANAL cohort study) were included in Iorio 2010 Systematic review (SR), thus will not be discussed separately.

Participants

Seven of the studies included patients with haemophilia A only. Two studies were conducted on patients with haemophilia B.

Intervention

Recombinant factor concentrates

Comparators

Plasma-derived factor concentrates

Outcome measures

Almost all the studies included in this review, evaluated inhibitor development except Kelly 1997 and Ewenstein 2002. Some of the studies also assessed the adverse events of treatment. No recent studies identified compared the risk of infection in the different source of concentrates.

Country

Three of the studies were conducted in United States of America, the HTA report was from Sweden, one study was conducted in Germany and one study was conducted in Canada.

Risk of bias

Two reviewers assessed the risk of bias of the included studies. The results was summarised in Figure 4.

All the studies were not randomised or the subjects were not selected randomly except Ewenstein 2002. Only one study was blinded. Five of the studies were prospective in design. Three of the studies were supported by industries. Overall, all the studies have high risk of bias.

Figure 4. Summary risk of bias of studies that compared recombinant and plasma-derived factors

	RANDOM SELECTION OF PARTICIPANTS	PROSPECTIVE STUDY	BLINDING	EXPLANATION ON LOSS TO FOLLOW UP	ANALYSIS TAKES INTO ACCOUNT CONFOUNDING FACTORS	"OTHER" POTENTIAL SOURCES OF BIAS
Kreuz 2002	−	+	−	−	?	?
Kelly 1997	−	+	−	+	−	−
Schwartz 1990	−	+	−	+	+	+
Gouw 2007	−	−	−	+	+	−
Goudemand 2006	−	−	−	−	+	+
Poon 2002	−	+	−	+	−	+
Ewenstein 2002	+	+	+	+	−	−
LEGEND	+ YES		− NO		? CAN'T TELL	

Efficacy

Berntorp et al in their systematic review assessed the differences in effects between recombinant and plasma-derived factor concentrates in treatment of patients with haemophilia A and B. Twenty seven studies met their inclusion and exclusion criteria which included single-arm studies, case studies and review articles. They concluded that the scientific evidence was insufficient to determine if there are any differences in effects between recombinant and plasma-derived factor concentrates for substitution treatment of haemophilia A and B.^{5 Level I}

Kelly et al conducted a prospective cross-over study to evaluate FVIII responses after infusion of Hemofil, a plasma-derived FVIII (pdFVIII) compared with infusion of Recombinate, a recombinant factor VIII (rFVIII) in 10 children with haemophilia A. A total of ten children aged 7 to 12 years old with severe factor FVIII deficiency were included. All the ten children had one recovery study for each product; 50 IU/kg Hemofil M for one study and 50 IU/kg Recombinate for the other study. Each FVIII concentrate was administered at least 72 hours apart and at least 48 hours after previous infusion of the other FVIII product. Before the infusion of the FVIII concentrate, a FVIII inhibitor titre, FVIII coagulant activity and haematocrit level were determined. The blood sample was obtained from each subject 30 minutes after the infusion. The response to FVIII was determined by calculating the difference between the plasma concentration of FVIII levels before and after infusion of the FVIII concentrate and divided by theoretical rise in the FVIII level. Based on the manufacturer's reports, with 50 IU/kg, the theoretical rise would be 100%; the ideal response is 2%. The recovery was determined by dividing the actual rise in FVIII level in plasma by the expected rise based on the amount administered. The mean response showed that Recombinate was significantly better than with Hemofil M which was $1.91\% \pm 0.14\%$ versus $1.50\% \pm 0.15\%$ with $p = 0.007$. Mean percentage of recovery was $100.5\% \pm 4.5\%$ with Recombinate and $78.7\% \pm 6.2\%$ with Hemofil M, $p = 0.007$. This study also found that there was moderate correlation between Recombinate and factors such as body surface area ($r = 0.762$), body weight ($r = 0.762$) and plasma volume ($r = 0.659$) but none for Hemofil A, where r was 0.494, 0.491 and 0.405 respectively.^{56 Level II-1}

Schwartz RS et al conducted prospective single-arm clinical trial to test safety and efficacy of rFVIII preparation for haemophilia A patients. A total of 107 subjects with severe or moderate haemophilia A were enrolled in the study which was conducted in three different parts. The first part was a pharmacokinetic comparison between rFVIII and pdFVIII which involved 17 asymptomatic adults. In this part the pdFVIII showed similar pharmacokinetics, with the exception that clearance and volume of distribution were slightly lower for rFVIII. The results were as follows: mean (\pm SD) incremental 10 minute recovery in-vivo for pdFVIII was 2.42 ± 0.33 percent per international unit of FVIII per kilogram. Meanwhile for rFVIII, the recovery values were assessed at weeks 1, 13 and 25. The values were 2.68 ± 0.52 ($p = 0.026$), 2.70 ± 0.61 ($p = 0.20$), and 2.92 ± 0.99 ($p = 0.017$) respectively. The second part of the study was to assess the efficacy and safety of rFVIII for home-treatment in 76 subjects (16 subjects from part 1). The efficacy showed that 73.9 percent bleeding episodes responded to a single-dose of rFVIII. Meanwhile the third part of the study was to evaluate the efficacy and safety of rFVIII in surgery in 26 subjects (17 subjects from Stage 1 and 2). The efficacy of rFVIII in 32 occasions for major surgical procedures showed that the haemostasis was excellent without need for any additional treatment.⁵⁷ Level II-2

Two studies compared the recovery of recombinant FIX concentrates and plasma-derived FIX concentrates. Ewenstein et al conducted a double blind cross-over study on pharmacokinetic in 15 centres in United States. Forty three moderate or severe haemophilia B, aged more than 5 years old with prior treatment with any type of FIX concentrate and absence of inhibitors were included. Analysis was conducted on 38 completed data. Thirty seven out of 38 patients received 48.3 to 50.8 IU per kg. One patient received 53.3 IU per kg. Mean recovery calculated from the peak level in the first hour was 1.71 ± 0.73 IU per dL per IU per kg for pdFIX and 0.86 ± 0.31 IU per dL per IU per kg for rFIX, $p < 0.0001$. Thirty six of the 38 patients (94.7%) had a recovery greater than 1.0 IU per dL per IU per kg after pdFIX infusion whereas only 31.6% had a recovery greater than 1.0 IU per dL per IU per kg following rFIX infusion and three patients (7.9%) had a recovery of less than 0.5 IU per dL per kg. Mean recovery after excluding two outliers was 1.57 for the pdFIX and 0.84 for the rFIX, there was significant difference in recovery of 0.73 (95% CI 0.63 - 0.84). The terminal T_{1/2} for pdFIX was 14.9 hours (range 7.2 - 22.7) compared with 16.8 hours (range, 10.8 - 26.1) for rFIX calculated from the FIX:C levels at 4, 24 and 48 hours. The plasma levels achieved with pdFIX remained 1.8 to 2.1 fold higher than with rFIX at each of these time points. The differences in recovery between pdFIX and rFIX were significant at all three time points. For each subject, a higher peak recovery was observed with pdFIX than with rFIX, irrespective of the sequence in which the study medications were administered. There was a significant positive correlation, $r = 0.62$, $p \leq 0.0001$; CI, 0.37 - 0.78) between the recoveries of the two products, implying that the large interpatient variability observed was caused by inherent differences among subjects. There was no significant correlation between baseline FIX:Ag and recovery, $r = 0.12$, $p = 0.33$.⁵⁸ Level I

Poon et al studied in-vivo FIX recovery among 200 haemophilia B patients where 126 patients received rFIX from 16 haemophilia centres across Canada and 74 patients received plasma-derived FIX from ten haemophilia centres across Canada. The mean recovery for all group was 0.77 (SD 0.19) for rFIX and 1.05 (SD 0.26) for pd-FIX. For patients aged ≤ 15 years old the mean recovery was 0.64 (SD 0.11) and 0.91 (SD 0.16) respectively. For patients aged ≥ 15 years old, the mean recovery was 0.84 (SD 0.21) and 1.11 (SD 0.29) respectively.⁵⁹ Level II-2

Safety

Plasma-derived factor VIII and factor IX are blood products and do not require approval from US Food and Drug Administration (US FDA) or other similar authority. US FDA through the Center for Biologics Evaluation and Research (CBER) regulates the collection of blood and blood components used for transfusion, or for the manufacture of pharmaceuticals derived from blood and blood components, such as clotting factors, and establishes standards for the products themselves.⁶⁰ Many recombinant factors such as Kogenate and ReFacto have received US FDA approval.⁶⁰

SR by Iorio A et al on rate of inhibitor development in previously untreated haemophilia A (HA) patients treated with plasma-derived (pdFVIII) or recombinant FVIII (rFVIII) concentrates included 24 prospective and retrospective studies. About 2,094 PUPs were involved in the analysis where 1,167 patients on pdFVIII and 927 patients on rFVIII. A total of 420 patients developed inhibitor. Out of the 420 patients, 160 (13.7%) were treated with pdFVIII and 260 were treated with rFVIII. High responding inhibitors were found in 252/1864 patients (101/1022 [9.8%] for pdFVIII and 151/842 [17.9%] for rFVIII). Meanwhile non-transient inhibitors were detected in 175/1117 patients (77/643 [12.0%] for pdFVIII and 98/474 [20.7%] for rFVIII). Pooled analysis of single-arm studies (16 pdFVIII and rFVIII arms) were performed and showed that the inhibitor development rate was significantly higher in patients treated with rFVIII compared with pdFVIII (27.4% versus 14.3%, Cochran Q = 11.7, $p < 0.001$). However, when the analysis was limited to patients with severe HA, the event rate was significantly higher (34.5%, 95% CI 29.3 – 40.1; for rFVIII and 15.9%, 95% CI 10.5 – 23.3 for pdFVIII with Cochran Q 14.2, $p < 0.001$). The event rate in moderate plus severe patients was 15.4% in pdFVIII and 28.5% in rFVIII with Cochran Q 13.6; $p < 0.001$.^{55 Level II-2}

This SR also looked into the effects of different pdFVIII and rFVIII concentrations towards the inhibitor incidence rate. For high purity pdFVIII concentrates, the inhibitor incidence rate was 10.2% (95% CI 6.5 – 15.6) and 15.9% (95% CI 11.4 – 21.6) for low purity with Cochran Q 3.0; $p = 0.221$. Meta-regression plots of inhibitor rate versus the study period showed a trend for higher inhibitor detection rate in more recent study period. Pooled analysis of six studies (1259 patients) that involved parallel cohorts treated with pdFVIII or rFVIII concentrates were conducted. There was no significant heterogeneity was found between those studies. The results showed that there were statistically significant associations of either high- or low titre inhibitors demonstrated for rFVIII versus pdFVIII. In high responding inhibitors, the relative risk (RR) was 1.7 (95% CI 1.3 – 2.7, $p < 0.001$; Cochran Q chi-squared = 1.97, $p = 0.853$) and for all inhibitors the RR was 2.0 (95% CI 1.5 – 2.6, $p < 0.001$; Cochran Q chi-squared = 3.03, $p = 0.695$). From the forest plot, it showed that HA patients that was initially treated with rFVIII had an increase risk of developing an inhibitor.^{55 Level II-2}

Another prospective long-term study by Kreuz W et al reported the development of inhibitors in PUP with severe (FVIII < 1%) and moderate (FVIII 1 to 5%) HA. The study was initiated in 1976 (updated January 1999). Seventy two paediatrics PUPs involved in the study. Each of them was exposed at least once to a single FVIII concentrate. By treatment, out of 51 patients who received pdFVIII; 18 patients (35%) developed inhibitors. Meanwhile, four patients out of 21 patients who received rFVIII developed inhibitor. If the severity considered, patients with residual FVIII activity less than 1% developed an inhibitor in 46% of the pdFVIII group and in 36% of the rFVIII group. In terms of frequency development of high-titre inhibitors, there was no significant difference detected between the pdFVIII and rFVIII patients.^{61 Level II-2}

Schwartz RS et al also reported on inhibitor development and adverse events in patients receiving recombinant versus plasma-derived factors. The adverse event assessment involved 56 subjects who completed five months of continuous home-treatment with a total of 1734 infusions of rFVIII. There were 18 (1%) adverse drug reactions (ADRs) reported which included an unusual metallic taste in the mouth accompanied by a burning sensation at the infusion site, mild dizziness or light headedness, erythema at infusion site, asymptomatic decrease in blood pressure, dryness of mouth, elevated serum aminotransferase level, chest discomfort and chest tightness with dyspnoea. Five of those reactions were claimed not specifically related to the administration of rFVIII. One patient who had elevated serum aminotransferase was withdrawn from the study. Another assessment conducted was on inhibitor development. Only two out of 86 subjects who were previously treated with pdFVIII concentrates developed inhibitor antibodies.^{57 Level II-2}

Poon et al reported results of anti-FIX antibody surveillance among 244 patients from 24 Canadian Haemophilia Centers. Two of the patients who had exposed to rFIX for 1-5 years had developed anti-factor IX antibodies associated with anaphylactic reactions. These two patients had not been previously exposed to pd-FIX and developed anaphylactic reactions with anti-factor IX antibodies detected on the 3rd and 14th exposure day respectively. It was mentioned that the incidence is similar to that reported for pdFIX. No other serious adverse event was reported.^{59 Level II-2}

Cost-effectiveness

There was no retrievable evidence on cost-effectiveness study that compare recombinant factors with plasma-derived factors. The price of plasma-derived FVIII per 250 IU ranged from [REDACTED] whereas the price of recombinant factor is [REDACTED] (Source: Pharmacy Department, Hospital Ampang and Hospital Kuala Lumpur)

Discussion

Nine studies met the inclusion and exclusion criteria. There were two systematic reviews identified which summarised non-randomised and observational studies. Three prospective non-randomised studies and two retrospective cohort studies on FVIII were included. A randomised controlled trial and a postmarketing surveillance study on FIX were also included. No study on cost-effectiveness was identified. The studies included have a high risk of bias, thus the results were not pooled.

Results of studies on efficacy suggested that recombinant factor VIII has better response and is correlated with body surface, body weight and plasma volume⁵⁶ which suggested that it may be easier to adjust the dosage with recombinant factors. While plasma-derived FVIII concentrates has better incremental recovery in 10 minutes when compared with recombinant factors which were evaluated after a week.⁵⁷ The effectiveness of recombinant FVIII in conjunction with surgery either in minor or major procedures was classified as good or excellent in one study with no difference between factor concentrates.⁷

Two studies on FIX showed that the recovery following rFIX was significantly lower compared to pdFIX which means that more rFIX concentrates is required to achieve therapeutic levels.^{58, 59}

Most of the studies evaluated the rate of inhibitor development. The SR showed that the rate was significantly higher in recombinant factors compared to plasma-derived factors but the two prospective smaller studies showed that the rate was higher in plasma-derived factors.^{55, 57, 61} Purity of plasma-derived factors did not affect inhibitor rate.⁵⁵ The use of different brands of rFVIII products also did not affect the risk of inhibitor development however the evidence was only available from one study.⁶² Thus it is still unclear whether the plasma-derived concentrate is better than the recombinant concentrate.

Safety in terms of preventing transmission of possible infections was not retrievable in this assessment, however as reported earlier the products have a high level of safety.^{5, 52} But issues has also been raised on how safe is safe. No plasma-derived FVIII has transmitted any documented viral illness since 1990. The safety concern now revolves around fear of transmission of prions or perhaps fear of “the next” as yet unidentified “virus”.⁵²

In many developed countries, recombinant factor concentrates are preferred especially in the young haemophilia populations, in a survey done among PedNet members representing 22 haemophilia centres in 16 countries in 2003, nine of the centres used only rFVIII concentrates for the treatment of patients with haemophilia A. Nine other centres used a recombinant concentrate in 80-99% of these boys. The choice of plasma-derived FVIII or rFVIII was balanced (40-60%) in the remaining four centres. Among the 18 centres where the boys were treated for haemophilia B, the recombinant product was used in 14 centres (78%) and it was prescribed for the majority of boys in nine centres.⁶³

In Canada, a survey done in 2006 among 25 HTC showed that 98% of patients receiving prophylaxis were using a recombinant product. Eleven patients (2%) were receiving plasma-derived factor concentrate: 10 patients with severe/moderate haemophilia B and one with severe haemophilia A.⁶⁴

In Spain, a study carried out in 2006 among 2400 haemophilia patients (85% of all Spanish haemophilia patients who require at least one annual visit) found that recombinant products are used by 54.2% of treated patients (57.3% of patients in the case of haemophilia A and 35.4% in haemophilia B) when compared with 44.2% of patients using plasmatic products. In population under 14 years of age, the use of recombinant factors increased to 83.5%.⁴⁹

Another important issue related to the choice of plasma-derived versus recombinant FVIII is that of the comparative efficacy of the two sources of replacement therapy in achieving immune tolerance, the best method to eradicate inhibitors through the long-term treatment of patients with replacement therapy with coagulation factors.⁶⁵ However we did not identify any comparative studies on this issue.

Another important factor to consider is the cost of the factor concentrates. Unfortunately, there was no retrievable evidence on cost-effectiveness and there was no local study on costing available. The price of plasma-derived factor concentrates is cheaper compared to recombinant factor concentrates but the actual cost is not known.

Our study has a few other limitations that should be considered, although abstract of studies in other languages were reviewed but finally only full text papers in English were included. The rigorous method of the review means that only papers that met our inclusion and exclusion criteria were included, thus we excluded single-arm studies, studies without comparison and narrative reviews. We did not pool the result of the studies due to the heterogeneity of the studies and the risk of bias.

Conclusion

There was insufficient evidence to answer the research question on the efficacy and safety of recombinant factor compared to plasma-derived factor concentrates. Only fair level of evidence with high risk of bias available for haemophilia A. The evidence showed inconsistent results for recovery of rFIX and pdFIX. Limited good level of evidence showed that recovery of rFIX was lower compared to pdFIX. As for safety, it cannot be concluded that plasma-derived factors has a lower risk of inhibitor development due to the inconsistency of the results.

There was no retrievable evidence on cost-effectiveness. Only the prices of the factors were available. There were other factors that may affect the cost such as the risk of inhibitors, infection rate, efficacy, hospitalisation and other adverse events which should be calculated into the cost.

Recommendation

No specific recommendation can be made. There was insufficient evidence addressing this decision problem. More primary research in the form of well designed and adequately powered RCTs is required.

CHAPTER 7 : TREATMENT OF PATIENTS WITH INHIBITORS

Introduction

Patients with severe haemophilia often developed a crippling joint disease as a result of frequent joint bleeds. Evidence suggests that factor replacement therapy aimed at preventing joint bleeds is extremely effective and results in prevention of haemophilic arthropathy. Unfortunately, some patients developed neutralising antibodies (inhibitors) to replacement factors (factor VIII (FVIII) or factor IX (FIX)) rendering such treatment ineffective.^{66, 67}

Incidence estimates suggest that inhibitors develop in 20 – 30% of patients with haemophilia A and in 5% of patients with haemophilia B.⁶⁶ In approximately half the number of patients, the levels are low and the inhibitors usually disappear after a period of “enhanced” prophylactic treatment. Others have high levels of inhibitors (high titres) that completely neutralise the administered factor concentrates, and they have no effect. The inhibitors usually appear within the first 10 to 30 treatment doses.⁵ Although these patients do not experience more bleeding episodes than those without inhibitors, haemostasis is more difficult to control when bleeding does occur.⁶⁶

Inhibitor eradication by immune tolerance induction (ITI) is generally accepted as the most preferred treatment options. During ITI, high doses of factor concentrate (100 - 200 IU per kg) are administered, and it takes 6 to 24 months. ITI is initiated as quickly as possible after inhibitors have been detected, but as a rule only after the titres have decreased spontaneously to below ten inhibitor units, which can take several months.⁵ In about 30% of haemophilia A patients and a larger proportion of patients with haemophilia B, who undergo ITI, failure to eradicate the inhibitor is observed. In addition, ITI treatment is very expensive and many patients will never be offered the opportunity to attempt to induce tolerance. In these patients, in those waiting for ITI to start, as well as in those undergoing ITI, acute bleeding episodes are generally managed by preparations containing activated coagulation factors. The use of these products is intended to achieve haemostasis independently of, i.e. by-passing, the FVIII and FIX activities.^{5, 68}

Currently there are two bypassing agents in the market namely recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC).^{5, 68} These agents are used to treat bleeding in patients with high responding inhibitors where traditional factor replacement is unlikely to be effective. For patients with low-responding inhibitors (with a Bethesda titre <5 BU mL) high doses of the replacement factor in which they are deficient may be enough to resolve a bleed.⁶⁶

Recombinant factor VIIa (rFVIIa) is a recombinant protein, similar in structure to coagulation factor VIIa derived from human plasma, but manufactured without using material of human origin. It has effects on both tissue factor dependent and -independent coagulation. In particular, at pharmacological concentrations, its main effect is to enhance thrombin generation on the surface of activated platelets, even in the absence of factors VIII and IX, which are deficient in patients with congenital haemophilia A and B, respectively. The thrombin induced by recombinant factor VIIa enhances platelet activation, fibrin formation, and inhibition of fibrinolysis. The effects of rFVIIa are localized to the site of vascular injury and it does not appear to enhance systemic activation of coagulation. Thrombotic events have been reported rarely. Antibodies to rFVIIa generally do not develop in patients with haemophilia, although there have been a few reports in patients with factor VII deficiency.⁶⁹

Activated PCC preparations, known as anti-inhibitor coagulant complex or FEIBA provides both factor II (prothrombin) and factor Xa for rapid and sustained thrombin generation. It also contains additional factors that target multiple sites within the coagulation system to help maintain the coagulation process. FEIBA restores haemostasis through multiple modes of action, including thrombin generation on the platelet surface.⁷⁰

The aim of this chapter is to compare the efficacy, safety and cost-effectiveness of rFVIIa with aPCC for haemophilia patients with inhibitors.

Characteristics of included studies

Study design

Twelve studies were included to answer research question 3 on the effectiveness and cost-effectiveness of recombinant activated FVII when compared to activated PCC for haemophilia patients with inhibitors. There were one meta-analysis, four systematic reviews, two RCT, three cost-minimisation analyses and two costing studies identified. Two systematic reviews with meta-analysis or meta-regression were excluded due to validity issue. The two RCT identified have been included in the reviews thus will not be discussed separately.

Participants

Haemophilia A and B patients with inhibitors, children and adults

Intervention

Studies comparing the efficacy, safety and cost-effectiveness of rFVIIa compared with aPCC were included.

Outcome measures

The outcome measures assessed include cessation of bleeding, quality of life, tolerance development and resource used.

Country

Most of the studies included in the systematic reviews included patients from North America and Europe. Two studies on costing were from the Republic of Czechoslovakia and United States of America. Two of the cost-minimisation studies were from the United States and the other one was conducted in Korea.

Risk of bias

Two reviewers assessed the risk of bias of the included studies. The criteria used were described in Chapter 3. The risk of bias of the primary papers reviewed was summarised in Figure 5 and Figure 6.

Figure 5. Summary risk of bias of RCTs comparing rFVIIa and aPCC

CRITERIA ASSESSED	SEQUENCE GENERATION	ALLOCATION SEQUENCE CONCEALMENT	BLINDING	EXPLANATION ON LOSS TO FOLLOW UP	INTENTION TO TREAT ANALYSIS	"OTHER" POTENTIAL SOURCES OF BIAS
Astermark 2007	?	?	-	+	-	+
Young 2008	+	?	+	+	-	-

LEGEND	YES	NO	CAN'T TELL
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In the RCTs, for sequence generation, Astermark 2007 mentioned that randomisation was performed in a block of patients equally divided into two which may allow investigator to guess and leads to high risk of bias. Young 2008. used permutation following the three dosing regimens and it was done in random. Both studies did not describe the method of concealment thus judgement cannot be made. Astermark 2007 was an open label study, thus not blinded. In Young 2008 study, assessment of rFVIIa was conducted in double blind methods whereas aPCC was not blinded. Both studies have a high risk of bias.

Both studies explained on loss to follow up. Astermark 2007 mentioned that intention to treat analysis was carried out, however they excluded four diaries with incomplete data. Young 2008 analysed results per protocol. Astermark 2007 stated that the study was supported by investigator-initiated unrestricted grant and all collections, management, and analysis of study data were completed independently by the investigators. Young 2008 study was sponsored by industry.

Figure 6. Summary risk of bias of non-RCTs comparing rFVIIa and aPCC

CRITERIA ASSESSED	RANDOM SELECTION OF PARTICIPANTS	PROSPECTIVE STUDY	BLINDING	EXPLANATION ON LOSS TO FOLLOW UP	ANALYSIS TAKES INTO ACCOUNT CONFOUNDING FACTORS	"OTHER" POTENTIAL SOURCES OF BIAS
Salaj 2012	−	−	?	−	+	−
Pokras 2012	+	−	−	+	+	−
You	−	−	−	?	+	−

LEGEND	YES	NO	CAN'T TELL
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Overall all the non-randomised studies have a high risk of bias. Pokras 2012 selected patients using the databases and included all the eligible patients whereas the other two studies did not mention how patients were selected into the study. All the studies were retrospective and did not blind the patients or the assessors. However, all the studies took into account confounding factors and conducted a multivariate analysis to control for confounding factor in the analysis. All the studies were sponsored by industries.

Efficacy

Iorio et al in their meta-analysis of clinical effectiveness of rFVIIa concentrate in comparison to plasma-derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors included two RCTs (Astermark 2007, Young 2008). The primary outcome measure was an early cessation of bleeding. They reported that Astermark 2007 study found no significant difference in the treatment efficacy judgement between the two treatments at 2, 6, 12, 24, 36 and 48 hours. However the outcome on bleeding stop showed significant difference between the two groups at 48 hours where 95.1% in aPCC group compared to 92.7% in rFVIIa, $p = 0.001$. Young 2008 study was reported to use an algorithm on pain and mobility scores and they did not find any significant difference between the treatment groups, pain scale ($p = 0.219$) and mobility scale ($p = 0.903$). Iorio et al also measured the number of participants requiring additional or alternative treatment. They reported that in Astermark 2007 study, two patients were administered with additional doses, first within the first 6 hours after onset of treatment and the other patient during the balance of the 48-hour observation period. In Young 2008 study, rescue medication was administered for: eight bleeding episodes for aPCC, two bleeding episodes for rFVIIa 270 mcg/kg and two bleeding episodes for rFVIIa 90 x 3 mcg/kg. The difference between rFVIIa 270 mcg/kg compared to aPCC was statistically significant ($p = 0.032$). However, the efficacy difference between aPCC and rFVIIa 90 x 3 mcg/kg did not reach statistical difference ($p = 0.069$). Iorio et al concluded that based on the separate analysis of the two RCTs, rFVIIa and APCC were found to be similar in efficacy and in causing a low risk of thromboembolic complications. Both drugs can be administered as single intravenous bolus (270 mcg/kg of rFVIIa, 75-100 IU/kg of aPCC).⁷¹ Level I

Berntop et al in their systematic review included 28 studies that address the effects of bypassing products. They concluded that the scientific evidence is insufficient to evaluate and to compare the effects of rFVIIa with aPCC, in the treatment of acute bleedings in patients with inhibitors. They reported that results from observational studies indicate that both available bypassing agents can prevent and control bleeding episodes, including surgical settings. Treatment failures were also reported. The clinical data suggested that the response may vary between individuals. Although two RCTs, FENOC study by Astermark 2007 and Young 2008 study were included in the review. Both studies were reported as of medium quality and relevance. They concluded that the scientific evidence is insufficient to assess the effect of prophylactic treatment with rFVIIa and aPCC on the potential to reduce the number of bleeding episodes and to prevent bleedings in patients with inhibitors.^{5 Level I}

Lyseng-Williamson et al in their systematic review included 13 studies including Astermark 2007. In Astermark 2007 paper reporting FENOC study, the equivalence of recombinant factor VIIa and aPCC in the treatment of joint bleeding episodes in haemophilia patients with inhibitors was not met. The criteria for equivalence (defined as a $\leq 15\%$ difference between recombinant factor VIIa and aPCC in the proportion of patients who reported effective or partially effective treatment within 6 hours of initiation of treatment). The efficacy of the products was rated differently by a substantial proportion of patients at all time points up to 48 hours.^{67 Level I}

The efficacy and time to bleeding resolution of rFVIIa and/or aPCC have been investigated in country-specific retrospective and/or prospective multicentre analyses validated by expert opinion. The efficacy of first line therapy in controlled bleeds was 87.1 - 100% for recombinant factor VIIa and 56.7 - 79% for aPCC.^{67 Level II-1}

Time to bleeding resolution after initiation of treatment was numerically shorter with rFVIIa than with aPCC (4.4 - 17.3 hours and 25.2 - 62.6 hours respectively). Sensitivity analyses showed that in order for the estimated length of time to successfully control a minor bleed to be shorter with aPCC than with rFVIIa, the time to control a bleed with rFVIIa would need to increase from 24 to 49 hours with home-treatment and from 24 to >54 hours for treatment of a day patient at a haemophilia care centre or the time to control a bleed with aPCC at home would have to decrease from 36 to < 13 hours.^{67 Level II-1}

Safety

Iorio et al assessed the adverse events related to rFVIIa and aPCC. They reported that Astermark 2007 did not report any study-related or study drug-related adverse effects in their study. Young 2008 did not report any thrombotic, fatal or clinical laboratory adverse events; however it did record 32 treatment emergent adverse events in 14 participants. Of these, three were in the rFVIIa 270 group, five were in the rFVIIa 90 x 3 group and six were in the aPCC group. None were considered related to the study.^{71 Level I}

Cost-effectiveness

Lyseng-Williamson in their systematic review found that on-demand treatment with rFVIIa for the management of mild to moderate bleeding episodes in patients with haemophilia with inhibitors was predicted to be associated with lower total medical costs than on-demand treatment with aPCC in pharmacoeconomics analyses across a number of countries. The lifetime costs of treating bleeding episodes were £200,000 (year 2001 values) lower with rFVIIa only regimen.^{67 Level II-1}

Knight et al included 12 studies in their systematic review of economic studies. Ekert 2001 the only CUA included in this review compared rFVIIa with the patients' usual treatment including aPCC for on-demand bleeding episodes showed that rFVIIa was the cost-effective alternative. rFVIIa resulted in a 63-92% reduction in the number of re-treatments, duration of painful episodes, delay up to initiation of treatment, days when crutches or wheelchair were required, emergency room visits and lost carer time. Overall incremental utility improvement associated with rFVIIa was 0.58.^{72 Level I}

The total average treatment cost, including health care resources, for the two rFVIIa phases was AUS\$219,214 which was AUS\$29,901 higher than the cost associated with “usual care” in phase 1 of the study. The incremental cost per QALY ratio was AUS\$51,533 which the author indicated was less than the ICER for hospital dialysis (AUS\$57,053) in Australia.^{72 Level I}

The other 11 cost-effectiveness analyses adopted similar model framework suggesting clinical acceptability of the approach. Knight 2003 study was over the patient’s life time, while the other studies estimated the average cost of treating a single bleed episode with either aPCC or rFVIIa. The estimates of efficacy varied between the models, especially for aPCC.^{72 Level I}

The average cost to resolve a bleed is lower using rFVIIa than aPCC in seven out of the nine economic analyses. The average amount that rFVIIa is lower than aPCC ranges between \$3,000 and \$17,000 per resolved bleed. The two studies that reported aPCC as having the lower mean cost to resolve a bleed both were said to have quality issues (Chung 2004 and Putnam 2005). Knight et al reported that sensitivity analysis was undertaken in the majority of the economic analyses and the results were found to be robust to realistic parameter variations.^{72 Level I}

Stephens et al published a systematic review which included 13 studies, six of the studies were on cost impact or general burden studies for rFVIIa and another seven studies were comparative economic analyses of rFVIIa versus plasma-derived agents. The comparative economic papers included were Joshi 2006, Dundar 2005, Putnam 2005, Knight 2003, Odeyemi 2002(a), Odeyemi 2002(b) and Ekert 2001. All the comparative economic analysis studies except Putnam 2005 showed that the cost of treatment with rFVIIa is lower when compared to aPCC. In Ekert et al study, the patients reported improvement in all components of the CHQ-CF80, with the exception of overall behaviour while receiving rFVIIa therapy. Similarly, parents reported improvement in all components of the CHQ-PF50 with rFVIIa therapy. A utility value of -0.11 was obtained for the scenario representing phase 1 (usual care) of this study. During this phase, there was a 37 hour delay in treatment, 131 hour of pain per bleed, 28 bleeds, 6 re-treatments in the initial 24 hours, and 96 days when crutches or a wheelchair were required. A mean utility value of 0.47 was obtained for the scenarios representing phases 2 and 3 (rFVIIa treatment) of this study. During these 2 phases (average of the 2 rFVIIa phases), there was only a 5 – 7 hour delay in treatment, 12 – 26 h of pain per bleed, 18 bleeds, < 1 rebleed, and between 34 and 36 days when crutches or a wheelchair were needed. The overall incremental utility improvement with rFVIIa was 0.58. The incremental cost per QALY ratio calculated was AUS\$51,533 which is less than the incremental cost per QALY ratio calculated for hospital dialysis (AUS\$57,053) in Australia.^{73 Level II-2}

The systematic review reported that Knight et al compared the cost-effectiveness of three ITI and three on-demand strategies using a Markov decision model. Overall treatment with any of the ITI strategies was more cost-effective than any on-demand strategies. However, of the on-demand therapies, rFVIIa had a lower average lifetime cost per patient (~£200,000 less). Odeyemi and Guest performed 2 modelling studies to determine the economic impact of rFVIIa compared with aPCC administration in adult patients with mild to moderate bleeds treated either at home or at a comprehensive care centre. The cost of rFVIIa treatment at home was estimated to be £12,944 and with aPCC £14,645; the cost of treatment at a comprehensive care centre with rFVIIa was estimated to be £11,794 and with aPCC £20,467. Dundar et al constructed a decision-analysis model to determine the economic impact of four different treatment regimens (high dose factor VIII or IX, PCC, aPCC, rFVIIa) for mild to moderate bleeds in patients with haemophilia and inhibitors. The medical chart data showed that fewer doses were required (3.6 versus 4.8), bleeding resolution time was shorter (17 versus 44 h), and efficacy higher (89% rFVIIa versus 67% aPCC) with rFVIIa versus aPCC. Total costs were US\$3000 lower per bleeding episode with rFVIIa administration compared with aPCC therapy. Putnam et al constructed a cost-minimisation model to compare the drug costs of the initial 24 h of treatment with aPCC versus rFVIIa in the home-treatment of minor bleeds. In this study, treatment costs for a bleeding episode with aPCC were US\$21,000 compared with US\$33,400 for rFVIIa. Finally, Joshi et al compared the cost-effectiveness of three different treatment regimens, consisting of first-, second- and third-line therapies used in the treatment of mild to moderate bleeds in patients with haemophilia and inhibitors. The total cost of therapy for an rFVIIa only strategy was estimated to be US\$28,076 compared with US\$30,883 – 32,150 for aPCC-based strategies.^{73 Level II-2}

Salaj et al conducted costing study using retrospective analysis data from two prospective, observational, nationwide registries based on health care payer perspective. Thirteen adults with congenital haemophilia a and b with high-titre inhibitors (≥ 5 BU) were included in this study. A total of 108 mild to moderate bleeds were treated with rFVIIa and 53 bleeds were treated with pd-aPCC. Four rFVIIa-treated joint bleeds of unknown severity were also included in the analysis, while 24 severe bleed were excluded. The pd-aPCC group demonstrated a significantly higher proportion of traumatic bleeds than rFVIIa group (18.9% versus 11.9%; $p = 0.001$). Target joint was affected in a significantly higher proportion of rFVIIa-treated bleeds (37.1% versus 20.0% in the aPCC group; $p = 0.037$). Mean time from bleeding onset to treatment initiation was significantly shorter for rFVIIa (4.1 h) than for aPCC (6.0 h; $p < 0.001$). There were significant differences in the time to bleed resolution: 93.8% of bleeds treated with rFVIIa were resolved in ≤ 12 h compared with only 60.4% of aPCC treated bleeds ($p < 0.001$). The mean total cost per bleeding episode was significantly lower with rFVIIa than with aPCC, €12,760 (11,001) versus €19,802 (12,928), $p = 0.002$. The mean cost of bypassing therapy was significantly lower in the rFVIIa than aPCC group €12,616 (11,011) versus €19,294 (12,928); $p = 0.003$, as were hospital costs (rFVIIa €144 versus €508; $p < 0.001$). Even when controlling for possible confounding factors in the General Linear Model (GLM) regression model, aPCC treated bleeds remained 29.4% more expensive than rFVIIa-treated bleeds, $p=0.052$.^{74 Level II-2}

Pokras et al conducted a costing study in the United States using Premier Perspective Database; the results showed that the median cost for treating an on-demand bleed in the hospital in the US is \$53,140 (including the cost of the BA, other pharmacy costs, room and board, supplies, lab/diagnostic and other related costs) with a mean of 6.1 days in hospital. Unadjusted analyses suggested that patients treated with aPCC versus rFVIIa had significantly longer inpatient stays ($p < 0.0001$), coupled with longer treatment duration ($p < 0.0001$), more infusions of BA administered ($p = 0.001$) and greater use of opioid-containing analgesics ($p < 0.001$). Stepwise multivariable regression showed that greater disease severity at the time of admission displayed the most significant explanatory power for both models, followed by hospital region outside the southern US, older age (cost model) and African-American race; after adjusting for BA, use of FVIII, source of hospital admission, hospital teaching status and size, and presence of arthropathy.^{75 Level II-3}

Three cost-minimisation analyses (CMA) was included in this review. Hay et al in their CMA included patients with mild to moderate bleeding episodes. They reported in the base case, the total medical cost to treat a bleed with aPCC and rFVIIa as first line medication were US\$25,969 and US\$35,838 respectively. When compared with rFVIIa, aPCC as first line therapy saves US\$9,869 per mild to moderate bleed. One way sensitivity analysis showed that results were insensitive to the efficacy of rFVIIa, unit price of aPCC or rFVIIa, switch rate, rebleed rate or body weight. The model was relatively sensitive to the dose of aPCC and rFVIIa and the efficacy of aPCC. The threshold analysis indicated that rFVIIa will reach cost neutrality when the efficacy of aPCC is as low as 60% or rFVIIa is infused only twice for each line or aPCC is infused three times for each line. If the unit price of aPCC is increased by 50% (from \$1.555 to \$2.354) or the rFVIIa unit price is reduced by one-third (from \$1.308 to \$0.864), rFVIIa will also be a dominant strategy. In two way sensitivity analysis, the results were quite sensitive to the assumed infusion frequency for both products. First line aPCC compared with rFVIIa can be a cost saving alternative for home-treatment of mild to moderate bleeding in haemophilia patients with inhibitors.^{76 Level II-3}

Bonnet et al conducted a CMA using decision analytic model based on payer perspective.^{77 Level II-3} They compared three scenarios:

Scenario 1

FEIBA/aPCC is used in the pre/intra and postoperative period

Scenario 2

rFVIIa is used in the pre, intra- and postoperative periods

Scenario 3

rFVIIa used in the pre- and intra-operative periods and FEIBA used in the postoperative period

In Scenario 1, a dosing of 85 U/kg throughout the perioperative period was selected for FEIBA, thus 6375 U of FEIBA would be used in the pre-operative period and 189750 would be used in the postoperative period. A total of 196,125 U would be consumed and the total drug cost would be \$339,296. In Scenario 2, a total of 526,500 µg; 6750 µg, 20,250 µg and 499,500 µg would be used in the pre-, intra- and postoperative periods respectively. The total drug cost would be \$810,810. In Scenario 3, during pre-operative and intra-operative periods, 6750 µg and 20,250 µg of rFVIIa would be used respectively. The postoperative period would use 189,750 U of FEIBA. The total drug cost of combination rFVIIa and FEIBA would equal \$369847. Using FEIBA instead of rFVIIa would decrease total drug cost by more than 50% and generate savings of over \$400,000 per major surgery. Sequential use of both bypassing agents increased total drug cost by 9% when compared with FEIBA alone but remain >40% lower than rFVIIa alone. Univariate sensitivity analysis confirmed the robustness of results.⁷⁷ Level II-3

You et al conducted a CMA based on Korean National Health Service perspective comparing rFVIIa and aPCC. They used data from prospective and retrospective observational studies. The mean effectiveness for new and re-bleeds was 87.1% in rFVIIa and 64% in aPCC. The mean cost of rFVIIa given as a first line therapy per individual bleeding episode was lower than the mean cost for aPCC (US\$9,276 versus US\$11,785). The mean total direct medical costs from initiation to cessation of bleeding were estimated to be US\$12311 for rFVIIa and US\$18085 for aPCC. The sensitivity analysis conducted showed that rFVIIa is cost-effective when simulating any value of the effectiveness of aPCC between 50% and 100%.⁷⁸ Level II-2

There was no economic evaluation comparing rFVIIa and aPCC has been conducted in Malaysia. The price of rFVIIa (1 mg) is [REDACTED] and for 2 mg the price is RM4,975.00. As for FEIBA (500 IU), the price is RM2,190.00. (Source: Pharmacy Department, Ampang Hospital, 2012)

Discussion

There were two RCT identified that compared head to head the rFVIIa and aPCC. These two RCTs have been included in most of the systematic reviews included in this review. Many of the primary studies and reviews included were sponsored by industries.

Overall the results showed that rFVIIa and aPCC were similar in efficacy in terms of preventing and controlling bleeding episodes and in causing low risk of thromboembolic phenomenon. Both can be administered as single intravenous bolus (270 µg/kg of rFVIIa, 75-100 IU/kg of aPCC).

There were four systematic reviews of economic studies and five primary papers included. All the systematic reviews and three of the primary papers showed that rFVIIa is more cost-effective when compared to aPCC.^{67, 75} Two cost-minimisation studies showed that aPCC is more cost-effective.^{77, 79} The results of the studies should be interpreted with caution since most of the studies were sponsored by industries.

A cross-sectional study published in 2007 assessed the used of bypassing agents in 22 haemophilia comprehensive care centres in 14 European countries. The study showed that rFVIIa was routinely used in all centres for both children and adults at dosages ranging from 90 – 250 µg/kg at an interval of 2 – 4 hour. aPCC was used in 85% of the centres in adults and in 25% of the centres in children with haemophilia A at dosages of 50 – 100 IU/kg every 6 – 12 hour. The corresponding figures for children and adults with haemophilia B were 40% and 15% of the centres, respectively.⁶⁸

All the studies included assessed the bypassing agents used as on-demand treatment for haemophilia patients with inhibitors. Currently the BAs are being studied for prophylaxis in haemophilia patients with inhibitors. However it has been described in only a small number of studies. Konkle et al evaluated whether secondary prophylaxis with rFVIIa can safely and effectively reduce the bleeding frequency as compared to conventional on-demand therapy in 38 male patients with inhibitors. Clinically relevant reductions in bleeding frequency during prophylaxis as compared to conventional on-demand therapy were achieved without raising safety concerns.⁸⁰

Given the time and resource available, there are limitations to our review that readers should bear in mind. We have conducted a comprehensive search to include all the relevant studies that fulfilled the inclusion and exclusion criteria, however finally only full text articles in English were included. We presented evidence from systematic reviews and meta-analysis and highlighted its strengths and weaknesses however; we did not access all the primary papers on which the systematic reviews and meta-analysis were based. We appraised and assessed the risk of biases of the studies but did not manage to analyse quantitatively the evidence based on the quality of the evidence.

Conclusion

Limited good level of evidence showed that rFVIIa and aPCC have similar efficacy and both can be administered as a single intravenous bolus. There was no higher risk of adverse events reported in rFVIIa compared to aPCC. Fair level of evidence suggested that rFVIIa is more cost-effective compared to aPCC.

Recommendation

The use of bypassing agents either rFVIIa or aPCC is recommended for treatment of any kind of bleeds in haemophilia patients with inhibitors since the limited good level of evidence showed that both the bypassing agents had similar efficacy.

Further well designed, high quality research is needed to study the relative effectiveness of rFVIIa compared to plasma-derived aPPC. A study among our population is strongly encouraged to provide better insight on the response to these bypassing agents.

CHAPTER 8 : COMPREHENSIVE HAEMOPHILIA CARE

Introduction

Haemophilia is a chronic and inherited X-linked bleeding disorder that requires lifelong medical care. Haemophilia treatment is costly and complex partly because of the cost of the factor concentrates used in replacement therapy. However, the vision of “Treatment for All” of the WFH is not based solely on achieving access to better treatment with safe factor concentrates: it also includes accurately diagnosing the disorder and providing specialised care by a multidisciplinary team of specialists trained in haemophilia management.⁸¹

The history of comprehensive care of haemophilia, embracing diagnosis, treatment and multidisciplinary support has evolved over the past 60 years paralleling the half century history of the WFH.⁸² It is defined as a continuing supervision of all medical and psychosocial factors affecting them and their family.⁸¹

In developed countries, haemophilia associations were originally established for the purpose of recruiting the donors needed to supply blood to be used for haemophilia patients. With the discovery of cryoprecipitate and subsequent development of clotting factor concentrates, increased the options of clinical management for patients.⁸³ Concentrates could be easily stored, administered at home and carried with patients during travel. These qualities allow early treatment of bleeding episodes before extensive joint damage occurred, and home-therapy quickly evolved as a management option. The increasing popularity of home-therapy necessitated the training and education of patients about disease management. Soon specialised centres that delivered a number of services, including home care and patient education began to emerge.⁸³

The concept of developing specialised centres for the care of people with haemophilia originated in the United Kingdom at the end of the 1940s. First established in 1954, the emphases of HTC were on diagnosis and need to avoid dangerous operations. These 18 HTCs did little more than diagnose the patients, issue special identity cards to them and provide them psychosocial support to protect them from the many hazards of hospital treatment.⁸⁴

Multidisciplinary management of patients with haemophilia started in USA in 1970 as an initiative of healthcare professionals committed to haemophilia treatment who had the support of patient associations.⁸¹ In 1975, through advocacy efforts led by those who treated haemophilia and parents affiliated with consumer advocacy organisation, the National Hemophilia Foundation (NHF), and based on the experience of early novel multidisciplinary approaches in Britain and California, Congress provided support to fund 26 comprehensive haemophilia specialty clinics through Health, Education and Welfare, now the US Department of Health and Human Services Maternal and Child Health Bureau.⁸⁵

In many developed countries the HTCs were made possible because of the advanced economic condition of these countries, provided comprehensive services including haemophilia care, orthopaedic and dental services and education, and psychosocial support.⁸³

The functions of the HTCs delineated in the WFH guidelines are:⁴³

- **To provide and coordinate inpatient (i.e. during hospital stays) and outpatient clinic and other visits) care and services to patients and their families.** Patients should be seen by all core team members at least yearly (children every six months) for a complete haematologic, musculoskeletal, psychosocial assessment and to develop, audit, and refine an individual’s comprehensive management plan. Referrals for other services can also be given during these visits.

- **To initiate, provide training for, and supervise home-therapy with clotting factor concentrates where available.**
- **To educate** patients, family members, and other caregivers to ensure that the needs of the person with haemophilia are met.
- **To collect data** on sites of bleeds, types and doses of treatment given, assessment of long-term outcomes (particularly with reference to musculoskeletal function), complications from treatment, and surgical procedures. This information is best recorded in a computerized registry and should be updated regularly by a designated person. Systematic data collection will facilitate the auditing of services provided by the HTC and support improvements to care delivery, help inform allocation of resources, and promote collaboration between centres in sharing and publishing data. Registries must be maintained in accordance with confidentiality laws and other national regulations.
- **Where possible, to conduct basic and clinical research.** Since the number of patients in each centre may be limited, clinical research is best conducted in collaboration with other haemophilia centres.

The core team should consists of the following members:⁴³

- a medical director (preferably a paediatric and/or adult haematologist, or a physician with interest and expertise in haemostasis)
- a nurse coordinator who:
 - coordinates the provision of care
 - educates patients and their families
 - acts as the first contact for patients with an acute problem or who require follow up
 - is able to assess patients and institute initial care where appropriate
- a musculoskeletal expert (physiotherapist, occupational therapist, physiatrist, orthopaedist, rheumatologist) who can address prevention as well as treatment
- a laboratory specialist
- a psychosocial expert (preferably a social worker, or a psychologist) familiar with available community resource

Although comprehensive care has evolved in developed countries since 60 years ago, in many developing countries, it is still evolving at various stages. The cost of optimum care for haemophilia is beyond the reach of individuals with haemophilia so that others, whether from government or private insurance must bear the cost.⁸⁶ By nature, the payers' focus is on the bottom-line economics, i.e "the most served with the least cost". In countries with emerging economies, economic issues will be the primary force determining how far patients and physicians can push their goals.⁸⁶

The aim of this review is to assess the effectiveness and cost implications of comprehensive care and other non-pharmacological treatment in patients with haemophilia.

Characteristics of included studies

We retrieved three studies that assessed the effectiveness of comprehensive care and a guidelines.

Study design

One of the studies included were prospective cohort study, one retrospective study and a cross-sectional study with costing.

Participants

Patients with haemophilia A or B

Intervention

Comprehensive haemophilia care or HTC user

Comparison

Non-comprehensive care or non-HTC user

Outcome measures

The outcome measures are the benefits or effectiveness of HTC or comprehensive care as measured by mortality and cost.

Efficacy

Smith et al published the first report on socioeconomic evaluation of a state-funded comprehensive haemophilia care program that was an affiliate of the national program in 1982. The study conducted in Rhode Island ascertained that by the fifth year of funding 77% of patients with haemophilia in the state received total care through this HTC where 28 of 43 patients converted to home infusion, most of whom had previously not had such self-infusion capacity available. The annual number of hospital days per patient has decreased from 12.6 to 3.5, and the number of visits to hospital facilities has fallen from 34 to 2.4. Numbers of days lost from school and work have decreased twofold and threefold, respectively. Best of all, comprehensive care has vastly improved the quality of life for patients with haemophilia in Rhode Island.⁸⁷ Level II-3

Smith et al reported a 5-year multicentre study examining the benefits of comprehensive care in 11 out of 22 federally funded comprehensive centres. 4682 patients were compared to 1333 patients who received care from the same providers before the creation of the comprehensive care model. The results showed that initially only 514 patients were knowledgeable and skilled enough to treat themselves with appropriate doses of intravenous blood product, by fiscal 1981, 2,001 had achieved this degree of proficiency. Thirty six percent of the surveyed population was unemployed at the outset as compared to 12.8% four years later. The number of days lost from work or school decreased from 14.5 per year (9.4 of which were spent in the hospital) prior to funding to 4.3, with hospital treatment needed in only 1.8. The average patient who could expect two hospitalisations per year before the program required admission only once every three to four years, five years later.⁸⁸ Level II-2

Soucie et al analysed data from the Haemophilia Surveillance System (HSS) which was a cooperative project between the Centers for Disease Control and Prevention (CDC) and the health departments in six states. From 1995-1997, 2950 males with haemophilia A and B were identified. Overall, 67% of patients received care in HTCs during the period. Thirteen percent received care primarily from private physicians or haematologist, 4% primarily from hospital- and nonhospital-based clinics, 8% received care only in hospitals or emergency rooms, and the rest received care from variety other sources.

During the study period, 236 (8%) persons with haemophilia died corresponding to an age-adjusted mortality rate of 40.4 deaths per 1000 person years. After multivariate analysis, medical care provided by HTC was found to be strongly associated with reduced mortality; persons who had received care in HTCs during the study period were 40% less likely to die than those who had not, RR 0.6 (95% CI 0.5 – 0.8). The mortality risk increased by 60% with each additional decade of age, (RR 1.6, 95% CI 1.4 – 1.7). Persons with severe liver disease had 2.4 times the risk of death (RR 2.4, 95% CI 1.5 – 3.9), those persons with HIV infection but without AIDS had nearly 5 times the risk (RR 4.7, 95% CI 3.0 – 7.2), and person with AIDS had 33 times the risk compared with persons without these conditions (RR 33.5, 95% CI 22.7 – 49.5). The life expectancy at birth was 38.7 years and the median age at death was 35 years. However, when HIV-infected persons were excluded from the cohort, the life expectancy rose to 64.1 years, and the median age at death nearly doubled to 67 years.^{89 Level II-2}

According to WFH guidelines, people with haemophilia are best managed in a comprehensive care setting. They stated that comprehensive care promotes physical and psychosocial health and quality of life while decreasing morbidity and mortality. The wide ranging needs of people with haemophilia and their families are best met through the coordinated delivery of comprehensive care by a multidisciplinary team of health care professionals, in accordance with accepted protocols that are practical and national treatment guidelines if available. They also recommended that patients should be seen by all core team members at least yearly (children every 6 months) for a complete haematologic, musculoskeletal and psychosocial assessment and to develop, audit, and refine an individual's comprehensive management plan. Referrals for other services can also be given during these visits.^{43 Level II-2}

Cost-effectiveness

There was no study on cost-effectiveness retrieved.

In Smith et al study in Rhode Island, the yearly cost of clotting factor per patient was stabilised at \$7,000, resulting in a net savings of approximately \$10,000 per patient primarily from reduced hospitalisation cost. Altogether, this has saved more than \$10,000 each year for treatment, despite the cost of rehabilitative surgery.^{87 Level II-2}

According to Smith et al study in 11 out of 22 HTCs in United States of America, the overall cost of care per patient per year before comprehensive care program introduced was \$15,800 and during the fifth year, it has reduced to \$5932. The details of the cost included in the costing was not reported in the paper.^{88 Level II-2}

Discussion

There were three observational studies and one guidelines retrieved that reported the benefits of comprehensive care. All the studies were from the United States. Nevertheless, the findings that HTCs significantly reduced the mortality rate of haemophilia patients supported the effectiveness of such centre in providing specialised specialist care. HTCs improved patients' knowledge and skills to help them manage themselves, reduced days of hospitalisation and days lost from work or office. These are the requisites to improve their quality of life.

Important elements of this effect were the availability of expertise for serious complications, availability of home-therapy, and consistent education of patients about their disease, all standard services at the comprehensive centres.⁸³

There was no full economic evaluation study on comprehensive haemophilia care identified. The studies retrieved showed that comprehensive care led to cost saving due to reduction in hospitals stays, hospital visits and management of complications.^{87, 88}

Economics greatly affects health care for haemophilia. During the past two decades, the cost of this care rose exponentially because improved safety of treatment products produced a 5 to 10 times increase in cost. It was reported that in the United States, the cost of haemophilia care is close to the median of the most developed countries. In 1996, the annual financial support of episodic care for an average haemophilia patient was about \$23,000 and for prophylaxis treatment \$76,000 (the medical provider cost was only 1.5% and hospital costs were only 1.7% of these costs).⁸⁶ In another study conducted in European countries in 1996-1998, the mean cost of haemophilia care in United Kingdom was €3,593 for prophylaxis care and €1,464 for on-demand care whereas in France the cost was €13,768 for prophylaxis care and €3,857 for on-demand care.³⁰

In countries with emerging economies, the effect of comprehensive care is dramatic. Frequently because of the limitation of resources, access to clotting factor concentrates is more restricted. In these situations, however, even the modest expenditures used to modify the structure and organisation of the care delivery (with emphasis on prevention), to educate medical personnel and patients and to modify blood bank practices to improve the safety and supply of therapeutic products yield huge economic and quality of life benefits.⁸⁶

The need for specialised care for patients with haemophilia was not unique in the United Kingdom and United States. Several French haematologists established a boarding school for boys with haemophilia, and two other schools were subsequently opened in 1963 and 1965. Out of this experience, a model of optimal care for haemophilia evolved in France that permitted each of these patients to benefit from the expertise of a full multidisciplinary team.⁸⁴

In Australia the concept of comprehensive care evolved in a more traditional fashion, similar to the pathway in the United States and United Kingdom models. Beginning in 1957, a specialised haemophilia clinic at the Royal Prince Alfred Hospital was developed with research and clinical component, with special expertise in blood banking and production of clotting factor concentrates locally. Japan. Italy and Israel developed independent HTC sites that evolved into nationwide networks.⁸⁴

European countries have come out with principles of haemophilia care. Amongst others, it stated that in each country, there should be a central organisation for haemophilia care supported by centres operating at the local level. These organisations should be responsible for accurate record keeping and the effective administration of haemophilia care. Such an approach also facilitates the exchange of best practice and the coordination of research. Each country should have a national haemophilia patient registry administered by the Central Haemophilia Organisation. Comprehensive Care Centres (CCCS) and HTC should be established to ensure that people with haemophilia have access to the full range of clinical specialties and appropriate laboratory services.⁴²

In 1997, the WFH produced a document defining the three levels of healthcare recommended for structuring a national healthcare plan for patients with haemophilia, from emergency hospital care to follow up at reference centres.⁸¹

WFH has also developed a model for national haemophilia care programmes (see Table 2). Emphasis was put on the inter-relationships of government, funders, clinicians and patients in developing care delivery. There are currently five pillars: obtaining government support, enhancing the care delivery system, improving medical expertise in the diagnosis and management, making safe and effective treatment products available and enhancing patient organisation capacity. A sixth pillar, improving data collection and outcomes analysis, is being added. All of these components are required not only for the success of a national programme but also in miniature for individual HTC⁸².

In Malaysia, currently there is no national program for haemophilia. Haemophilia treatment varies from no treatment to fresh frozen plasma (FFP) to fractionated products or recombinant FVIII depending on patients' access to treatment. However, comprehensive care has been initiated in Ampang hospital.

This review has certain limitations. We intend to compare comprehensive care with non-comprehensive care, thus longitudinal studies without comparison were not included. In view of time constraint we did not assess the role of the team members in comprehensive care but assessed the collective approach. We conducted a comprehensive search in several databases as mentioned earlier, however, finally we only include full text articles in English. There was no high quality study identified on this decision problem.

Conclusion

The fair level of evidence showed that comprehensive care reduced the mortality rate in haemophilia patients, reduced the hospitalisation days and reduced the number of days lost from school or work. There was insufficient evidence on cost-effectiveness, however the fair level of evidence suggested that comprehensive care leads to cost saving.

Recommendation

Based on the available evidence and the current practice of haemophilia management worldwide, comprehensive care for haemophilia patients is recommended and seemed to be the way forward to improve the quality of care and prevent complications.

A national haemophilia program should be introduced in Malaysia to address several issues pertaining to management of haemophilia patients such as care delivery, medical expertise and treatment products. WFH steps to set up a national haemophilia program (see Table 2) may be used as a guide.

Table 2. World Federation of Haemophilia steps for developing national haemophilia care programmes

GOVERNMENT SUPPORT	CARE DELIVERY	MEDICAL EXPERTISE	TREATMENT PRODUCTS	PATIENT ORGANIZATION
Objectives				
<ul style="list-style-type: none"> To obtain government support for national hemophilia care program within the health system 	<ul style="list-style-type: none"> To set up a national haemophilia care program (national plan defined with key treaters and NGO). To make the organisation of haemophilia treatment more efficient 	<ul style="list-style-type: none"> To provide accurate diagnosis and appropriate treatment 	<ul style="list-style-type: none"> To obtain the best quality blood products in sufficient quantity at an affordable cost. Develop and improve regulatory knowledge 	<ul style="list-style-type: none"> To develop a strong patient organisation for advocacy and education
Development steps				
<ol style="list-style-type: none"> No government support or interest in haemophilia care. Government recognition of main HTC as a reference centre. Some level of government involvement in haemophilia care (e.g. haemophilia committee or task force). Limited central or regional government resources allocated for haemophilia care. Official government commitment to haemophilia care. Government contributes substantial financial support for haemophilia care. Hemophilia is a line item in a country's annual healthcare budget. Government is a key partner in sustainable national haemophilia care program. 	<ol style="list-style-type: none"> Isolated doctor in major city works with no resources. Basic treatment is possible in hospital(s) in major city Regular haematology outpatient clinic with follow up offered Creation of a core team within hospital that forms the basis of a full haemophilia treatment centre (HTC) Core team within hospital (HTC) has a medical patient registry & treatment guidelines/ protocols Additional HTCs with core teams for children and/or adults in major cities. Coordinated network of designated HTCs with national treatment protocols. Full comprehensive haemophilia care team is formed in the major HTC(s) Basic teams formed in other areas/regions Established national medical patient registry. Established sustainable national haemophilia care program. 	Medical treatment <ol style="list-style-type: none"> Basic medical knowledge in haematology (includes paediatricians and general practitioners) Doctor specialised in haematology Haematologist(s) assigned to haemophilia care Key haematologist(s) trained in haemophilia Specialised haemophilia core team (haematologist, nurse, physiotherapist, orthopedist, lab technologist) Education provided to patients Home care available for patients Specialised comprehensive care team (social worker, dentist, psychologist, infectious diseases specialist, genetic counsellor) Education offered to general medical community. 	<ol style="list-style-type: none"> Local production of: <ol style="list-style-type: none"> Whole blood Plasma Fresh frozen plasma (FFP) Cryoprecipitate Freeze dried cryoprecipitate Combination of local production of cryo and/or FFP and some purchase of plasma-derived factor concentrates: <ol style="list-style-type: none"> Less than .2 IU per capita of concentrates Between .2 and .5 IU Between .5 and 1 IU Between 1 and 2 IU Proper national tender system in place Examine feasibility of contract fractionation of plasma-derived concentrates Examine feasibility of local fractionation of plasma-derived concentrates Purchase of plasma-derived concentrates (>2 IU per capita) Examine feasibility of combined purchase of plasma-derived and recombinant concentrates 	<ol style="list-style-type: none"> Organisation formed by a nucleus of patients Organisation structured, recognised/registered with a constitution. Organisation holds regular meetings with a core group of volunteers and educates patients and families in major city. NMO patient registry. Organises activities including: <ol style="list-style-type: none"> educational services fundraising training membership volunteer recruitment advocacy budgeting Outreach to other regions of the country to identify new patients Regional chapters are formed National organisation follows a strategic plan National organisation is a partner in national haemophilia care program

Source : Street A. Developing models of haemophilia care

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APPENDIX 1 : HTA PROTOCOL

TITLE: Management of Haemophilia and rare bleeding disorders

1. BACKGROUND INFORMATION

Haemophilia is an inherited bleeding disorder that results from a low level of proteins needed for normal blood clotting. There are two main types of haemophilia, haemophilia A, which is caused by a lack or decrease of clotting factor VIII (FVIII); and haemophilia B, which is caused by a lack or decrease of clotting factor IX (FIX). These X-linked disorders represent the large majority of inherited deficiencies of clotting factors, occurring in approximately one per 5000 and one per 50,000 male births, with no racial predilection. According to their residual endogenous FVIII/FIX concentrations, individuals with a factor level <1 IU/dL are classified as severe haemophiliacs and represent about half of diagnosed cases. Subjects with factor levels between 1-5 IU/dL and >5 IU/dL have moderate and mild haemophilia, respectively.¹ Together with von Willebrand disease, a defect of primary haemostasis associated with a secondary defect in coagulation factor VIII (FVIII), these X-linked disorders include 95% to 97% of all the inherited deficiencies of coagulation factors.

Rare bleeding disorders (RBDS) are heritable abnormalities of haemostasis that may present significant difficulties in diagnosis and management to haemophilia centre clinicians.² RBDs represent 3-5% of all the inherited deficiencies of coagulation factors. Their distribution is variable in the world, with a prevalence of the presumably homozygous forms in the general population ranging from approximately 1 in 2 million for prothrombin (factor II, FII) and FXIII deficiency (the rarest) to 1 in 500,000 for FVII deficiency (the most common). Exceptions are countries with large Jewish communities where FXI deficiency is much more prevalent. In Middle Eastern countries and Southern India, with a higher rate of consanguineous marriage, autosomal recessive traits occur more frequently in homozygous state.³

According to World Federation of Hemophilia, the reported haemophilia A and haemophilia B prevalence varied considerably among countries. The prevalence of haemophilia A (per 100,000 males) for high income countries was 12.8 ± 6.0 (mean \pm SD) whereas it was 6.6 ± 4.8 for the rest of the world. The prevalence of Haemophilia A in Malaysia has increased from 5.6 in 1998 to 6.6 in 2006, the mean was 5.9 ± 0.4 .⁴ As for haemophilia B for the highest income country was 2.69 ± 1.61 whereas the prevalence for the rest of the world was 1.20 ± 1.33 . The reported prevalence for Malaysia was 1.00 ± 0.11 .⁵

Replacement of haemostatic concentrations of the deficient factor is the mainstay of treatment for bleeding episodes, according to the type and severity of bleeds and until complete resolution of symptoms.¹ Recurrent joint bleeds, inevitably leading to crippling arthropathy were the hallmark of these diseases before 1970s, when plasma fractions containing FVIII or FIX were still not available. At that time the mortality of bleeding was very high and the life expectancy of persons with haemophilia was much lower than that of general population.¹

Haemophilia care does not consist only of replacement therapy and haematologic follow up. The haematologist's clinical and laboratory expertise should be conjugated to other diagnostic and therapeutic facilities for the management of bleeding at various sites, surgery and chronic complications. The need for multidisciplinary integrated approach at specialised centres for this rare congenital disease requiring complex management has been recognised since 1960s.¹

In the western world today, it is possible for a child with haemophilia receiving adequate treatment to live a near normal life. An accurate diagnosis is quickly established, the family is educated on the management and the child is put either on prophylactic factor replacement or on-demand replacement given at home.⁶ But, this level of treatment is expensive. In Sweden for example, it costs US\$100,000 per year to provide prophylactic factor replacement for one child with haemophilia.⁶

In Malaysia, currently there is no national standard or holistic approach in management of patients with haemophilia to ensure high quality multidisciplinary approach to improve patient outcomes and optimise resource utilisation.

The review was requested by a Senior Consultant Paediatric Haemato-oncologist in order to improve the quality of care of haemophilia patients in the country.

2. POLICY QUESTION

Should a national haemophilia program be introduced in Malaysia?

Research Questions

1. Is screening programme effective for haemophilia and bleeding disorders and who are the target groups?
2. What is the most cost-effective diagnostic approach for bleeding disorders?
3. Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and other rare bleeding disorders and what are the resource implications?
4. Is recombinant factor VIII and factor IX more cost-effective compared to plasma-derived?
5. What is the role of non-pharmacological in a comprehensive care (dental, physiotherapy, orthopaedic, genetic counselling, psychologist, rehabilitation, nutrition, nursing) for haemophilia?

3. OBJECTIVES

The following are the objectives of this review:

1. To assess the effectiveness of screening program and diagnostic strategies for haemophilia and rare bleeding disorders
2. To assess the efficacy and resource implications of prophylaxis treatment when compared to on-demand treatment for patients with haemophilia and other rare bleeding disorders
3. To assess safety, effectiveness and cost-effectiveness of recombinant factors compared to plasma-derived
4. To assess the effectiveness of non-pharmacological management for haemophilia and other rare bleeding disorders patients

4. METHODS

Systematic reviews following the principles used by Cochrane Collaboration will be conducted to achieve the objectives of this review.

4.1 Search Strategy

- i. Electronic database will be searched for published literatures pertaining to management of haemophilia and rare bleeding disorders which includes screening, diagnosis, treatment -prophylaxis versus on-demand, programme of other countries.
- ii. The following databases will be used to carry out the search of evidence:- MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), PubMed, Horizon Scanning, INAHTA Database, HTA database and FDA database.
- iii. Additional literatures will be identified from the bibliographies of the relevant articles.
- iv. Expert in this area will be contacted when necessary to get further information.
- v. Handsearching of evidence will be conducted if necessary to find unpublished evidence.
- vi. General search engine might be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
- vii. There will be no limitation applied in the search such as year and language.
- viii. The detail of the search strategy will be presented in the Appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

a. Study design :

For systematic review on screening and diagnosis, HTA reports, systematic reviews, RCT, diagnostic accuracy studies, cohort studies, case-control studies and cross-sectional studies with gold standard will be included.

For systematic review on clinical effectiveness, systematic reviews, meta-analysis, RCT and non-randomised comparative studies will be included.

For systematic review on cost-effectiveness of haemophilia program, which will include prophylaxis versus on-demand treatment, all cost-effectiveness study of satisfactory quality will be included.

b. Population :

Patients with all type of Haemophilia and clotting factor deficiency/coagulation bleeding disorders

c. Intervention :

- i. targeted/ genetic screening
- ii. treatment – prophylaxis
- iii. recombinant factor
- iv. non-pharmacological management

d. Comparators :

- i. on-demand treatment
- ii. plasma-derived
- iii. different prophylaxis approach

e. Outcome

One or more of the following outcome measures will be assessed

- i. Effectiveness of the screening and/or haemophilia programme as measured by detection rate, mortality rate, survival rate, quality of life, and quality adjusted life years (QALY) gained
- ii. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of screening method or diagnosis methods
- iii. Effectiveness and adverse events of the prophylaxis and on-demand treatment as measured by joint bleeds, quality of life, clinical scale on joint functions, arthropathy
- iv. Cost, cost-benefit, cost-effectiveness, and cost-utility of the haemophilia programme and treatment strategies

f. Publication

Full text articles published in English

4.2.2 Exclusion criteria

- i. Animal study
- ii. Narrative review
- iii. Laboratory study
- iv. Non-English full text articles
- v. Platelet disorders
- vi. Connective tissue diseases

4.3 Data extraction strategy

Data will be extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements will be resolved through discussion. A third person, whose decision is final will be consulted when disagreements persists after discussion.

4.4 Quality assessment strategy/Assesment of risk of bias

The validity of the eligible studies will be assessed by two reviewers independently using Critical Appraisal Skill Programs checklists criteria according to the study designs.

The quality of the evidence will be graded according to US/Canadian Preventive Services Task Force Grading System.

4.5 Methods of analysis/synthesis

Data will be summarised in evidence table. If the data is suitable for statistical pooling, meta-analyses of the main outcomes will be performed. Otherwise data for the outcomes will be reported narratively.

5. REPORT WRITING

6. REFERENCES

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APPENDIX 2 : ELECTRONIC BIBLIOGRAPHIC DATABASES SEARCHED

1. MEDLINE
2. EMBASE
3. Cochrane Central Database of Controlled Trials (CENTRAL)
4. Cochrane Database of Systematic Reviews (CDSR)
5. NHS Database of Abstracts of Reviews of Effectiveness (DARE)
6. NHS Economic Evaluation Database (NHS EED)
7. NHS Health Technology Assessment (HTA) Database

APPENDIX 3 : **OTHER SOURCES CONSULTED**

1. Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP-S)
2. National Institutes for Health and Clinical Excellence (NICE)
3. Clinical Practice Guidelines and Protocols in British Columbia
4. Columbia British
5. Swedish Council on Health Technology Assessment
6. Canadian Agency for Drugs and Technologies in Health (CADTH)
7. International Network of Agencies for Health Technology Assessment (INAHTA)
8. World Health Organisation (WHO)
9. Google
10. EuroSCAN
11. Australia and New Zealand Horizon Scanning Network
12. Guidelines International Network (G-I-N)
13. ClinicalTrials.gov
14. International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

APPENDIX 4 : **SEARCH STRATEGIES USED IN THE MAJOR ELECTRONIC BIBLIOGRAPHIC DATABASES**

MEDLINE/EMBASE/PubMED

Recombinant versus plasma-derived

1. exp hemophilia a/ or exp hemophilia b/ or exp coagulation protein disorders/
2. ha?mophilia a.tw.
3. (factor VIII adj1 deficienc\$).tw.
4. ha?mophilia.tw.
5. ha?mophilia b.tw.
6. acquired hemophilia.tw.
7. blood Coagulation Disorders, Inherited/
8. hereditary\$ coagulation disorder\$.tw.
9. blood coagulation factor deficiencies.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. recombinant factor VIII.tw.
12. plasma derivatives.tw.
13. 11 or 12
14. 10 and 13

Prophylaxis versus on-Demand

1. exp hemophilia a/ or exp hemophilia b/ or exp coagulation protein disorders/
2. ha?mophilia a.tw.
3. (factor VIII adj1 deficienc\$).tw.
4. ha?mophilia.tw.
5. ha?mophilia b.tw.
6. acquired hemophilia.tw.
7. blood Coagulation Disorders, Inherited/
8. hereditary\$ coagulation disorder\$.tw.
9. blood coagulation factor deficiencies.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Prophylaxis.tw.
12. on-demand.tw.
13. 11 or 12
14. 10 and 13

APPENDIX 5 : RISK OF BIAS ASSESSMENT

RISK OF BIAS ASSESSMENT FOR RCT

CRITERIA ASSESSED			
Sequence generation	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Allocation sequence concealment	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Blinding	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Explanation on loss to follow up	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Intention to treat analysis	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
"Other" potential sources of bias	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>

RISK OF BIAS ASSESSMENT FOR COMPARATIVE OBSERVATIONAL STUDIES

CRITERIA ASSESSED			
Random selection of participants	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Prospective study	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Blinding	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Explanation on loss to follow up	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
Analysis takes into account confounding factors	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>
"Other" potential sources of bias	Yes <input type="checkbox"/>	Can't tell <input type="checkbox"/>	No <input type="checkbox"/>

RISK OF BIAS ASSESSMENT FOR ECONOMIC EVALUATION PAPERS

CRITERIA ASSESSED	Paper ID
1. Was a well-defined question posed?	Yes . Can't tell . No
2. Comprehensive description of the competing alternatives	Yes . Can't tell . No
3. Effectiveness established	Yes . Can't tell . No
4. Effects of the intervention identified, measured and valued appropriately?	Yes . Can't tell . No
5. All relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	Yes . Can't tell . No
6. Were costs and consequences adjusted for different times at which they occurred (discounting)	Yes . Can't tell . No
7. What were the results of the evaluation?	Yes . Can't tell . No
9. Was an adequate sensitivity analysis performed?	Yes . Can't tell . No
10. Is the programme likely to be equally effective in your context or setting?	Yes . Can't tell . No
11. Are the costs translatable to your setting?	Yes . Can't tell . No
12. Is it worth doing in your setting?	Yes . Can't tell . No

APPENDIX 6 : DESIGNATION OF LEVELS OF EVIDENCE

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

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 7 : **PETTERSSON RADIOLOGIC SCORE**

Finding	Score
Osteoporosis	
Absent	0
Present	1
Enlarged epiphysis	
Absent	0
Present	1
Irregular subchondral surface	
Absent	0
Partially involved	1
Totally involved	2
Narrowing of joint space	
Absent	0
Present, joint space > 1 mm	1
Absent, joint space ≤ 1 mm	2
Subchondral cyst formation	
Absent	0
Present	1
Erosions at joint margins	
Absent	0
1 Cyst	1
> 1 Cyst	2
Gross in congruence of articulating bone ends (angulation or displacement between articulating bone ends)	
Absent	0
Slight	1
Pronounced	2
Joint deformity	
Absent	0
Slight	1
Pronounced	2

Source: Ng WH, Chu WCW, Shing MK, et al Role of imaging in management of hemophilic patients. American Journal of Roentgenology. 2005 May 1, 2005;184(5):1619-23.

APPENDIX 8 : EVIDENCE TABLES

This Appendix contains the evidence tables with data extracted from the 49 studies included in this HTA report. The evidence tables are arranged in four parts.

- Part 1** is the evidence tables on efficacy and resource implications of prophylaxis treatment when compared to on-demand treatment for patients with haemophilia and other rare bleeding disorders.
- Part 2** is the evidence tables on safety, effectiveness and cost-effectiveness of recombinant factors compared to plasma-derived
- Part 3** is the evidence tables on efficacy and resource implications of recombinant activated FVII when compared to activated PCC and what are the resource implications
- Part 4** is the evidence tables on the effectiveness of comprehensive care for haemophilia patients

PART 1

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	1. Iorio A, Marchesini E, Marcucci M, et al Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database of Systematic Reviews. 2011;9:CD003429.
Study type and methods	Systematic Reviews with meta-analysis
LE	1
Number of patients & Patient characteristics	<p>Six studies were included</p> <p>Aronstam 1976 Aronstam 1977 Carlsson 1997 Gringeri 2011 (ESPRIT) Manco-Johnson 2007 (JOS) Morfini 1976</p> <p>Children and adults with congenital haemophilia A or B, including all ages and all degrees of severity. People with factor VIII and IX inhibitors were excluded</p>
Intervention	Prophylaxis treatment with clotting factor concentrates in any formulation such as FFP, cryoprecipitate, lyophilised plasma-derived clotting factor concentrate, or recombinant clotting factor concentrate in any concentration, frequency or dosage
Comparison	On-demand, placebo or alternative prophylaxis
Length of follow up (if applicable)	Up to 58 months
Outcome measures/ Effect size	<p>Bleeding frequency Significant statistical reduction of total bleeding in patients treated on prophylaxis versus those treated on-demand. Rate ratio 0.30 (95% CI 0.12 to 0.76) I² 99% (Chi² 196.78, p < 0.00001)</p> <p>Radiologic joint score Patients on PP in ESPRIT study showed statistical significant protection from joint damage when compared to standard on-demand (risk difference 0.70 (95% CI 0.39 to 1.01). The difference in JOS study was borderline RD 0.15 (95% CI -0.01 to 0.31)</p> <p>QoL ESPRIT trial showed that overall QoL was 22.2 (SD 8.2)</p> <p>Clotting factor concentrate usage Significant increased consumption of factor VIII in the patients treated with prophylaxis when compared to those treated on-demand. MD 5270 IU/month per patient (95% CI 4230 to 6320) I² 0% (Chi² 0.24, p=0.62)</p> <p>Economic evaluation Cost analysis with societal perspective was conducted in ESPRIT study. ICER per bleeding events avoided in patients on prophylaxis was EUR 7537 whereas for maintaining all joints unaffected over the whole treatment period was EUR 201,601.12</p> <p>Adverse events Rate of infections per treatment group- non-significant difference against prophylaxis RD 0.14 (95% CI -0.14 to 0.42), I² 75% (Chi² 4.04, p=0.04)</p> <p>Inhibitor rate – not significantly higher in patients on prophylaxis RD 0.06 (95% CI -0.03 to 0.15) I² 0% (Chi² 0.06, p=0.81)</p>
General comments	Very old studies included. More recent observational studies should be included in this review.

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders

: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and other rare bleeding disorders, and what are the resource implications?

Is recombinant factor VIII and IX more cost-effective compared to plasma-derived?

Bibliographic citation	2. Berntorp E, Astermark J, Baghaei F, Bergqvist D, Holstrom M, Ljung R, et al Treatment of Hemophilia A and B and von Willebrand Disease. Stockholm, Sweden: Swedish Council on Health Technology Assessment; 2011.
Study type and methods	Systematic Review/HTA report
LE	1
Number of patients & Patient characteristics	<p>Numerous articles included</p> <p>Haemophilia A – 27 studies, 7 reviews</p> <p>Haemophilia B – 4 studies</p> <p>Long-term effects of haemophilia A and B – 9 studies</p> <p>Bypass products – 24 studies, 16 reviews</p> <p>Immunotolerance treatment – 24 studies, 8 reviews</p>
Intervention	<ol style="list-style-type: none"> 1. Prophylaxis 2. Recombinant 3. Bypassing agent
Comparison	<ol style="list-style-type: none"> 1. On-demand 2. Plasma-derived
Length of follow up (if applicable)	-
Outcome measures/ Effect size	<ul style="list-style-type: none"> • Number of bleeding episodes • Quality of life • Tolerance development • Resource used <p>Results were not pooled</p> <p>Treatment of haemophilia A and B</p> <ul style="list-style-type: none"> • Insufficient to determine <ul style="list-style-type: none"> - differences between recombinant and plasma-derived factor concentrates - differences between different dosing strategies - risk of developing inhibitors in prophylaxis compared to on-demand - differences in long-term effects of different treatment regime - insufficient to determine which doses and dosing intervals are the most effective <p>Treatment of patients with inhibitors</p> <ul style="list-style-type: none"> • Insufficient evidence <ul style="list-style-type: none"> - To determine the effects of treating acute bleedings with the bypass agents' - To assess the effects of prophylactic treatment with the bypass agents - To assess the effects of immunotolerance induction using factor VIII or IX concentrates <p>Treatment of von Willebrand Disease</p> <ul style="list-style-type: none"> • Insufficient evidence to determine the effects of prophylaxis and on-demand treatment, different dosing strategies and different factor concentrates <p>Economic aspects</p> <ul style="list-style-type: none"> • Insufficient evidence <p>Ethical aspects</p> <ul style="list-style-type: none"> • Includes risk of blood contamination and the high cost of treatment
General comments	Reviews, studies without controls were also included

Evidence Table

Question

: Management of haemophilia and rare bleeding disorders

: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	3. Gringeri A, Lundin B, von Mackensen S, et al A randomized clinical trial of prophylaxis in children with hemophilia a (the esprit study). Journal of Thrombosis & Haemostasis. 2011 Apr;9(4):700-1
Study type and methods	RCT + cost-effectiveness analysis Open label pragmatic trial Italy
LE	1
Number of patients & Patient characteristics	45 patients (5 withdrew before intervention commence) Haemophilia A (FVIII <1%) without inhibitors h/o < 2 bleeding episodes
Intervention	21 patients Prophylaxis with recombinant FVIII concentrate Recombinate (up to 2004) then ADVATE 25 IU/kg three times a week on non-consecutive days
Comparison	19 patients On-demand 25 IU/kg or more of same product within 6 hour from the event, repeated every 12-24 hour until complete resolution of bleeding episode
Length of follow up (if applicable)	Mean Prophylaxis group - 72.5 months On-demand group - 76.0 months 28.8% loss to follow up
Outcome measures/ Effect size	Mean bleeding events per patient/year Prophylaxis = 4.0 On-demand = 12.0 (p <0.01) Mean haemarthroses per patient/year P = 1.0 O = 5.5 (p<0.01) Radiographic findings Patients with joint damage, no (%) P = 6 (29%) O=14 (74%) (p<0.05) NNT: 2 Total no of FVIII units infused P = 13,477,251 O = 5,749,085 (p<0.01) ICER per bleeding event avoided in patients on prophylaxis was 7537€ (10,049.6 IU x 0.75€) ICER for maintaining all joints pristine over the whole treatment period was 201,601.12€ Adverse events 10 of 20 patients on prophylaxis required indwelling catheter, six infected. None in on-demand group 5(12.5%) develop inhibitors, 3 from prophylaxis
General comments	Industry funded Included in Berntorp 2011 and Iorio 2011

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	4. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. New England Journal of Medicine. 2007 Aug 9;357(6):535-44.
Study type and methods	RCT open label US
LE	1
Number of patients & Patient characteristics	65 patients Haemophilia A, FVIII < 2 U/dL, without inhibitors h/o < 2 bleeding episodes
Intervention	Prophylaxis with recombinant FVIII Kogenate or Kogenate FS 25 IU/kg every other day 32 patients
Comparison	Enhanced episodic therapy 40 IU/kg of same product at the time of joint haemorrhage and 20 IU at 24 hours and 72 hours after the first dose. Encourage to continue infusions of 20 IU of FVIII every other day until joint pain and impairment of mobility had completely resolved for a max of 4 weeks 33 patients
Length of follow up (if applicable)	Mean 49 months 25% loss to follow u
Outcome measures/ Effect size	<p>Preservation of index joint Prophylaxis group 25/27 (93%), Enhanced episodic group 16/29 (55%), NNT 3 (Need to treat three patients to prevent one joint damage) RR 6.1 (95% CI 1.5 to 24.4)</p> <p>Mean joint haemorrhages per person /year Prophylaxis 0.63 ± 1.35 EET 4.89 ± 3.57 $p < 0.001$</p> <p>Mean total haemorrhages per person/year Prophylaxis 3.27 ± 6.24 EET 17.69 ± 9.25 $p < 0.001$</p> <p>Total no of FVIII units infused Prophylaxis $352,793 \pm 150,454$ EET $113,237 \pm 65,494$ $p < 0.001$</p> <p>Adverse events CVAD was placed in 54 children (83%). In 12 of these boys (22%) at least one device-related infection occurred 2 patients develop inhibitors (both received prophylaxis, $p = 0.24$)</p>
General comments	Included in Iorio 2011

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	5. Hacker MR, Page JH, Shapiro AD, et al Central venous access device infections in children with hemophilia: A comparison of prophylaxis and episodic therapy. Journal of Pediatric Haematology/Oncology. 2007 Jul;29(7):458-64.
Study type and methods	RCT Multicentre United States
LE	I
Number of patients & Patient characteristics	65 Haemophilia A, FVIII < 2 U/dL, without inhibitors h/o < 2 bleeding episodes
Intervention	Prophylaxis with recombinant FVIII Kogenate or Kogenate FS 25 IU/kg every other day 32 patient
Comparison	Enhanced episodic therapy 40 IU/kg of same product at the time of joint haemorrhage and 20 IU at 24 hours and 72 hours after the first dose. Encourage to continue infusions of 20 IU of FVIII every other day until joint pain and impairment of mobility had completely resolved for a max of 4 weeks 33 patients
Length of follow up (if applicable)	Up to 49 months
Outcome measures/ Effect size	The number of participants with a CVAD who developed a CVAD-related infection while on study was 6 (21%) in the prophylaxis arm and 6 (24%) in the episodic arm. Seven of these children developed more than one infection, resulting in a total of 22 incident infections. Years CVAD was indwelling before first infection on study, mean (95% CI) Prophylaxis 1.6 (0.2 – 2.9) Episodic Therapy 0.7 (0.2-1.2) The crude and adjusted rate ratios for first CVAD-related infection per 1000 CVAD days associated with episodic therapy versus prophylaxis were 1.42 (95%CI 0.46-4.40) and 1.23 (95%CI 0.33-4.56), respectively. Among 12 children with a CVAD-related infection, 3 had an inhibitor ≥ 0.5 BU
General comments	Data from Joint OutcomeStudy – Manco-Johnson <i>et. al.</i>

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	6. Dmoszynska A, Kuliczowski K, Hellmann A, et al Clinical assessment of Optivate[registered], a high-purity concentrate of factor VIII with von willebrand factor, in the management of patients with haemophilia A. Haemophilia. 2011 May;17(3):456-62.
Study type and methods	Multicentre open label, non-randomised prospective study Poland and UK
LE	II-2
Number of patients & Patient characteristics	N=70 Male ≥ 12 years old with haemophilia A (<2% basal FVIII activity at time of diagnosis) Without inhibitors, with at least 20 exposure days (ED)
Intervention	n= 11 Prophylaxis treatment with Optivate At least two prophylactic doses per week
Comparison	n= 59 On-demand with Optivate
Length of follow up (if applicable)	2 years
Outcome measures/ Effect size	11320 Optivate infusions were used Mean number of bleeds per patient was 23.5 for prophylaxis group (mean 0.24 (95% CI 0.08 – 0.40) new bleeds per week per patient) compared to 70.4 for on-demand patients (mean 0.75 (95% CI 0.65 – 0.86) new bleeds per week per patient) Total number of bleeds Prophylaxis - 258 On-demand – 4151 Mean dose per infusion/patient IU/kg Prophylaxis – 41.5 (95% CI 4.90, 14.12) On-demand – 26.0 (95% CI 22.15, 29.90) Safety 22 treatment-related AEs occurred in seven patients (one on prophylaxis) (10%) which include headaches (4%), dizziness (3%) All patients had negative screens for inhibitors to FVIII throughout the studies, no virus transmission occurred and no significant change in laboratory values.
General comments	Industry sponsored

Evidence Table

Question

: Management of haemophilia and rare bleeding disorders

: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	7. Collins P, Faradji A, Morfini M, et al Efficacy and safety of secondary prophylactic vs. On-demand sucrose-formulated recombinant factor VIII treatment in adults with severe hemophilia a: Results from a 13-month cross-over study. Journal of Thrombosis & Haemostasis. 2010 Jan;8(1):83-9.
Study type and methods	Open label prospective trial Cross-over trial United States and Europe
LE	II-1
Number of patients & Patient characteristics	N=20 Male patients aged 30-45 years with severe haemophilia (FVIII < 1 IU/dL) with an average of two relevant bleeds per month Without inhibitor Mean age 36.4 ± 3.5 years
Intervention	Prophylaxis treatment with rFVIII-FS (Kogenate) for 7 months 20 – 40 IU/kg three times per week Administered at home by slow intravenous infusion at a maximum rate of 2 mL/min Break through bleeds were treated with a dose of 20 – 100 IU/kg according to bleeding severity (n=20)
Comparison	On-demand treatment with rFVIII-FS (Kogenate) for 6 months (n=19)
Length of follow up (if applicable)	13 months
Outcome measures/ Effect size	<p>Mean (SD) number of all bleeds in previous 6 months 17.1 (9.0)</p> <p>Mean (SD) FVIII consumption in previous 6 months 60438 (44078)</p> <p>rFVIII-FS consumption On-demand – 581 infusions Prophylaxis – 1650 89.8% of infusions were administered for treatment of spontaneous or trauma bleeds during the on-demand period (and 7.7% for preventive prophylaxis), only 3.2% of infusions were for spontaneous or trauma bleeds during prophylaxis period (94.4% were for regular or preventive prophylaxis)</p> <p>Total consumption per patient was 70421 ± 43057 and 211933 ± 54725 IU respectively.</p> <p>All bleeds, Median (IQR) On-demand – 20.5 (14-37) Prophylactic – 0 (0-3) p<0.001</p> <p>Joint bleeds, median (IQR) On-demand – 15.0 (11-26) Prophylactic – 0 (0-3) p<0.001</p> <p>Gilbert score Baseline 24.8 ± 15.1 Month 6 25.3 ± 11.7 Month 13 19.8 ± 11.7 p<0.001</p> <p>Safety 51 adverse events were reported in 13 patients (65%) 26 AEs occurred during the on-demand period and 25 during prophylaxis. 94% of AEs were mild to moderate and none lead to withdrawal of study. Six SAEs occurred in two patients during the study (one patient during each treatment period) and not considered to be treatment-related and no inhibitor formation was detected during either treatment period.</p>
General comments	Industry sponsored

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	8. Fischer K, van der Born JG, Molho P, et al Prophylactic versus on-demand treatment strategies for severe haemophilia: A comparison of costs and long-term outcome. Haemophilia. 2002 Nov;8(6):745-52.
Study type and methods	Retrospective Cohort Two cohort studies were combined
LE	II-2
Number of patients & Patient characteristics	155 subjects with severe haemophilia (FVIII/FIX activity < 0.01 IU/ml) without history of antibodies to FVIII/FIX
Intervention	Prophylaxis treatment, n=49 (Netherlands) Intermediate dosages of 15-25 IU/kg two or three times weekly (haemophilia A) or 30-50 IU/kg once or twice weekly (haemophilia B)
Comparison	On-demand treatment, n = 106 (France) Treatment given per bleeding episode
Length of follow up (if applicable)	22 years
Outcome measures/ Effect size	Mean annual clotting factor consumption Prophylaxis – 1488 ± 783 IU/kg/year On-demand – 1612 ± 1442 IU/kg/year Patients primarily treated with prophylaxis had fewer joint bleeds per year (median 2.8 versus 11.5), a higher proportion of patients without joint bleeds (29% versus 9%), lower clinical scores (median 2.0 versus 8.0), and less arthropathy as measured by Pettersson score (median 7 points versus 16 points)
General comments	Not concurrent control Partially sponsored by industry

Evidence Table

Question

: Management of haemophilia and rare bleeding disorders

: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	9. Steen Carlsson K, Hojgard S, Glomstein A, et al On-demand vs. Prophylactic treatment for severe haemophilia in Norway and Sweden: Differences in treatment characteristics and outcome. Haemophilia. 2003 Sep;9(5):555-66.
Study type and methods	Retrospective cohort study (conducted from 1989-1999)
LE	II-2
Number of patients & Patient characteristics	156 patients with severe haemophilia A and B in Norway and Sweden Born between 1949 and 1989 (for prophylaxis group) and between 1939 and 1981 (on-demand group). Without inhibitor
Intervention	Primary Prophylaxis (n=95) Regular injections of factor concentrates at least twice weekly for haemophilia A and at least once weekly in haemophilia B
Comparison	On-demand (n=61) Injections when haemorrhaging occurred but also include periods of prescribed secondary prophylaxis
Length of follow up (if applicable)	11 years
Outcome measures/ Effect size	<p>Clotting factor consumption Median annual factor concentrate consumption in the prophylaxis population was about three times as large as for the on-demand patients. For adults the median total IU/kg per annum was for prophylaxis 3024 IU (IQR 2328 – 3864) and for on-demand 780 IU (IQR 400 – 1303).</p> <p>Hospitalisation – patients on on-demand treatment had more total number of hospital days (320 versus 246) and undergone more invasive procedures (121 versus 48)</p> <p>Employment – On-demand patients were more on 100% sick leave/early retirement in 1999 (33% versus 9% in the prophylaxis group)</p> <p>Panel data analysis</p> <ul style="list-style-type: none"> patients on prophylactic treatment had 50 percentage units lower probability of undergoing a major surgical procedure a person who had been on prophylactic treatment all the time between 2 and 188 years old had a 74 percentage units lower risk of having a longer period of loss of working days due to haemophilia compared with a person who did not have any prophylaxis between 2 and 18 years ($p < 0.01$) Factors associated with variations in annual factor concentrate use <ul style="list-style-type: none"> on-demand – being adults (18+), the prescribed dose per kg when haemorrhaging, number of weeks on secondary prophylaxis during the year children (prophylaxis) – having haemophilia A, weighed relatively more than other children in the same age prophylaxis (adults) – increasing the dose per kg bodyweight by 1 IU increased annual consumption of factor concentrate by 2580 IU.
General comments	Industry sponsored

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	10. van den Berg HM, Fischer K, van der Bom JG. Comparing outcomes of different treatment regimens for severe haemophilia. Haemophilia. 2003 May;9 Suppl 1:27-31
Study type and methods	Retrospective cohort Sweden, France, the Netherlands
LE	II-2
Number of patients & Patient characteristics	156 patients with severe haemophilia born between 1970 and 1980 were compared
Intervention	High dose prophylaxis regime (Swedish cohort, n=19) 25-40 IU/kg three times a week for haemophilia A and 30-50 IU/kg twice a week for haemophilia B. Intermediate dose cohort (Dutch cohort, n=21) 15-25 IU/kg two to three times per week for haemophilia A and 30-50 IU/kg once or twice weekly for haemophilia B.
Comparison	On-demand treatment (French cohort, n= 116) Treatment given per bleeding episode. Short courses of prophylaxis were given in case of chronic synovitis or after orthopaedic surgery.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Annual number of joint bleeds Swedish – 3 Dutch – 5.3 French – 16.3 Pettersson score Swedish – 6.5 Dutch – 6.0 French – 18.8 Orthopaedic joint score Swedish – 2.4 Dutch – 2.0 French – 7.7 Clotting factor consumption (IU/kg/year) Swedish – 3713 Dutch – 1828 French – 1634 Age at start of prophylaxis Swedish – 2.6 Dutch – 4.6 French – NA Age at start of home-treatment Swedish – NA Dutch – 9.1 French – 8.9 *mean (SEM)
General comments	

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	11. Fischer K, Van Den Berg M. Prophylaxis for severe haemophilia: Clinical and economical issues. Haemophilia. 2003 Jul; 9(4):376-81.
Study type and methods	Retrospective cohort Sweden, France and the Netherlands
LE	II-2
Number of patients & Patient characteristics	179 patients with severe haemophilia born between 1970 and 1980 were compared. No history of inhibitor
Intervention	High dose prophylaxis regime (Swedish cohort, n=24) 25-40 IU/kg three times a week for haemophilia A and 30-50 IU/kg twice a week for haemophilia B. Intermediate dose cohort (Dutch cohort, n=49) 15-25 IU/kg two to three times per week for haemophilia A and 30-50 IU/kg once or twice weekly for haemophilia B.
Comparison	On-demand treatment (French cohort, n= 106) Treatment given per bleeding episode.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Median annual number of joint bleeds High dose – 0.5 (0.2 – 1.8) Interm. Dose – 2.8 (0 – 7.8) On-demand – 11.5 (3.8 – 24.0) Median Pettersson score High dose – 4 (0 – 15) Interm. Dose – 7 (3 – 15) On-demand – 16 (8 – 28) Median Clinical score High dose – 0 (0 – 1.0) Interm. Dose – 2.0 (0.3 – 5.0) On-demand – 8.0 (3.3 – 14.0) Clotting factor consumption High dose – 4301 (3034 – 4726) Interm. Dose – 1550 (824 – 1968) On-demand – 1260 (630 – 2130)
General comments	

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	12. Morado M, Villar A, Jimenez-Yuste V, et al Prophylactic treatment effects on inhibitor risk: Experience in one centre. Haemophilia. 2005 Mar;11(2):79-83.
Study type and methods	Retrospective cohort Spain
LE	II-2
Number of patients & Patient characteristics	50 patients with severe haemophilia A who were born between 1993 to 2003
Intervention	Prophylaxis High doses of FVIII, 25 -40 IU/kg three times a week to maintain FVIII activity levels above 1%
Comparison	On-demand
Length of follow up (if applicable)	Up to 10 years
Outcome measures/ Effect size	15 patients developed inhibitors (30%) (12 high responders, 3 low responders) Mean age at time of inhibitor appearance was 2 years (21 months) and ranged from 10 days to 6 years. Response to immunotolerance treatment ranges from 50% to 75%. All the patients with inhibitors were on-demand treatment at the time of inhibitor development. 78% of on-demand patients showed an inhibitor as opposed to none of the 31 patients receiving prophylaxis treatment.
General comments	?universal sampling

Evidence Table**Question**: **Management of haemophilia and rare bleeding disorders**: **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	13. Liou WS, Tu TC, Cheng SN, et al Secondary prophylaxis treatment versus on-demand treatment for patients with severe haemophilia a: Comparisons of cost and outcomes in Taiwan. Haemophilia. 2011 Jan;17(1):45-54.
Study type and methods	Retrospective cohort Taiwan
LE	II-2
Number of patients & Patient characteristics	50 Severe haemophilia A without inhibitors Median age; Prophylaxis-17.0 (5.7 – 50.0) On-demand- 38.3 (18.4-63.7)
Intervention	Secondary prophylaxis (n=13) Under the age of 18 years, taking 25-40 IU/kg of FVIII three times a week or if over 18 years, they were taking it twice a week
Comparison	On-demand (n=37)
Length of follow up (if applicable)	Median- 50 months in prophylaxis and 45 months in on-demand
Outcome measures/ Effect size	<p>Median no of bleeding episodes (min-max value) Prophylaxis – 7.76 (1.18-18.22) On-demand – 31.91 (16.36-78.21) p<0.0001</p> <p>Median no of joint bleeding episodes Prophylaxis – 5.18 (0.94 – 17.33) On-demand – 27.12 (3.47 – 73.24) p<0.001</p> <p>Regression analysis after adjusting for age, weight, month followed up and age squared - patient treated on-demand would be expected to have 24.6 more bleeding episodes per year than a patient on prophylaxis treatment</p> <p>Median annual FVIII utilisation (IU/kg/year) Prophylaxis – 1824 On-demand – 1324 p<0.01</p> <p>Total medical cost (USD\$/kg) Prophylaxis – 1615.78 (1042.49 – 4022.12) On-demand – 1210.25 (167.63 – 6217.84) p<0.05</p> <p>Total factor VIII cost (USD\$/kg) Prophylaxis – 1598.27 (1034.28 – 4007.38) On-demand – 1139.6 (160.43 – 5724.63) p<0.05</p> <p>Predictive modelling of scenarios Scenario1 – all patients with severe haemophilia A receive on-demand therapy Scenario 2 – all patients with severe haemophilia A receive secondary prophylaxis therapy Scenario 3 – 26% of patients receive secondary prophylaxis, 74% receive on-demand therapy Scenario 4 – 30% of patients who are on secondary prophylaxis will switch to on-demand therapy during adulthood (after 18 years old) Scenario 5 – 30% of the 26% of patients receiving secondary prophylaxis switch to on-demand after 18 years old. 74% stay on on-demand</p> <p>Mean annual total cost per patient Scenario 1 – US\$14815692 Scenario 2 – US\$16894513 Scenario 3 – US\$15357816 Scenario 4 – US\$14904077 Scenario 5 – US\$14889478</p>
General comments	Partial industry funded

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	14. Miners AH, Sabin CA, Tolley KH, et al Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease. Journal of Internal Medicine. 1998 Dec;244(6):515-22.
Study type and methods	Retrospective cohort (United Kingdom)
LE	II-2
Number of patients & Patient characteristics	179 patients with severe (<1 IU/dL) haemophilia A, B and vWD (1980-95) A subgroup of these patients 25 adults and 22 children who had previously received treatment on-demand and who had switched to treatment with prophylaxis were studied in order to examine the effects of change.
Intervention	Prophylaxis
Comparison	On-demand
Length of follow up (if applicable)	16 years
Outcome measures/ Effect size	<p>Between 1980 and 1995, a total of 38104 bleeds occurred (63% joint bleed). Overall median number of bleeds per patient for 16-year period was 162 (range 1-1096).</p> <p>In 1980, patients had a median of 23.5 bleeds (range 1-107) but by 1995 this has dropped to 14 (range 0-52). In 1980, there was a median of 20 (range 1-67) joint bleeds per patient, but 1995 this had fallen to 8 (0-45), both decreases were significant ($p<0.0001$).</p> <p>Effect of switching from treatment on-demand to prophylaxis</p> <p>Adults (n=25) – Prior to prophylaxis, median of 37 bleeds (range 11-132) per year and used a median of 560 (range 196-3120) IU/kg/year of clotting factor. Year 0 – 13 bleeds (range 0-92), 65% reduction, Clotting factor usage 1935 (range (592-3376) IU/kg/year, 350% increase</p> <p>Children (n=22) – prior to prophylaxis median of 21 (range 3 – 64) bleeds per year and used a median of 1974 (range 700-3750) IU/kg/year of clotting factor. Year 0 – 11 bleeds (range 0 – 49). Clotting factor usage increased to 2967 (range 1742-5472) IU/kg/year</p> <p>Cost-effectiveness analysis</p> <p>The ICER for prophylaxis compared with treatment on-demand was £547 per bleed avoided (£76683-£27751)/192.5-103)</p>
General comments	Policy to introduce PP treatment in 1990s.

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	15. Tagliaferri A, Franchini M, Coppola A, et al Effects of secondary prophylaxis started in adolescent and adult haemophiliacs. Haemophilia. 2008 Sep;14(5):945-51.
Study type and methods	Retrospective cohort Italy
LE	II-2
Number of patients & Patient characteristics	84 severely affected haemophiliacs, who had switched from on-demand to prophylaxis during adolescent or adulthood because they bleed frequently and/or had developed target joints. Absence of inhibitors
Intervention	Secondary prophylaxis
Comparison	On-demand
Length of follow up (if applicable)	Median of 4.8 years
Outcome measures/ Effect size	<p>Total bleeds/year (SD) Prophylaxis – 4.2 (3.7) On-demand – 35.8 (24.8), $p<0.01$</p> <p>Joint bleeds/years Prophylaxis – 3.3 (3.1) On-demand – 32.4 (23.1), $p<0.01$</p> <p>Orthopaedic score Prophylaxis – 13.8 (12.6) On-demand – 18.1 (13.1), $p=0.13$</p> <p>Pettersson score Prophylaxis – 13.7 (16.0) On-demand – 13.9 (16.9) $p=0.73$</p> <p>Concentrate consumption Prophylaxis – 3987 (876) On-demand – 2871 (2049) $p<0.01$</p> <p>Overall cost of concentrate Prophylaxis – 2990 (657) On-demand – 2153 (1537), $p=0.01$</p>
General comments	Each patient acts as their own control

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	16. Smith MP, Giangrande P, Pollman H, et al A postmarketing surveillance study of the safety and efficacy of ReFacto (st louis-derived active substance) in patients with haemophilia a. Haemophilia. 2005 Sep;11(5):444-51.
Study type and methods	Open label multicentre postmarketing surveillance study Europe and New Zealand
LE	II-2
Number of patients & Patient characteristics	60 Previously treated and untreated patients with moderate to severe haemophilia A (FVIII < 5%) Without inhibitor
Intervention	Prophylaxis treatment with Refactor, strength and frequency determined by the treating doctor Required units = body weight (kg) x desired FVIII rise (%) x 0.5 IU/kg N=32
Comparison	On-demand treatment with ReFactor N=28
Length of follow up (if applicable)	6 months or 50 exposure days
Outcome measures/ Effect size	Mean Spontaneous bleed (SD) per year in prophylaxis group was 10.33 (10.63) ReFacto resolved 81.7% of breakthrough bleeds with one or two infusions On-demand – 542 bleeding episodes occurred, 95.2% of bleeds were resolved with one or two infusions Safety Five treatment-related, non-SAEs were reported in three patients (one patient had dizziness and phlebitis, one had drug effect decreased and another had drug effect decreased and back pain) A total of seven SAEs were reported. Four SAEs were considered not related to ReFacto which include gastroenteritis, haemorrhage, myocardial ischaemia and suspected ICH. The remaining three SAEs were inhibitor cases; two had to be withdrawn from the study.
General comments	This study assessed the efficacy of ReFacto. Short duration

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	17. Schramm W, Royal S, Kroner B, et al Clinical outcomes and resource utilization associated with haemophilia care in Europe.[erratum appears in haemophilia. 2002 Sep;8(5):733]. Haemophilia. 2002 Jan;8(1):33-43
Study type and methods	Cross-sectional study
LE	II-3
Number of patients & Patient characteristics	1005 subjects (837 haemophilia A, 166 haemophilia B) from 18 HTC in 10 European countries (Germany, UK, Italy, France, Spain, the Netherlands, Switzerland, Sweden, Greece and Israel) Severe or moderate haemophilia who were not currently enrolled on an immune-tolerance regimen; who had a minimum age of 12 years
Intervention	Prophylaxis (n=335) Those who were treated with factor concentrate at least 2-3 times per week Precise regimen varies between HTCs
Comparison	On-demand (n=670)
Length of follow up (if applicable)	6-month reporting period
Outcome measures/ Effect size	After multivariate analysis controlling for age, haemophilia type, severity, inhibitor status, HIV status and type of employment, people treated on-demand were 3.4 times more likely to suffer a joint bleed during the 6-month reporting period than those treated prophylactically. OR 3.4 (95% CI 2.43 to 4.76) After stratifying for age - subjects who are 30 years old and younger, and who were treated on-demand, had an average 7.55 more joint bleeds than subjects treated prophylactically, after adjusting for each of the other independent variables, OR 7.55 (95% CI 5.02, 10.08). - subjects who are over 30 years old and who were treated on-demand had 3.33 more joint bleeds, on average, than subjects treated prophylactically after adjusting for each of the other independent variables, OR 3.33 (95% CI 1.94, 4.72) Cost of care in 6 countries In countries where there were relatively similar numbers of subjects treated on-demand and those treated prophylactically (Germany, Sweden, United Kingdom), the cost for factor replacement therapy was significantly higher for subjects treated prophylactically.
General comments	Convenience sampling Industry sponsored

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	18. Lucia JF, Aznar JA, Abad-Franch L, et al Prophylaxis therapy in haemophilia a: Current situation in Spain. Haemophilia. 2011 Jan;17(1):75-80.
Study type and methods	Cross-sectional multicentre study Spain
LE	III
Number of patients & Patient characteristics	2081 patients with hemophila A and B on active follow- up at any Spanish Hospital by 2006.
Intervention	Prophylaxis - Definition follows PEDNET
Comparison	On-demand treatment.
Length of follow up (if applicable)	-
Outcome measures/ Effect size	<p>32.8% were severe, 13.9% moderate, 53.3% mild cases.</p> <p>399 (19.2%) on prophylaxis; 81 (20.3%) on primary prophylaxis (PP), 303 (75.9%) secondary (SP) and 15 (3.7%) undetermined.</p> <p>Half of 682 severe HA patients (45.9%;313) were on prophylactic treatment.</p> <p>Joint status EHA was proved for 555/1228 (45.2%) patients.</p> <p>142/313 (45.4%) severe HA on prophylaxis were detected to have EHA but only in 2.9% of patients under PP versus 59% of patients receiving SP. No EHA in adult severe HA patient on PP, whereas 70.4% on SP had joint damage ($p<0.00001$)</p> <p>Recombinant FVIII administered for prophylaxis to 71.4% of HA patients and plasma-derived products were used in 28.6%</p>
General comments	

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	19. Royal S, Schramm W, Berntorp E, et al Quality of life differences between prophylactic and on-demand factor replacement therapy in european haemophilia patients. Haemophilia. 2002 Jan;8(1):44-50.
Study type and methods	Cross-sectional study Multicentre Europe
LE	II-3
Number of patients & Patient characteristics	1033 subjects with severe or moderate haemophilia who were not treated with an immune-tolerance protocol, and who had a minimum age of 12 years. Treated at 18 HTC's across Europe
Intervention	Prophylaxis treatment Those who were treated with factor concentrate at least 2 – 3 times per week
Comparison	On-demand
Length of follow up (if applicable)	-
Outcome measures/ Effect size	Final population for multivariate analysis 903. Quality of life measured by SF-36 Adjusted overall multivariate model showed significance differences in the two treatment groups when all eight dimensions were tested simultaneously ($p < 0.001$). The significant dimensions were: <ul style="list-style-type: none"> • Less bodily pain • Better general health • Physical functioning Subjects were also stratified by HIV status. HIV-negative subjects differed significantly by treatment group and reported significantly lower bodily pain, better general health and scored higher in physical functioning, mental health and social functioning. HIV-positive subjects who were treated on-demand scored higher than subjects treated prophylactically in vitality dimension.
General comments	Loss to follow up 12.6% Industry sponsored Non-random

ECONOMIC evaluation

Evidence Table : **Management of haemophilia and rare bleeding disorders**
Question : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	20. Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia a. Haemophilia. 2009 Jul;15(4):881-7.
Study type and methods	Cost-utility analysis with Markov modelling UK NHS perspective
LE	III
Number of patients & Patient characteristics	100 hypothetical cohort with severe haemophilia A (<1 IU/dL)
Intervention	Prophylaxis 25-40 IU/kg three times per week over a person's entire life time
Comparison	On-demand
Length of follow up (if applicable)	70 year time horizon/lifetime Discount rates 3.5%
Outcome measures/ Effect size	The mean expected costs of treating on-demand and with PP over a 70-years time horizon were approximately £644,000 and £858,000 respectively. The associated QALY is 13.95 and 19.58 respectively. The ICER is £38,000 per QALY Based on CEAC, the probability of PP being cost-effective at £30,000 per additional QALY is 13%, rising to over 90% at a willingness to pay per additional QALY of £100,000. The CEAC moves sharply to the left (indicating more favourable cost-effectiveness for prophylaxis) following reductions in the clotting factor price, the discount rate for future QALYs and the time between prophylactic infusions of FVIII.
General comments	Industry funded Update of 2002 paper

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	21. Miners AH, Sabin CA, Tolley KH, et al Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759-74.
Study type and methods	Cost-utility analysis with Markov modelling UK Societal perspective Utility estimated using a series of equation based on 1999 cross-sectional study
LE	III
Number of patients & Patient characteristics	100 patients with severe haemophilia A and B Without inhibitors Hypothetical cohorts
Intervention	Primary Prophylaxis
Comparison	On-demand
Length of follow up (if applicable)	Lifetime/70 years time horizon
Outcome measures/ Effect size	Clotting factor accounted for the largest proportion of total cost – 58 to 96% depending on the clotting factor type (FVIII or FIX) and the time between prophylactic doses of clotting factor Baseline analysis produced ICER for individuals receiving FVIII and FIX of £46,500 per QALY gained and £8600 per QALY gained respectively. Results were highly sensitive to a number of variables: unit clotting factor cost, the time between prophylactic doses of clotting factor and the discount rate.
General comments	Based on hypothetical cohort. Many assumptions

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
: **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	22. Risebrough N, Oh P, Blanchette V, et al Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia a. Haemophilia. 2008 Jul;14(4):743-52.
Study type and methods	Cost-utility analysis Societal perspective Canada Markov modelling with 3-month cycles
LE	III
Number of patients & Patient characteristics	Hypothetical cohort of males with severe haemophilia A (FVIII < 2%) Began treatment at age 1 and continued for 5 years No inhibitors
Intervention	Standard Prophylaxis (SP) 25 FVIII units/kg on alternate days Tailored (escalating dose) prophylaxis (EscDose) Began prophylaxis with 50 FVII units/kg once a week. Escalated to 30 FVIII units/kg twice a week if children met the escalation criteria. Escalated to 25 FVIII units/kg on alternate days if escalation criteria met. Escalation criteria: developing three bleeds into anyone joint in a 3-month period or four clinically significant soft tissue or joint bleeds
Comparison	On-demand 40 U/kg upon presentation of bleeding and 20 U/kg on days 1 and 3 postbleed.
Length of follow up (if applicable)	5 years
Outcome measures/ Effect size	The expected cost of 5 years of SP was \$569,835 per child compared to \$443,185 for EscDose and \$277,209 for on-demand. Cost for FVIII accounted for 82% and 86% of EscDose and SP respectively. Compared with on-demand, EscDose decreased bleeding episodes by 52 joints-bleeds at an additional cost of \$165,976 (\$33,195 per year) Compared to Demand SP decreased bleeding by 65 joint bleeds at an additional cost of \$292,626. ICER to prevent a joint bleed with EscDose compared to demand was \$3192. Each additional joint bleed avoided with SP compared to EscDose, cost \$9046. The cost for avoiding a TJ was \$244,082 for EscDose compared with on-demand and \$361,857 for SP compared with EscDose. Comparing Demand to EscDose the ICUR was \$542,938 per QALY gained The incremental cost per QALY gained for EscDose compared with SP was >\$1000000/QALY gained. Sensitivity analysis showed that cost of FVIII was a cost driver in the model
General comments	Efficacy data derived from two retrospective case-control studies and one prospective studies Industry funded

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	23. Carlsson KS, Hojgard S, Lindgren A, et al Costs of on-demand and prophylactic treatment for severe haemophilia in norway and Sweden. Haemophilia. 2004 Sep;10(5):515-26.
Study type and methods	Cost evaluation study Together with a retrospective cohort study Societal perspective
LE	II-2
Number of patients & Patient characteristics	156 patients with severe haemophilia A and B (factor VIII/IX activity <1%) in Norway and Sweden Born between 1949 and 1989(for prophylaxis group) and between 1939 and 1981 (on-demand group). Without inhibitor
Intervention	Primary Prophylaxis (n=95) Regular injections of factor concentrates at least twice weekly for haemophilia A and at least once weekly in haemophilia B
Comparison	On-demand (n=61) Injections when haemorrhaging occurred but also include periods of prescribed secondary prophylaxis
Length of follow up (if applicable)	11 years
Outcome measures/ Effect size	The mean cost for an adult (18+) patient-year for on-demand was EUR 51,518 ± 36,035 (mean ± SD) and for prophylaxis EUR 147,939 ± 65,963 (590 and 504 patient-years for on-demand and prophylaxis respectively). Factor concentrate was the major source of costs in both strategies (74% and 94%, respectively). Both other health care cost and costs in other sectors were greater for on-demand (EUR 1807 and 11,358, respectively) than for prophylaxis (EUR 1126 and 7530, respectively) Panel data analysis The average predicted annual cost or a 30 year old on-demand patient was EUR 51,832 (95% CI 44,324-59,341) and for prophylaxis EUR 146,118 (95% CI 129,965-162,271) - The expected annual costs were nearly three times higher for prophylaxis than for on-demand treatment
General comments	Not a full economic evaluation paper. Industry sponsored

Evidence Table
Question

: **Management of haemophilia and rare bleeding disorders**
 : **Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?**

Bibliographic citation	24. Carlsson KS, Hojgard S, Lethagen S, et al Willingness to pay for on-demand and prophylactic treatment for severe haemophilia in Sweden. Haemophilia. 2004 Sep;10(5):527-41.
Study type and methods	Willingness to pay study Sweden
LE	III
Number of patients & Patient characteristics	609 Swedish households Interviewed by telephone
Intervention	Prophylaxis
Comparison	On-demand
Length of follow up (if applicable)	11 years
Outcome measures/ Effect size	<p>The mean estimated WTP (year 2002) was EUR 39 (95% CI 31-47) for on-demand and EUR 65 (95% CI 55- 73) for prophylaxis. The WTP for on-demand and prophylaxis exceeded the calculated cost of treatment per taxpayer of providing on-demand and prophylactic treatment.</p> <p>The estimated WTP varied in different subsamples of individual characteristics but confidence intervals always overlapped that of the main results.</p> <p>Sensitivity analysis showed that the ranking of the two treatment alternatives was robust in that the WTP was greater for prophylaxis in all possible subsets.</p>
General comments	<p>Drop outs – 24.7%</p> <p>Industry sponsored</p>

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	25. Daliri AAK, Haghparsat H, Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia a in Iran. International Journal of Technology Assessment in Health Care. 2009 Oct;25(4):584-7.
Study type and methods	Cost-effectiveness study Third party payers perspective Retrospective chart review Iran
LE	II-2
Number of patients & Patient characteristics	25 Patients with severe haemophilia (factor level < 1%) Without inhibitor or HIV infection. Maximum age of 9 years receiving care at the HTC between September 2007 and 20 March 2008. Mean age 5.31±2.37 in prophylaxis and 5.42 ± 1.50 in on-demand
Intervention	Prophylaxis (n=11) Uninterrupted, schedules administration of factor VIII at least three times weekly for a minimum of six consecutive months
Comparison	On-demand (n=14)
Length of follow up (if applicable)	6 months
Outcome measures/ Effect size	<p>Total Factor consumption Prophylaxis 250,500 IU (59.75%) On-demand 168,750 IU (40.25%)</p> <p>Mean (±SD) Prophylaxis 22772.73 (±11203.48) On-demand 12053.57 (±6776.78)</p> <p>Mean per patient per month Prophylaxis 3795.45 IU On-demand 2008.92 IU</p> <p>Total bleeding episodes Prophylaxis 17 (6.88%) On-demand 230 (93.12%)</p> <p>Mean (±SD) Prophylaxis 1.54 (±1.69) On-demand 16.42 (±8.65)</p> <p>Mean per patient per month Prophylaxis 0.25 On-demand 2.73</p> <p>The incremental cost per avoided bleed was 3,201,656 Rials (€213.45) over 6 months in Iran. The results were insensitive to changes in price of clotting factor</p>
General comments	Small sample Only cost of clotting factor included in the assessment

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is prophylaxis approach more effective when compared to on-demand approach in managing haemophilia and what are the resource implications?

Bibliographic citation	26. Lippert B, Berger K, Berntorp E, et al Cost-effectiveness of haemophilia treatment: A cross-national assessment. Blood Coagulation & Fibrinolysis. 2005 Oct;16(7):477-85.
Study type and methods	Cost-effectiveness analysis Third party payer perspective Germany, Sweden, United Kingdom and The Netherlands Data based on multicentre cross-sectional survey (18 HTC's)
LE	II-2
Number of patients & Patient characteristics	N= 506 Patients with severe haemophilia A and B (factor level <1%) Without inhibitor Minimum age of 14 years and receiving medical care at the HTC between January 1996 and January 1998 Mean age 35 ± 13 years (range 14-83)
Intervention	Prophylaxis Treating with coagulating factor at least two to three times per week and for a minimum of 6 months
Comparison	On-demand
Length of follow up (if applicable)	6 months observation period Time horizon 1 year
Outcome measures/ Effect size	<p>With prophylactic treatment the incremental cost per avoided bleeding was €6650 for patients 30 years and younger, €11731 for patients more than 30 years old in Germany. In Sweden the incremental costs per avoided bleed for patients aged more than 30 years was €14138.</p> <p>In the Netherlands, the incremental costs per avoided bleed for patients aged 30 years and older was €10,833.</p> <p>In United Kingdom the incremental cost per avoided bleeding was €9315 for patients 30 years and younger and €14001 for patients aged more than 30 years.</p> <p>ICER for prophylaxis versus on-demand treatment in 1 year HIV-infected patients 30 years or less - ranged from €1.24 million per QALY in German to €1.73 million per QALY in the United Kingdom.</p> <p>HIV-negative patients 30 years or younger ICER ranged from €2.21 million per QALY in Germany to €3.10 million per QALY in the United Kingdom.</p> <p>HIV-negative patients over 30 years – ranging from €4.77 million per QALY in Germany to €5.7 million per QALY in Sweden and the United Kingdom.</p>
General comments	On-demand treatment dominant

PART 2

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is recombinant factors more effective when compared to plasma-derived factor in patients with haemophilia and what are the resource implications?

Bibliographic citation	1. Iorio A, Halimeh A, Holzhauser S et al Rate of Inhibitor Development in Previously Untreated Hemophilia A Patients Treated with Plasma-Derived or recombinant Factor VII Concentrates: A Systematic Review. Journal of Thrombosis and Haemostasis. 2010; 8: 1256-1265
Study type and methods	Systematic review 24 Prospective and retrospective studies. The studies characteristics and quality were evaluated using Newcastle-Ottawa scale.
LE	II-2
Number of patients & Patient characteristics	Haemophilia A patients that: - PUPs - Previous exposure to blood components other than plasma derivatives - Patients with inhibitors were also included 2094 PUPs (1167 on pdFVIII and 927 on rFVIII) - Pts were analysed in 3 groups: i) All pts (all FVIII: C levels and all degrees of severity. ii) Severe HA (FVIII: C < 1%) iii) Severe plus moderate HA (FVIII: C ≤ 5%) All types of inhibitors also included
Intervention	rFVIIIa (n=927)
Comparison	pdFVIII (n=1167)
Length of follow up (if applicable)	-
Outcome measures/ Effect size	- 420 pts developed inhibitor, 160 (13.7%) treated with pdFVIII and 260 (28.0%) treated with with rFVIII - High responding inhibitors 252/1864 pts (101/1022 [9.8%] for pdFVIII and 151/842 [17.9%] for rFVIII) - Non-transient inhibitors 175/1117 (77/643 [12.0%] for pdFVIII and 98/474 [20.7%] for rFVIII)

<p>Outcome measures/ Effect size</p> <p>(cont.)</p>	<p>Pooled Analysis of single-arm studies</p> <ul style="list-style-type: none"> - Inhibitor development rate in pts treated with rFVIII was significantly higher than in pts treated with pdFVIII (27.4% versus 14.3%, Cochrane Q = 11.7, P<0.001) <p>Sensitivity Analysis</p> <p><i>Disease severity</i></p> <p>The event rate was significantly higher when limit the analysis in severe HA:</p> <ul style="list-style-type: none"> - pdFVIII = 15.9%, 95% CI 10.5-23.3 - rFVIII = 34.5%, 95% CI 29.3 – 40.1 - Cochrane Q = 14.2, P<0.001 <p>While limit the analysis to Moderate plus severe pts:</p> <ul style="list-style-type: none"> - pdFVIII = 15.4%, 95% CI 11.1-21.0 - rFVIII = 28.5%, 95% CI 25.1-32.2 - Cochrane Q = 13.6, P<0.001 <p><i>Inhibitor development rate increased in relation to HA severity in both treatments – significantly higher in rFVIII than pdFVIII.</i></p> <p>Incidence inhibitor rate if exclude studies that used multiple concentrations</p> <ul style="list-style-type: none"> - rFVIII = 25.2% (95% CI 20.6-30.4) incidence rate - pdFVIII = 8.5% (95% CI 5.7-12.4) - Cochrane Q 25.6, P<0.001 <p><i>Incidence inhibitor rate in cohorts using single concentrates was lower in both treatments.</i></p> <p>Pooled Analysis of studies involving parallel cohorts treated with pdFVIII or rFVIII concentrates</p> <ul style="list-style-type: none"> - 6 studies (1259 pts) – no heterogeneity was found between studies. - Statistically significant associations of either high or low titre inhibitors for both rFVIII versus pdFVIII: <p>In high responding inhibitors – RR = 1.7 (95% CI 1.3-2.7, P<0.001; Cochran Q chi-squared = 1.97, P=0.853)</p> <p>In all inhibitors – RR = 2.0 (95% CI 1.5-2.6, P<0.001; Cochrane Q chi-squared = 3.03, P = 0.695)</p> <p><i>From forest plots – pts that initially treated with rFVIII had an increased risk of developing inhibitor</i></p>
<p>General comments</p>	<p>On-demand treatment dominant</p>

**Evidence Table
Question**
: Management of haemophilia and rare bleeding disorders
: Is recombinant factors more effective when compared to plasma-derived factor in patients with haemophilia and what are the resource implications?

Bibliographic citation	2. Kelly KM, Butler RB, Farace L et al Superior in-Vivo Response of Recombinant Factor VII Concentrate in Children with haemophilia A. Journal Paediatric. 1997; 130: 537-540
Study type and methods	Prospective Cross-over Study Recovery Studies with each product: according to cross-over design (72 hrs apart and at least 48hrs after previous infusion of factor VIII product) – - 50IU/kg of pdFVIII in one study - 50IU/kg of rFVIII in another study
LE	II-1
Number of patients & Patient characteristics	10 pts - 7 – 12 years old) - From Children's Hospital of Philadelphia Hemophilia Clinic - Severe HA (factor VIII level < 1%) - Enrolled June-Oct 1995
Intervention	Recombinate (rFVIII) 50 IU/KG
Comparison	Hemofil M (pdFVIII) 50 IU/KG
Length of follow up (if applicable)	
Outcome measures/ Effect size	Response and Recovery of Hemofil M and Recombinate: - Mean response after infusion with Recombinate was significantly better than with Hemofil M (1.91% ± 0.14% versus 1.50% ± 0.15%, P=0.007) - Correlations Recombinate and: Body surface area – r = 0.734, P = 0.015 Body weight – r = 0.762, P = 0.01 Plasma volume – r = 0.659, P = 0.03 - No correlations between response to Hemofil M and: Body surface area – r = 0.494, P = 0.15 Body weight – r = 0.491, P = 0.05 Plasma volume – r = 0.405, P = 0.25 Infusion of pdFVIII and rFVIII showed similar response rate (2.5% and 2.7% respectively)
General comments	Industry sponsored – Baxter Non-randomised

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: Is recombinant factors more effective when compared to plasma-derived factor in patients with haemophilia and what are the resource implications?

Bibliographic citation	3. Gouw SC, Van Ver Bom JG, Auerswald et al Recombinant versus Plasma-Derived Factor VII Products and the Development of Inhibitors in Previously Untreated Patients with Severe Haemophilia A: the CANAL Cohort Study. The American Society of Haematology. Blood. 2007; 109(11):4693-4697
Study type and methods	Multicentre Retrospective cohort - To describe inhibitor risks according to different FVIII product types - To examine whether switching between FVIII products affected the risk of inhibitor development - In 13 European Centre an 1 Canadian Centre
LE	II-1
Number of patients & Patient characteristics	316 pts - With severe haemophilia A Born between 1990 and 2000 Treated in one of participating centres
Intervention	rFVIII
Comparison	pdFVIII
Length of follow up (if applicable)	-
Outcome measures/ Effect size	- 12,918 exposure days (pts received FVIII products) = 8,493 (66%) exposures days on rFVIII - pts developed inhibitors after median of 14 exposure days (interquartile range (IQR) 8-19 days) and at median age of 15 months (IQR, 10-12months) - 82 pts (26%) developed clinically relevant inhibitors: <ul style="list-style-type: none"> • 66 pts developed high-titre inhibitors • 16 pts developed low titre inhibitors 1) <i>Compared inhibitor risk between rFVIII and pdFVIII products</i> - Risk of inhibitor development was not clearly lower in pdFVIII compared with rFVIII products (RR = 0.8 , 95% CI 0.5 – 1.3) - Among high-titre inhibitor, possible reduction risk was lower (RR = 0.9 , CI 0.5 – 1.5) 2) <i>VWF association with risk of inhibitor development</i> - Compared to rFVIII, the inhibitor dev was similar in pdFVIII containing considerable quantities of VWF (RR = 1.0 , CI 0.6 – 1.6) - 70% decreased in pts received pd-FVIII containing small quantities of VWF (RR = 0.3 , CI 0.1 – 1.1) (table 2) 3) <i>Risks of inhibitor development according to different brands of rFVIII products</i> - Risk of pts received B-domain deleted rFVIII (ReFacto) was not statistically significantly higher compared with pts received full-length rFVIII (Kogenate) (RR = 1.4 , CI 0.8 – 2.6) (table 2) 4) <i>Effect of switching of FVIII products</i> - 104 pts (33%) switched to another FVIII product brand - 66% switched to another product once with unknown reason - Changed products for the 1st time after median of five exposure days (IQR 2 – 15 days, range 2 – 48 days) - Risk of inhibitors development was not increased after the switched (adjusted RR = 0.9 , CI 0.6 – 1.6) (figure 1 and table 3)
General comments	

**Evidence Table
Question**

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	4. Kreuz W, Ettingshausen CE, Zyschka A. Inhibitor Development in Previously Untreated Patients with haemophilia A: A Prospective Long-Term Follow-Up Comparing Plasma-Derived and Recombinant Products. <i>Seminars in Thrombosis and Hemostasis</i> . 2002; 28(3): 285-290
Study type and methods	Prospective long-term study (19)
LE	
Number of patients & Patient characteristics	<p>72 PUP</p> <ul style="list-style-type: none"> - From haemophilia centre Department of Paediatrics, University Hospital Frankfurt am Main - Severe (FVIII < 1%) or moderate (FVIII 1 to 5%) haemophilia A - No previous exposure to blood or any blood products (PUP) - No detectable inhibitor prior to first exposure to FVIII concentrate - Informed consent
Intervention	<p>rFVIII</p> <ul style="list-style-type: none"> - 21 pts
Comparison	<p>pdFVII</p> <ul style="list-style-type: none"> - 51 pts
Length of follow up (if applicable)	<p>23 year (1976 -2002)</p>
Outcome measures/ Effect size	<ul style="list-style-type: none"> - Median 270 ED (range 1-3,051) <p>Inhibitor Development</p> <ul style="list-style-type: none"> - 22 (31%) developed inhibitor after a median of 15 ED (range 4 – 195) <ul style="list-style-type: none"> • 5 (23%) were low responders (LR) • 17 (77%) were high responders (HR) • By the treatment – pdFVIII = 18/51 pts (35%) – HR = 13 (72%), LR = 5 (28%) – 7% of the entire cohort rFVIII = 4/21 pts (19%) – HR = 4 (100%) - Among 46 severe pts – inhibitor formation occurred in 20 pts (43%) - If the severity considered – pts with residual FVIII activity less than 1 % developed an inhibitor in 46% of the pdFVIII grouped and in 36% of the rFVIII group - Distribution of high- and low- responding inhibitors differed significantly comparing to pdFVIII and rFVIII groups. <p>Frequency of the High-titre inhibitors development</p> <ul style="list-style-type: none"> - No significant difference comparing pdFVIII (37%) and rFVIII (36%) - No transient inhibitor formation <p>Exposure status of non-inhibitor as an indicator for the risk of further inhibitor development differed significantly comparing both groups (table 5)</p>
General comments	

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	5. Schwartz RS, Abildgaard CF, Aledort LM et al Human Recombinant DNA-derived Antihaemophilic (factor VIII) in the Treatment of haemophilia A. The New England Journal of Medicine. 1990; 323: 1800-1805
Study type and methods	Prospective single-arm clinical trial - Conducted in 3 stages: i) Stage 1 – Compare pharmacokinetics of pdFVIII and rFVIII ii) Stage 2 – Assessed the efficacy and safety of home-treatment iii) Stage 3 – Assessed the efficacy and safety of treatment during surgical procedures or for serious haemorrhage
LE	
Number of patients & Patient characteristics	107 pts - With haemophilia A (20 PUPS) - Patients with inhibitors were excluded Stage 1 – 17 asymptomatic adults with haemophilia A (16 severe and one moderate) Stage 2 – 76 subjects (16 from Stage 1 and 60 new subjects) Stage 3 – 26 subjects included (9 new subjects and 17 have been enrolled in Stage 1 or 2)
Intervention	rFVIII
Comparison	pdFVIII
Length of follow up (if applicable)	-
Outcome measures/ Effect size	<p>Stage 1</p> <ul style="list-style-type: none"> - Recovery: <ul style="list-style-type: none"> • pdFVIII – incremental 10 minutes recovery (in-vivo) = $2.42 \pm 0.33\%$ per international unit of FVIII per kg • rFVIII – at weeks 1 [2.68 ± 0.52 (P = 0.026)], 13 [2.70 ± 0.61 (P 0.020)] and 25 [2.92 ± 0.90 (P = 0.017)] - aPT time: <ul style="list-style-type: none"> • lengthened beyond normal range in all pts • similar degree of shortening of aPT time after administration both treatment - Mean residence time and elimination half-life of rFVIII equalled or exceed of pdFVIII - Clearance and volume of distribution at steady state for rFVIII were slightly lower than pdFVIII <p>Stage 2</p> <ul style="list-style-type: none"> - 76 pts involved in home-treatment with rFVIII – 56 completed - Mean incremental in-vivo recovery values of the challenges doses of rFVIII (50IU/kg) given at weeks 5, 9, 13 and 25 ranged from 2.49 ± 0.70 to $2.92 \pm 0.99\%$ per international unit of FVIII administered per kg and were not statistically different - Over 6 months the 56 pts had 540 separate bleeding episodes; 399 (73.9%) required only one treatment with rFVIII – mean dose used was 26.8 ± 13.4 IU of FVIII per kg - Immunologic monitoring – none of 52 pts who had negative-baseline studies had any evidence of antibody formation to FVIII <p>Stage 3</p> <ul style="list-style-type: none"> - 26 pts (17 from stage 1 or 2 and 9 new pts) – received rFVIII on 32 occasions. - On 32 occasions – haemostasis was excellent without additional treatment <p>Inhibitor</p> <ul style="list-style-type: none"> - Inhibitor antibodies developed in only two of the 86 subjects who had previously treated with pdFVIII concentrates <p>ADRs</p> <ul style="list-style-type: none"> - 1734 rFVIII infusions – 18 ADR reports (1%) = unusual metallic taste in mouth, burning sensation at infusion site, mild dizziness, light headedness, elevated serum aminotransferase levels (1 was withdrawn due to this) etc.
General comments	

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	6. Ewenstein Bruce M, Joist JH, Shapiro Amy D, et al Pharmacokinetic analysis of plasma-derived and recombinant factor IX concentrates in previously treated patients with moderate or severe hemophilia B. Transfusion. 2002;42(2):190-7.
Study type and methods	Double blind cross-over study on pharmacokinetic. Multi-centre in US. 7 days washout period.
LE	I
Number of patients & Patient characteristics	43 moderate or severe haemophilia B, aged more than 5 years old. Prior treatment with any type of FIX concentrate, absence of inhibitors.
Intervention	Recombinant factors IX.
Comparison	Plasma-derived FIX.
Length of follow up (if applicable)	at least 15 exposure days.
Outcome measures/ Effect size	<p>Analysis conducted on 38 completed data. 37 out of 38 patients received 48.3 to 50.8 IU per kg. One patient received 53.3 IU per kg. Mean recovery calculated from the peak level in the first hour was 1.71 ± 0.73 IU per dL per IU per kg for pd-FIX and 0.86 ± 0.31 IU per dL per IU per kg for rFIX, $p < 0.0001$</p> <p>94.7% had a recovery greater than 1.0 IU per dL per IU per kg after pd-FIX infusion whereas only 31.6% had a recovery greater than 1.0 IU per dL per IU per kg following rFIX infusion and three patients (7.9%) had a recovery of less than 0.5 IU per dL per kg.</p> <p>Mean recovery after excluding two outliers was 1.57 for the pd-FIX and 0.84 for the rFIX, significant difference in recovery of 0.73 (95% CI 0.63-0.84)</p> <p>The terminal $T_{1/2}$ for pd-FIX was 14.9 hours (range 7.2 – 22.7) compared with 16.8 hours (range, 10.8 -26.1) for rFIX calculated from the FIX:C levels at 4, 24 and 48 hours. The plasma levels achieved with pd-FIX remained 1.8 to 2.1 fold higher than with rFIX at each of these time points. The differences in recovery between pd-FIX and rFIX were significant at all three time points.</p> <p>For each subject, a higher peak recovery was observed with pd-FIX than with rFIX, irrespective of the sequence in which the study medications were administered.</p> <p>There was a significant positive correlation, $r = 0.62$, $p \leq 0.0001$; CI, 0.37-0.78) between the recoveries of the two products, implying that the large interpatient variability observed was caused by inherent differences among subjects.</p> <p>No significant correlation between baseline FIX:Ag and recovery, $r = 0.12$, $p = 0.33$</p>
General comments	Funded by Aventis Behring.

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	7. Poon M-C, Lillicrap D, Hensman C, et al Recombinнат factor ix recovery and inhibitor safety: A Canadian post-licensure surveillance study. Thromb Haemos. 2002;87:431-5.
Study type and methods	Post-licensure Surveillance study 2 parts – In-vivo Factor IX recovery and Anti-factor IX antibody surveillance
LE	II-2
Number of patients & Patient characteristics	200 haemophilia B patients
Intervention	rFIX n= 126 (age range 1 – 74, mean 27.5, median 26.5) from 16 haemophilia centres across Canada.
Comparison	Plasma-derived FIX n=74 (age range 2 – 74, mean 28.3, median 28) from ten haemophilia centres across Canada.
Length of follow up (if applicable)	-
Outcome measures/ Effect size	Mean Recovery (SD) All age group rFIX – 0.77 (0.19) pd-FIX – 1.05 (0.26) ≤15 years old rFIX – 0.64 (0.11) pd-FIX – 0.91 (0.16) ≥15 years old rFIX – 0.84 (0.21) pd-FIX – 1.11 (0.29) anti-FIX antibody surveillance 2 of 244 patients from 24 Canadian haemophilia Centres exposed to rFIX for 1-5 years had developed anti-factor IX antibodies associated with anaphylactic reactions. These two patients had not been previously exposed to pd-FIX and developed anaphylactic reactions with anti-factor IX antibodies detected on the 3 rd and 14 th exposure day respectively. No other serious adverse events reported.
General comments	

PART 3

Evidence Table

Question

: Management of haemophilia and rare bleeding disorders

: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	1. Iorio A, Matino D, D'Amico R et al Recombinant Factor VIIa Concentrate versus Plasma-Derived Concentrates for the Treatment of Acute Bleeding Episodes in People with haemophilia and Inhibitors. Wiley Publishers. The Cochrane Collaboration. 2011
Study type and methods	Meta-analysis - 2 studies included (RCTs and quasi-randomised controlled clinical trials) i) Astermark 2007 ii) Young 2008
LE	I
Number of patients & Patient characteristics	i) Astermark 2007 (66 pts-41 completed the study) – adults and children with severe haemophilia A with inhibitors ii) Young 2008 (42 pts-21 completed the study) – adults and children with severe haemophilia A & B with inhibitors.
Intervention	rFVIIa i) Young 2008 - rFVIIa 90mcg/kg (at 0, 3 and 6 hrs) - rFVIIa 270mcg/kg single iv bolus (followed by two placebo infusion) ii) Astermark 2007 - rFVIIa 90-120mcg/kg (target 105mcg/kg as iv bolus repeated after 2 hrs)
Comparison	aPCC i) Young 2008 - aPCC 75IU/kg single iv bolus ii) Astermark 2007 - aPCC 75-100IU/kg (target 85IU/kg) as single iv bolus Other drugs used - analgesic
Length of follow up (if applicable)	
Outcome measures/ Effect size	Primary Outcome: i) Early cessation of bleeding a) Changes on any subjective or objective pain and mobility scale: Astermark 2007 – there was no significant difference in the treatment efficacy judgement between the two treatments at 2, 6, 12, 24, 36 and 48 hours. However the outcome on bleeding stop showed significant difference between the two groups at 48 hours where 95.1% in aPCC group compared to 92.7% in rFVIIa, p=0.001. Young 2008 – Algorithm on pain and mobility scores - did not find any significant difference between the treatment groups, pain scale P = 0.219 and mobility scale P = 0.903 b) Changes in the volume of haematoma assessed radiologically at any point in the first 48 hours – not assessed by both study

<p>Outcome measures/ Effect size (cont.)</p>	<p>Secondary Outcome</p> <p>i) Number of participants requiring additional or alternative treatment</p> <p>Astermark 2007 2 pts were administered with additional doses within the first 6 hours after onset of treatment The other pt during the balance of the 48-hour observation period</p> <p>Young 2008 Rescue medication administered for: 8 bleeding episodes for aPCC 2 bleeding episodes for rFVIIa 270mcg/kg 2 bleeding episodes for rFVIIa 90 x 3mcg/kg</p> <ul style="list-style-type: none"> - Difference between rFVIIa 270mcg/kg versus aPCC was statistically significant (P = 0.032) - Efficacy difference between aPCC and rFVIIa 90 x 3mcg/kg did not reach statistical difference (P = 0.069) <p>ii) Number of participants with AE (thromboses; allergic reactions) Astermark 2007 – no report</p> <p>Young 2008 – no report on thrombotic, fatal or clinical lab. AE. Report 32 treatment emergency AE in 14 participants (3 in rFVIIa 270 group, 5 in rFVIIa 90 x 3 group and six in aPCC group) – none related to the study.</p> <p>iii) Correction of abnormal haemostatic laboratory test results – not assessed in both</p>
<p>General comments</p>	

Evidence Table
Question

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Bibliographic citation	2. Berntorp E, Astermark J, Baghaei F, Bergqvist D, Holstrom M, Ljung R, et al Treatment of Hemophilia A and B and von Willebrand Disease. Stockholm, Sweden: Swedish Council on Health Technology Assessment; 2011.
Study type and methods	Systematic Review/HTA report
LE	I
Number of patients & Patient characteristics	28 studies were included to assess the effect of bypassing products Including Astermark 2007 Young 2008
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	-
Outcome measures/ Effect size	<ul style="list-style-type: none"> • Number of bleeding episodes • Quality of life • Tolerance development • Resource used <p>Results were not pooled</p> <p>Treatment of patients with inhibitors</p> <ul style="list-style-type: none"> • Insufficient evidence <ul style="list-style-type: none"> - To determine the effects of treating acute bleedings with the bypass agents' - To assess the effects of prophylactic treatment with the bypass agents - To assess the effects of immunotolerance induction using factor VIII or IX concentrates <p>Economic aspects</p> <ul style="list-style-type: none"> • Insufficient evidence
General comments	Reviews, studies without controls were also included

Evidence Table
Question

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Bibliographic citation	3. Lyseng-Williamson KA, Plosker GL. Recombinant factor VIIa (eptacog alfa): A pharmacoeconomic review of its use in haemophilia in patients with inhibitors to clotting factors viii or ix. Pharmacoeconomics. 2007;25(12):1007-29.
Study type and methods	Systematic review
LE	I
Number of patients & Patient characteristics	Haemophilia patients with inhibitors. Astermark 2007 Dundar 2005 Hart 2002 Ozelo 2007 Plyush 2006 Yoo 2007 Hilgartner 1990 Odeyemi 2002a Odeyemi 2002b Ekert 2001 Knight 2003 Huth-Kuehne 2006 Joshi 2006
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	
Outcome measures/ Effect size	<p>In Astermark 2007 paper reporting FENOC study, the equivalence of recombinant factor VIIa and aPCC in the treatment of joint bleeding episodes in haemophilia patients with inhibitors was not met. The criteria for equivalence (defined as a $\leq 15\%$ difference between recombinant factor VIIa and aPCC in the proportion of patients who reported effective or partially effective treatment within 6 hours of initiation of treatment). The efficacy of the products was rated differently by a substantial proportion of patients at all time points up to 48 hours.</p> <p>The efficacy and time to bleeding resolution of recombinant factor VIIa and/or aPCC have been investigated in country-specific retrospective and/or prospective multicentre analyses validated by expert opinion. The efficacy of first line therapy in controlled bleeds was 87.1-100% for recombinant factor VIIa and 56.7-79% for aPCC.</p> <p>Time to bleeding resolution after initiation of treatment was numerically shorter with recombinant factor VIIa than with aPCC (4.4-17.3 hours versus 25.2-62.6 hours). Sensitivity analyses showed that in order for the estimated length of time to successfully control a minor bleed to be shorter with aPCC than with recombinant factor VIIa, the time to control a bleed with recombinant factor VIIa would need to increase from 24 to .49 hours with home-treatment and from 24 to >54 hours for treatment of a day patients at a haemophilia care centre or the time to control a bleed with aPCC at home would have to decrease from 36 to <13 hours.</p> <p>On-demand treatment with recombinant factor VIIa for the management of mild to moderate bleeding episodes in patients with haemophilia with inhibitors was predicted to be associated with lower total medical costs than on-demand treatment with aPCC in pharmacoeconomics analyses across a number of countries.</p> <p>The lifetime costs of treating bleeding episodes were £200,000 (year 2001 values) lower with rFVIIa only regimen than with the regimens that used aPCC as first line or first and second line treatment</p>
General comments	

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	4. Astermark J, Donfield SM, DiMichele DM, et al A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: The feiba novoseven comparative (fenoc) study. Blood. 2007 Jan 15;109(2):546-51.
Study type and methods	Prospective, open label, randomized, cross-over trial Equivalence study - a difference in efficacy of no more than 15% was determined to be clinically acceptable magnitude of equivalence.
LE	I
Number of patients & Patient characteristics	48 patients with congenital haemophilia A, an inhibitor and the need for bypassing agents in the treatment joint bleeding Mean age 27.5 years (range, 8 – 55 years).
Intervention	rFVIIa 2 doses of Novoseven (90-120 µg/kg body weight; target dose, 105 µg/kg x 2)
Comparison	aPCC one dose of FEIBA (75-100 IU/kg body weight; target dose, 85 IU/kg)
Length of follow up (if applicable)	48 hours after treatment.
Outcome measures/ Effect size	Data for 96 bleeding episodes contributed by 48 participants were analysed. Haemostatic effect. At 6 hours after infusion (primary outcome), the confidence interval only slightly exceeded the 15% boundary (90% CI -11.4%, -15.7%), p=0.059 The proportion of discordant pairs (one treatment effective/the other not effective) ranged from a high of 43.8% at the 2 hour time-point to a low of 9.8% at the 36 hour time-point. The outcome on bleeding stop showed significant difference between the two groups at 48 hours where 95.1% in aPCC group compared to 92.7% in rFVIIa, p=0.001 The highest proportion of discordant pairs, 40.4% was observed at the 2-hour time-point. The rate of discordant decreased to 7.3% by the 48-hour evaluation.
General comments	Intention to treat analysis.

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	5. Young G, Shafer FE, Rojas P, et al Single 270 microg kg(-1)-dose rFVIIa vs. Standard 90 microg kg(-1)-dose rFVIIa and aPCC for home-treatment of joint bleeds in haemophilia patients with inhibitors: A randomized comparison. Haemophilia. 2008 Mar;14(2):287-94.
Study type and methods	Randomised , multicentre, cross-over, double blind study to evaluate the efficacy and safety of rFVIIa (by two different blinded dose schedules) and an open label aPCC (FEIBA).
LE	I
Number of patients & Patient characteristics	42 patients with haemophilia A and B and inhibitors with a history of two or more joint bleeds during the preceeding 12 months.
Intervention	rFVIIa 270 µg/kg single bolus or three doses of 90 µg/kg
Comparison	aPCC 75 IU/kg
Length of follow up (if applicable)	9 hour after treatment
Outcome measures/ Effect size	<p>Efficacy</p> <p>The percentage of patients requiring additional haemostatic medication to control bleeding within 9 h of first trial product administration was significantly greater for the aPCC treatment group than for the rFVIIa 270 µg/kg group ($p=0.032$) with 36.4% of patients in the aPCC group requiring such medication. The efficacy difference between the aPCC and rFVIIa 90 x 3 µg/kg group approached, but did not reach statistical significance, $p=0.069$.</p> <p>Successful response to treatment was assessed by 37.5% of patients receiving rFVIIa 270 µg/kg, 54.5% of patients receiving 90 µg/kg x 3 rFVIIa and 27.3% of patients receiving aPCC</p> <p>Positive response to pain were 45.8%, 54.5% and 27.3% for the rFVIIa 270 µg/kg, rFVIIa 90 µg/kg x 3, and aPCC treatment groups respectively ($p=0.219$).</p> <p>For mobility ; 25%, 45.5% and 22.7% for rFVIIa 270 µg/kg, rFVIIa 90 x 3 µg/kg, and aPCC. $P=0.903$.</p> <p>Safety</p> <p>No patients withdrew from treatment due to adverse events or serious adverse events, and no thrombotic, fatal, or clinical laboratory adverse events were reported. All adverse events were judged unlikely to be related to study treatment by the investigating physicians.</p> <p>A total of 32 treatment-emergent adverse events were experienced by 14 subjects; seven events reported by three patients treated with the rFVIIa 270 µg/kg, 11 events reported by five patients treated with the rFVIIa 90 µg/kg x 3 and 14 events reported by six patients treated with aPCC.</p>
General comments	<p>Sponsored by Novo Nordisk</p> <p>Intention to treat analysis.</p>

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
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Bibliographic citation	6. Knight C, DanØ AM, Kennedy-Martin T. A systematic review of the cost-effectiveness of rFVIIa and aPCC in the treatment of minor/moderate bleeding episodes for haemophilia patients with inhibitors. Haemophilia. 2009;15(2):405-19.
Study type and methods	Systematic Review of cost-effectiveness study
LE	I
Number of patients & Patient characteristics	<p>Patients with haemophilia A and B and inhibitors</p> <p>12 studies included</p> <p>Ekert 2001</p> <p>Knight 2003</p> <p>Joshi 2006</p> <p>Odeyemi and Guest 2002</p> <p>Odeyemi and Guest 2002</p> <p>Huth-Kuehne 2006 (abstract)</p> <p>Chung 2004 (abstract)</p> <p>Carlsson 2006 (abstract)</p> <p>Dundar 2005</p> <p>Ozelo 2007</p> <p>Yoo 2007 (abstract)</p> <p>Putnam 2005</p>
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	
Outcome measures/ Effect size	<p>Ekert 2001 the only CUA included in the review compared rFVIIa with the patients' usual treatment including aPCC for on-demand bleeding episodes showed that rFVIIa was the cost-effective alternative. rFVIIa resulted in a 63-92% reduction in the number of re-treatments, duration of painful episodes, delay up to initiation of treatment, days when crutches or wheelchair were required, emergency room visits and lost carer time.</p> <p>Overall incremental utility improvement associated with rFVIIa was 0.58.</p> <p>The total average treatment cost, including health care resources, for the two rFVIIa phases was AUS\$219,214 which was AUS\$29,901 higher than the cost associated with "usual care" in phase 1 of the study. The incremental cost per QALY ratio was AUS\$51,533 which the author indicate is less than the ICER for hospital dialysis (AUS\$57,053) in Australia.</p> <p>The other 11 cost-effectiveness analyses adopted similar model framework suggesting clinical acceptability of the approach. Knight 2003 study was over the patient's life time, while the other studies estimated the average cost of treating a single bleed episode with either aPCC or rFVIIa. The estimates of efficacy varied between the models, especially for aPCC.</p> <p>The average cost to resolve a bleed is lower using rFVIIa than aPCC in seven out of the nine economic analyses. The average amount that rFVIIa is lower than aPCC ranges between \$3000 and \$17000 per resolved bleed. The two studies that reported aPCC as having the lower mean cost to resolve a bleed both were said to have quality issues (Chung 2004 and Putnam 2005).</p> <p>Sensitivity analysis was undertaken in the majority of the economic analyses and the results were found to be robust to realistic parameter variations.</p>
General comments	Sponsored by Novo Nordisk

Evidence Table
Question

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Bibliographic citation	7. Stephens JM, Joshi AV, Sumner M, et al Health economic review of recombinant activated factor vii for treatment of bleeding episodes in hemophilia patients with inhibitors. Expert Opinion on Pharmacotherapy. 2007 Jun;8(8):1127-36.
Study type and methods	Systematic review of economic studies
LE	II-2
Number of patients & Patient characteristics	<p>Haemophilia patients with inhibitors</p> <p>13 studies met inclusion criteria for the review including six cost impact or general burden studies for rFVIIa (3 prospective, 3 retrospective) and seven comparative economic analyses of rFVIIa versus plasma-derived agents</p> <p>Comparative economic analyses papers included were</p> <p>Joshi 2006</p> <p>Dundar 2005</p> <p>Putnam 2005</p> <p>Knight 2003</p> <p>Odeyemi 2002</p> <p>Odeyemi 2002</p> <p>Ekert 2001</p>
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	
Outcome measures/ Effect size	<p>All the comparative economic analyses studies except Putnam 2005 showed that the cost of treatment with rFVIIa is lower when compared to aPCC.</p> <p>Ekert et al - Patients reported an improvement in all components of the CHQ-CF80, with the exception of overall behavior while receiving rFVIIa therapy. Similarly, parents reported an improvement in all components of the CHQ-PF50 with rFVIIa therapy. A utility value of -0.11 was obtained for the scenario representing phase 1 (usual care) of this study. During this phase, there was a 37 h delay to treatment, 131 h of pain per bleed, 28 bleeds, 6 re-treatments in initial 24 h, and 96 days when crutches or a wheelchair were required. A mean utility value of 0.47 was obtained for the scenarios representing phases 2 and 3 (rFVIIa treatment) of this study. During these 2 phases (average of the 2 rFVIIa phases), there was only a 5 – 7 h delay to treatment, 12 – 26 h of pain per bleed, 18 bleeds, < 1 rebleed, and between 34 and 36 days when crutches or a wheelchair were needed. The overall incremental utility improvement with rFVIIa was 0.58. The incremental cost per QALY ratio calculated was AUS\$51,533 which is less than the incremental cost per QALY ratio calculated for hospital dialysis (AUS\$57,053) in Australia.</p> <p>Knight et al compared the cost-effectiveness of three ITI and three on-demand strategies using a Markov decision model. Overall treatment with any of the ITI strategies was more cost-effective than any on-demand strategies. However, of the on-demand therapies, rFVIIa had a lower average lifetime cost per patient (~£200,000 less)</p> <p>Odeyemi and Guest performed 2 modelling studies to determine the economic impact of rFVIIa compared with aPCC administration in adult patients with mild to moderate bleeds treated either at home or at a comprehensive care centre. The cost of rFVIIa treatment at home was estimated to be £12,944 and with aPCC £14,645; the cost of treatment at a comprehensive care centre with rFVIIa was estimated to be £11,794 and with aPCC £20,467.</p> <p>Dundar et al constructed a decision-analysis model to determine the economic impact of four different treatment regimens (high dose factor VIII or IX, PCC, aPCC, rFVIIa) for mild to moderate bleeds in patients with haemophilia and inhibitors. The medical chart data showed that fewer doses were required (3.6 versus 4.8), bleeding resolution time was shorter (17 versus 44 h), and efficacy higher (89% rFVIIa versus 67% aPCC) with rFVIIa versus aPCC. Total costs were US\$3000 lower per bleeding episode with rFVIIa administration compared with aPCC therapy.</p> <p>Putnam et al constructed a cost-minimisation model to compare the drug costs of the initial 24 h of treatment with aPCC versus rFVIIa in the home-treatment of minor bleeds. In this study, treatment costs for a bleeding episode with aPCC were US\$21,000 compared with US\$33,400 for rFVIIa.</p> <p>Finally, Joshi et al compared the cost-effectiveness of three different treatment regimens, consisting of first-, second- and third-line therapies used in the treatment of mild to moderate bleeds in patients with haemophilia and inhibitors. The total cost of therapy for an rFVIIa only strategy was estimated to be US\$28,076 compared with US\$30,883 – 32,150 for aPCC-based strategies.</p>
General comments	Funded by Novo Nordisk

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	8. Salaj P, Penka M, Smejkal P, et al Economic analysis of recombinant activated factor vii versus plasma-derived activated prothrombin complex concentrate in mild to moderate bleeds: Haemophilia registry data from the czech republic. Thrombosis Research. 2012;129(5):e233-e7.
Study type and methods	Pharmacoeconomics study using retrospective analysis data from two prospective , observational, nationwide registries. Health care payer perspective Year costing 2009 All resource unit costs were derived from reimbursement lists.
LE	II-2
Number of patients & Patient characteristics	13 adults with congenital haemophilia a and b with high-titre inhibitors (≥ 5 BU) Paediatric patients, and adults with acquired haemophilia were excluded Mean age 38.1years (range 21-63; SD 13.5)
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	
Outcome measures/ Effect size	<p>108 mild to moderate bleeds were treated with rFVIIa and 53 with pd-aPCC. Four rFVIIa-treated joint bleeds of unknown severity were also included in the analysis, while 24 severe bleed were excluded.</p> <p>Bleed characteristics The pd-aPCC group demonstrated a significantly higher proportion of traumatic bleeds than rFVIIa group (18.9% versus 11.9%;$p=0.001$)</p> <p>Target joint were affected in a significantly higher proportion of rFVIIa-treated bleeds (37.1% versus 20.0% in the aPCC group; $p=0.037$)</p> <p>Mean time from bleeding onset to treatment initiation was significantly shorter for rFVIIa (4.1 h) than for aPCC (6.0 h; $p<0.001$)</p> <p>Treatment outcomes Significant differences in the time to bleed resolution: 93.8% of bleeds treated with rFVIIa were resolved in ≤ 12 h compared with only 60.4% of aPCC treated bleeds ($p<0.001$)</p> <p>Costs of care Mean total cost per bleeding episode was significantly lower with rFVIIa than with aPCC, €12,760 (11,001) versus €19,802 (12,928), $p=0.002$</p> <p>Mean cost of bypassing therapy were significantly lower in the rFVIIa than aPCC group €12,616 (11,011) versus €19,294 (12,928);$p=0.003$, as were hospital costs (rFVIIa €144 versus €508; $p<0.001$).</p> <p>Even when controlling for possible confounding factors in the GLM regression model, aPCC treated bleeds remained 29.4% more expensive than rFVIIa-treated bleeds, $p=0.052$.</p>
General comments	Industry sponsored Novo Nordisk

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	9. Pokras SM, Petrilla AA, Weatherall J, et al The economics of inpatient on-demand treatment for haemophilia with high responding inhibitors: A us retrospective data analysis. Haemophilia. 2012;18(2):284-90.
Study type and methods	Costing study Retrospective based on Premier Perspective Database United States
LE	II-3
Number of patients & Patient characteristics	N= 267 1322 inpatient stays, of which 821 received rFVIIa and 397 received aPCC Mean age 23.0 years Male haemophilia A patients with a primary or secondary ICD-9 diagnosis code of 286.0 (congenital FVIII disorder). Presence of high responding inhibitors was ascertained through dispensation of Bas during the inpatient stay. Stays with any surgical costs were excluded.
Intervention	rFVIIa
Comparison	aPCC
Length of follow up (if applicable)	
Outcome measures/ Effect size	Median cost for treating an on-demand bleed in the hospital in US is \$53,140 (including the cost of the BA, other pharmacy costs, room and board, supplies, lab/diagnostic and other related costs) with a mean of 6.1 days in hospital. Unadjusted analyses suggested that patients treated with aPCC versus rFVIIa had significantly longer inpatient stays ($p<0.0001$), coupled with longer treatment duration ($p<0.0001$), more infusions of BA administered ($p=0.001$) and greater use of opioid-containing analgesics ($p<0.001$) Stepwise multivariable regression showed that greater disease severity at the time of admission displayed the most significant explanatory power for both models, followed by hospital region outside the southern US, older age (cost model) and African-American race; after adjusting for BA, use of FVIII, source of hospital admission, hospital teaching status and size, and presence of arthropathy.
General comments	Funded by Novo Nordisk

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	10. Hay JW, Zhou ZY. Economical comparison of apcc vs. Rfvila for mild to moderate bleeding episodes in haemophilia patients with inhibitors. Haemophilia. 2011:e969-e74.
Study type and methods	<p>Cost-minimisation analysis</p> <p>US third party payer perspective</p> <p>Decision analytic model</p> <p>Drug cost from Medicare Part B payment limits</p> <p>Cost of hospitalisation from 2006 national Statistics by Healthcare cost and Utilisation Project for DRG397 and multiplied by the cost to charge ratio calculated using US CMS MEDPAR data.</p>
LE	II-3
Number of patients & Patient characteristics	Mild to moderate bleeding episodes in haemophilia patients with inhibitors
Intervention	<p>rFVIIa</p> <p>90 µg/kg given every 2 – 3 h</p>
Comparison	<p>aPCC</p> <p>50-100 IU/kg body weight and up to 200 IU/kg/day</p>
Length of follow up (if applicable)	
Outcome measures/ Effect size	<p>In the base case, the total medical cost to treat a bleed with aPCC and rFVIIa as first line medication were US\$25,969 and US\$35,838 respectively.</p> <p>Compared with rFVIIa, aPCC as first line therapy saves US\$9869 per mild to moderate bleed.</p> <p>One way sensitivity analysis showed that results were insensitive to the efficacy of rFVIIa, unit price of aPCC or rFVIIa, switch rate, rebleed rate or body weight. The model was relatively sensitive to the dose of aPCC and rFVIIa and the efficacy of aPCC. The threshold analysis indicated that rFVIIa will reach cost neutrality when the efficacy of aPCC is as low as 60% or rFVIIa is infused only twice for each line or aPCC is infused three times for each line.</p> <p>If the unit price of aPCC is increased by 50% (from \$1.555 to \$2.354) or reduce the rFVIIa unit price by one-third (from \$1.308 to \$0.864), rFVIIa will also be a dominant strategy.</p> <p>In two way sensitivity analysis, the results were quite sensitive to the assumed infusion frequency for both products. First line aPCC compared with rFVIIa can be a cost saving alternative for home-treatment of mild to moderate bleeds in haemophilia patients with inhibitors.</p>
General comments	Funded by Baxter

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	11. Bonnet PO, Yoon BS, Wong WY, et al Cost minimisation analysis to compare activated prothrombin complex concentrate (apcc) and recombinant factor VIIa for haemophilia patients with inhibitors undergoing major orthopaedic surgeries. Haemophilia. 2009;15(5):1083-9.
Study type and methods	Cost-minimisation analysis Decision analytic model Payer perspective Based on review of published literature Drug cost derived from 2006 US average wholesale prices
LE	II-3
Number of patients & Patient characteristics	Haemophilia patients with inhibitors undergoing major orthopaedic surgeries such as knee or hip arthroplasty
Intervention	Scenario 1 FEIBA/aPCC used in the pre/intra and postoperative period Scenario 3 rFVIIa used in the pre- and intra-operative periods and FEIBA used in the postoperative period
Comparison	Scenario 2 rFVIIa used in the pre, intra- and postoperative periods
Length of follow up (if applicable)	14 day treatment period
Outcome measures/ Effect size	Scenario 1 A dosing of 85 U/kg throughout the perioperative period was selected for FEIBA 6375 U of FEIBA would be used in the pre-operative period and 189750 would be used in the postoperative period. A total of 196125 U would be consumed and the total drug cost would be \$339,296. Scenario 2 A total of 526,500 µg; 6750 µg, 20250 µg and 499500 µg would be used in the pre-, intra- and postoperative periods respectively Total drug cost would be \$810,810 Scenario 3 During pre-operative and intra-operative periods, 6750 µg and 20,250 µg of rFVIIa would be used respectively. The postoperative period would use 189,750 U of FEIBA. The total drug cost of combination rFVIIa and FEIBA would equal \$369847 Using FEIBA instead of rFVIIa would decrease total drug cost by more than 50% and generate savings of over \$400,000 per major surgery. Sequential use of both bypassing agents increase total drug cost by 9% when compared with FEIBA alone but remain >40% lower than rFVIIa alone. Univariate sensitivity analysis confirmed robustness of results.
General comments	Only drug cost included Funded by Baxter

Evidence Table
Question

: Management of haemophilia and rare bleeding disorders
: In patient with inhibitors is recombinant activated FVII more effective when compared to activated PCC and what are the resource implications?

Bibliographic citation	12. You CW, Lee SY, Park SK. Cost and effectiveness of treatments for mild to moderate bleeding episodes in haemophilia patients with inhibitors in Korea. Haemophilia. 2009;15(1):217-26.
Study type and methods	Cost minimisation study Korean National Health Service perspective Decision-analysis approach Based on retrospective and prospective observational studies
LE	II-2
Number of patients & Patient characteristics	Haemophilia patients with inhibitors 25 bleeding episodes in 16 patients treated with aPCC as a first line therapy between May 2003 and May 2005, and from a prospective analysis of 31 bleeding episodes in 11 patients treated with rFVIIa as a first line therapy between July 2005 and December 2005
Intervention	rFVIIa n=11
Comparison	aPCC n= 16
Length of follow up (if applicable)	Up to 5 days
Outcome measures/ Effect size	Mean effectiveness for new and re-bleeds 87.1% in rFVIIa and 64% in aPCC. The mean cost of rFVIIa given as a first line therapy per individual bleeding episode was lower than the mean cost for aPCC (US\$9,276 versus US\$11,785) Mean total direct medical costs from initiation to cessation of bleeding were estimated to be US\$12311 for rFVIIa and US\$18085 for aPCC Sensitivity analysis conducted showed that rFVIIa is cost-effective when simulating any value of the effectiveness of aPCC between 50% and 100%.
General comments	Sponsored by Novo Nordisk Korea Only direct medical cost included

PART 4

Evidence Table : **Management of haemophilia**
Question : **Is comprehensive haemophilia care effective?**

Bibliographic citation	1. Soucie JM, Nuss R, Evatt B, et al Mortality among males with hemophilia: Relations with source of medical care. <i>Bloods</i> . 2000;96:437-42
Study type and methods	Cohort study
LE	II-2
Number of patients & Patient characteristics	2950 males with haemophilia A or B
Intervention	HTC care (67%)
Comparison	Non-HTC care -13% care from private physicians or haematologists 4% from hospital –and non-hospital based clinics, 8% -received care only in hospitals or emergency rooms Other 8% - variety other sources
Length of follow up (if applicable)	3 years
Outcome measures/ Effect size	<p>236 (8%) persons with haemophilia died corresponding to an age-adjusted mortality rate of 40.4 deaths per 1000 person years.</p> <p>After multivariate analysis – medical care provided by HTCs was strongly associated with reduced mortality; persons who had received care in HTCs during the study period were 40% less likely to die than those who had not. RR 0.6 (95% CI 0.5-0.8).</p> <p>Mortality risk increased by 60% with each additional decade of age RR 1.6 (95% CI 1.4 – 1.7). Persons with severe liver disease had 2.4 times the risk of death RR 2.4 (95% 1.5 – 3.9), those persons with HIV infection but without AIDS had nearly 5 times the risk RR4.7 995% CI 3.0 – 7.2), and person with AIDS had 33 times the risk compared with persons without these conditions RR 33.5 (95% CI 22.7 – 49.5).</p> <p>The life expectancy at birth was 38.7 years and the median age at death was 35 years. However, when HIV-infected persons were excluded from the cohort, the life expectancy rose to 64.1 years, and the median age at death nearly doubled to 67 years.</p>
General comments	

Evidence Table : **Management of haemophilia**
Question : **Is comprehensive haemophilia care effective?**

Bibliographic citation	2. Smith PS, Levine PH. The benefits of comprehensive care of haemophilia: A five-year study of outcomes. Am J Public Health. 1984;74(6):616-7.
Study type and methods	Cohort study
LE	II-2
Number of patients & Patient characteristics	4682 patients with haemophilia A or B
Intervention	HTC care
Comparison	Non-HTC care (historical)
Length of follow up (if applicable)	5 years
Outcome measures/ Effect size	<p>Initially only 514 patients were knowledgeable and skilled enough to treat themselves with appropriate doses of intravenous blood product, 2,001 had achieved this degree of proficiency by fiscal 1981.</p> <p>Thirty six percent of the surveyed population were unemployed at the outset as compared to 12.8% four years later.</p> <p>The number of days lost from work or school decreased from 14.5 per year (9.4 of which were spent in the hospital) prior to funding to 4.3, with hospital treatment needed in only 1.8. The average patient who could expect two hospitalisations per year before the program required admission only once every three to four years, five years later.</p> <p>The overall cost of care per patient per year before the program was \$15,800 and during the fifth year, \$5932.</p>
General comments	Details of costing not provided

Evidence Table : **Management of haemophilia**
Question : **Is comprehensive haemophilia care effective?**

Bibliographic citation	3. Smith PS, Keyes NC, Forman EN. Socioeconomic evaluation of a state-funded comprehensive hemophilia care program. New England Journal of Medicine. 1982;306(10):575-9.
Study type and methods	Retrospective cohort Data from a three-year experience with such a program in Rhode Island with those from the preceding year
LE	
Number of patients & Patient characteristics	43 patients with haemophilia
Intervention	Comprehensive care
Comparison	Non-comprehensive care (historical)
Length of follow up (if applicable)	3 years
Outcome measures/ Effect size	<p>77 per cent of the patients with severe haemophilia in the state received total care through the Hemophilia Centre.</p> <p>28 of the 43 patients now treat themselves, the annual number of hospital days per patient has decreased from 12.6 to 3.5, and the number of visits to hospital facilities has fallen from 34 to 2.4.</p> <p>The yearly cost of clotting factor per patient has remained about \$7,000. Altogether, this has saved more than \$10,000 each year for treatment, despite the cost of rehabilitative surgery.</p> <p>Numbers of days lost from school and work have decreased twofold and threefold, respectively. Best of all, comprehensive care has vastly improved the quality of life for patients with haemophilia in Rhode Island.</p>
General comments	

APPENDIX 9 : LIST OF EXCLUDED STUDIES

1. Abshire TC, Brackmann HH, Scharrer I, et al Sucrose-formulated recombinant human antihemophilic factor VIII is safe and efficacious for treatment of hemophilia a in home-therapy--international kogenate fs study group. *Thrombosis & Haemostasis*. 2000;83(6):811-6.— No comparison
2. Ahnstrom J, Berntorp E, Lindvall K, et al A 6-year follow-up of dosing, coagulation factor levels and bleedings in relation to joint status in the prophylactic treatment of haemophilia. *Haemophilia*. 2004 Nov;10(6):689-97.- no comparison
3. Aledort LM, Navickis RJ, Wilkes MM. Best evidence on b-domain deletion and the immunogenicity of recombinant factor VIII. *Journal of Thrombosis & Haemostasis*. 2011;9(11):2325-7. — Review paper
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5. Anonymous. "Factor VIII--Baxter: rAHF-PFM, recombinant anti-haemophilic factor--protein-free method, recombinant factor VIII--protein-free." *Drugs in R & D*. 2003;4(6): 366-368. — Review paper
6. Astermark J, Petrini P, Tengborn L, et al Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *British Journal of Haematology*. 1999 Jun;105(4):1109-13.-no comparison
7. Astermark J, Rocino A, Von Depka M, et al Current use of by-passing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors. *Haemophilia*. 2007;13(1):38-45. — narrative review
8. Astermark J, Voorberg J, Lenk H, et al Impact of inhibitor epitope profile on the neutralising effect against plasma-derived and recombinant factor VIII concentrates in vitro. *Haemophilia*. 2003 Sep;9(5):567-72. — Laboratory study
9. Astermark J. When to start and when to stop primary prophylaxis in patients with severe haemophilia. *Haemophilia*. 2003 May;9 Suppl 1:32-6; discussion
10. Auerswald G, Depka Prondzinski M, Ehlken B, et al Treatment patterns and cost-of-illness of severe haemophilia in patients with inhibitors in Germany. *Haemophilia*. 2004;10(5):499-508.-Review paper
11. Bajwa N, Enriquez MM, Gorina E, et al Cumulative analysis of inhibitor formation in patients with haemophilia a treated with sucrose-formulated recombinant factor VIII. *Haemophilia*. 2009 Mar;15(2):597-600.— No comparison
12. Barnes C, Rivard GE, Poon MC, et al Canadian multi-institutional survey of immune tolerance therapy (itt) -- experience with the use of recombinant factor VIII for itt. *Haemophilia*. 2006 Jan;12(1):1-6 — No comparison
13. Bergman GE. Progress in the treatment of bleeding disorders. *Thrombosis Research*. 2011 Jan;127 Suppl 1:S3-5.— Review paper
14. Berntorp E, Archey W, Auerswald G, et al A systematic overview of the first pasteurised vwf/fviii medicinal product, Haemate p/ humate -p: History and clinical performance. *European Journal of Haematology*. 2008 May;Supplementum. (70):3-35-narrative review
15. Berntorp E, de Moerloose P, Ljung RCR. The role of prophylaxis in bleeding disorders. *Haemophilia*. 2010 Jul;16 Suppl 5:189-93.- narrative review

16. Berntorp E. Joint outcomes in patients with haemophilia: The importance of adherence to preventive regimens. *Haemophilia*. 2009 Nov;15(6):1219-27. Narrative review
17. Berntorp E. Prophylactic therapy for haemophilia: Early experience. *Haemophilia*. 2003 May;9 Suppl 1:5-9; discussion
18. Berntorp, E. "Differential response to bypassing agents complicates treatment in patients with haemophilia and inhibitors." *Haemophilia* 2009;15(1): 3-10. – Review paper
19. Berntorp, E. Prophylaxis and treatment of bleeding complications in von Willebrand disease type 3. *Seminars in Thrombosis & Hemostasis* 2006;32(6): 621-625. – Review paper
20. Bjorkman S, Folkesson A, Jonsson S. Pharmacokinetics and dose requirements of factor VIII over the age range 3-74 years: A population analysis based on 50 patients with long-term prophylactic treatment for haemophilia a. *European Journal of Clinical Pharmacology*. 2009 Oct;65(10):989-98.-no comparison
21. Blanchette P, Rivard G, Israels S, et al A survey of factor prophylaxis in the Canadian haemophilia a population. *Haemophilia*. 2004 Nov;10(6):679-83. – no comparison
22. Blanchette VS, Shapiro AD, Liesner RJ, et al Plasma and albumin-free recombinant factor VIII: Pharmacokinetics, efficacy and safety in previously treated pediatric patients. *Journal of Thrombosis & Haemostasis*. 2008 Aug;6(8):1319-26.– No comparison
23. Blatny J, Kohlerova S, Zapletal O, et al Prophylaxis with recombinant factor VIIa for the management of bleeding episodes during immune tolerance treatment in a boy with severe haemophilia a and high-response inhibitors. *Haemophilia*. 2008;14(5):1140-2.– Case series
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25. Brecelj J, Bole V, Benedik-Dolnicar M, et al The co effect of prophylaxis and radiosynovectomy on bleeding episodes in haemophilic synovitis. *Haemophilia*. 2008 May;14(3):513-7.- no comparison
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29. Chuansumrit A., Angchaisuksiri P., Sirachainan N et al Critical Appraisal of the Role of Recombinant Activated Factor VII in the Treatment of Haemophilia Patients with Inhibitors. *Journal of Blood Medicine*.2010;1: 37-48 – No comparison
30. Cooper DL, Seremetis S, Carr ME, Jr. Re: Discordant pair analysis of rFVIIa and pd-aPCC response. *Haemophilia*. [Comment Letter]. 2011;17(2):323-335. – Review paper

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32. Di Minno G, Cerbone AM, Coppola A, et al Longer-acting factor VIII to overcome limitations in haemophilia management: the PEGylated liposomes formulation issue. *Haemophilia*. [Research Support, Non-U.S. Gov't Review]. 2010;16 Suppl 1:2-6. – Narrative review
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34. Djulbegovic B, Marasa M, Pesto A, et al Safety and efficacy of purified factor ix concentrate and antifibrinolytic agents for dental extractions in hemophilia b. *American Journal of Hematology*. 1996 Feb;51(2):168-70.
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48. Fischer K, Van den Berg HM, Thomas R, et al Dose and outcome of care in haemophilia--how do we define cost-effectiveness? *Haemophilia*. 2004 Oct;10 Suppl 4:216-20. – no comparison
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50. Fischer K, Van Der Bom JG, Prejs R, et al Discontinuation of prophylactic therapy in severe haemophilia: Incidence and effects on outcome. *Haemophilia*. 2001 Nov;7(6):544-50. – no comparison
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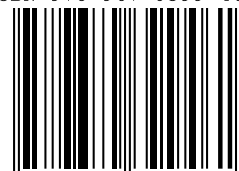
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