

Consumption of factor VIII (FVIII) concentrates in Scottish haemophiliacs (1989-2003).

Eisa Hamouda Hamid

Submitted to:

**Public Health Sciences
University of Edinburgh**

**As required for completion of Master of Epidemiology degree
September 2003**

Declaration

I, Eisa Hamouda Hamid, Declare that the following MSc Epidemiology dissertation completed in September 2003 is entirely my own work.

12th September 2003

Acknowledgments

There are many people to whom I am greatly indebted, and without whom this work could not have been completed:

Firstly, I would like to express my thanks and gratitude to my supervisor, Professor Robin Prescott, who has been a constant source of support and encouragement throughout this work. He has guided me with substantial advice, and through meticulous and vigorous discussions. Furthermore, he has also been an enormous strength in helping me deal with the bad news of my father's cancer, and when I need to return urgently to Sudan.

I would also like to thank Professor Christopher Ludlam, New Royal Infirmary, for giving me the opportunity, relatively rare, to do applied research, and also for sharing with me his years of experience in haemophilia care and research.

I am grateful to many other people including Mrs Pam Warner, my course organiser, for her comments on the proposal; Mr Eric Evan, Haemophilia Centre Data Manager, for his great help and patience during data collection, and endless checking and rechecking of the numbers; Mrs Jane Pelley, from the Protein Fractionation Centre, for her help with data and interpretations of the findings; Dr Rose Dennis, Haemophilia centre, for her invaluable interpretations of the findings on individual patients' usage; Ms Marshall, Erskine Medical Library, for the clinic on systematic literature review.

Finally, I would like to express my thanks to my sponsor, the Chevening Scholarship Scheme of the Foreign and Commonwealth Office, for enabling me to continue my education at an institution of the highest calibre.

Abstract

Introduction

Haemophilia is a rare condition, yet its treatment is a costly, lifelong commitment on the part of the provider, payer and patients. A large proportion of this expense is attributable to the cost of factor VIII infusion. Moreover, clotting factor use has risen steadily over the past decades. Evaluation of clotting factors consumption is essential in order that future resources are allocated appropriately.

Objective

To examine historical trends of use of factor VIII (FVIII) concentrates, its monthly variability in the Scottish haemophiliacs between 1989 and 2003, and examine individual patients' consumption in order to assess the influence of factors such as severity of haemophilia A, prophylaxis, on-demand treatment, surgery, immune tolerance treatment as well as to compare home and hospital usages.

Methods

Data on total monthly use of FVIII was collected in the Protein Fractionation Centre (PFC, Edinburgh, and UK) between 1989 and 2003, and individual data on patients from the Haemophilia Centre database (Haemophilia and thrombosis Centre, Royal infirmary, Edinburgh) was made available.

Results

This is the most recent study to examine the consumption of FVIII concentrates in Scotland. During this 14 year-period the annual clotting factor consumption has increased by over 350 %. This may be attributed to increase in life expectancy of the haemophiliacs and to more rigorous treatment approaches including prophylaxis

treatment. Another finding in this work was that the clotting factor consumption in East coast, especially in the latter years, had grown faster than the West coast of Scotland. Produced for the first time during this period, the use of genetically-engineered bloods products have grown very sharply while the use of plasma-derived clotting factor has steadily decreased.

In order to examine the variation in clotting factor use, two models were fitted. The first model covers the whole period while the second cover the period after the start of recombinant clotting factor. Both models have shown that 95% of the time the monthly consumption will be within 2 SD of the trend line corresponding to 0.42 and 0.46 million international units of FVIII respectively.

From the FVIII consumption in individual patients, 42 % whom have severe haemophilia, the impact of severity, prophylaxis, surgery and patients on immune tolerance on the clotting factor consumption have been quantified.

Conclusion and recommendation

To facilitate a 'constructive dialogue' between those providing the funding and those delivering the health care, establishment of a monitoring system to track variation in clotting factor usage is recommended. To help collection of consistent data and improve the recording and storage of information on clotting factor consumption, the design of an internal database for clotting factor use is recommended to replace the present spreadsheet based approach. Further studies applying cohort designs are needed to assess the impact of all potential factors on clotting factor usage

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Table of Abbreviations

ART	Anti Retroviral Therapy
FVIII	Factor VIII
GNP	Gross National Product
HCV	Hepatitis C Virus
HIV	Human Immune Deficiency Virus
IU	International Unit
MRB	Marketing Research Bureau
PFC	Protein Fractionation centre
SD	Stand Deviation
SNBTS	Scottish National Blood Transfusion Centre
SPC	Statistical Process Charts
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia centre Doctors' Organisation
USA	United States Of America
vWD	von Willebrand Disease
WFH	World Federation of haemophilia

Chapter I: Introduction

Haemophilia is a rare condition. The World Federation of Haemophilia (www.wfh.org) documents more than 100,000 people with haemophilia in 89 countries. Most of these people do not have access to adequate treatment. World-wide there are an estimated half million people with haemophilia, less than a third of whom are diagnosed (O'Mahoney B, 2002). There are approximately 5,000 patients with Haemophilia A and 1,000 with haemophilia B (Christmas disease) in the United Kingdom (UK) (Rizza CR, Spooner RJ; Giangrnde PL, 2001). The treatment of haemophilia aims to reduce disability and prolong life, to facilitate general social and physical well being and to help each patient achieve their full potential, whilst causing them minimal harm (Kasper et al, 1989). However, only countries of the so-called Western World have implemented successful haemophilia care (Mannucci PM, 1998). As a result, an improvement in both the longevity and quality of life of patients has become apparent. Despite this, the treatment of haemophilia is a costly, lifetime commitment on the part of the provider, payer and patients. Several studies have demonstrated that high percentages of haemophilia care costs are attributable to the cost of factor VIII infusion (Smith PS et al, 1996; Szucs TD, Offiner A, Schramm T et al, 1996; Molho P, Rolland N, Lebrun T et al, 2000). For instance, as reported in Globe et al (2003) has shown, in the USA infusion of FVIII concentrates infusion comprised 72% of the total cost (range 45 - 83%). In the UK £48 million was spent on clotting factors in 1994 (Miners HA et al, 1998). In addition, clotting factor use has risen steadily over the decades. 63 million units of FVIII were used in 1981 to treat haemophilia A patients but the consumption had risen to over 149 million units by 1996 (Rizza CR, Spooner RJ; Giangrnde PL, 2001).

In Scotland, a comprehensive study was conducted to assess the demographic characteristics, treatment and clinical outcome of those with haemophilia living in central Scotland between 1980 and 1994. The number of patients increased from 162 in 1980 to 206 in 1994. The prevalence of blood product treated haemophilia A in 1980

was 0.04, and in 1994 was 0.052 per 1000 person, respectively (Ludlam CA, Lee R J, Prescott R J et al 2000). Apart from a single study in mid nineteen seventies, however, (Cash JD, Spencely M, 1976), the use of coagulation factor concentrates has not been studied. Data on clotting consumption is necessary for both monitoring and ensuring that future resources to be appropriately allocated.

This project was facilitated by Professor Robin Prescott. His communication with Professor Christopher Ludlam yielded that there was a need to examine trends of FVIII consumption in Scotland, with special focus on the monthly variations. This need most probably stemmed from the disparity between the rising clotting factor use and the limited financial resources. Following a discussion with Professor Prescott and Professor Ludlam, it has been decided that this project examines FVIII consumption in Scottish haemophiliacs focusing specifically on two aspects:

Historical trends of FVIII consumption and monthly variability.

Influence of haemophilia A severity, prophylaxis, surgery and immune tolerance on FVIII consumption.

This dissertation consists of seven main chapters. In chapter one, there is an introduction to the whole work. This is followed by a chapter on a literature review, in which epidemiological and clinical aspects of haemophilia A are covered to help show the size of the problem and also put any terms that will be used in their proper context. Relevant literature on consumption and economics of FVIII are incorporated. Chapter three covers the aim and objective of the project. In chapter four, a detailed account of the methodology is given. The results of the data analysis are given in chapter five. This is followed by discussion of the findings in chapter six. Finally the conclusion and recommendations are presented in chapter seven.

Chapter II: Literature review

2.1 Literature review Process

After a discussion concerning the aim of the project with Professor Robin Prescott at the Public Health Sciences and Professor Christopher Ludlum from the Haematology Department New Royal Infirmary, the following two strategies were employed during the literature review process:

- National policy document review
- Computerised literature search

2.1.1 National policy document review

Internet searches and consultation with haemophilia professionals revealed a selection of relevant national policy documents. (United Kingdom Haemophilia Centres Directors' Organisation, 1994; Inhibitor Working Party United Kingdom Haemophilia Centres Directors' Organisation, 1996; Executive Committee United Kingdom Haemophilia Centres Directors' Organisation, 1997; United Kingdom Haemophilia Centres Directors' Organisation, 1997; Genetic Working Party United Kingdom Haemophilia Centres Directors' Organisation, 1997). These documents explained the present UK guidelines and recommendations for haemophilia treatment. The United Kingdom Haemophilia Centres Directors' Organisation, now known as United Kingdom Haemophilia Centres Directors' Organisation (UKHCDO) works with patients and other organisations (the Haemophilia Society and Haemophilia Alliance) to provide standardised and optimum care for patients across the UK and ensures the continuous development of guidelines.

2.1.2 Computerised literature search

- Literature searches were carried out utilising the following databases available through the University of Edinburgh library:
- Medline:1966-present
- Web of science:1981-present
- Embase:1980-present
- Biosis:1969-present
- CINAHL:1982-present

Key word combined terms relating to haemophilia or FVIII with terms relating to the following words were used (appendix):

- Epidemiology
- Global
- UK
- Scotland
- Economics

The above terms were investigated as:

- *Medical subject heading*(MeSH)
- Key words in either document title or abstracts
- The primary focus of document.

Additional databases available on the internet was searched using the search terms listed above:

- Cochrane Library Database
- Health technology assessment database (HTA).
- NHS health Economic database (NHS EED).

Further keyword searching of the WWW was undertaken using the 'Google' search engine, giving coverage of grey literature. These included marketing research agencies, guideline-producing agencies and specialist haematological sites:

- Haemophilia Society UK

- MRB (Market Research Bureau, USA)
- OHC (Oxford Haemophilia Centre)
- Department of Health UK
- WFH (World Federation of Haemophilia)

2.2 Findings from the literature review

Combining information obtained from both strategies of literature review yielded information on many aspects of Haemophilia. Those considered to be most relevant to this study were:

- clinical aspects of Haemophilia
- Global and UK Haemophilia trends.
- Haemophilia in Scotland
- Haemophilia treatment protocols and modalities
- Economics of Haemophilia and factor VIII consumption estimates.

2.3 Clinical aspects of Haemophilia

2.3.1 Definition

The general term 'haemophilia' describes a group of inherited blood disorders in which there is a life-long defect in the clotting mechanism of the blood. A more precise definition can be given in terms of which part of the clotting mechanism is defective. The clotting factors, which are present in normal blood, are numbered with Roman numerals from I to XIII (e.g. Factor VIII = 8). A person can be deficient in any factor but the most well known are deficiencies of factor VIII (haemophilia A) and factor IX (haemophilia B), both of which show X-linked inheritance. The commonest inherited bleeding disorder is von Willebrand's disease (vWD), a defect in the quantity or quality of the von Willebrand factor, present in perhaps as many as 1% of the general population. This disorder is generally mild, but it is an important cause of menorrhagia in affected blood relatives (as in Paula HB, Pasi KJ, 2003).

Acquired haemophilia and other related bleeding disorders: These are rare conditions, occurring particularly in elderly individuals, may arise as a result of acquired deficiencies due to dysfunction of the immune system or as adverse reactions to external agents, infections or drugs. This definition of acquired bleeding disorders does not include secondary haemorrhagic conditions often associated with anticoagulant therapy and well defined primary disorders e.g. liver disease, renal disorders, disseminated intravascular coagulation and neoplasia.. This condition may require the frequent administration of very costly blood products or recombinant coagulation factor preparations for effective management.

Both types of haemophilia share the same symptoms and inheritance pattern, only blood tests can differentiate which factor is deficient/affected.

2.3.2 Severity

The bleeding tendency is related to the measured concentration of the factor and is classified as mild, moderate, or severe (White GC II et al, 2001). This classification generally predicts bleeding risk, guides the optimum management plan, and predicts outcome. Traditionally, severity is expressed in terms of percentage of the average normal clotting activity. More recent mode of expression uses numbers of international units (IUs) of clotting factor per millilitre, leading to a different definition of severity (WFH, 1998). Where there is $< 1\%$ ($< .01$ IU/ml) of the normal factor activity present the condition is described as 'severe'. Between 1% and 5% ($0.01-0.05$ IU/ml) of normal activity is classed as 'moderate', and $> 5-40\%$ ($> .05-40$ IU/ml) is described as 'mild' (as in Paula HB, Pasi KJ, 2003). Those who have mild or moderate haemophilia generally only experience bleeding problems after an obvious injury or an operation, and many mild cases have only been discovered after, for example, a tooth extraction or surgery.

Although most patients with severe haemophilia need regular replacement therapy, a few rarely bleed and need only occasional treatment. 15% of patients with severe

haemophilia in the UK had no record of treatment in a year of observation (Rizza CR, Spooner RJ; Giangrnde PL, 2001).

2.3.3 Pathophysiology.

Factor VIII is a complex plasma glycoprotein of 2351 amino acids that is synthesised primarily by hepatocytes, although kidney, sinusoidal endothelial cells, and lymphatic tissues can also synthesise small amounts of factor VIII (as in Paula HB, Pasi KJ, 2003). The protein contains a large B domain of unknown function that is not required for coagulant activity. It is one of the largest and least stable coagulation factors, circulating in plasma in a non-covalent complex with von Willebrand factor. Factor VIII has a half-life of about 12-hours in adults (shorter in children). Von Willebrand factor protects factor VIII from premature proteolytic degradation and concentrates it at sites of vascular injury.

Bleeding occurs in haemophilia owing to failure of secondary haemostasis. Primary haemostasis, formation of the platelet plug, occurs normally but stabilisation of the plug by fibrin is defective because inadequate amounts of thrombin are generated. Factor VIII is known to be central to the process of blood coagulation and for the adequate generation of thrombin.

2.3.4 Molecular genetics of haemophilia.

The gene for factor VIII was cloned in 1984 (as in Paula HB, Pasi KJ, 2003). These advances in cloning have further resulted in significant advances in the molecular characterisation of the defects that cause the haemophilia and made possible the production of recombinant clotting factor concentrates for therapeutic use.

2.3.5 Inhibitor risk and molecular defect.

Inhibitors are antibodies to factor VIII, which prevent therapy from being effective. They appear almost exclusively in patients with moderate and severe haemophilia.

Inhibitor risk is associated with the type of mutation present. In haemophilia A, patients with mutations that severely truncate or prevent production of factor VIII (intron 22 inversion, large deletions, non-sense mutations) have a much higher frequency (about 35%) of inhibitor development than those carrying mis-sense mutations and small deletions (about 5%) in whom some protein may be produced (as in Paula HB, Pasi KJ, 2003).

2.3.6 Diagnosis.

Haemophilia is diagnosed either because of a known family history (which is absent in a third of haemophiliacs) or after presentation with bleeding. A blood sample from the newborn baby can be used to make a diagnosis. Cases of severe haemophilia may become apparent and be diagnosed at an early age as a result of surgery or injury. For example, prolonged bleeding may follow circumcision, routine blood sampling or routine childhood vaccinations. More often the first symptom of a bleeding tendency is in the form of extensive bruising as the child bruises learning to crawl or walk (Pollmann H et al, 1999).

Moderate and mild haemophilia may not be diagnosed until later into childhood or in some cases even in adulthood. Because there is some clotting factor available more minor injuries will heal normally and it may not be until a major injury occurs that the deficiency is revealed. The process of diagnosis involves many complex laboratory tests on blood samples and takes several days to complete.

Factor VIIIIC deficiency due to haemophilia A must be distinguished from von Willebrand's disease by assays of von Willebrand factor. The family history (autosomal inheritance) and bleeding symptoms (menorrhagia, easy bruising, and epistaxis) differ. Most cases of von Willebrand's disease are mild; haemarthroses and muscle bleeds occur only in the most severe type (uncommon) in which von Willebrand factor is absent and the factor VIIIIC concentration is very low (Rodeghiero F, 2002).

2.3.7 Inheritance

Haemophilia is an inherited condition. However, it is possible for the condition to appear in any family - it is thought that at least 30% of people with haemophilia have no family history of a bleeding disorder. It is difficult to be exact about this because of the way in which haemophilia is inherited. Technically, it has a 'sex-linked recessive' inheritance pattern. This means that while only males are affected by the condition, it is passed through the female member of the family. Women with a haemophilic gene are called carriers. Each daughter of a carrier mother has a 50% chance of being a carrier, and each son of a carrier has 50% chance of having haemophilia.

2.3.8 Signs and Symptoms of haemophilia

Severe haemophilia usually manifests in the first year of life with raised unsightly bruises, at circumcision or when prolonged bleeding suggests something unusual, often from minor lesions in the mouth (WFH, 1998). In most cases, minor cuts and scratches do not pose any problems for a person with haemophilia. A little pressure is usually enough to stop the bleeding. For those severely affected, the major problem is internal bleeding into joints, muscles and soft tissues (Rodriguez-Merchan EC, 1999). These types of bleeding are sometimes described as 'spontaneous' because it is impossible to identify the exact injury that caused them.

An ache, irritation or tingling in an affected area is the usual indication that a person with haemophilia gets when bleeding into the body tissue begins. This is followed by definite pain and stiffness, limitation of use, and the site of the bleed will get hot, swollen and progressively more tender. In the case of joint bleeding, the blood that has escaped into the joint has a very damaging effect on its surface. Once a joint becomes damaged then bleeding will occur more frequently resulting in a 'target joint'. The majority of bleeds in joints and muscles occur in the lower limbs, with knees and ankles being the worst affected in most people.

2.3.9 Management

2.3.9.1 Basic management

The goals of treatment of haemophilia, as stated by the World Federation of the Haemophilia, are to minimise disability and prolong life, to facilitate general social and physical wellbeing and to help each patient to achieve full potential, while causing no harm (as in Giangrande PLF, no publication year).

Plasma-derived FVIII concentrates became widely available in the 1970s, resulting in the development of home therapy plans. Continued manufacturing advances resulted in clotting factors of higher purity (Pelley G, personal communication 20030). Viral inactivation steps were introduced in 1986 to eradicate transmission of HIV and HCV (Lee CA, Sabin CA, Miners AH, 1997). Recombinant factor VIII concentrates became available from 1992. In the UK, recombinant products are the treatment of choice because they eliminate the risk of transmission of human and animal infectious agents (UKHCDO, 1997).

The basis of treatment is to raise the concentration of the missing factor sufficiently to arrest spontaneous and traumatic bleeds (on demand treatment), given regularly to prevent bleeds occurring (prophylactic treatment) or to cover surgery .

2.3.9.2 Prophylactic Treatment

Patients with severe haemophilia treated on-demand can expect to treat 30 – 35 bleeds per year using 30-35 iu/kg of FVIII per acute bleeding incident (As in Miners AH et al, 1998). However, by infusion of 24 – 40 iu/kg of clotting factor prophylactically three times a week, it is possible to prevent acute bleeding, thus preventing arthropathy(Nilsson IM et al, 1992). Pioneered in Sweden, prophylactic treatment is now the recommended strategy for children with severe haemophilia (Nilsson IM et al, 1992). Many other studies have confirmed the benefit of regular and adequate treatment (three times a week, or alternate days, in haemophilia A). This approach prevents joint bleeds and therefore their long-term consequences (Yee TT, Beeton K, Griffioen A, et al, 2002; Van Den Berg HM et al, 2002). However, limited information is available on lifestyle and quality-of-life issues (Royal S, Schramm W, Berntorp E et al 2002; Naraine VS, Risebrough NA, Oh P et al, 2002).

2.3.9.3 Comprehensive care

Comprehensive care involves a variety of treatment and careful monitoring (bleeding incidents, treatment, inhibitor assays, musculoskeletal and immunological assessments, physiotherapy and exercise assessments, and psychosocial adjustment among other things). Comprehensive care team works to prevent problems, or to address them at early stages before they affect the health or well being of the individual. In the UK, a network of centres was initiated in 1968 and has been progressively developing since then with the establishment of 22 comprehensive care centres.

2.3.9.4 Inhibitor treatment

The appearance of inhibitors may complicate treatment and make it much more expensive. However, inhibitors develop in a minority of patients, often early in life after relatively few treatments. The prevalence in haemophilia A in the UK is 6% (Rizza CR, Spooner RJ, Giangrande PL, 2001). Factor VIII inhibitors may be either low-titre (commonly transient) antibodies, overcome by increased or continuing treatment with factor VIII concentrates, or more serious high-titre, highly responding antibodies, which preclude treatment with factor concentrates (Dennis R, personal communication 2003). Acute bleeding episodes may respond to plasma-derived activated-prothrombin complex concentrates that include a mixture of activated clotting factors that may be able to bypass factor VIII activity. However, recombinant activated factor VII is effective for acute joint bleeds (Dennis R, personal communication 2003).

2.3.10 Complications of Haemophilia

Inadequately treated individuals suffer from recurrent joint bleeding leads to chronic arthropathy, with fixed flexion and other deformities particularly of the large hinge joints. Death from haemorrhage is also a recognised fatal complication of haemophilia. The benefits of clotting factors came at a significant cost. Hepatitis (B and C) and HIV viruses have been recognised as complications of plasma-derived concentrates made from large plasma pools (Ludlam CA, personal communication 2003; Lee C, Dusheiko

G, 2002; Makris M et al, 1996). HCV has serious late complications. Most adults have chronic infection with slow progression to cirrhosis of the liver and, in some, malignant disease.

HIV infection in haemophilia was reported in 1981, and in the UK more than 1200 individuals were infected by blood-product infusions between 1979 and 1985 when viral inactivation steps were introduced. More than half these individuals have died. No new cases of HIV infection from virally inactivated blood products have been detected since 1986 (Racoosin JA, Kessler CM, 2002; Wilde JT et al, 1999; Wilde JT, 2002).

Mortality statistics showed that the commonest cause of death in haemophilia changed from intracranial haemorrhage before the availability of effective treatment to treatment-related deaths in the 1980s and 1990s, mainly related to HIV infection and liver disease (Rizza CR, Spooner RJ, Giangrande PL, 2001).

Development of antibodies that make treatment ineffective as mentioned earlier is also a recognised complication of replacement therapy.

2.3.11 Gene therapy for haemophilia

Haemophilia is an ideal target for gene therapy because only a small rise in factor concentrations to more than 1-2% above normal would achieve the goals of prophylaxis without regular infusions of concentrate, and would deliver a substantial improvement in lifestyle for patients with severe haemophilia (Paula HB, Pasi KJ, 2003).

The ultimate gene therapy for haemophilia A or B would be direct correction of the molecular defect in the mutated gene. Such direct gene modification has been demonstrated, but for haemophilia A or B this approach remains a long way in the future (Paula HB, Pasi KJ, 2003). It is also reported that more than 25 patients with haemophilia have now been treated in phase I gene-therapy protocols. No study has

conclusively shown that therapeutic concentrations of factors VIII and IX can be reliably obtained, although none have highlighted significant safety concerns.

2.4 Global Epidemiology of Haemophilia

In 1998, the World Federation of Haemophilia (WFH) began collecting information on haemophilia care throughout the world. This surveys, called the WFH Global Surveys, collect basic demographic information, data on resources of care and treatment products, and information on the prevalence (the percentage of the population affected) and infectious complications such as HIV and HCV.

Globally, the WFH has documented more than 100,000 people with haemophilia in 89 countries. World wide, however, there are an estimated half million people with haemophilia, less than a third of whom are diagnosed. Most of these people do not have access to adequate treatment (O'Mahoney B, 2002).

The outlook for people with severe haemophilia differs substantially between countries with a strong economy and those with major economic constraints. FVIII concentrates may not be easily provided, but a considerable effect on quality of life and life expectancy can be made by development of national haemophilia programmes and local blood transfusion services (O'Mahoney B, 2002). Data from the WFH demonstrate that survival into old age is significantly increased not only by the development of treatment centres but also by the use of clotting factors. Optimum survival is reported to be associated with a rate of use of replacement therapy of at least 1 international unit per head, such as in the USA and Europe (table 1). It reported that in countries with weaker economies (such as Iran, Russia, and Egypt), many individuals can be diagnosed but the rate of use of clotting factor is lower. In countries with major financial constraints (such as India and Bangladesh) most people with haemophilia remain undiagnosed, and the provision of effective treatment is very little.

The World Federation of Haemophilia, through the Global Alliance for Progress, contributes towards improving the in haemophilia care in some of the poorer countries by assisting the implementation of national haemophilia programmes. The objectives

Table 1. Global comparisons in the provision of haemophilia centres and treatment*

Country	Population (millions)	% of patients diagnosed	Number of haemophilia treatment centres	Factor VIII use per head
Australia	19	95	15	3.00
USA	278	87	140	3.40
Germany	82	82	6	5.50
Iran	63	82	10	0.50
Russia	146	81	4	0.10
Egypt	63	75	7	0.10
South Africa	42	52	10	0.60
India	998	12	56	0.01
China	1227	5
Indonesia	207	4	8	0.01
Bangladesh	128	2

* Data from World Federation of Haemophilia Global Survey, 2002.

are to introduce or improve national programmes in 30-40 countries, increase the number of people diagnosed from 120,000 to 170,000 to ensure that these newly identified patients have access to basic care, and to ensure that those currently diagnosed but untreated have access to basic care(O'Mahoney B, 2002).

2.5 Epidemiology of Haemophilia in the UK

According to Rizza et al (2001), the UK Ministry of Health designated 36 'haemophilia diagnostic and registration centres' in 1968. Three of these Centres (Oxford, Manchester and Sheffield) were designated special treatment centres. By 1976, the number of haemophilia centres had grown to 52. In 1993, two tiers of haemophilia centre were created in accordance with guidelines published by the Department of Health, and 22 centres were designated as comprehensive care centres (Rizza CR, Spooner RJ, Giangrande PL, 2001).

The number of people with haemophilia A registered at UK Haemophilia has increased steadily from 3943 in 1981 to 4826 in 1996 (figure1), of whom only 1546 (32%) were severely affected(Rizza CR, Spooner RJ, Giangrande PL, 2001). However, the proportion of patients with severe haemophilia has been falling since 1981. This most likely reflects the relatively greater impact of HIV on severely affected patients, who were more likely to be exposed to blood products (Darby SC et al, 1995).

2.5.1 The incidence of inhibitory antibody

The proportion of patients with haemophilia A who are known to have developed inhibitors to FVIII has remained constant at around 6% from the time when information was first collected in 1969(Biggs R, 1974). By 1996, a cumulative total of 249 of 4826

(5%) patients with haemophilia A who were alive were known to have developed inhibitory antibodies at some stage (Rizza CR, Spooner RJ, Giangrande PL, 2001).

2.5.2 HIV Status

HIV infection in haemophilia was reported in 1981, and in the UK more than 1200 individuals were infected by blood-product infusions between 1979 and 1985 when viral inactivation steps were introduced. More than half these individuals have died. No new cases of HIV infection have been detected since 1986 (Ludlam CA, personal communication 2003).

2.5.3 Acquired haemophilia

It has been reported that, between 1985 and 1996, 240 patients with acquired haemophilia A were registered and treated at UK haemophilia centres, of which 151 are known to have died. The age of the patients at diagnosis ranged from 20 to 99 years and 125 (52%) of the 240 cases reported were female.

2.5.4 Deaths

A total of 1190 patients with haemophilia A have died during 1981-96 (Rizza CR, Spooner RJ, Giangrande PL, 2001). The main cause of death during that period was AIDS, which accounted for 38% deaths and has been the commonest cause of death for people with haemophilia in the UK since 1987. Cerebral haemorrhage was the second most common cause of death (10%), followed by cancer (9%), myocardial infarction and other forms of heart disease (6%), and respiratory problems, including pneumonia (6%). Seventy-eight patients died of liver disease, 28 had casualties and 15 committed suicide.

2.6 Epidemiology of Haemophilia in Scotland

A comprehensive study, covering the period from 1980 to 1994, was undertaken to assess demographic characteristics, treatment and clinical outcome of those with haemophilia living in central Scotland, (Ludlam CA, Lee R J, Prescott R J et al 2000).

The number of individuals with haemophilia A increased throughout the period 1980 - 1994. In 1980 there were 162 patients with haemophilia A; by 1994 this had become 206. The main rise occurred during the period 1980-85 mostly represents the referral of patients previously cared for at outlying hospital to the Haemophilia Centres in Edinburgh and Glasgow. After 1985 there was only a minimal 2.5% increase in the total number of treated patients. The prevalence of blood product treated haemophilia A patient in 1980 was 0.04, and in 1994 was 0.052 per 1,000 persons, respectively.

The age distribution of haemophilia A patients in 1980 and 1994 was compared with that of the general population of central Scotland. In 1980 the age distribution of patients was similar to the normal population apart from the paucity of patients with haemophilia over 60 years (3.7 % vs. 15.6 %) while by 1994 there had been an increase in this older age group (9.9 % vs 17.1 %).

2.6.1 The incidence of inhibitory antibody

The number of patients with FVIII inhibitors detected in any year was relatively constant (range between 12 and 17) with a cumulative total of 30 patients during the period 1980 to 1994. Of this total 83% had severe Haemophilia A.

2.6.2 HIV Status

There were no HIV positive patients in 1980. By 1985, 53 patients with haemophilia A who had become HIV positive. In 1994 the number of HIV positives among haemophilia A patients had declined to 38 patients. The prevalence of HIV among severe haemophilia A was 39 %. This is lower than reported figures from for the UK as a whole (59 %) and to some other countries (90 %) (UKHCDO, 1986; Goedert JJ et al, 1985). Fewer patients become infected with HIV in early 1980s, because the virus was

not endemic in the general population in Scotland at that time and because the majority of patients were treated with FVIII containing blood products derived from locally collected plasma (Melbye et al, 1984; Ludlam CA et al, 1985).

2.6.3 Hospital admission

There was an increase in the total annual hospital admission of patients with haemophilia A from 103 to 168 over the 15-year period. The number being admitted primarily because of acute bleeding was reasonably constant during the entire 15-year period. After 1985 the increase was largely due to HIV and from HCV. The largest numbers of admission were seen in those with severe haemophilia A. The number of surgical admission was small (4 – 21 per annum) and those relating to haemophilia (2 – 9 per annum) were mainly orthopaedics. The number of bed days per 100 patients per annum was examined. It was reported that the rate for those with severe haemophilia A was 80 per 100 compared with 50 and 35 for moderate and mild severity haemophilia A.

2.6.4 Deaths

There was an increasing number of deaths during the 1980-1994 with the rise being largely due to HIV and HCV. During the study period there were a total of 53 deaths of haemophilia A. Nevertheless, the mortality trends are similar to those for larger populations (Darby SC et al, 1995; Darby SC et al, 1997). The number of deaths from acute bleeds remained constant over the study period while they increased markedly for those with HIV, and were beginning to increase due to HCV.

2.7 Economics of Haemophilia

Haemophilia is a disorder of special economic interest, because care is both expensive and life long (Schram W, Berger K, 2003). Haemophilia is a rare disease (0.006% of total population in developed countries) and each patient must be managed by an individualised algorithms. It was reported that in the countries with the highest gross

national product (GNP), adequate haemophilia care requires 2-3 times the health resources available for the average citizen. However, data from some countries showed that considerable percentages of patients use no clotting factors at all. In the UK Rizza et al (2001) reported that in any one year 15 % of severely affected patients apparently did not receive replacement therapy. Similarly, US data from 1998 shows that 23% of patients use no clotting factors at all, 48% of FVIII is used for patients with any kind of prophylaxis (Evatt B, 2002).

Factor replacement therapy in haemophilia is believed to account for 50 – 80% and in some reports up to 93% of the total cost of the haemophilia care (Ross-Degnan D et al, 1995; Smit SP et al, 1996). Over the last decade the use of clotting factor concentrates in developed countries has risen sharply. This increase is because of clotting factors of availability of high quality and safety. Patient demand has augmented the prophylactic use of factor concentrates. clinical studies and analysis of the quality of life of haemophilia patients have shown significant improvement in outcomes (e.g. avoidance of joint and other bleeding and reduced disability) and better quality of life for patients treated prophylactically (Lovqvist et al, 1997; Molho P, Rolland N, Lebrun T et al, 2000; Nilsson IM et al, 1992; van den Berg HM et al, 2001; Royal S, Schram W, Berntorp E et al, forthcoming; Miners AH et al, 1999). However, those improvements were attained at a significant cost. Few studied have examined the relationship of cost and effectiveness. A US study reported cost-effectiveness as US\$ 1,400 per additional joint bleed avoided and a UK study analysing the cost-effectiveness of switching to prophylaxis reported cost of US\$ 900 per averted bleed (Smith PS et al, 1996; Miners AH, Sabin CA, Tolley KH, Lee CA, 1998).

The prices of concentrates fluctuate significantly in relation to many factors. The distribution systems, the number of intermediaries, the custom duties and the state regulation controlling the product import are among the recognised factors. The current selling prices vary tremendously from one country to another. For example, as of April 1996 the price per IU ranged from US 0.20 cents for intermediate purity to \$1.0 for recombinant (WFH, 2001). In the UK Lee et al (1997) reported that while intermediate

purity plasma clotting factor cost 32 pence per unit and is exempted from value added tax, recombinant cost 52 pence per unit and is liable to 17.7% VAT.

2.7.1 Global FVIII concentrate consumption

The majority of people with Haemophilia in the world have inadequate care (Jones P, 1995). Limitations of financial resources are the foremost reason for inadequate haemophilia care in developing countries (Chandy M, 1995; Kar A, Potnis-Lele M, 2001; Srivastava A, 1998; Srivastava A et al, 1998). However, the survival of patients with haemophilia A can increase sharply with the incremental increases of clotting factor usage (Evatt BL, 2002; Evatt BL, Robillard L, 2000).

The Marketing Research Bureau (MRB), an independent market research firm specialized in the field of human blood and plasma products, has been tracking plasma-derived and recombinant FVIII products on a world wide basis since 1974. MRB provides syndicated reports for the FVIII concentrate market estimating the annual units sold and the revenue for FVIII concentrates at the country level based on industry and government interviews. In 2002 the MRB reported that production of plasma-derived factor VIII has climbed about 60% in the last 18 years (from 1.3 billion to 2.1 billion IUs) as a result of fractionation. Moreover, the introduction of recombinant factor VIII has dramatically increased the quantity of FVIII available to haemophilia patients. Today, recombinant factor VIII represents roughly 42% of the quantity available to haemophilia patients. Almost all the recombinant concentrate (88%) is sold in North America and Europe.

Plasma-derived factor VIII concentrate is now increasingly used in emerging markets (South America, Middle East and Asia Pacific) where access to therapy becomes easier (MRB 2002). Factor VIII usage has been multiplied by a factor of seven between 1990 and 2000 in South America, by a factor of nine in the Middle East and more than doubled in Asia & the Pacific.

In a recent study of FVIII concentrate consumption in 110 countries it has been found that there is a clear correlation between the availability of FVIII concentrates for a country and its economic capacity (Stonebraker JS, Amand RE, Nagle AJ, 2003). For example, countries with the lowest gross national product (GNP) per capita are the least likely to establish health-care programmes for patients with haemophilia. Indexes were developed to estimate the level of FVIII concentrate consumption and economic capacity for each of the 110 countries. This has demonstrated that despite limited economic capacities, a number of countries are consuming more FVIII concentrate units per capita than expected. This latter findings, agree with the conclusion reached by Evatt and Robillard (2000) that even for countries with economic challenges, modest spending on haemophilia care can considerably improve the level of haemophilia care.

2.7.2 Clotting factor consumption in the United Kingdom

In the United Kingdom, concentrates of FVIII have been available since the 1960s (Rizza CR, Spooner RJD, Giangrande PLF, 2001). Commercial FVIII concentrates became available in the UK from the early 1970s. At first, these products were supplied free of charge but budgets were devolved to individual centres in England and Wales in 1993, which offers a choice of products. All haemophilia centres in the UK now have devolved budgets that allow choice of a wider range of products. In the UK the choice of clotting factors is determined by the individual physician, who is also responsible for purchasing concentrates for use at home as well as at hospital (Rizza CR, Spooner RJD, Giangrande PLF, 2001).

The use of concentrate in the United Kingdom has been growing significantly. In a study of treatment of haemophilia in the UK, covering the period 1981-1996, Rizza CA et al (2001) reported that there had been a consistent rise each year of approximately 10 % in the usage of FVII. A total of 63.2 million of FVIII were used in 1981 to treat haemophilia patients but the consumption rose to 149.7 million IUs by 1996. Treatment with recombinant FVIII was launched in 1994, and by 1996 16% of FVIII used was recombinants.

For reasons of infection safety recombinant FVIII is the treatment of choice (UKHCDO, 1997). However, genetically engineered FVIII costs more than twice as much as intermediate purity FVIII. In one UK centre it was reported that where the median annual use of concentrate of an adult is 72 000 units, the annual cost per patients would be £2300 for intermediate purity plasma derived concentrate but £4400(including VAT) for recombinant FVIII (Lee CA, Sabin CA, Miners AH, 1997).

Changes in treatment policy, particularly the introduction of prophylaxis for children, have big impact on haemophilia cost. Studies showed that shifting from on demand treatment to prophylaxis requires a fourfold increase in clotting factors use (Nilsson IM et al, 1992; Allan J-P, 1979). In a comprehensive care centre, study of the changing pattern of FVIII and factor (FIX) concentrates usage, between 1980 and 1994, shown that dramatic increases in the clotting factor has largely been due to the introduction of prophylactic regimens(Miners AH et al,1998). Also, Savidge GF (1995) estimated that the additional clotting factor required for a patient with severe haemophilia A weighing 30 kg to changing from on-demand to a prophylaxis regime costs £10,560 to £29,700 per annum, depending on the purity of product used.

Sterilization of concentrates has added considerably to the cost of treatment. Also, it is reported that patients with end stage AIDS consume upwards of 50% more clotting factor than when they are asymptomatic (Kennelly J, 1995). With the advent of antiretroviral therapy (ART) the cost of drug treatment increases, as duration of life will add to the costs of caring for these patients. Furthermore, individuals infected with HCV if the condition progress to liver disease increased amount of factor VIII is needed when liver.

3 Chapter III: Aim and objectives

3.1 Aim

To examine the consumption of Factor VIII (FVIII) concentrates over time.

3.2 Objectives:

3.2.1 To examine historical trends of FVIII consumption and its monthly variability.

3.2.2 To examine individual patients' consumption in order to assess the influence on further consumption of:

- severity of the condition
- prophylactic use
- surgical use
- immune tolerance treatment of FVIII inhibitors

4 Chapter IV: Methodology

4.1 Study design

Consumption of factor VIII (FVIII) concentrate in the Scottish haemophiliacs was examined using:

- Data on total monthly use of FVIII collected in the Protein Fractionation Centre (PFC, Edinburgh, and UK) between April 1989 and March 2003. In the PFC-collected data the year starts in April and ends in March next year.
- Individual data on patients from the Haemophilia Centre database (Haemophilia and thrombosis Centre, Royal infirmary, Edinburgh) between April 1989 and December 2003.

4.1.1 Study populations

- For the total monthly FVIII consumption the population was that covered by all haemophilia centres in Scotland reporting to the PFC. This covers all haemophilia patients in Scotland.
- For data collected from the Edinburgh Haemophilia Centre; the population was all individuals with haemophilia A, unspecified haemophilia A, and von Will brand's Disease (vWD) and were registered at the Haemophilia Centre. Patients with von Willebrand disease were included in the population to evaluate the influence of those individuals on total FVIII consumption. The Edinburgh centre deals with all haemophilia patients in the South-East of Scotland and covers approximately 20 % of all patients in Scotland.

4.2 Data collection

The data on the factor consumption was obtained from the following sources:

1. Protein Fractionation Centre: Protein Fractionation Centre (PFC, Edinburgh) is the manufacturing division of the Scottish National Blood Transfusion Service (SNBTS). Founded in early 1970's, the centre provides a range of fractionated plasma products and related services to the UK NHS and commercial and non profits organisations world-wide.

Each haemophilia centre in Scotland collects monthly data on factor usage on special forms (Monthly Return, PFC), that are then sent to the centre. The information is then stored both as paper document and on a database. The information collected from the returned records includes centre name, month, year, amount and type of product amount issued.

Data on monthly clotting factor use between April 1989 to March 2003 was obtained in Microsoft excel spreadsheets from the Product Services Manager at the PFC. Products were classified as either plasma-derived or recombinant. Similarly, centres were categorised as West and East Coasts of Scotland. This categorisation was made for administrative purposes, as there are two directors responsible for haemophilia care in those two areas. Moreover, the clotting factors are given in total quotas for both areas, which are then distributed (purchased) to (by) other centres within the area. For the East Coast the products are distributed by the Edinburgh Haemophilia Centre, whilst the Glasgow Haemophilia Centre distributes to the West.

Haemophilia Centres which its data were obtained were as follows:

East Coast: Edinburgh, Dundee, Aberdeen, Ninewell, Raigmore

West Coast: Glasgow, Yorkhill, Dumfries and Galway.

2. The Haemophilia Centre Database in Edinburgh Royal infirmary

The database contains data on patients on hospital and home treatment. For those patients on home treatment, the data are collected on a home treatment record, which is then returned monthly to the haemophilia centre. Data on patients who received their treatment in hospital are collected by the haemophilia nurse in a

special record. This information is then entered and stored on the haemophilia database. The information collected from patients on hospital treatment includes the date of birth (DOB), date and time of infusion, reason for infusion, location of bleeds, type and amount of treatment administered by the manufacturer, number of vials used and batch number. Information on diagnosis and weights of each patient was obtained from the data manager of the centre. Dates of death (DOD) were obtained from the haemophilia doctor. For the purposes of this study, diagnosis was categorised into severe, other haemophilia A, and vWD (other haemophilia A includes mild, moderate, acquired and unspecified). Products were categorised as plasma-derived and recombinant. FVIII usage was categorised as either on-demand (this includes spontaneous and trauma bleedings), surgical, dental, procedure, physiotherapy or prophylaxis.

Apart from the reason for infusion being omitted, data of patients on home treatment includes similar information to the hospital.

4.3 Data analysis

4.3.1 Data cleaning, checking data quality.

During the course of our study, we were repeatedly told that data cleaning takes more time than the actual or definitive analysis. This was never clear to me when I started working on this project. Moreover, it appears that data collection (even if stored in an electronic format) takes a similar significant amount of time! Below is a brief description of the process of data cleaning and checking of validity and consistency.

The data from PFC was obtained in 14 excel sheets, each of which covers one year's data and contains the information for the nine haemophilia centres in Scotland in addition to that of Northern Ireland. This information includes the monthly amount of each of 25 commercial products (covering FVIII, FIX and other replacement products) for each centre. Each excel sheet contains approximately 1,000 line of data, but in a format that did not allow straightforward transfer to a statistical package. Text and data were interspaced, and

the factor VIII products were entered with inconsistent spelling and use of upper and lower case, requiring substantial editing. Three diskettes were needed to collect this data.

Out of those PFC data, information concerning FVIII usage was extracted in new modified spreadsheets. Later those sheets were collapsed into a single spreadsheet that included the monthly usage of eight commercial clotting factors. The data was modified into an 'analysable' format. For example, the month was recoded to number of month since the start of the study from the original text in the 14 of the spreadsheets. This yielded 168 months data for each of the nine centres that consume eight types of FVIII products.

The overall quality of PFC data was excellent apart from some duplication in the reported usage of the West Coast use. In some periods figures had been reported from Glasgow that included FVIII that issued to Yorkhill hospital although the latter were also reported. Clarification (and correction) of this over-reporting was only obtained in August 2003.

In contrast, the information on individual patients' consumption, stored in a database, was less complicated to handle. There were huge amounts of raw information, but annual tables of any variable of interest could be extracted by the data manger. Nevertheless, the data again needed extra cleaning, such as excluding patients with other coagulation disorders and had to be put into a proper format and transferred to SPSS for analysis.

Data for both PFC and individual patients' usage was analysed using SPSS 11.0 for Windows.

4.4 Ethical approval and data protection

This project is part of an internal NHS audit of the haemophilia which makes no requirement for ethical approval. To protect patients' privacy identifiers were separated from the data.

5 Chapter V: Results

5.1 FVIII concentrates consumption in Scottish haemophiliacs 1989-2003

5.1.1 Trends in FVIII concentrate consumption

The total amount of FVIII used between 1989 and 2003 in Scotland is shown in figure 1. In 1989/1990 a total of 7.6 million IU of FVIII were used. By 2002/2003 this had increased to 26.7 million IUs, an increase of over 350 %. This gives Scotland an increase in FVIII usage of 9.6 % each year. This trend has almost identical increase rate to the rest of the UK trend, where clotting factors consumption had been reported to rise approximately by 10% each year (Rizza CR, Spooner RJ, Giangrnde PL, 2001).

When divided into East and West coast areas as defined in chapter IV, figure 2 shows that an almost identical trend pattern for total consumption for both areas until 1998. From 1999 the consumption in the East witnessed a very sharp increase. However, the consumption in the West, apart from a sharp decrease in 99/00 remained almost static. These findings on area consumption showed that during the 14-year period the annual FVIII consumption in the East Coast grew by almost 500 % (from 3.7 million IUs in 1989 to 18 million IUs in 2003), whereas the West coast witnessed an increase of only 300% (from almost 4 million IUs in 1989 to 11.7 million IUs in 2003). There were slight decreases in consumption in 1998 and 2000 in the East Coast, and in 1999 in the West. For the East these were partly explained by a decrease in surgical and immune tolerance used in those years (Dennis R, personal communication 2003).

Fig.3 shows the trend by type of factors used. The use of recombinant factors has sharply grown over 6200 % since 1995. In contrast, since 1995 the consumption of plasma-derived factors has sharply declined to reach just over 10 % in 2003 of total FVIII consumption. However an increase in plasma-derived concentrates was clearly observed for the years

2000 to 2002, This increase in plasma-derived factors corresponded with a shortage in supply of recombinant factors, where some patients had to go back on to plasma-derived products. The shortage was because of the close down of Bayer's manufacturing plant pending major changes because of unspecified irregularities. This caused extreme shortages as Bayer has approximately half the market share in Europe (Pelley J, personal communication 2003).

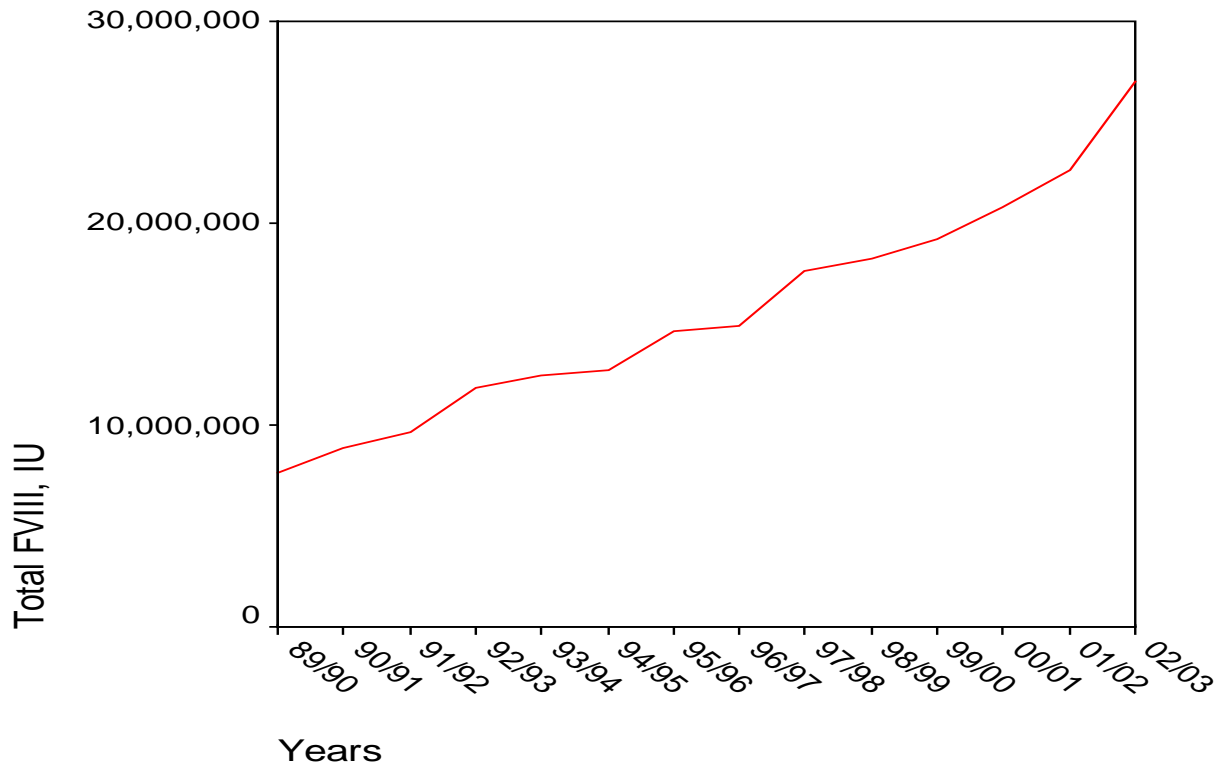


Figure 1. Historical trend in FVIII consumption, Scotland 1989-2003. (NB: all time divisions are complete years, starts in April and ends in March next year)

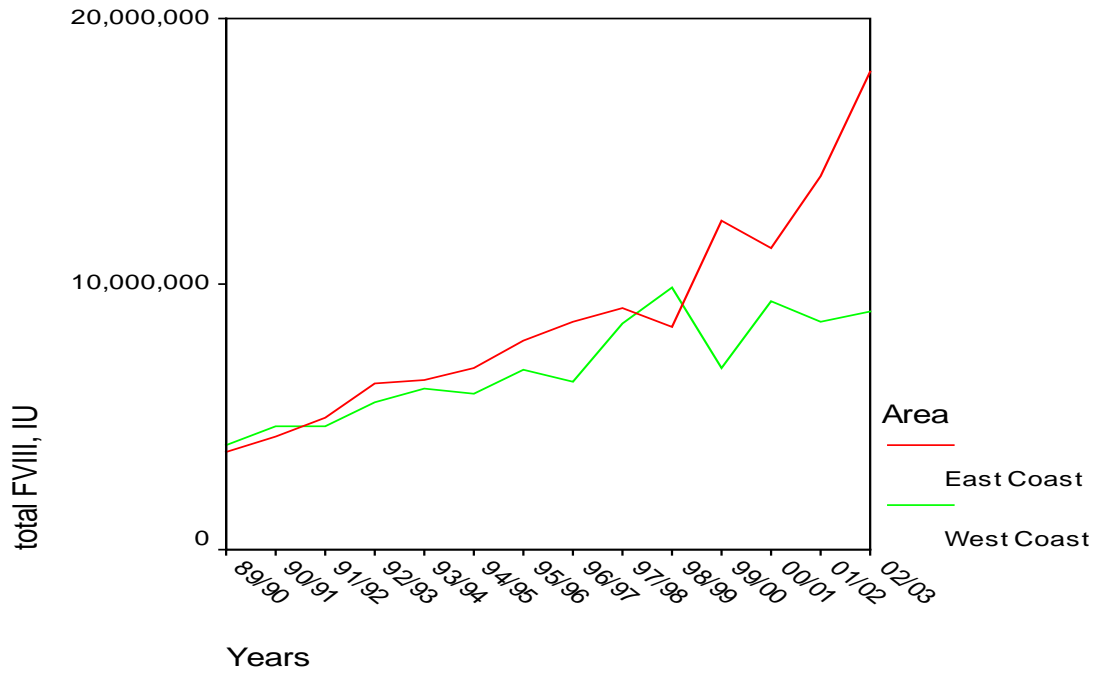


Figure 2. Trends in FVIII consumption subdivided by area, Scotland 1989-2003. (NB: all time divisions are complete years, starts in April and ends in March next year)

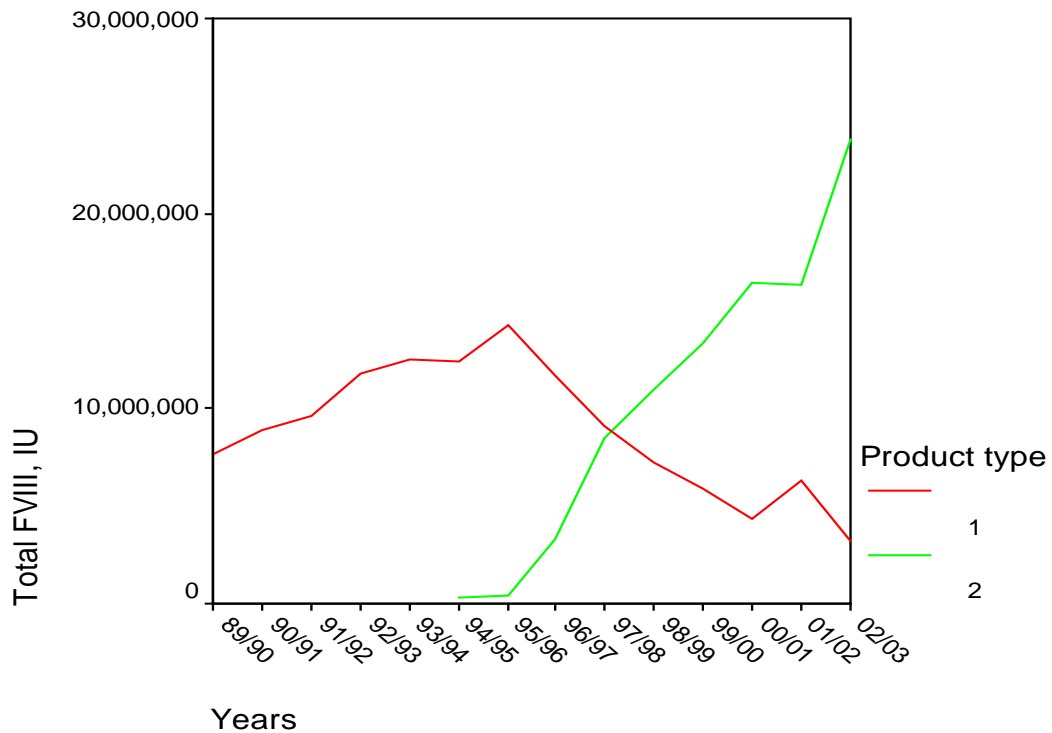


Figure 3. Trends in FVIII consumption by product type, Scotland 1989-2003. (NB: all time divisions are complete years, starts in April and ends in March next year)

5.1.2 The variability of FVIII consumption

To examine the variability of total monthly FVIII consumption, two models were developed. The first (model 1) included the total monthly amount for the whole period of the study (1989-2003) and the second (model 2) for the period from the start of use of recombinant factor concentrates until the end of the study period only. The latter model was built, as there is preference in use of recombinant clotting factors over the plasma-derived ones.

Models were, also built to examine the variability of clotting factor consumption for each area (East & West Coast) after the start of recombinant factors.

Regression methods (curve estimation) were conducted (figure 4). Different curve fitting were used (linear and exponential). R2 was derived each - this is the percentage of variation explained by the model.

The residuals were checked with standard diagnostic methods and were found to be approximately normally distributed. (Figures 5 and 6). Outliers were set as variables with standard deviation of more than 3. The models were checked by repeating the fitting procedure after removal of the outliers. Models 1 and 2 were unaffected. (Only the original analysis is reported.) However, for the area models the outliers have influenced both the coefficient and the residual statistics. As the interest of the study was the variation in monthly usage, the outliers were not excluded and the original analysis is reported.

Dependent variable: The dependent variable was the total amount of monthly use. For the area models the monthly amount corresponds to that of the area after the start of the recombinant products.

Independent variable: The independent variable was the months within the period under study (168 months for model 1; and 108 months for model 2 and area models).

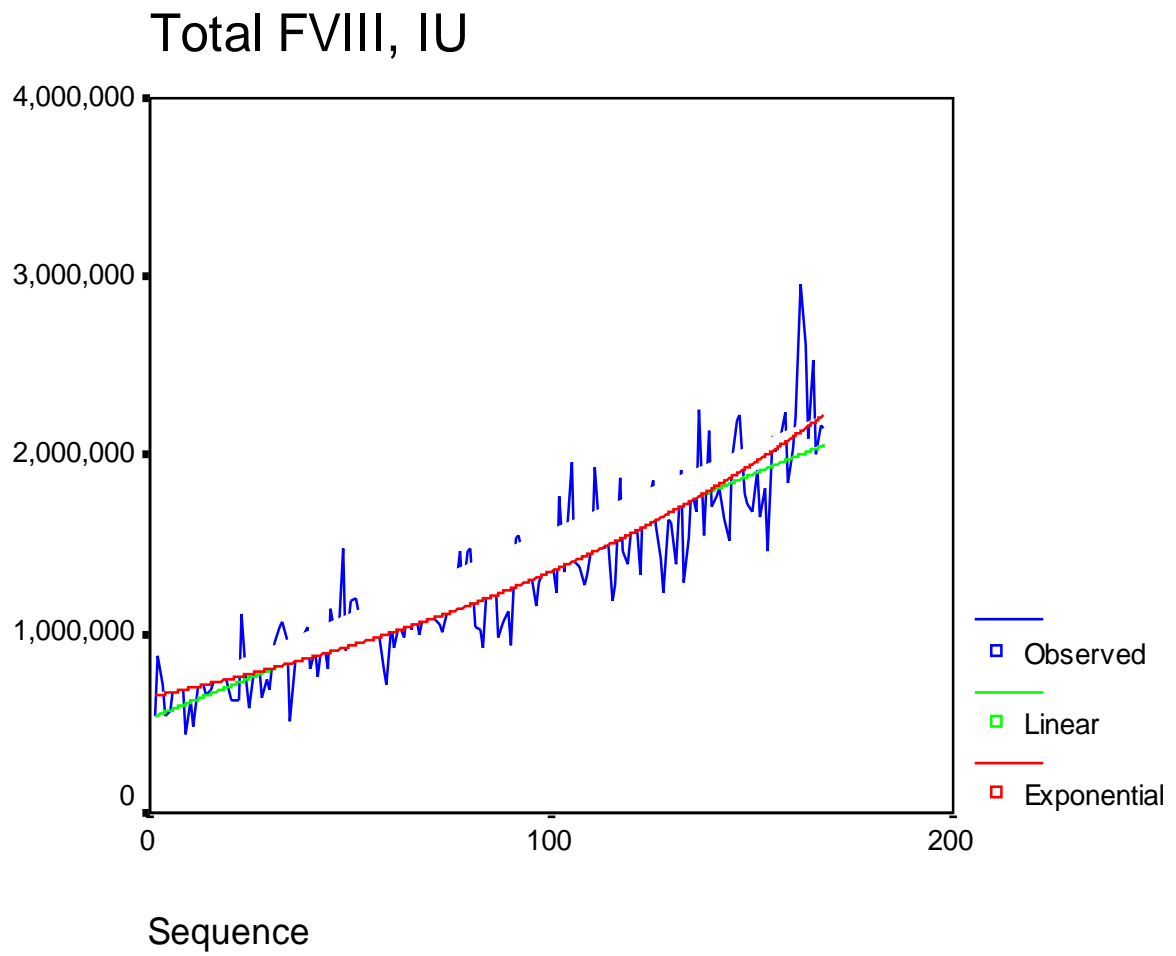


Figure 4. Estimation for both exponential and linear models. The months cover the whole study period (168 months).

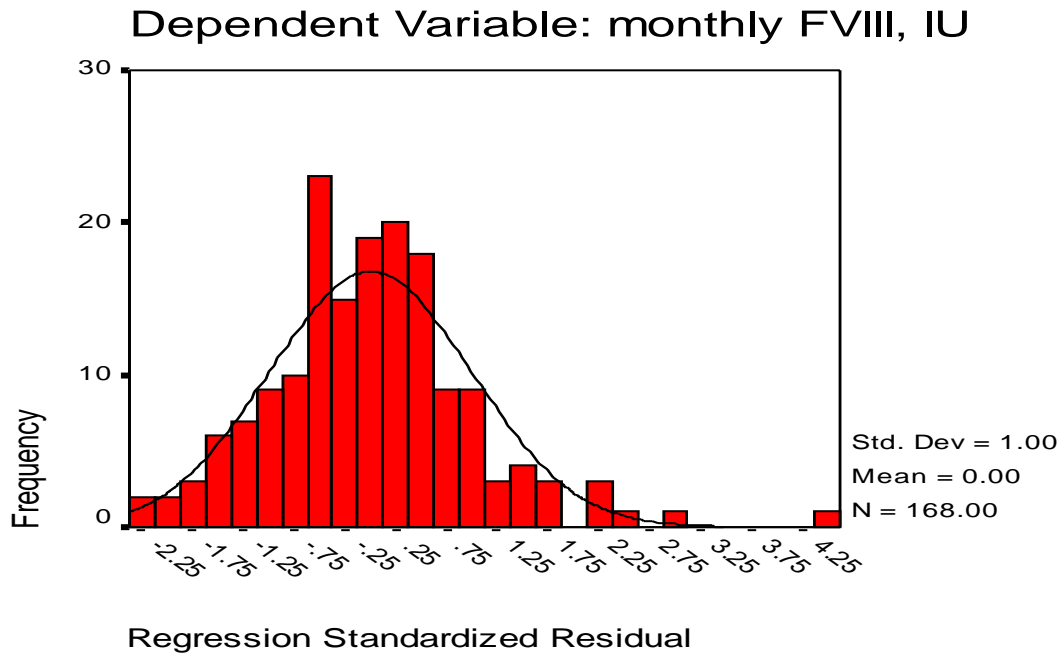


Figure 5. Distribution of residuals for the linear model, showing one outlier.

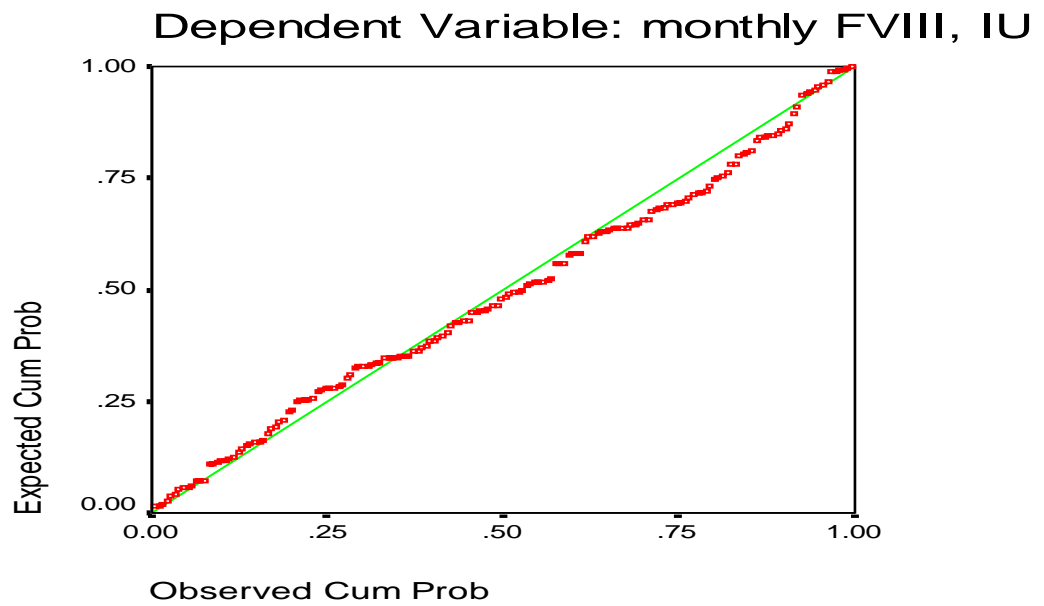


Figure 6. Normal probability plot of regression standardized residuals.

5.1.2.1 Regression statistics

For all models, the total monthly consumption was found to follow an exponential trend. Figure 4 shows the result when the monthly consumption for the whole period was analysed. However, a linear trend was also reasonable with no major difference from the exponential one. Although both curve estimates are reported, it would not be expected that demand would continue to follow an exponential trend. For that reason and for simplicity too, the linear model could be chosen for projected estimates of variability of demand.

For the exponential model the R^2 was 0.83, while for the linear estimates the R^2 was 0.81. The regression coefficients, i.e. the expected monthly change in FVIII were 15,000 and 9,100 IUs the exponential and linear respectively. Substantial difference was noticeable in the regression coefficients. This is because while the increase in the linear model is absolute that for the exponential model is proportional.

Table 2, shows the result of the linear regression for both model 1 and model 2. For model 1, based on monthly consumption for the whole 14-year period, the R^2 was 0.81. For model 2, after the start of the recombinant clotting factors, the R^2 was 0.68. There were small differences in the monthly variation of clotting factor usage between the two models. As the distributions are approximately Normal, on 95 % of occasions the monthly consumption will be within two standard deviations (2 SD) of the trend line, corresponding to 0.42 million and 0.46 million IUs of FVIII for model 1 and model 2 respectively.

When examined for each area separately, the variations in the monthly consumption were found to differ between the two areas (Table 3). In the East coast the monthly variation of FVIII consumption within one SD was 0.21 million whereas that for the West coast increase was 0.16 million IUs. From the trend (figure 2) the clotting factor consumption was lower in the West coast; this probably explains the smaller variation seen in this area.

Table 2. Results of linear regression analysis: variation in monthly consumption of FVIII. Regression Coefficients and Residuals SD are in million IU.

Variable	Regression coefficient* (95% CI)	P value	Residuals SD
Model 1: the whole study period(168 months) $R^2 = 0.81$			
Month	0.0091 (0.0084 to 0.0098)	<0.001	0.21
Model 2: start of the recombinant factor (108 months) $R^2 = 0.68$			
Month	0.011 (0.0094 to 0.012)	<0.001	0.23

*Coefficients represent expected change in FVIII amount for a given change in the months (e.g. from the first month to the second month).

Table 3. Results of linear regression analysis: variation in monthly consumption of FVIII for East and West Coasts. Regression Coefficients and Residuals SD are in million IU.

Variable	Regression coefficient (95% CI)	P value	Residuals SD
Model 1: East coast monthly variability(108 months) $R^2 = 0.60$			
Month	0.0082(0.0070 to 0.0095)	<0.001	0.21
Model 2: West coast monthly variability(108 months) $R^2 = 0.45$			
Month	0.0025(0.0016 to 0.0035)	<0.001	0.16

5.2 FVIII usage by individual patients, Edinburgh Haemophilia Centre 1989 - 2002.

5.2.1 Patient details

Details of total hospital and home treated patients between 1989 and 2003 are shown in table 4. These figures represent the number of patients where a clotting diagnosis for haemophilia A or vWD is available. Others factors and fields which have been left blank are factors that have been excluded. Almost all patients (165/166) received treatment at hospital at some point during the 14-year period. 42 % of patients had severe haemophilia. During the study period there were 31 births and 21 deaths. Figure 7 shows the number of patients who received at least 1 IU of clotting factor between 1989 and 2003. The median age of the patients in 1989 was 42 (range 16 - 85) years; by 2003 this had increased to 50 (range 7 - 86) years.

5.2.2 Consumption by diagnosis

The total amount of FVIII used in the Edinburgh haemophilia centre between 1980 and 2002 is shown in figure 8. Increases in FVIII were seen irrespective of the severity of disorder or diagnosis (vWD). However, a sharp decline in factor usage, for all diagnosis, was observed during 1998. According to the haemophilia doctor, this due to the decrease in surgical use for that year (figure 11) (Dennis R, personal communication 2003). However, this decline also corresponds to shortage of the recombinant products mentioned earlier.

For the patients with severe haemophilia A, there was a sharp increase between 1989 and 2003 (2.6 million IUs and almost 8 million IUs). When calculated as a percentage of the total usage for all types of coagulation diagnosis, usage by severe haemophiliacs accounted for almost 75% in 1989 and 85% in 2003. However, the noticeable declines observed in 1998 and 2001 commented upon earlier, were also apparent here. Those declines were also

evident in the general graph of total clotting factor usage for the East coast (figure 2), indicating that FVIII consumption on the East coast was greatly influenced by the Edinburgh usage.

Similarly, for the combined group of patients, other haemophilia A, the consumption was steadily increasing between 1989 and 2002 (0.6 up to 2 million IU respectively). Interestingly, the 1998 and 2001 declines seen in usage of patients with severe haemophilia A, is also evident here. These declines could also be, (though to a lesser extent) attributed to the decrease in certain categories in the reasons for infusion in their treatment- mainly the surgical and prophylactic uses.

Total FVIII consumption for people with vWD showed a small absolute increase during the study period (from 0.08 – 0.4 million IU).

Table 4. Edinburgh Haemophilia Centre Patients statistics, 1989-2003.

Diagnosis	No.(%)	Births	Deaths	Immuno -tolerance status
Severe haemophilia A	70(42)	14	14	10
Other haemophilia A(mild, moderate, Acquired & unspecified)	67(40)	16	7	4
vWD	29(18)	1	0	0
Total	166(100)	31	21	14

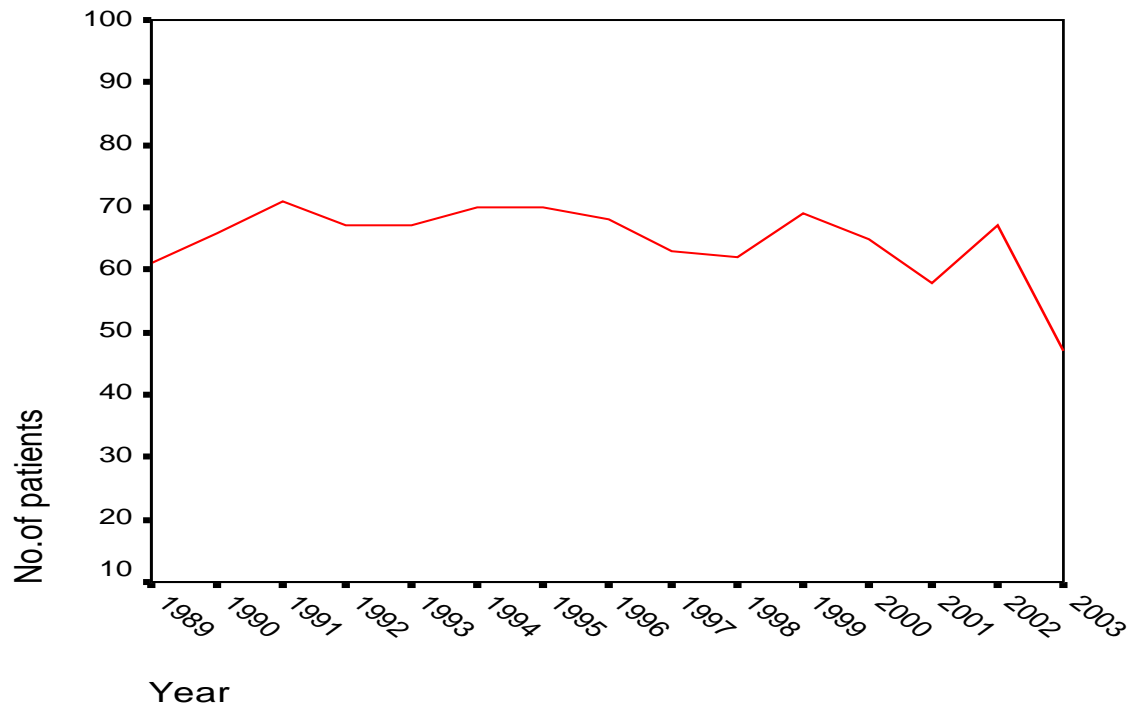


Figure 7. Annual no of patients treated at Edinburgh Haemophilia centre, 1989-2003(NB: in 1989 data for 9 months only and 3 months respectively).

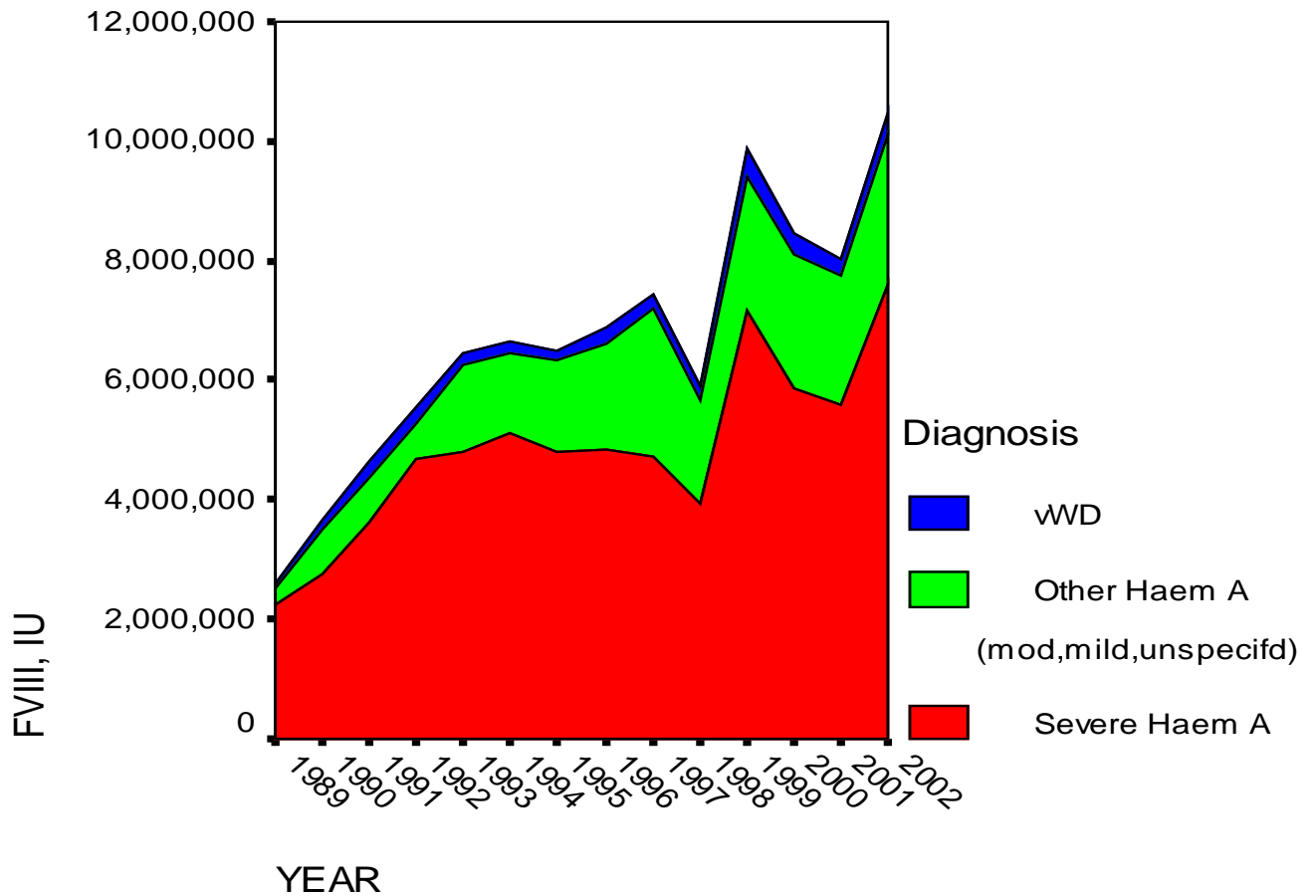


Figure 8. Total FVIII consumption by diagnosis for both hospital and home treated patients, Edinburgh Haemophilia centre 1989-2002(NB: in 1989 data for 9 months only).

5.2.3 Hospital Vs Home treatment

Total FVIII consumption for patients on hospital treatment (figure 9), irrespective of the severity of Haemophilia A, experienced a sharp increase between 1989 and 1993 (from 2 to almost 5 million IUs respectively). The clotting factor consumption continued to decline from 1994 up to 1998 whereupon it started to fluctuate. Decreased levels of FVIII consumption seen in 1998 and 2001 (slightly over 1 million IUs for each). The reasons behind those declines were different. While in 1998 there was a noticeable decrease in surgical usage of FVIII; in 2001 there was a decrease in the prophylactic usage (figure 11).

In contrast, trends in total clotting factor consumption for patients on home treatment, irrespective of the severity of the disorder, continued to sharply increase until the end of the study period (figure 10). In comparison, in 1989 patients with severe haemophilia A on home treatment used 1.0 million while patients with severe haemophilia on hospital treatment used nearly 1.5 million IUs of FVIII. By 2002 FVIII usage of home treated patients had increased to over 6.0 million while that of hospital treated one had increased to only 2.5 million IUs. This resulted in an increase of over 600% for home usage and only 60 % for hospital usage. When calculated as percentages of the total FVIII consumption, the home treatment usage had risen from 40 % in 1989 to over 70% in 2003 reflecting that increasing number of patients was taking treatment at home.

As expected, the clotting factor usage for the combined group of patients (other haemophilia A), for both home and hospital was fluctuating. Patients with mild and moderate haemophilia A can go for many years without treatment.

There were no significant differences between hospital and home usage for people with vWD. However, the consumption was mainly by in hospital, probably due the needs of patients with severe vWD.

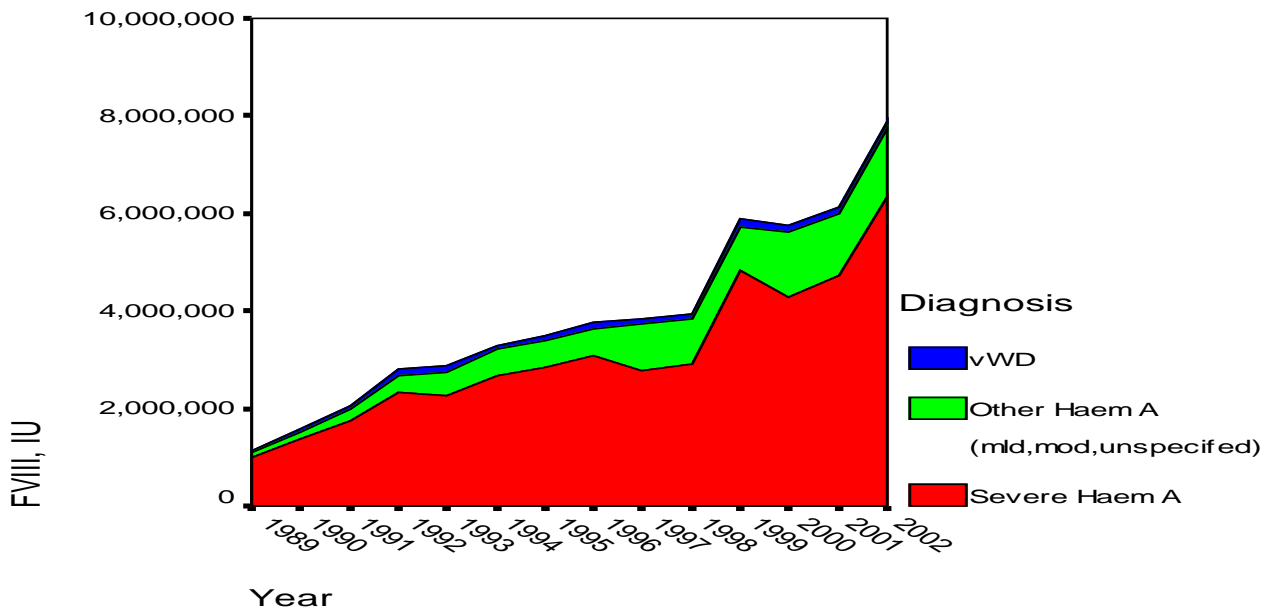
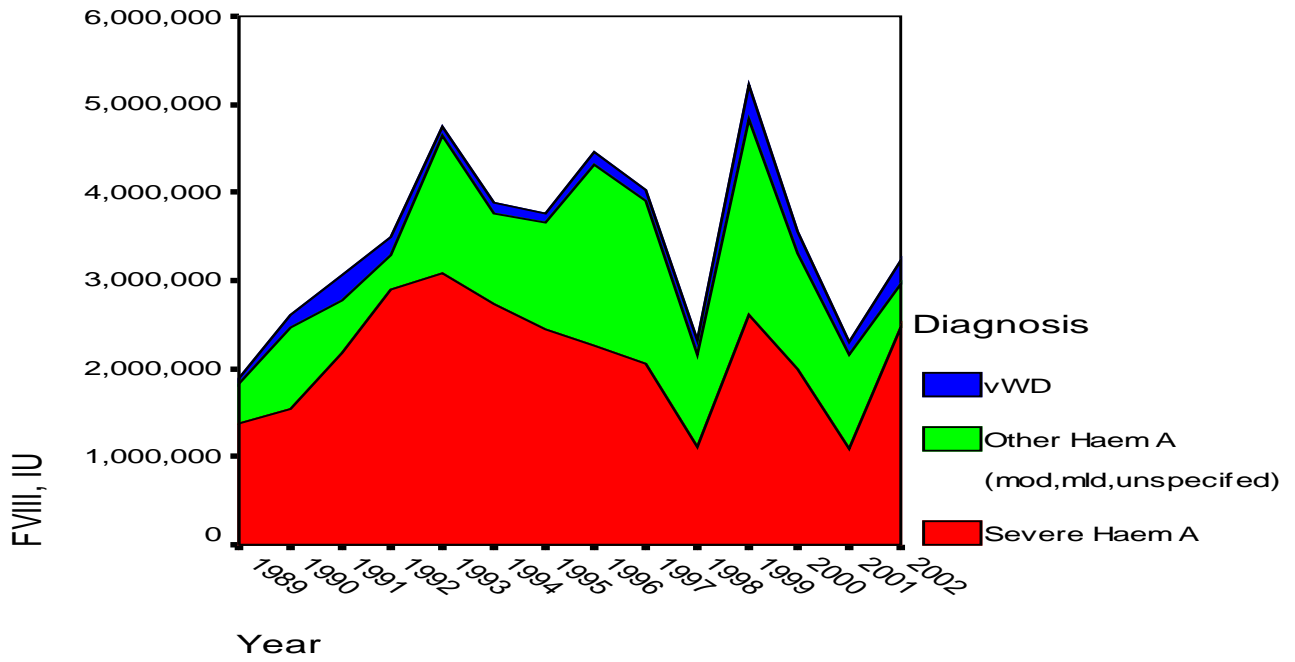


Figure 9. Total FVIII consumption by diagnosis for hospital treated patients, Edinburgh Haemophilia centre 1989-2002(NB: in 1989 data for 9 months only).

Figure 10. Total FVIII consumption by diagnosis for home treated patients, Edinburgh Haemophilia centre 1989-2002(NB: in 1989 data for 9 months only).

5.2.4 Consumption by reasons for infusion

Figure 11 shows the clotting factor usage and the reasons for treatment. These results were only for patients who were treated in hospital, as data concerning reasons of infusion for home treated patients was not available during the time of this work. Apart from sharp increases in the early 1990's, the clotting factor consumed for spontaneous and trauma bleeding, i.e. on demand treatment, considerably decreased. In 1993 2.8 million IUs of FVIII were used by this reason, but by 2002 this had come down to 1.5 million IUs (over 50% decreases). This could be explained in part by the increased use of prophylactic treatment, which is evident in figure 11. When calculated as a proportion of the total amount of clotting factor used in hospital, on-demand treatment had declined from just over 70 % in 1989 to less than 50% in 2002. It is not known, however, due to lack of data if on-demand treatment has also declined in those treated at home, as home treatment will also be for spontaneous or traumatic bleeds.

The total amount of FVIII used for prophylaxis between 1989 and 1999 had increased by over 850 % (0.2 and 1.7 million IUs respectively). The apparent fall in the prophylactic usage between 1999 and 2002 may be because home treatment had no reasons for use recorded, but use for prophylaxis would certainly be a substantial amount. With the lack of data on home infusion, it would not be easy to demonstrate any relevant inference on whether the decline of prophylactic usage was due to this lack of data or decreases over time and stability in the amount of FVIII used in prophylaxis. However it is generally believed that prophylactic use continued to increase after 1999.

With the increase in life expectancy of haemophiliacs it is predictable that the need for surgical resources would increase and hence an increase in need for clotting factors. In this study the median age of patients had increased from 42 years in 1989 to 50 years in 2002. Throughout the 14-year period, in all years but one the surgical use of FVIII continued to increase. In 1989 slightly over 0.1 million IUs of clotting were used for

surgical reasons. By 2002 this had increased to 0.6 million IUs. The sharp decline seen in 1998 in FVIII amount (0.06 million IUs) used by this group could possibly be attributed to fluctuations in the number of operations. Interestingly the 1998 decrease in surgical use of clotting factor coincides with shortage of the recombinant products. This probably patients were reluctant to use plasma-derived product. In 2002 surgical use accounted for over 20% of the total FVIII used in hospital.

The clotting factor consumption for the rest of recorded reasons such as physiotherapy, dental, minor procedures or other, was fairly constant over the study period, ranging between 0.0007 million IUs to 0.1 million IUs. However, an increasing amount of FVIII had 'missing reasons' impeded the analysis and interpretation of the results. In 1989 there were 0.2 million IU with missing reasons By 2002 this amount reached 0.7 million IU. These amounts were at some points higher than those of the surgical or prophylactic use, underlining the need for better recording.

A summary for the changes in infusion reasons between 1989 and 1999 is given in figure (12). Data for the latest year, 2002, was not used in this summary for reasons of data quality.

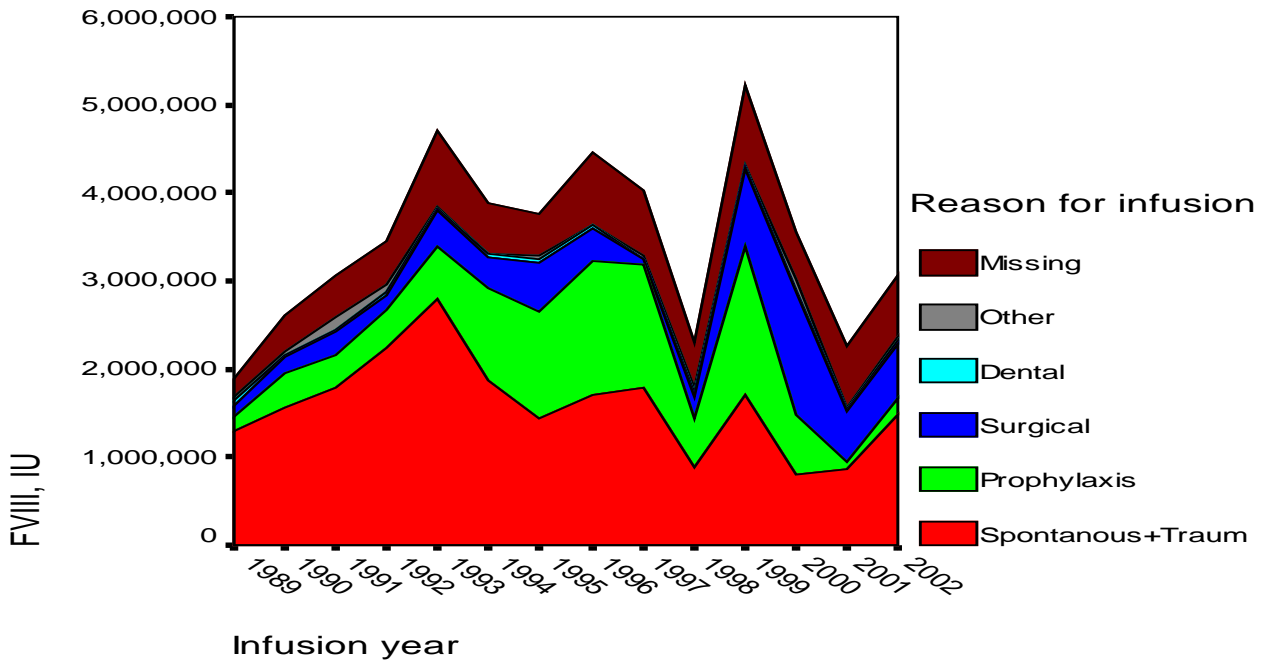


Figure 11. Total FVIII consumption by reasons for treatment for hospital treated patients, Edinburgh Haemophilia centre 1989-2002(NB: in 1989 data for 9 months only).

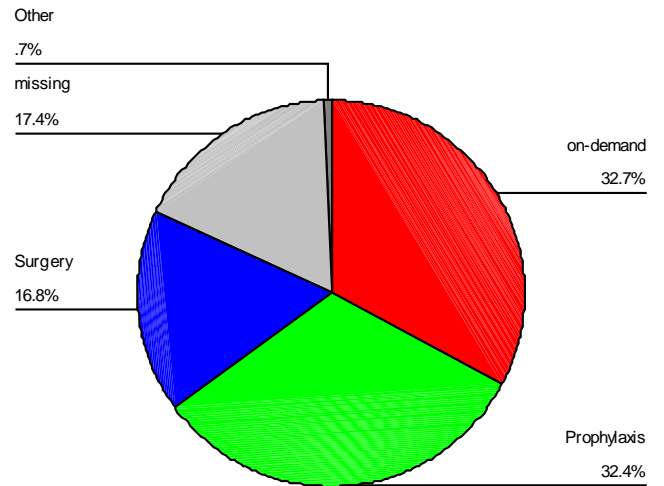
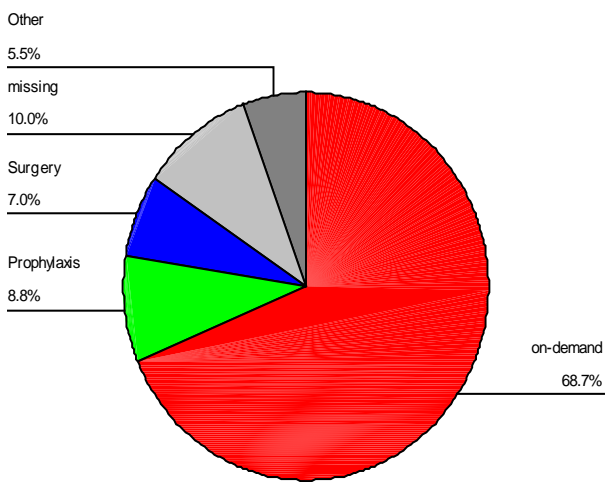


Figure 12. Reasons for FVIII infusion (% of total) in hospital treated patients, Edinburgh Haemophilia Centre 89 and 99(NB: in 1989 data for 9 months only)

5.2.5 FVIII usage by immune-tolerance group.

In this study 14 patients (< 10%) were reported to have FVIII inhibitors, very few of them being on immune tolerizing regimen. However, figure 13 show that patients with immune-tolerance status consumed a significant amount of FVIII. In 1999, almost one-quarter (2.2/8.9 million IUs) of the total factor usage for all patients with severe haemophilia was consumed by this group of patients. Discussions with the professionals at the haemophilia centre indicated that it was one heavily treated child who greatly magnified this high amount of FVIII (Ludlam, personal communication 2003). This clearly shows the impact on the trends of total FVIII consumption from individual patients.

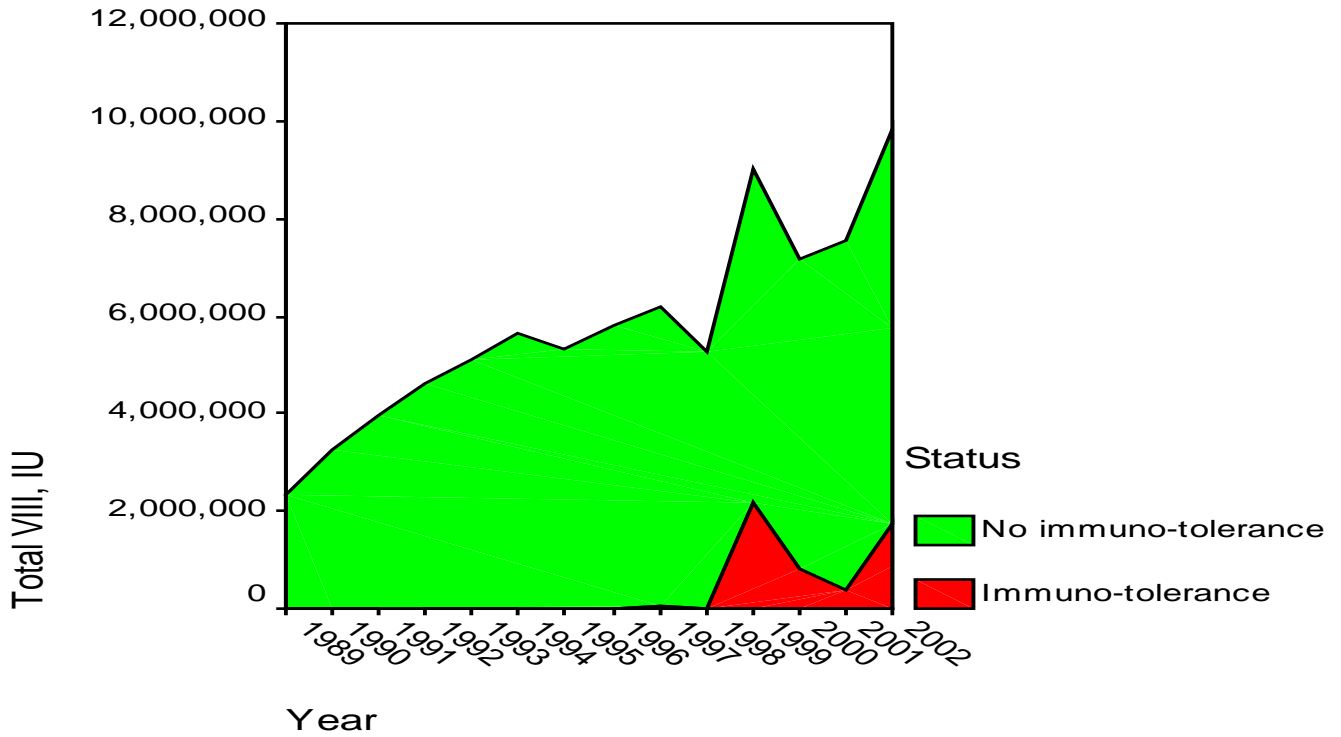


Figure 13. Total FVIII consumption by patients with immuno-tolerance compared with others treated at haemophilia centre Edinburgh 1989-2002(NB in 1989 data for 9 months only)

6 Chapter VI: Discussion

6.1 Trends in FVIII concentrate consumption in Scotland 1989-2003.

Several studies have documented increasing trends in clotting factor usage in developed countries (Miners A H, et al 1997, & Rizza CR, Spooner R J; Giangrnde P L, 2001). Availability of clotting factors of high quality and safety, improved methods of administration as well as the financial conditions in developed countries have enabled an increase in the amount of clotting factors used per patient (Schramm W, Berger K, 2003). Moreover, prophylaxis as the preferred method of treatment, especially in children, adds to the increase in use of clotting factors (Nilsson IM et al 1992, Allain J-P 1979). Rational planning and decision making for haemophilia cares needs, in addition to reliable data on demographic and clinical characteristics, consistent data on changing pattern, and variations in clotting factors usage (Ludlam CA, Lee R J, Prescott R J et al, 2000).

Since the mid nineteen seventies there have been no studies on the use of coagulation factors use in Scotland (Cash JD, Spencely M, 1976). It was found that from 1961 to 1975 the demand for fresh frozen plasma (FFP), cryoprecipitate (CP), and antihæmophilic factor (AHF) increased by seven and a half times. Patients with severe hæmophilia A received about 85% of the factor VIII issued in 1971-1974, most of which was used on demand. A patient with severe hæmophilia A on unlimited on-demand home treatment would need about 500 units of factor VII/kg body weight/year.

This study, covering the period from 1989-2003, aims to examine FVIII consumption and trends in Scottish hæmophiliacs. Scotland is considered to have a stable population and is also a moderately large population for this study (Scotland populations is 4.7 million,

census 2001). This work has shown the size of the increases in FVIII consumption between 1989 and 2003 in Scotland. In 1989/1990 a total of 7.6 million IUs of FVIII were used. By 2002/2003 this had increased to 26.7 million IUs, an increase of over 350 % (al 1997).

With this recent increase the Scottish consumption of FVIII per capita has risen from 1.5 in 1989 to 5.3 in 2003, over a three-fold increase. This figure is higher than the recently reported figures of FVIII consumption per head for USA and Australia and almost the same as Germany (Table 1). In the global comparisons of the provision of haemophilia centres and treatment conducted by the World Federation of Haemophilia, FVIII consumption per capita was 3.0 Australia, 3.4 for USA and 5.5 for Germany (WFH global survey, 2002)

As the data for the overall trend were the monthly totals, and as no demographic or clinical data were available for analysis, it may not be possible to illustrate specific reasons for this increase in the overall trend. Nevertheless, information from the literature suggests that this increase in clotting factors has been largely due to change in treatment policy (adoption of prophylactic treatment and introduction of immune tolerance regimen for patients with inhibitors). Increase in the prevalence of haemophilia and increase in life expectancy of haemophiliacs has also been influential (Ludlum CA, Lee RJ, Prescott RJ et al, 2000; Miners AH et al, 1997; Rizza CR et al, 2001). In Scotland, prior to 1980 there were noticeable small number of haemophiliacs over 60 years of age in Scotland, most likely reflecting reduced life expectancy due to bleeds in severe haemophiliacs (Ludlum CA, Lee RJ, Prescott RJ et al, 2000). By 1994 there was over three times the number of individuals living beyond the age of 60. In Scotland, too, the effect of HIV on the total number of patients, particularly with severe haemophilia A is less than in many other countries. This is because the prevalence of HIV in 1985 was 39% among those with severe haemophilia A compared with 59% for UK as a whole and approximately 90% in some other countries (Ludlam CA, Lee RJ, Prescott RJ et al, 2000). As expected, with the advent of antiretroviral therapy (ART), fewer numbers of deaths from HIV are observed (Ludlum CA, personal communication 2003). The growing numbers of elderly patients are increasing the demand for surgical resources and hence clotting factor concentrates.

Interesting findings were observed when the national trend was subdivided into area (East and West coasts) each of which displayed significant differences from the national pattern (fig 2). From the late 1990s it was the consumption in the East Coast that substantially influenced the national trend. In early 1990's the total annual usage of FVIII on the West coast was slightly greater than that of the East. But, since then, apart from a short period 1996-1998, the usage has been growing faster in the East than that of the West coast. In 1989 4.0 and 3.7 million IUs of FVIII were used, but by 2003 this had reached 11.7 and 18.0 in West and East coast respectively. Again, the scope of this project has its limitations in explaining those observed differences. Moreover, although a considerable number of comparative studies between east and west of Scotland have been done in other health issues we are unaware of any comparative data with regard to haemophilia care. But one of the inferences in explaining those differences was that there are larger numbers of patients treated on the East than on West Coast (Ludlam CA, personal communication 2003). Findings from individual patients' usage for Edinburgh Haemophilia Centre (below) may shed light on the causes behind increased FVIII consumption on the East coast of Scotland. Duplicating this work at individual centres would offer improved assessment of FVIII consumption.

The preference of recombinant clotting factor products, clearly demonstrated by a very sharp increase since their introduction (figure 3), has been supported for safety reasons (UKHCDO, 1997). However, this has its financial implications for haemophilia care. While intermediate purity plasma-derived clotting factor costs 32 pence per unit and is exempt from value added tax (VAT), recombinant FVIII costs 52 pence per unit and is liable to 17.5% VAT (Lee CA, Sabin CA, Miners AH, 1997). The answer to the question whether the recombinant factors will totally replace the plasma-derived factors will depend on many factors such as the development of new treatments, and product pricing or availability. The latter factor was clearly illustrated in this work by recombinant products being shortened by the closing down of Bayer's manufacturing plant. This led to increases in usage of plasma-derived concentrates.

6.2 The monthly variation in FVIII consumption.

As mentioned previously, many works have described the changing trends and patterns in clotting factors usage (Miners AH et al 1997; Rizza CR, Spooner RJ, Giangrnde PL, 2001), yet we are unaware of any work on variability on demands of clotting factor concentrates. Therefore, this study represents the most extensive work so far about the variations in FVIII consumption.

As stated elsewhere, the cost of providing care for haemophilia is high and rising partly because of the increasing amount of factor used per patient. Clotting factors account for a high percentage of direct cost of haemophilia care (Smith PS, Teutsch SM, Shaffer PA, Rolka H, Evatt B, 1996; Szucs TD, Offiner A, Schramm T et al, 1996; Molho P, Rolland N, Lebrun T et al, 2000; Lee CA, Sabin CA, & Miners AH, 2003). Therefore, an estimation of variability in demand for clotting factors would be of great help in rational decision making on allocation of budgets. Moreover, determination of the variability in demand provides useful estimates of over dispersion for establishing monitoring systems for factor usage. This is of great interest too for the decision-makers to track whether any possible increases fall within an acceptable level or not. In other words, what are known in industry as ‘in-control’ and ‘out of control’ processes. Statistical methods that could be used in establishing monitoring system for clotting factors usage will be described latter.

This work showed that despite substantial differences in the predicted values between the models, monthly increase in FVIII consumption fits well for both exponential and linear models (figure 4). Both models explained 81 % and 68% respectively of variability in monthly usage of clotting factor concentrates. In the exponential model, the monthly FVIII is predicted to increase by 15,000 IUs (0.74 % per month), while in the linear model the monthly predicted value is 9,100 IUs. Nonetheless, for simplicity the linear model could be chosen for projected estimates of variability of demand.

An interest of haemophilia care decision-makers in Scotland is to estimate the monthly clotting factors usage varies, and to assess whether that variation lies within an acceptable limits (in control). The results of this study (table 2) showed that 95 % of the time the monthly consumption will be within 2 SD of the trend line, corresponding to 0.42 million IUs of FVIII. However, the variation was slightly greater (2SD= 0.46 million) when the

period was limited to the time from the start of the recombinant products. For operational reasons, the latter figure would be the more useful than the former, as it is more likely that the recombinant clotting factors will replace the plasma-derived factors in the future.

Once again this work established differences between the East and West coasts of Scotland. As shown in the results chapter, the predicted a monthly change in factor VIII consumption differs substantially between the two areas (5,900 IUs, for the East and 2,700 IUs for the West). Similarly, within 2 SD the consumption in the East is expected to vary by 0.21 million for the East, while that of the West vary by 0.16 million within its trend line.

6.3 FVIII consumption by individual patients, Edinburgh Centre 1989 - 2002.

The purpose of examining individual patients' consumption was to assess further influences of severity, reasons for infusion and patients with FVIII inhibitors on the clotting factor consumption, as well as comparing hospital and home treatment usage.

Increases in FVIII were seen irrespective of the severity of disorder or diagnosis (vWD). This was quite consistent with the findings of other reports (Miners A.H., et al 1998). As expected, FVIII consumption was highest among severe haemophiliacs, as individuals with mild and to some extent moderate haemophilia A are unlikely to use significant resources. In this work FVIII usage of patients with severe haemophilia accounted for over 75% and 85% of the total usage of haemophiliacs in 1989 and 2002 respectively. Findings on reasons for infusion in this study provide interpretations for these increases in the clotting factor concentrates for hospital treatment.

Of interest is the fact that although almost every patient in this work had used the hospital resources at least once during this study period, FVIII usage of home treated patients had increased from 1.0 to over 6.0 IUs of the clotting factor, an increase of 600% during this 14-year period. Moreover, when calculated as a proportion of the total usage (home and hospital), home treatment had risen from 30% to over 70% during that period, reflecting that increasing number of patients were taking treatment at home. Although lack of data on

reasons for home treatment had greatly impeded the analysis, it was still possible to assume that most patients on home treatment were on prophylactic regimen. Introduction of prophylactic treatment policy has been reported to remarkably decrease the rate of acute bleeds and other complications of haemophilia that may necessitate a hospital treatment (Colvin BT, Hay CRM, Hill FE, 1995; Ehrenforth S, Kreuz W, Scharrer et al, 1992). In Scotland, the drop in hospital usage of clotting factor is may be due to decline in HIV and HCV patients' hospitalisation. In the study of haemophilia in central Scotland the annual number of hospital admission rose by nearly 50% between 1980 and 1994. This was reported to be principally due to increases in HIV and HCV (Ludlum C.A., Lee RJ, Prescott RJ et al, 2000). It is unlikely that other reasons for hospital usage, such as surgery, has dropped as the consumption of the clotting factor apart from a single year continued to increase during the period of this work (figure 11).

As mentioned elsewhere in this project, patients with severe haemophilia A can be treated either by regular infusion of FVIII 2-3 times per week (prophylaxis) or only in case of acute bleed incidents (on demand). In Scotland prophylactic treatment has been adopted as the standard treatment for children with severe haemophilia (Ludlam CA, personal communication 2003). Thus, as expected, this work demonstrated a large increase in the level of FVIII concentrates used by patients on prophylactic treatment between 1989 and 1999(over 850 %). This has resulted in clotting factor consumption almost three times higher than it would be if there were no prophylactics. This finding was consistent with other reports and predictions (Pettersson H, 1993; Bohn RL, Avond J, Glynn RJ et al, 1998). However, many studies show that the annual clotting factor consumption per kilogram body weight for prophylaxis is very high in early childhood, but decreases over time to stabilise in adulthood (Nilsson IM et al, 1992, Lofqvist T et al, 1997; Fischer K et al, 2001). Additionally, other parameters were also reported to have a large impact on clotting factor consumption: clotting factor can be decrease by 82% if infusions are given daily rather than three times a week (Carlsson M et al, 1993). Due to unavailability of data on reasons for home uses, it is not easy to conclude whether the prophylactic usage is decreasing over time and whether the decline of prophylactic usage was due to this lack of data alone or due to decreases over time and stability in the amount of FVIII used in prophylaxis.

The findings mentioned above to account for an increase in prophylactic usage corresponded with a decrease in the amount of clotting factor used for acute bleed (spontaneous and traumatic). In 2002 FVIII consumption for spontaneous and traumatic bleeds reached less than 50 % of the total amount used for all reasons for infusion. This may further corroborates findings that prophylactic reduces the number of bleeds and hence arthropathy ((Nilsson IM et al, 1992). Interestingly, the amount of FVIII for surgical use continued to increase, probably due to medical conditions unrelated to haemophilia. This increase in the amount of FVIII used for surgical purposes was predictable, as the need for surgical resources increases with the increase in life expectancy of haemophiliacs (Ludlam C.A., Lee R.J, Prescott R.J et al 2000). The sharp decline seen in 1998 in FVIII amount, where only 0.06 million IUs were used could possibly be attributed to fluctuations in the number of operations. The coincidence of this little FVIII use with Bayer's shortage of the recombinant products period, may be due to some patients were reluctant to use plasma-derived factors.

Finally, the findings on FVIII consumption by immune tolerance group (figure 13) shows that this small group of patients have a great impact on the total annual clotting factor consumption. In 1999, this group of patients consumed 2.2 million IUs of FVIII to represent over 25 % of the total clotting factor used for that year. Consistent with other findings, these figures demonstrate how patients with inhibitors, especially the ones on immune tolerizing regimens, impact haemophilia treatment cost (Rivard GE, Vick S, 1994; Chang H et al, 1999). However, it was also reported that in the majority of patients with FVIII inhibitor, product costs were not excessive in comparison with those patients without inhibitors. This was suggested to be due to the fact that heavily treated outlying inhibitor patients very much magnified the overall costs of treating this group, due to high per-unit cost of the products (Chang H et al, 1999)

6.4 Limitations of the study

The present analysis was limited by two important factors. Firstly, as highlighted in the discussion analysis of some variables was impeded by the quality of the data, especially the data of individual patients. Secondly, this study is also limited by unmeasured factors.

6.4.1 Limitations due to data quality

Missing information for some patients, such as reasons for infusion, the diagnosis or amount of FVIII received impeded the analysis of all patients at Edinburgh centre. Also, systematic lack of data on reasons for infusions in home treated patients has impeded the clarifications of variations in FVIII consumptions trend for the individual patients' usage at Edinburgh centre. Although it likely that those home usages will be for prophylactic treatment, it also likely that some patients at least may be infused for some spontaneous and traumatic bleedings. This missing data may have potential influences on FVIII consumption trends in Edinburgh.

6.4.2 Unmeasured factors

Examination of individual patients' consumption in Edinburgh has helped interpretation the variations of FVIII consumption on the East coast. However, small interpretations were made for the variation in the clotting factor in the West coast this because data from Glasgow was unavailable for analysis coupled with lack of comparative literature on haemophilia in East and West coasts of Scotland.

For the data from Edinburgh patients, although many important factors that have a big influence on FVIII consumption, (like prophylactic use, surgical use, immune tolerance group, on-demand treatment were examined) yet the influences of other factors like patients with HIV and/or HCV and patients weights were not measured. Using other study design like cohort of patients' consumption would also improve the assessment of FVIII increase

7 Chapter VII: conclusion and recommendations

7.1 Conclusion

This is the most recent study to examine the consumption of FVIII concentrates in Scotland. During this 14 year-period the annual clotting factor consumption has increased by over 350 %. This may be attributed to increase in life expectancy of the haemophiliacs and to more rigorous treatment approaches including prophylaxis treatment. Another finding in this work was that the clotting factor consumption on East coast, especially in the latter years, had grown faster than the West coast of Scotland.

Produced for the first time during this period, the use of genetically-engineered bloods products has also grown very sharply whilst the use of plasma-derived clotting factors have steadily decreased.

In order to examine the variation in clotting factor use, two models were fitted. The first model covers the whole period while the second covers the period after the start of recombinant clotting factor. Both models have shown that on 95% of occasions the monthly consumption will be within 2 SD of the trend line corresponding to 0.42 and 0.46 million I Us of FVIII respectively.

In terms of FVIII consumption in individual patients, 42 % of them patients with severe haemophilia revealed that the factors such as prophylaxis, surgery and patients on immune tolerance have a big impact on clotting factor consumption. These findings agree with other studies.

7.2 Recommendations

7.2.1 Operational

- To facilitate a 'constructive dialogue' between those providing the funding and those delivering the health care, establishment of a monitoring system to track variation in clotting factor usage is recommended. Such a system will help to examine whether any increases fall within an acceptable level or not; what is described in industry as 'in-control' and 'out of control' processes. Such a system could be set at national as well as local level. The estimation of the variability in demand as performed in this dissertation will help to set up such a system.
- As emphasized earlier in this study national as well as local planning for haemophilia care requires quality data. To improve the record and storage of information on clotting factor consumption the design of an internal database for clotting factor is recommended. Moreover, use of the database facilitates the retrieval of information, generation of data summaries more easily and in different electronic formats such as Access and Excel. To reduce any possible errors in the data entry, such duplication of data, better data management system with in built error checking is suggested
- Improvement in records at the haemophilia centres and avoidance of subjective mistakes by staff will ensure the integrity of the data and help in auditing and research.

7.2.2 Research

- Repeating this study on individual patients' usage at both Glasgow and Yorkhill hospitals will shed light on factors that impact FVIII on the West coast of Scotland. This will also help comparison of haemophilia care between the two coasts of Scotland.
- Also, studies applying other designs like the cohort study are needed to assess the impact of a wider range of factors on clotting factor usage.
- Due to limited information on prophylaxis treatment and lifestyle and quality-of-life issues, studies in this area will help the funders recognise the relevance of prophylactic treatment.

To help establish the recommended monitoring system, the following summary provides an introduction to the features of the cumulative sum tests (cusum) and its application. Also included here are some reservations about its use in monitoring health outcome processes.

The cusum test: designing a system for monitoring clotting factors usage

Control charts were originally invented to monitor the quality of manufacture products. The cumulative sum tests (cusum), a type of statistical process control charts, test based on cumulative sum of deviation from the target has been a success in this respect (von Dobben de Bruyn CS, 1968). This has been followed by another related success of the sequential tests for acceptance sampling.

The sequential analysis methods are one of the statistical methods that can be used to detect unusual changes in the level of an underlying process. The distinctive feature of this method is that data accumulate over time and analysis is repeated at every time point.

As recommended in this study, a monitoring system could be set to quickly detect unusual variations in the underlying clotting factor consumption. To design such system requires that the expected or acceptable variation in consumption to be defined, corresponding to what is termed in-control process (given symbol k) in control chart studies. Criteria must be defined decided to define when the observed consumption is sufficiently different from that expected to warrant special attention, corresponding to consumption rate being out of control (given symbol h). Both k and h will always be expressed in standard deviations of the observations (e. g monthly consumption in this case). Consumption that considered out of control could be followed up to seek explanations for the causes of the variability.

The following are the key features of statistical process control (SPC) charts as summarised in Alyin et al (2003):

- Test statistic calculated for the unit at each time point: this statistic is function of the difference between the observed outcome at given time and that of the expected

under in-control distribution. The statistics may also depend on previous values of these residuals, leading to a cumulative sum.

- Predefined alarm threshold: if the test statistic exceeds the threshold at some time t , a warning or alarm is triggered and the chart is said to signal that the process being monitored has become out of control
- Some measures of the performance of the chart: the ability of the chart to detect when the underlying process is truly in and out of control must be measured. Such chart performance measures take the place of the more familiar type I and type II error rates and are used, in all but the Shewart's chart, to inform the choice of alarm threshold h .

However, in a pilot study to use the control charts to establish a system to monitor the mortality rates in primary care (the Shipman's Inquiry), Aylin et al (2003) have expressed some reservations in the using these control charts. These reservations would also be applicable in the case of clotting factor use and warrant consideration. As pointed out by them, the characteristics of industrial processes are very different from those of a health outcome process. Most processes in industrial settings are well characterised in sense that a process is in control, the only source of variation is random. By contrast, health outcome processes are far more complex. Even when in control, the process is subject to many non-random sources of variation. They have concluded that an efficient SPC chart for monitoring the health outcome processes should specify an acceptable in-control performance level and an acceptable amount of variation about this level. Specification of these levels could be estimated from historical data. They also think these acceptable levels could be chosen subjectively by taking into account the degree of variation in outcomes that would be expected.

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Appendix