THE ECONOMICS OF REPLACEMENT THERAPY FOR INDIVIDUALS WITH BLEEDING DISORDERS

THESIS

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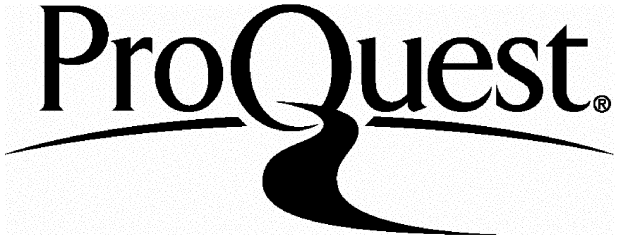

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ABSTRACT

Individuals with haemophilia are deficient in essential clotting factors resulting in an increased tendency to bleed. Repeated bleeding into joints may cause haemophilic arthritis (HA). However, there is considerable interest from providers of haemophilia care in treating some individuals on a prophylactic basis to prevent bleeds, and hence joint damage, from occurring in the first instance. Prophylaxis was first administered at the Katharine Dormandy Haemophilia Centre (KDHC) in the late 1970s to some individuals with severe haemophilia, although full-time regimes were not introduced until the early 1980s.

Data from individuals with severe haemophilia who were registered for treatment at the KDHC showed that following prophylaxis, the median incidence of bleeding had decreased significantly from 23.5 bleeds (range 1-107) per year in 1980 to 14 bleeds (range 0-52) per year by 1995 ($P<0.0001$). This said, however, individuals with severe haemophilia still recorded lower levels of health-related quality-of-life (HR-QoL) than individuals with mild / moderate haemophilia or the general UK male population even after adjusting for differences in age. Thus, significant scope exists for HR-QoL to be improved further. Using a unit clotting factor cost of 32.5 p/iu, a cost-utility analysis (CUA) showed that it cost an additional £46,500 per quality-adjusted life-year (QALY) and £8,600 per QALY to treat individuals with severe haemophilia A / vWD and severe haemophilia B with primary prophylaxis instead of on-demand respectively. However, the results from the CUA were not robust and both incremental cost-effectiveness ratios were found to be highly sensitive to a number of parameters including the unit clotting factor cost, the time between maintenance clotting factor infusions and the decision to discount future QALYs. Thus, further research over longer time periods is required to provide more accurate estimates of cost-effectiveness.

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1 GENERAL INTRODUCTION

1.1 Haemophilia

> *"The haemophilic population in the United Kingdom comprises of a group of patients whose medical management is both costly and complex. Some of the complexity arises due to the rarity of the condition, its life long nature, its variable severity and the fact that patients do not appear 'ill' in the accepted sense of the term. It may not always be understood that the lack of prompt, appropriate treatment may lead to prolonged hospitalisation and the misuse or even on occasion the wastage, of expensive blood products."*[1]

Haemophilia was first described as long ago as the fifth century in the Babylonian Talmud. However, modern knowledge of the disease is accredited to an American doctor named Otto who in 1803 reported on a group of patients who displayed a prolonged tendency to bleed[2]. In Germany, the disease soon became known as *Haemorrhaphilia*, denoting a disease characterised by a 'love of blood'. Haemophilia, as the condition is now known, is a rare X-chromosome linked recessive condition that affects 1 in every 6-10,000 males but is passed on to off-spring by female carriers of the defective gene[3]. If male, a child has a 50% chance of being born with the condition. Despite significant advances in patient management there is no cure.

In individuals without haemophilia, a number of proteins including clotting Factor VIII (FVIII), Factor IX (FIX) and von Willebrand factor (vWF), are produced by the liver. Following a bleed, the body uses these clotting factors to form a clot in order to stop the bleeding. Individuals with haemophilia A and B (or Christmas Disease) do not produce sufficient quantities of FVIII and FIX respectively whereas vWD is characterised by a quantitative or qualitative abnormality of vWF[3]. These clotting factor deficiencies mean that the coagulation time, the time it takes for a bleed to stop, increases and, could in some instances, prove fatal.

1.1.1 Epidemiology of haemophilia in the UK

In the UK, the three most common clotting disorders are haemophilia A, haemophilia B and von Willebrands Disease (vWD). vWD, or vascular haemophilia, is a related

disorder to haemophilia and is usually referred to as such. In 1994 it was estimated that 5,418, 1,109 and 3,794 individuals with these clotting factor disorders were registered with UK haemophilia treatment centres (Table 1.1)[4]. These figures equate to prevalence rates of one person with haemophilia A, B and vWD per every 10,000, 50,000 and 16,000 individuals respectively. Therefore, the prevalence of haemophilia A is one and half times greater than that of vWD and five times greater than that of haemophilia B.

Table 1.1: Epidemiology of haemophilia in the UK. Figures are taken from the United Kingdom Haemophilia Centre Returns, 1994[4]

	Haemophilia Type			
	Haemophilia A	**Haemophilia B**	**vWD**	**Total**
Number	5,418	1,109	3,374	9,901
% <2 iu/dl*	36	32	1	24
UK prevalence**	1/10,000	1/50,000	1/16,000	1/5,500
New+	151	17	306	190
Deaths	139	5	15	159

* **individuals with haemophilia A and vWD FVIII levels of <2 iu/dl whereas individuals with haemophilia B, FIX levels of <2 iu/dl**

** **assuming that the UK population is 56 million**

\+ **previously unseen patients and individuals from abroad who registered for treatment at a UK haemophilia treatment centre in the UK**

Depending on their baseline *in vivo* clotting factor level, individuals with haemophilia A or B are described as having either mild, moderate or severe haemophilia. Individuals without haemophilia produce between 50-150 international units (of FVIII, FIX and vWF) per decilitre of plasma (iu/dl). Individuals with mild haemophilia have baseline *in vivo* clotting factor levels of between >5-49 iu/dl, those with moderate haemophilia have levels of between 1-5 iu/dl and those with severe haemophilia have levels of less than 1 iu/dl[5]. Individuals with mild or moderate haemophilia will experience relatively few bleeding episodes but even mild trauma may cause bleeding in those patients with severe haemophilia and bleeding may also be spontaneous. Individuals with vWD are classified according to a combination of their factor FVIII, von Willebrand antigen, von Willebrand activity and ristocetin-induced platelet aggregation levels. vWD is usually manifested as a mild to moderate bleeding tendency but a minority of patients with vWD suffer from acute bleeding episodes in the same manner as patients with severe haemophilia. Bleeding episodes are usually into the joint cavity, muscle or other soft

tissue and are often painful. When bleeding into the joint cavity occurs, the joint becomes swollen and is held in flexion until the swelling is reduced. With adequate treatment the joint will return to its pre-haemorrhage status without causing any damage. However, when a joint fails to recover fully between bleeding episodes the synovium grows abnormally large (hypertrophies) and further bleeding is precipitated. The likely result of this cycle of events is the development of haemophilic arthropathy (HA). This is a chronically painful and debilitating condition resembling progressive osteoarthritis that can be arbitrarily defined as chronic synovitis for more than six months.

1.1.2 The evolution of replacement products and therapy

To compensate for these clotting factor deficiencies individuals with haemophilia and vWD require replacement (or substitution) therapy with an appropriate product. Some of the first treatments used in the early 1900s included the addition of traces of normal plasma to haemophilic blood and the bubbling of carbon dioxide through haemophilic blood[6]. However, modern treatment of these conditions began with the use of blood transfusions to treat bleeding episodes in patients with haemophilia in the late 19th century. Whilst, fractionation of plasma was begun in 1901[7], it wasn't until the 1960s[8] that cryoprecipitate, a crude refinement of clotting factor, was first fractionated from fresh frozen plasma and was used to treat patients with haemophilia A and vWD. By the late 1960s prothrombin complex's had also been isolated and were used to treat patients with haemophilia B. Following the advent of these more portable clotting agents, treating at home became the accepted place for administering treatment for all individuals whose bleeds occurred often enough for the patient or his family to maintain the necessary skills. 'Home treatment' has led to considerable improvements in life expectancy; prior to 1960 individuals with severe haemophilia had a median life expectancy of only 10.2 years whilst with the impact of viral infections aside, the average life expectancy is now almost equivalent to that of the general male population[9].

1.1.3 Modern replacement products

Nowadays, individuals with severe haemophilia A or manifestly severe vWD usually receive replacement therapy with clotting FVIII or FVIII rich in vWF whereas individuals with haemophilia B receive treatment with FIX. Replacement products are characterised by being of intermediate purity, high purity, or are super pure

(recombinant). Because plasma-derived products continue to transmit hepatitis A and B19 parvovirus, and because of concern over as yet unknown future viruses, recombinant clotting factors, where available, are now considered by most haemophilia treating specialists as the treatment of choice. However, recombinant clotting factors are considerably more costly to purchase than plasma derived clotting factors, they are liable to value added tax (unlike plasma derived clotting factors) because they are not derived from blood and their additional clinical benefit is the subject of much debate[10-13].

1.1.4 Modern methods of clotting factor delivery (replacement therapy)

Irrespective of the type of clotting factor being used, patients usually receive treatment following a bleed (on-demand therapy) in order to abort it. However, there is increasing interest in giving clotting factor to individuals prophylactically in order to prevent bleeds, and hence joint damage, from occurring in the first instance. When clotting factor is administered prophylactically prior to any signs of joint damage, this process is referred to as 'primary prophylaxis'. 'Secondary prophylaxis' denotes prophylaxis with clotting factor started after the onset of serial bleeding when joint damage is already manifest.

The advent of suitable replacement products has also enabled individuals with haemophilia and vWD to undergo invasive surgery including corrective orthopaedic surgery. Individuals with these clotting factor deficiencies who undergo any invasive procedure must receive replacement therapy with clotting factor before, during and after the procedure in order to prevent any problematic bleeding. For some time it has been customary to administer clotting factor to these individuals using bolus infusions at suitable time intervals. However, interest is growing in supplying the necessary clotting factor on a 'continual' basis for the duration of treatment; a process known as continuous infusion.

1.1.5 Recent policy recommendations

Since 1998 and 1999, it has been mandatory in England and Wales for NHS purchasers and providers to treat all individuals with severe haemophilia A and B aged 16 years or younger with recombinant clotting factor respectively. In Scotland it is also planned that all patients with severe haemophilia should be in recepit of recombinant clotting factors by the end of March 2001.

Primary prophylaxis is now advocated as the method of replacement therapy of choice for all individuals with severe haemophilia or manifestly severe vWD by the UK Haemophilia Centre Directors Organisation[14]. However, treatment with primary prophylaxis is not mandatory in the UK. Primary prophylaxis has also been advocated as the treatment of choice by the United States National Hemophilia Foundation's Medical and Scientific Advisory Council[15] and the Canadian Hemophilia Society[16]. Although precise figures do not exist, it is estimated that only 1% of the world's population of individuals with severe haemophilia has received treatment with primary prophylaxis.

1.2 The growing need for economic evaluations

Ever increasing pressures on health care budgets has made it important for health care technologies not only to demonstrate their safety and efficacy but also to show that they represent an efficient use of resources. Economic evaluations provide information on efficiency by comparing the costs and benefits of one health care programme to the costs and benefits of a programme that it is ultimately seeking to replace. Economic analyses represent a set of formal quantitative methods used to inform, but not to make, resource allocation decisions[17].

Economic evaluations can be used to either assess *technical* (operational) or *allocative efficiency*. *Technical efficiency* involves the selection between alternative means of achieving the same ends, and may therefore, be interpreted as the pursuit of a maximum output for a given level of cost or a minimum cost for a given level of output. Economic evaluations for assessing *allocative efficiency* are used to judge whether an activity is worth pursuing in the first instance and to also consider the scale at which a programme should operate. The implicit recommendation here is that resources should be allocated towards those technologies that are believed to represent an efficient (or cost-effective) use of resources and away from those technologies thought to be relatively inefficient. Therefore, where health care budgets are limited, resources should be allocated towards those technologies where the marginal benefits to the population of interest are greatest relative to the marginal costs. Theoretically, allocating resources on this basis would ensure a Utilitarian objective of maximising societal health from the limited resources available.

In countries such as Australia and Canada, the presentation of economic data for pharmaceutical reimbursement negotiations is now mandatory and some Governments and journals have established guidelines for the performing and reporting of economic studies. Many research funding bodies, including the Medical Research Council (MRC) and the NHS Research and Development (R&D) programme, require justification for not including economic evaluations alongside clinical studies. The present UK government has also established a new body, the National Institute for Clinical Excellence (NICE), part of whose remit is to produce and to disseminate evidence on the cost-effectiveness of selected drugs, medical devices, surgical and health promotion interventions[18].

In more recent years the focus of much methodological debate has surrounded the incorporation of economic evaluations into randomised controlled trials (RCTs) because they are thought to produce the least biased estimated of efficacy. However, Banta and Sculpher have suggested that economic assessment should be iterative and that it should commence much earlier than alongside an RCT. The rationale given for this (re)iterative approach to economic evaluation is threefold. Firstly, it has been suggested that adopting this approach will help to facilitate the controlled diffusion of new technologies by helping to allocate R&D funds towards those technologies that are expected to provide the greatest value for money in the future as R&D resources are themselves scarce. Secondly, through the use of extensive sensitivity analysis, the results from 'early' (ie. prior to evaluation alongside an RCT) economic evaluations can be used to help design 'efficient' economic studies if further economic research is warranted. Thus, it has also been suggested that economic evaluations have a role to play in setting and designing research priorities as well as a role in the R&D process itself. Thirdly, a continuous evaluative process should help to produce progressively firmer estimates of cost-effectiveness by incorporating increasingly more accurate data into the analysis.

1.3 The context of the thesis

With the recent advent and subsequent clinical endorsement of more costly clotting factors and more resource intensive methods of replacement therapy (such as primary prophylaxis), individuals with these clotting factor deficiencies can now be extremely costly to manage. Despite these high costs, however, allocating resources towards high-

cost low-volume areas, such as certain types of haemophilia treatments, can still be justified on economic grounds if the resulting health outcomes are sufficiently large.

Only a small number of replacement therapy programmes for individuals with clotting factor disorders have been subject to economic analysis. Moreover, published studies addressing these issues are of variable quality. The most likely explanation for this dearth in economic studies is that measuring the costs and effects of lifelong treatments is difficult, particularly when the underlying condition is also rare. However, decision-makers require assessments of the cost-effectiveness of these treatments to be made irrespective of these informational difficulties, as a number of authors have already noted[19-21].

1.4 Project aims and objectives

The main aim of this thesis was to assess the cost-effectiveness of primary prophylaxis for individuals with severe clotting factor disorders. Secondary objectives were:

1. To assess the outcome of prophylaxis with clotting factor for individuals with severe clotting factor disorders who were registered for treatment at the Katherine Dormandy Haemophilia Centre (KDHC).
2. To describe and to analyse the current situation with regards to health-related quality-of-life (HR-QoL) in individuals with haemophilia who are registered at the KDHC and, in doing so, to provide baseline HR-QoL data for future research.
3. To assess the extent to which primary prophylaxis could reduce the demand for hospital visits and indirect resources.
4. To assess whether continuous infusion with clotting factor during surgery versus bolus infusions represents a technically efficient use of resources.
5. To assess the cost-effectiveness of primary prophylaxis versus treatment on-demand.
6. To assess the scope for new technologies and treatment programmes to improve the cost-effectiveness of primary prophylaxis.
7. To suggest which data should be collected to aid future economic analyses of replacement therapies with clotting factor.

1.5 Outline of the thesis

The thesis has been divided into nine chapters. Chapter 2 contains the literature review in which existing evidence on the costs and benefits of the replacement therapies is

presented and discussed. Chapter 3 contains a description of the methods and data used in the thesis. Data on bleeding patterns and clotting factor use are analysed in Chapter 4 in order to ascertain how effective prophylaxis has been in reducing the incidence of bleeding for individuals with severe haemophilia who were registered at the KDHC. Chapter 5 assesses current levels of HR-QoL in individuals with mild, moderate and severe haemophilia and compares these levels to those recorded by two general populations. Chapter 6 assesses the extent to which primary prophylaxis for individuals with severe haemophilia could reduce the demand for hospital visits and patient / family resources. Chapter 7 contains an economic evaluation of continuous infusion with clotting factor versus bolus infusions during surgery and, principally using the data and results from Chapters 4-7, Chapter 8 contains a cost-utility analysis of primary prophylaxis. Finally, Chapter 9 contains a general discussion of all the issues and final remarks.

2 LITERATURE REVIEW

2.1 Introduction

The aim of this literature review was to gather all the available evidence on the benefits (ie. health-related quality-of-life and patient preferences), effectiveness, costs and cost-effectiveness of treatment on-demand with clotting factor, (primary or secondary) prophylaxis and continuous infusion. However, since clotting factor concentrate is an integral component of replacement therapy, the literature review also included an overview of the different types of clotting factor concentrates.

The methods used to conduct the literature review and the results of the literature review are described in sections 2.2 and 2.3 respectively and a summary and discussion of the main findings of the review is contained in section 2.4.

2.2 Methods

It was thought prior to conducting the literature review that the search would yield relatively few suitable studies given that haemophilia is a rare lifelong condition. Therefore, no specific inclusion or exclusion criteria were stipulated for any part or sub-part of the review except that the studies had to contain at least some patient-based data rather than purely theoretical analyses.

2.2.1 Search techniques and terms

The following electronic databases were searched: Medline, the Bath Information and Dissemination Service (BIDS), the NHS Economic Evaluation Database (NEED) and the NHS Database of Abstracts of Reviews of Effectiveness (DARE). References made in articles were also used as a literature source and hand searching of relevant haematological journals was also performed. Various combinations of the following textwords and MeSH headings were used to search the electronic databases (the underlined words were used as textword and MeSH headings):

Haemophilia, hemophilia, von Willebrands Disease, episodic, on-demand, replacement therapy, substitution therapy, prophylaxis, pharmacokinetics, continuous infusion, clotting factor, FVIII, FIX, factor VIII, factor IX, inhibitor, antibody, complication, venous access device, catheter, port-a-cath, cannula, economics, economic evaluation,

cost, arthropathy, joint, arthritis, bleed, haematoma, hematoma, haemarthrosis, hemarthrosis, mortality, morbidity, effectiveness, quality-adjusted life-year, QALY, quality-of-life, HR-QoL, preferences, benefit, adherence, compliance, infection, virus, human immunodeficiency virus (HIV), hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), parvovirus and iatrogenic.

2.3 Results

2.3.1 The clotting factors

The majority of available clotting factors are either derived from human plasma or are synthetic (recombinant). Clotting factors are characterised by being of intermediate-purity, high-purity[22] or are super-pure (recombinant)[23]. The term purity is taken to refer to the contaminating protein content of the clotting factor and is usually expressed in term of iu/mg proteins[22]. Increased purity is also generally associated with increased acquisition costs[14]. Low purity products, such as cryoprecipitate, exist but they are generally no longer given to individuals with haemophilia in developed areas of the world because they cannot be virus inactivated to satisfactory levels[3].

2.3.1.1 Plasma-derived clotting factors

Intermediate-purity FVIII clotting factors are prepared solely with conventional precipitation methods and are subject to heat treatment methods of viral inactivation whereas high-purity FVIII and FIX clotting factors are subject to solvent detergent methods of viral inactivation followed by chromatographic purification techniques[3,22]. High-purity clotting factors do not contain such large quantities of plasma proteins and alloantigens such as immunoglobulins, fibrinogen and immune complexes compared to intermediate-purity products[3,22,24]. Indeed, there is some evidence to suggest that the cellular component of the immune system declines less slowly in individuals with haemophilia who are HIV seropositive who have been treated with high-purity clotting factors than individuals who have been treated with intermediate-purity products. However, it remains unclear whether this difference leads to differences in clinical manifestations of the infection or in survival[25-35].

Prior to the introduction of high-purity FIXs in the late 1980s, individuals with haemophilia B were treated with prothrombin complex concentrates (PCCs). However, PCCs contained quantities of activated factors that are believed to have caused

thromboembolic complications and myocardial infarctions[36,37]. High-purity FIX products are thought not to contain these activated factors thus they are considered to be safer products than PCCs[38] although additional clinical experience is necessary to establish this conclusively[22,37,39,40].

Between the years 1965-1985, almost all individuals with severe haemophilia who had received untreated, large-pool blood products became infected with hepatitis C (HCV)[41]. Moreover, approximately 60% of these individuals also became infected with HIV[42-44]. Since this time, the introduction of improved methods of viral inactivation (particularly solvent / detergent techniques), progress in donor selection and blood screening methods has almost eliminated reports of lipid-enveloped viral infection (HIV, HCV or hepatitis B) secondary to treatment with plasma-derived clotting factor[45-48]. However, they continue to transmit heat resistant non lipid-enveloped viruses such as hepatitis A (HAV) and B19 parvovirus[38,49-55]. Although the incidence of infection with HAV and B19 are both thought small and the clinical impact of infection with HAV is minor in most instances of infection[56], infection with B19 is thought to have caused chronic anaemia in some individuals with haemophilia who were immunocompromised[56,57]. Perhaps more importantly, however, the continued transmission of HAV and the B19 parovirus serves as a reminder that despite all efforts, plasma-derived clotting factors could transmit as yet unknown viruses with a higher degree of clinical significance to individuals with haemophilia in the future[58-60].

2.3.1.2 Recombinant clotting factors

Recombinant clotting factors are synthetically derived alternatives to plasma derived products. A recombinant FVIII was first licensed in the US in 1992 and in the UK in 1994. Three recombinant FVIIIs are currently available in the UK, both have had their biological and haemostatic characteristics and efficacy well established and documented to date[61-65]. A recombinant FIX was first licensed in the UK in 1999. Because they are synthetic, recombinant clotting factors are believed to be safer to use than plasma derived alternatives as they are less likely to transmit any blood borne viruses. Nonetheless, although there has never been a reported case of viral transmission secondary to infusing with a recombinant clotting factor, there remains a theoretical risk of transmission as some recombinant clotting factors are produced using human albumin and animal cells[13] and reports of the presence B19 parvovirus DNA in recombinant FVIII have been made[55]. A further suggested advantage of recombinant

clotting factors is that they may also slow the decline of the cellular component of the immune system in individuals with haemophilia who are HIV positive to a greater extent than high-purity plasma clotting factors. However, no patient based evidence could be found to support this claim.

2.3.1.3 Clotting factors and current UK clinical guidelines

Recombinant clotting FVIII and FIX are now considered by the United Kingdom Haemophilia Centres Directors Organisation (and other national haemophilia organisations) to be the treatment of choice for all individuals with severe haemophilia A and severe haemophilia B. Since 1998 and 1999, it has been mandatory in England and Wales for NHS purchasers and providers to treat all individuals with severe haemophilia A and B aged 16 years or younger with recombinant clotting factor respectively. In Scotland it is also planned that all patients with severe haemophilia should be in recepit of recombinant clotting factors by the end of March 2001[66,67].

2.3.2 Methods of replacement therapy

Traditionally, individuals have treated themselves with clotting factor following an episode of bleeding (on-demand) using bolus techniques in order to stop the bleeding. However, interest is growing in supplying the necessary clotting factor prophylactically to individuals with severe bleeding clotting factor deficiencies in order to prevent spontaneous bleeds occurring in the first instance and the long-term damage caused to the joints by bleeding.

2.3.2.1 Treatment on-demand (following a bleed) with clotting factor

Since the advent of more portable clotting factors in the 1960/70s, individuals with clotting factor disorders such as haemophilia have been able to treat themselves with clotting factor at home on-demand following a bleed. A study performed by Allain *et al.*[68] in 70 individuals with severe haemophilia A showed that 99% of bleeds could be stopped by administering a single bolus infusion of 31 iu/kg body weight of FVIII. However, no further studies were found that confirmed the efficacy of this dosage and none could be found that examined the efficacy of this dosage in stopping bleeds or any other size dose of FIX for treating individuals with haemophilia B following a bleed.

2.3.2.1.1 Clinical effectiveness

In 1975, the US congress passed the Haemophilia Act in which financial support was provided to support comprehensive care programmes for individuals, which included

treatment on-demand with clotting factor. Over the following ten years, the number of individuals treating on-demand increased from 514 to 2517[69-71]. As a result, the average number of days individuals were absent from work or school decreased by 73%, the number of adults entering the labour market increased by 74%, the number of inpatient admissions per year decreased by 89% and the average number of days individuals spent in hospital per year decreased by 83%. Moreover, prior to 1960 the median life expectancy for individuals with severe haemophilia was less than 30 years of age[72-74] but by the early 1980s it had more than doubled[72,75-79].

Despite these dramatic improvements in mortality and morbidity, the major limitation of treating individuals on-demand is that repeated bleeding into the joint cavity causes the joint to become swollen. With adequate treatment, the joint may return to its prehaemorrhage status without causing any damage. However, when a joint fails to recover fully between bleeding episodes the synovium may grow abnormally large (hypertrophies) precipitating further bleeding. The likely result of this cycle of events is the development of haemophilic arthropathy (HA)[80]; arbitrarily defined as chronic synovitis for more than six months[81]. HA is a chronically painful and debilitating condition that resembles progressive osteoarthritis[71,82,83]. Approximately two-thirds of reported bleeds are into the joint space (haemarthrosis) whereas the remaining one-third is into the muscle (haematoma) or surrounding soft tissue. The knees, ankles and elbows are the joints most prone to bleeding[84] and hence the most prone to developing HA. In 1980, Steven *et al.*[85] estimated the prevalence of HA individuals with severe haemophilia to be in excess of 55% although the prevalence was shown to be highly correlated with increasing age. Although adults with severe haemophilia can expect to treat a mean of 30-35 bleeds per year, Åhlberg[86] and Kreuz[70,71] have demonstrated that as few as 10 and 5 bleeds into a single joint may cause a clinically significant deterioration in joint status respectively. Moreover, a significant prevalence of HA in individuals with mild / moderate haemophilia also suggests that infrequent or mild bleeding episodes might be sufficient to initiate a change in joint condition[85]. In instances of severe HA, individuals may undergo corrective orthopaedic surgery. However, procedures of this nature in individuals with clotting factor disorders such as haemophilia are thought to rank amongst the most costly forms of orthopaedic surgery[87].

The specific impact of treatment on-demand on joint function has only been examined in a limited number of studies[86,88-90] and only one study was found which examined the impact of treatment on-demand on health-related quality-of-life (it is discussed in section 2.3.2.3.4 as it contains a comparative analysis with prophylactic treatment). A Finnish retrospectively controlled cross-sectional study performed in 1982[91] examined the degree of clinical impairment of the joints in 62 individuals with severe haemophilia who had been treated on-demand. The degree of joint impairment was evaluated by recording crepitation, deformities and loss of movement. The individuals had a mean age of 15.5 years at the time of the assessment (between 1957-59). The results from this group were compared to scores recorded in a group of 70 individuals with a mean age of 24 years recorded between 1978-79. Permanent joint changes were observed in 50 (81%) of the individuals in the 1959 series and 70 (86%) in the 1979 series despite adequate supplies of lyophilised cryoprecipitate being available (no reference is made to a specific treatment protocol). However, few differences in the degree of joint impairment between the two groups were noted. The authors concluded that treatment on-demand could at best, delay, but not prevent, the onset of HA.

The Orthopaedic Outcomes Study[84] examined the impact of increasing clotting factor use on joint status. This 5-year multicentre study compiled data on 477 individuals under twenty-five years of age with severe haemophilia A who were inhibitor free. All individuals were grouped into one of four treatment regimes according to the mean annualised amount of clotting factor they had infused over the study period (0-499 iu/kg, 500-999 iu/kg, 1,000-1,999 iu/kg and 2,000+ iu/kg/year). Participants' elbows, knees and ankles were assessed using World Federation (WFH) of Haemophilia orthopaedic and radiological[82,83] scoring systems. Using the orthopaedic scoring system, each of the six joints receives a score between 0 (best) and 15 (worst) meaning that each individual could receive a maximum orthopaedic score of 90. The radiological scale is similar to the orthopaedic scoring system but the elbows, knees and ankles each receive scores between 0 (best) and 13 (worst) meaning that the maximum radiological score per person is 78. The orthopaedic examinations were performed in each of the six study years but the radiological assessments were only performed in the initial and final years of the study.

On entry to the study, 10% (n=48) of individuals recorded clinically perfect orthopaedic and radiological joint scores. However, 55% of individuals showed deterioration in both scores by the end of the 5-year study period. Analysis of the data showed that both initial and final orthopaedic and radiological joint scores were correlated with age ($P<0.05$). The number of joint bleeds was also shown to correlate with the change in orthopaedic joint score over the study period whereas the total number of bleeds was shown to correlate with the change in the radiological score after adjusting for age differences ($P<0.05$ in both instances). The authors concluded that although a small proportion of individuals who were treated on-demand retained clinically perfect joints, this method of treatment could not prevent the development of haemophilic arthritis even if individuals received large doses of clotting factor.

2.3.2.2 Prophylaxis with clotting factor

The term 'prophylaxis' refers to the instance where individuals receive clotting factor in an attempt to prevent bleeding from occurring. Primary prophylaxis refers to the situation where patients receive clotting factor prior to any signs of any joint damage and is usually started at 1-2 years of age. Secondary prophylaxis refers to the instance where patients receive prophylaxis after the first signs of serial joint bleeding and where joint damage is already manifest[5,92].

2.3.2.2.1 The rationale for primary prophylaxis

The rationale for primary prophylactic treatment was the observation in the 1960s that chronic arthropathy was less frequent and less severe in moderate haemophilia (ie. FVIII / FIX concentrations between 1-5% of normal levels) than in severe haemophilia (ie. FVIII / FIX concentrations <1% of normal levels)[86,93,94]. It was hypothesised, therefore, that bleeding and the onset of haemophilic arthropathy could be prevented in individuals with severe haemophilia if trough *in vivo* clotting factor levels could be maintained at or above 1 iu/dl at all times.

2.3.2.2.2 Clinical effectiveness: the early studies

During the 1960s and 1970s, a number of studies were published which reported that secondary prophylaxis (usually with cryoprecipitate) could reduce bleeding frequency under certain conditions (Table 2.1). For example, in one case study[95] an individual with severe haemophilia A received one bag of cryoprecipitate every 12 hours for three months and one bag of cryoprecipitate per day for the following three months. In the

six month prior to receiving prophylaxis, the patient had been admitted to hospital 15 times following various haemorrhagic episodes. During the first three-month period of prophylaxis however, the patient did not require hospitalisation, stated that he was free of muscle pain and for the first time was able to attend school on a regular basis. The individual also sustained trauma at least twice without any signs of bleeding. During the second three-month period the individual suffered three spontaneous joint bleeds, complained of discomfort in various muscles but still did not require hospitalisation. Aronstam *et al.*[96] also reported on the success of prophylaxis in reducing bleeding frequency in a double blind controlled trial which involved nine individuals with severe haemophilia A. Individuals were initially randomised to a once weekly prophylactic regime receiving either a concentrate calculated to raise baseline FVIII activity levels to 2.5 iu/dl or a concentrate calculated to increase the activity level to no more than 1 iu/dl. All nine individuals received both treatment regimes for approximately two school terms (24 weeks) each. Bleeding frequency was reduced by 15% ($P<0.05$) whilst the individuals received the higher-dose regime compared to their pre-trial statistics but the lower-dose regime didn't produce any significant reductions in bleeding frequency. Various other studies also reported that prophylaxis in individuals with severe haemophilia reduced or prevented bleeding in patients who had previous histories of bleeding.

These early studies were the first to provide evidence that secondary prophylaxis had the potential to reduce frequency of bleeding. However, it is difficult to form any general conclusions on the effectiveness of prophylaxis from these studies because they are not of similar design, their sample sizes were small, only one study was controlled and in most the duration of follow-up was less than a year[92].

2.3.2.2.3 Clinical effectiveness: orthopaedic outcome

A further limitation of the early clinical studies was that they focused on bleeding when the ultimate goal of prophylactic treatment is to modify the progression of haemophilic arthropathy. In one prospective study, the effect of prophylaxis on this outcome was studied in two groups of seven children with severe haemophilia A who had received prophylaxis from a mean age of 5 years and 3 years respectively[97]. Both groups received bolus infusions of FVIII two or three times per week with an average annual consumption of over 3,000 iu/kg/year. The children in both groups were examined

between the ages of 5-12 years. At the time of investigation the children in the older and younger groups were a mean age of 9 and 8 years respectively. In the older age group, radiological changes were found in the ankles of five and in the knees of four patients. However, in the group who had started prophylaxis at an earlier age, only one case of ankle damage was detected; the results were not tested for statistical significance.

In a similar study, Dzinaj *et al.*[98] collected data on two groups of individuals with haemophilia A. The first group comprised of 8 individuals with severe and 2 individuals with moderate haemophilia who had a median age of 6.2 years (range: 3-14 years) who had all been less than 2 years old when they started to receive primary prophylaxis. The second group comprised 4 individuals with severe haemophilia and 3 with moderate haemophilia who had received treatment on-demand until a median age of 10.3 years (range: 6-13 years). To determine the outcome of treatment on joint status, individuals were assessed using the WFH radiological scoring system (previously described in section 2.3.2.1.1). At the time of assessment, individuals who had started prophylaxis at the older age recorded a mean radiological score of 2 (range: 0-33) whereas individuals who had started prophylaxis at the younger age recorded a median score of 0 (range: 0-2), the difference in scores was significant (P=0.01). However, the radiological scores were not adjusted for differences in age, which could explain the observed differences.

Table 2.1: The early studies of secondary prophylaxis

Author and year	Study design	Patients treated Clotting factor level	Age (years)	Notes	Outcome
Robinson, 1967[95]	Case study	N=1 1 iu/dl	19	One bag of cryoprecipitate every 12 hours for 3 months then every day for a further 3 months.	No hospitalisations required during this time. Patient able to go to school on regular basis for first ever time and reported a reduction in pain
Bellingham, 1967[99]	Case report	N=1 <1 iu/dl	21	Prophylaxis with cryoprecipitate following hip replacement.	Operation and subsequent period was uneventful.
Shanbrom, 1969[100]	Case study	N=1 <1 iu/dl	39	Antihemophilic factor given to increase levels to between 80%-100% of normal using various regimens for 12 months.	Patient had a history of bleeding. Prophylaxis completely prevented joint bleeding but patient died possibly due to increased fibrinogen.
Van Creveld, 1969[101]; Van Creveld, 1971[102]	Two case reports (1971 study)	N=2	-	Prophylaxis with cryoprecipitate 2-3 times a week (900-1,500 iu weekly) for 2.5-3 years	Reduced episodes of bleeding and hospital admissions. No progression of joint problems.
Hirschman, 1970[103]	Four case reports	N=4 2 iu/dl or less	12-34	Two individuals had vWD. Various prophylactic regimens with cryoprecipitate tried.	The two individuals with haemophilia A experienced fewer bleeds compared to pre-prophylaxis levels but those with vWD did not.
Kasper, 1970 [104]	Prospective	N=5 all <1 iu/dl	14-34	Four FVIII schedules were used for approximately 2 months each. (1) 250 iu per day (2) 2,000 iu once a week (3) 1,500 iu three times per week (4) 500 iu every morning.	(1) bleeding reduced in all but one patient (4) reduced bleeding slightly more. (2 and 3) no bleeds in first 48 hours following infusion. All bleeds tended to be in previously affected joints.
Morfini, 1976[105]	Prospective*	N=10 <1 iu/dl		Two different schedules of freeze dried factor IX (1) 7.5 iu/kg twice per week (2) 15 iu/kg once per week.	Prophylaxis reduced bleeding frequency ($P<0.05$) compared to pre-trial period. (1) was significantly more effective than (2) ($P<0.01$).
Aronstam, 1976 [96]	Prospective cross over trial	N=9 all <1 iu/dl	13-17	Individuals received one infusion per week of FVIII to raise clotting factor levels to at least 0.01 and 0.25 iu/dl for one school term respectively.	The higher does regime reduced bleeding frequency compared to pre-trial levels by 15% ($P<0.05$). The lower dose regime had no affect on bleeding frequency compared to pre-trial levels.

The Dutch experience of prophylaxis was described in a 6-year retrospective study in individuals with severe haemophilia who were registered at the van Creveld Clinic, Utrecht[106]. The group of individuals studied were born between 1974 and 1990 and consisted of 75 and 7 individuals with haemophilia A and haemophilia B, respectively. At the beginning and end of this period, 68 individuals who had received prophylaxis from a median age of 4 years (range: 0.5-16.5 years) underwent a radiological examination using the WFH radiological scoring system although only the most clinically affected joint was assessed in each patient. At the beginning of the study, individuals recorded a median radiological score 0 but at the end of the 6-year period this score had increased to a median of 2.5 despite consuming 1,753 iu/kg of clotting factor per year on average. The authors also noted that the number of bleeds compared to pre-prophylaxis levels had declined but no figures are provided.

The impact of prophylaxis on orthopaedic outcome was also assessed in a Turkish study[107]. This study consisted of 7 children with severe haemophilia A (n=6) and B (n=1) who started to receive prophylaxis at a mean age of 5 years (1.5-7 years) with 20-50 iu/kg of clotting factor twice weekly. Data relating to the same group of patients one year prior to starting prophylactic therapy were collected retrospectively to act as a control, as were data for a group of ten individuals with severe haemophilia A (n=7) and B (n=3) who had been 'sporadically' treated on-demand (ie. treatment was not always available when clinically indicated). In the year prior to prophylaxis, the seven individuals experienced a mean of 10.5 (sd. 3.2) bleeds per year, and recorded mean orthopaedic and radiological scores of (sd. 0) and 1.1 (sd 1.2) respectively and consumed a mean of 2,073 (sd. 1,032) iu/kg/year of clotting factor. After receiving prophylaxis for a mean period of 14.5 months (range: 6-24 months) bleeding frequency had declined to 4.5 (sd. 3.6) bleeds per year but the mean clotting factor usage per patient had increased to 3,489 (sd. 960) iu/kg/year and the orthopaedic and radiological scores remained largely unchanged. However, marked differences in orthopaedic and radiological joint scores were observed between these individuals and the individuals in the 'on-demand' control group. At the time of assessment individuals in this control group were a mean of 12.5 years of age (1-22 years) and had experienced a mean of 9.8 (sd. 3.9) bleeds per year and recorded mean total orthopaedic and radiological scores that ranged between 5-20 and 10-20 respectively.

A number of studies have also reported the effect of treatment with secondary prophylaxis on orthopaedic outcome[70,84,108-110]. In one study[108], 14 individuals with severe haemophilia who had a mean age of 7.2 years (range: 2-12.5 years) at the time of assessment were switched to a secondary prophylactic treatment regime which consisted of 20 iu/kg of FVIII three times per week and 40 iu/kg of FIX twice a week for individuals with severe haemophilia A and B respectively. Prior to prophylaxis all had some clinical indications of joint damage. After a mean period of 1.5 years (range; 0.3-4) years of receiving secondary prophylaxis, bleeding into target joints stopped for many individuals and most individuals demonstrated clinical improvements in joint functioning. However, radiological abnormalities did not improve in any of the evaluated joints and, indeed, disease status progressed in two joints, although it is not possible to state what percentage of the total number of joints these account for. Similar findings were reported by Schramm *et al.* [110] and Aledort *et al.*[84].

More recently, a prospective cohort study was performed to consider the impact of prophylactic treatment on 27 children with severe haemophilia A who were registered for treatment at a London comprehensive care centre[21,111]. Both bleeding frequency and musculoskeletal outcome were assessed but the precise method used to score musculoskeletal outcomes was not provided in the report. 'Significant' bleeds were defined as bleeding episodes that occurred spontaneously or after minimal trauma and caused pain or loss of function. At the start of the study all 27 children had been on prophylaxis for a minimum of 6 months. Four of the children were infected with HIV but only one had an AIDS-defining diagnosis. The median age at the start of treatment was 6.2 (range 1.3-15.9) years and the mean follow-up period was 30 (range 7-76) months. Individuals with haemophilia A received a mean of 31.8 iu/kg (range 12.5-52.6 iu/kg) three times per week whereas the individual with haemophilia B received 31.8 iu/kg of FIX twice a week. Prior to receiving prophylaxis, the average annual number of significant bleeds was 14.7 (range 3.7-35.4) per patient but on prophylaxis this average reduced to 1.5 (range 0-12.5) ($p<0.001$). The authors also reported that whilst all seven individuals who had started prophylaxis prior to any signs of joint damage maintained normal joint status up to the end of the follow-up period, the joints of the remaining 20 individuals with evidence of arthropathy prior to starting prophylaxis, all improved with prophylactic treatment. This finding was in contrast to the other findings from other studies[84,108,110].

Data for a subgroup of patients included in the Orthopaedic Outcomes Study[84] (previously described in section 2.3.2.1.1) also demonstrated the impact of prophylaxis on orthopaedic outcome. In this analysis, orthopaedic scores for 66 individuals and radiological scores for 53 individuals who had received full-time prophylaxis (defined as prophylaxis for >45 weeks in each year) for the entire 5-year study period were examined. The results from the analysis showed that these individuals recorded significantly fewer bleeds ($P<0.0001$) than the remaining individuals in the study. Moreover, individuals who received full-time prophylaxis also recorded significantly superior orthopaedic scores ($P=0.002$) and radiological scores ($P<0.0001$) after adjusting for age differences between the two treatment groups.

2.3.2.2.4 Clinical effectiveness: evidence from the Malmö Treatment Centre, Sweden

The most comprehensive evidence[92] regarding the ability of primary prophylaxis to modify the progression of haemophilic arthritis is from a series of articles originating from the Malmö Centre, Sweden, where prophylaxis has been practised in individuals with severe haemophilia A since 1958 and in individuals with haemophilia B since 1976[112-119].

In 1992, Nilsson *et al.* reported the results of a study in which a cohort of 60 individuals with severe haemophilia had received prophylaxis for between 2-25 years[115]. The individuals in the study were divided into three different groups according to their age (Table 2.2). The individuals in the youngest age group had received primary prophylaxis from a mean age of 1.2 years of age (range: 0.5-2.0 years) with between 25-40 units of clotting factor three times and twice per week for individuals with haemophilia A and B respectively, whereas individuals in the remaining two groups started prophylaxis at an older age and had received less intensive treatments. The more intensive regimen meant that treatment had prevented the trough *in vivo* clotting factor level from falling below 1 iu/dl in all individuals in the youngest age group; this was not the case for individuals in the two older groups. At the time of the study, each individual was assessed using the WFH orthopaedic and radiological joint scoring systems. The results from the analysis showed that the 15 individuals in the youngest group had experienced less joint bleeds per year and recorded lower orthopaedic and radiological joint scores compared to the 45 individuals in the two older groups. Indeed, each individual in the youngest age group recorded a clinically perfect

orthopaedic and radiological joint score. The effectiveness of the higher dose prophylactic regimen received by individuals in the younger age group was also assessed by comparing their orthopaedic and radiological joint scores to the scores recorded by individuals in the older age groups (n=30) when they were of an equivalent age and to similar age-adjusted scores for a group of individuals who had only received treatment on-demand. The mean orthopaedic scores for the individuals who had received the higher dose prophylactic regime were shown to be markedly better than the scores recorded by individuals in the remaining two groups. However, no tests for statistical differences were performed in any part or subpart or the study.

Table 2.2: Prophylactic treatment of 60 individuals with severe haemophilia from the Malmö Centre, Sweden (mean values and ranges)[115]

	Age		
	3-12 years	**13-17 years**	**18-32 years**
Number of patients (haem. A/B)	15 (13/2)	20 (17/3)	25 (22/3)
Age at start of prophylaxis	1.2 (0.5-2.0)	2.6 (1.0-4.5)	6.2 (3.0-13.0)
Joint bleeds / year	0.1 (0.0-4.0)	3.0 (0.1-16.6)	5.2 (0.5-16.0)
Annual dose range of FVIII/FIX (iu/kg)	1,000-9,000	800-6,600	200-6,000
Pre-infusion FVIII/FIX: C (iu/dl)	1.0 (1.0-5.0)	<1.0-3.0	<1.0-2.5
Orthopaedic joint score	0 (0-0)	1.2 (0.0-7.0)	5.1 (0.0-15.0)
Radiological joint score	0 (0-0)	4.8 (0.0-22.0)	18.0 (0.0-41.0)

The latest publication from the Malmö Centre utilised prospective data collected between 1990-1995 on 34 individuals with severe haemophilia who were between 6-21 years of age[114]. In a similar manner to the previous study, individuals in this study were divided into three groups according to their age (Table 2.3). The youngest two groups comprised of 15 individuals with severe haemophilia who had started primary prophylaxis between the ages of 1.0-2.0 years with 24-40 iu/kg of FVIII three times a week for individuals with haemophilia A and 25-40 iu/kg of FIX twice a week for individuals with haemophilia B. The elbows, knees and ankles were again assessed using the WFH orthopaedic and radiological scoring systems. By the end of 1995, individuals in the two younger aged groups had, on average, experienced fewer bleeds than the individuals aged 16-22 years. Additionally, the individuals in the two youngest groups recorded clinically perfect orthopaedic and radiological joint scores although this was not the case among individuals in the oldest group who had received less intensive prophylaxis and from a later age. Similarly to the 1992 study by Nilsson *et al*, the

authors of this study concluded that haemophilic arthropathy could be prevented if trough *in vivo* clotting factor levels were maintained above 1 iu/dl at all times. However, it is interesting to note that the trough *in vivo* clotting factor levels recorded in the youngest group of individuals was between 1-9 iu/dl which suggests that the *in vivo* level required to prevent the onset of haemophilic arthritis might be above 1 iu/dl. It is also possible that age differences between the groups could explain some or all of the observed differences in joint status.

Table 2.3: Prophylactic treatment of 34 individuals with severe haemophilia followed up from 1990 to 1995 from the Malmö Centre, Sweden (mean scores and ranges)[114]

Patient details	Group I	Group II	Group III
Age at end of study (years)	16-22	11-15	7-10
Number of patients (haem. A/B)	19 (16/3)	9 (8/1)	6 (5/1)
Age at start of prophylaxis	2.6 (1.5-1.4)	1.3 (1.0-2.0)	1.2 (1.0-1.5)
Joint bleeds / year	2.2 (0.0-19.8)	0.1 (0.0-0.4)	0.4 (0.0-0.8)
Annual dose of FVIII/FIX (iu/kg)	3,713 (2,848-4,619)	5,741 (4,730-7,817)	6,354 (5,305-8,915)
Pre-infusion FVIII/FIX: C (iu/dl)	3.8 (2.0-8.0)	4.8 (1.0-9.0)	3.4 (3.0-4.0)
Orthopaedic joint score 1990/95	1.2 (0.0-7.0) / 2.4 (0.0-18.0)	0.0 / 0.0	0.0 / 0.0
Radiological joint score 1990/95	4.8 (0.0-22.0) / 6.5 (0.0-31.0)	0.0 / 0.0	0.0 / 0.0
Annual absence from work / school	0.9 (0.6-7.0)	0	0

2.3.2.2.5 When should individuals begin to receive primary prophylaxis?

A key issue in treating individuals with primary prophylaxis is when treatment should commence. A number of studies have suggested that treatment should begin between the ages of 1-3 years of age prior to any signs of repeated joint bleeding[21,70,98,111,112,115,116,118-121]. However, it has also been suggested that treatment should be withheld until an individual has experienced three joint bleeds or two successive bleeds in the same joint, because not all individuals with severe haemophilia 'behave' as clinically severe[21].

In one study from the Malmö Centre, joint bleeding frequency and WFH orthopaedic joint scores were evaluated in 121 individuals with severe haemophilia who had started prophylactic treatment with clotting factor concentrates at least once a week before the age of 10 years[112]. No significant differences were seen in the annual number of joint bleeds and the development of arthropathy before the age of 3 years. However, age at

start of prophylaxis was found to be an independent predictor for the development of arthropathy (P=0.0002), whereas dose size and infusion interval at were not.[109,110]

2.3.2.2.6 Methods of reducing clotting factor use

Although the evidence suggests that prophylaxis with 24-40 iu/kg of clotting factor 2-3 times per week may prevent haemophilic arthropathy in patients with severe haemophilia, treatment is thought to be extremely costly because it involves the use of large amounts of clotting factor. Interest is growing, therefore, in developing techniques that reduce the amount of clotting factor required for prophylaxis without compromising the effectiveness of treatment.

Once infused, clotting factors are known to show wide intersubject variability in terms of pharmacokinetic behaviour[122]. It has been suggested, therefore, that tailoring prophylactic regimes to individual patient's pharmacokinetic properties might be one method of reducing clotting factor use. Pharmacokinetic dosing, as this process is known, can be seen as a method of 'fine-tuning' clotting factor requirements in terms of size and frequency of dose.

The feasibility of using pharmacokinetic dosing to fine-tune prophylactic regimes has been assessed by Carlsson *et al.* in two separate studies performed at the Malmö Centre[123,123,124,124]. One of these two studies was a prospective crossover study that comprised 21 individuals with haemophilia A. With the exception of one individual who had a baseline clotting factor level of 1.5 iu/dl, all patients had severe haemophilia A; participants were a median of 17 years of age (range 8-42 years). At the beginning of the study, participants were randomised to receive either 25-40 iu/kg of FVIII three times per week or a modified schedule based on individual pharmacokinetic data requiring a dosing interval of two days. The aim of both treatment regimes was to prevent *in vivo* FVIII levels from falling below 1 iu/dl. The study lasted for a total of 12 months; patients switched treatment regimes after 6 months. Spontaneous joint bleeding episodes and clotting factor usage were the outcomes assessed.

In order to obtain the necessary pharmacokinetic information needed for the modified dosing schedules, venous blood samples were taken from each patient. FVIII concentration was measured using a chromogenic assay. To verify these data, checks were made on each patient at least four times during the study. *In vivo* clotting factor

levels were assessed each time a participant required maintenance infusion. Doses were calculated as:

$$C = \sum_{i=1}^{n} A_n \cdot e^{-k_n \cdot t}$$

Where C is the *in vivo* clotting factor concentration at time *t*, A is the y-axis intercepts and k*n* is the rate constants of the exponential term (half-life=ln2/k).

Data from only 14 participants were analysed, as the remainder did not complete the treatment protocol. During the periods of pharmacokinetic dosing the mean *in vivo* trough level increased from 0.89 iu/dl to 2.2 iu/dl ($P<0.005$); a slight decrease in bleeding frequency was also observed but the difference was not significant. Furthermore, during these periods, reported FVIII consumption decreased from a mean of 124,000 iu to 84,000 iu ($P<0.005$), a reduction of 32% over the six month period.

Although no adverse events, such as inhibitor development, were observed in any of the 21 patients, 7 (33%) patients did not complete the study. Two individuals were withdrawn from the study, one following an (unrelated) accident and the other because he changed treatment centres. One individual did not consent to using the reduced rate pharmacokinetic regime, one individual did not wish to receive injections every two days and in another patient it was not possible to maintain an *in vivo* clotting factor level above 1 iu/dl with a dosing interval of two days. Of the remaining two individuals, one started with the modified regime and subsequently refused to allow longer intervals between doses and the other individual found that attempting to reduce clotting factor use when starting the pharmacokinetic regime was not worthwhile given the size of the clotting factor vials. Therefore, although this non-completion rate is high (33%) and there is some concern as to patient acceptability due to the increased need for venipuncture, reduced rate treatment regimes based on individual pharmacokinetic details were technically feasible in all but one person.

Carlsson *et al.* also performed a similar crossover study in eight individuals with severe haemophilia B over two two-week periods[124]. The results showed that compared to infusing with FIX every 3 days, infusing every 2 days reduced total clotting factor use

by 25%. Moreover, compared to the 3-day programme, infusing every day reduced the total amount of FIX used by 34%.

Based on the same pharmacokinetic principles, it has been suggested that supplying patients with a continuous infusion (CI) of FVIII would further reduce consumption during standard prophylaxis (ie. 24-40 iu/kg 2-3 times per week) and bolusing using pharmacokinetic information every other day by as much as 92% and 86% respectively[123-125]. However, a practical application of this process, which would probably require the use of an implantable micro-pump and reservoir system, is yet to be marketed. Additionally, although the Swedish series of studies suggest that it is possible to prevent the onset of degenerative haemophilic arthritis in individuals with severe haemophilia, studies have shown that a small number of individuals with mild / moderate forms of the condition have developed HA[85]. Thus, it is yet to be proved that reducing or removing the peaks in *in vivo* clotting factor activity would be clinically insignificant[92].

Although long-term CI is yet to become a practical treatment option, an alternative to bolusing during surgery is to use short-term CI. Indeed, CI has previously been used as a method of supplying clotting factor during a range of different invasive procedures and has also been used to treat potentially life-threatening bleeds such as cerebral haemorrhage in individuals with and without inhibitors[71,125-138].

The theoretical advantage of CI over bolusing is that it maintains a constant *in vivo* clotting factor level above which there is little or no risk of bleeding and in some instances has reduced clotting factor consumption by 30%-75%[126,127,132,134,139,140]. It has also been suggested that CI may allow individuals to be discharged earlier from hospital compared to bolusing because wounds are thought to heal quicker and because of the use of more ambulant therapy programmes[133].

A study by Hathaway *et al.*[139] in 6 individuals with severe haemophilia A showed that a mean 0.04 iu/kg/hour (range 0.12-0.56 iu/kg/hour) FVIII was required to raise clotting factor levels by 1 iu/dl/hour. Bona *et al.*[128] also demonstrated the safety and efficacy of this infusion rate in 11 patients with haemophilia A and also demonstrated that two patients with haemophilia B required a mean 0.075 iu/kg/hour of FIX to achieve the

same objective. There is some evidence to suggest that clearance rates reduce during the course of treatment meaning that progressively less clotting factor is required in order to maintain a given *in vivo* clotting factor level. Martinowitz *et al.*[133] demonstrated in 10 patients with haemophilia A that clearance rates decreased from a median post-operative level of 3.2 ml/kg/hour to 1.7 ml/kg/hour on day 5 after which time the clearance rate levelled off for the remainder of treatment (range of treatment 4-21 days). In a separate study of 4 individuals with severe and moderate haemophilia B, 3 patients experienced a progressive decrease in clearance rates[71]. When infusion rates are adjusted to take account of decreased clearance rates, the process is usually referred to as *adjusted dose CI.*

One of the reported side effects of CI has been local thrombophlebitis around the cannula site. However, there is reason to believe that in the majority of instances infusing a small dose of diluted heparin concurrently with the clotting factor can prevent cannula irritations and infections. A further limitation of this approach is that CI requires clotting factor to remain in solution in plastic containers for periods of time. Efficacy must be established and a license granted before a clotting factor can be stored and used in this manner. At present the greatest published experience is for Monoclate P (a very high purity FVIII) and Mononine (a very high purity FIX). However, the suitability of using a recombinant FVIII for CI is currently being investigated.

2.3.2.3 Prophylaxis compared with treatment on-demand

2.3.2.3.1 Prophylaxis versus treatment on-demand and inhibitor (antibody) development

A possible side effect of replacement therapy with clotting factor is inhibitors to treatment. Inhibitor antibodies reduce the effectiveness of treatment with FVIII or FIX. An inhibitor of one Bethesda Unit (BU) is defined as the amount of antibody needed to destroy 50% of the clotting factor activity in the normal pool in two hours[141]. In 1994, 280 (5.2%), 10 (0.8%) and 4 (0.01%) of individuals with haemophilia A, B and vWD registered at haemophilia centres in the UK developed inhibitors to treatment[4]. However, two prospective studies have shown that inhibitors developed in 28%-52% of individuals with haemophilia A[142,143]. A large US study has also shown that the prevalence of FIX inhibitors was much lower than for individuals with haemophilia A with a prevalence rate of between 1.5%-3.0%[144].

Low responding (titre) inhibitors, those that do not usually go above 5 BU[141], are often transient and usually disappear spontaneously over time. In the majority of instances these individuals do not present a difficulty in terms of treatment and may, over the short-term, be treated with higher doses of clotting factor. Individuals with high titre inhibitors, however, are a serious concern, as patients may not achieve measurable levels of clotting factor activity despite receiving large doses of clotting factor. Treating these individuals can be an extremely complex and costly process[145-147].

A number of factors are believed to place individuals at increased risk of inhibitor development such as the number of exposure days to clotting factor, race and particular mutations in the FVIII gene[23,92,148]. It has also been suggested that increased clotting factor purity is also associated with an increase in the risk of inhibitor development[149] but available evidence is inconclusive[150]. Moreover, no evidence could be found that to suggest that prophylactic treatment is associated with an increased risk of inhibitor development[142].[61,143,151]

2.3.2.3.2 Prophylaxis versus treatment on-demand, venous access and adherence to treatment

Prophylaxis requires regular access to the central venous system. However, this can sometimes be problematic in young children and in the elderly. To aid prophylactic treatment, young patients may be fitted with a percutaneous central venous catheter such as Brovaic or Hickman catheter, or an implantable venous access device such as a Port-A-Cath. The use of such devices is not automatic however, because of the risk of infection[3,112].

A number of studies have reported on the long-term feasibility of fitting patients with severe haemophilia with venous access devices such as Port-A-Caths[21,121,152-158]. In a study by Ljung *et al.*[157], 25 individuals with haemophilia of mean age 1.6 years (range 6 months to 7.4 years) had Port-A-Caths fitted for a mean period of 2.4 years (range: 1 month to 8.3 years). Seven children had developed inhibitors prior to having the devices fitted of which six were high responding inhibitors. The Port-A-Caths were implanted in an operating room under aseptic conditions, general anaesthesia and under the haemostatic cover of clotting factor. The position of the catheter was confirmed by X-ray and sealed with a small injection of heparin. Antibiotics were administered on

the first post-operative day to all but one patient. No post-operative complications were reported for 20 of the individuals but one individual developed an infection, one individual experienced bleeding around the port on the day after the operation and one individual experienced both bleeding and infection. All three complications were treated without the need to replace the Port-A-Cath systems. In the remaining two individuals, septicaemia and the malposition of the catheter meant that both individuals required their Port-A-Caths to be replaced, both without complication.

In the study by Liesner *et al.*[21] (described in section 2.3.2.2.3), nine of 27 (33%) children with severe haemophilia who were treated with prophylaxis were fitted with venous access devices. Eight of these nine children were fitted with a Port-A-Cath and one child was fitted with a Hickman line. The catheters were fitted to the children when they were aged between 1.3 and 5.2 years but no details are given concerning the length of time the devices were fitted. Four of the nine (44%) children developed catheter infections, two of whom required the Port-A-Cath to be removed and reinserted after two weeks and four years; no subsequent complications were reported.

Other studies have reported the incidence of minor infection to be between 10% and 25% [154,158] but otherwise trouble free use. Blanchette *et al.*[159] reported an infection rate of 48% or 0.7 infections per 1,000 patient days. One patient in this study experienced persistent pain associated with needle access of the port[159]. Zappa *et al.*[160] reported an infection rate of 10% but stated that in every instance patients or their parents expressed a preference for catheter insertion. Most stated that they would have another catheter fitted if the present device had to be removed following infection. A recent review of the literature also concluded that the highest risk of an infection approximtely two years after fitting a venous access device was 29%[161]. However, the risk of developing an infection was shown to be almost three times as large for individuals who were fitted with a device for the purposes of immune tolerance (treatment for inhibitors) than for individuals who were receiving routine prophylaxis. Moreover, it would also appear that individuals are at increased risk of infection if they are HIV seropositive or have been fitted with an external device such as a percutaneous device[154]. No deaths have been reported in individuals with haemophilia as the result of a catheter-related infection.

2.3.2.3.3 Prophylaxis versus treatment on-demand and mortality

Although the primary objective of prophylaxis is to modify the progression of haemophilic arthropathy, it has been suggested that prophylaxis might also reduce mortality because it reduces the probability of individuals experiencing potentially life-threatening bleeding episodes and because the probability of individuals undergoing surgery is also likely to decreased.

Only one study was found that used patient based information to examine the impact of prophylaxis on mortality[9]. The study used data on 919 Dutch individuals with haemophilia collected between January 1st 1986 and June 1st 1992. Of the 45 individuals who died between these dates, 27% were due to AIDS related events, 33% to cerebrovascular disease and haemorrhagic events and 11% to liver disease and cirrhosis. The results from the analysis showed that individuals with severe haemophilia had a life expectancy equivalent to that of the Dutch general male population once the impact of HIV and HCV were removed from the analysis. Further multivariate analysis using a Cox proportional hazards model showed that individuals receiving prophylaxis had a relative risk of death of 0.5 (95% CI 0.1-2.6) compared to individuals treated on-demand, meaning that altough prophylaxis reduced the risk of death by 50% the finding was not significant. However, it is feasible that as the number of individuals who die as a result of HIV or HCV infection declines, the proportion of individuals who die from haemorraghic events may increase thus the difference in mortality between the two methods of treatment might theoretically increase over time. It is also likely that individuals who received prophylaxis were unrepresentative of individuals with severe haemophilia, expereiencing more severe bleeding, and thus the ability of prophylaxis to reduce mortality has been underestimated.

2.3.2.3.4 Prophylaxis versus treatment on-demand and health-related quality-of-life

Two studies were found in which the relative impact of prophylaxis and treatment on-demand on health-related quality-of-life (HR-QoL) for individuals with haemophilia had been assessed[162,163]. The first study[162], published as an abstract, examined HR-QoL in 566 individuals with haemophilia from 16 European haemophilia treatment centres using the Medical Outcome Study (MOS) Short Form 36 (SF-36) health survey questionnaire[164,165]. The MOS SF-36 questionnaire is a generic instruments that can be used to assess HR-QoL within as well as between different conditions. It measures HR-QoL on eight multi-item dimensions and scores on each dimension from 0 (worst health) to 100 (best health) (see section 5.2 for a more detailed description of this

questionnaire). Individuals were divided into two groups according to whether they had been treated on-demand or with prophylaxis but no more clinical or treatment details are provided. The results from univariate analyses showed that individuals who were treated on-demand recorded significantly lower scores on the physical functioning dimensions ($P<0.05$) and the general health dimension ($P<0.05$) than individuals who had been treated with prophylaxis but there were no significant differences on any of the remaining six scales. The abstract presented no further comparative analysis.

The second HR-QoL study, by Szucs *et al.*[163], included 50 individuals with haemophilia who had completed the Rosser-Watts disability \ distress matrix[166] questionnaire in addition to the MOS SF-36[162,163]. Similarly to the MOS SF-36, the Rosser \ Watts matrix is a generic HR-QoL instrument where scores of 1 and 0 are equivalent to perfect health and death respectively[166]. The 50 individuals in the study were divided into those who had received treatment on-demand (n=39) and those who had received prophylaxis (n=11). Nineteen individuals were known to be HIV seropositive. Prophylaxis was defined as prophylactic treatment with clotting factor 12-18 iu/kg three times per week but no further treatment details, such as duration of prophylaxis, were provided. The majority of individuals (92%) had severe haemophilia but clotting factor levels ranged between <1-5 iu/dl and it was unclear what proportion of individuals with severe haemophilia were in each treatment group. The results from the SF-36 questionnaire were also compared to normative data for males aged between 31-40 years although the source of this general population data was not referenced.

Individuals treated with prophylaxis and on-demand produced median utility values of 0.53 (range: 0.43-0.87) and 0.53 (range: 0.28-0.87) respectively but no adjustments were made for age differences between the two treatment groups and viral (HIV or HCV) status in multivariate analyses. Similarly, the authors claimed that individuals with severe haemophilia recorded significantly lower scores on the SF-36 dimensions that recorded physical functioning, physical role limitation, pain and general health compared to their normative counterparts. However, no tests for significant differences between the two groups were performed, no measures of variance were quoted for either set of SF-36 scores and no adjustments were made for the effects of HIV or HCV infection on the scores.

2.3.2.3.5 Prophylaxis versus treatment on-demand: costs and cost-effectiveness.

Four studies were found that examined the costs of treating individuals with prophylaxis or on-demand (Table 2.4). Three of these four studies also examined the cost-effectiveness of prophylaxis. A number of other studies which examined at least the costs of treatment were also found but they were excluded from this section of the review because they did not include any patient-based data or did not report their results in sufficient detail to warrant further appraisal[167-172]. One further study was excluded from this section of the review because it only referred to resource use and not costs[173].

The European cross-sectional study by Szucs *et al.* (previously described in section 2.3.2.3.4) reported that it cost £11,400 and £17,700 per patient-year (PPY) to treat individuals with severe haemophilia on-demand or with (secondary) prophylaxis respectively, when the direct and indirect costs of treatment were included in the analysis; no tests for statistical differences between the two treatment groups were performed. The analysis also showed that irrespective of the method of delivery, clotting factor provision accounted for almost 95% of total annual costs whereas the indirect costs accounted for no more than 4%. This study also produced an incremental cost effectiveness ratio (ICER) per averted joint bleed of £800. However, the limitations of this study are that neither treatment protocol is described in sufficient detail to know exactly what was being evaluated and it is impossible to assess how individuals were assigned to treatment groups. Thus, any comparisons between treatment groups might be biased. Moreover, no attempt was made to extrapolate the findings if the study and no sensitivity analysis was performed thus. Thus, it is difficult to attach any certainty to these cost or cost-effectiveness estimates.

In addition to examining the clinical impact of prophylaxis, data from the retrospective Orthopaedic Outcomes study (previously described in section 2.3.2.1.1) were also used to examine the health care and indirect costs of treating individuals with haemophilia A with prophylaxis. All individuals included in the original study were stratified according to one of three treatment groups according to how long they had received prophylaxis for 0-5 weeks (no prophylaxis), 6-45 weeks (partial prophylaxis), or greater than 46 (full prophylaxis) weeks per year respectively. The study included resource data on inpatient days, surgery and days lost from work or school and was valued using a combination of US cost data, US charge data and US average earnings. The individuals had a mean age of 15 years (sd. 6.9 years).

The results from the analysis showed that the costs of clotting factor provision accounted for £19,700, £50,800 and £56,200 PPY for individuals receiving no, partial or fulltime prophylaxis respectively. The costs associated with disability-related outcomes (hospital visits and lost production) were shown to be £1,000, £1,400 and £500 PPY for these three treatment groups respectively. However, the study contains no other analyses, statistical tests between treatment groups or adjusts costs for differences in age or viral status.

The costs of providing clotting factor to individuals with haemophilia on a prophylactic basis has also been examined in two separate studies performed by Carlsson *et al.*[123,124] (previously described in section 2.3.2.2.6). However, it should be noted that the primary purpose of both studies was to demonstrate the efficacy of reducing the interval between maintenance doses of clotting factor rather than estimating the costs of treating individuals with prophylaxis *per se*. The first of these two studies was a prospective cross over study that comprised of 21 individuals with haemophilia A[123].

Data from only 14 participants were analysed, as the remainder did not complete the treatment protocol. During the periods of pharmacokinetic dosing the mean *in vivo* trough level increased from 0.89 iu/dl to 2.2 iu/dl ($P<0.005$); a slight decrease in bleeding frequency was also observed but the difference was not significant. Furthermore, during these periods, reported FVIII consumption decreased from a mean of 124,000 iu to 84,000 iu ($P<0.005$), a reduction of 32% over the six month period. Moreover, the pharmacokinetic dosing programme reduced the annual cost of clotting factor provision from £62,600 per annum to £42,400 per annum, a decrease of 32%.

Although no adverse events such as inhibitor development were observed in any of the 21 patients, seven (33%) patients did not complete the study. Two individuals were withdrawn from the study one following an (unrelated) accident and the other because he changed treatment centres. One individual did not consent to using the reduced rate pharmacokinetic regime, one individual did not wish to receive injections every two days and in another patient it was not possible to maintain an *in vivo* clotting factor level above 1 iu/dl with a dosing interval of two days. Of the remaining two individuals, one started with the modified regime and subsequently refused to allow longer intervals

between doses and the other individual found that attempting to reduce clotting factor use using the pharmacokinetic regime was not worthwhile given the size of the clotting factor vials. Therefore, although this non-completion rate is high (33%) and there is some concern as to patient acceptability due to the increased need for venipuncture, reduced rate treatment regimes based on individual pharmacokinetic details were technically feasible in all but one person. Carlsson *et al.* also performed a similar crossover study in eight individuals with severe haemophilia B over 2x2 week periods[124]. Annualising the study results produced costs of £80,600, £46,600 for individuals receiving FIX twice a week and every three days respectively.

Table 2.4: The costs and cost-effectiveness of replacement therapy: results from the literature search

				Cost per patient-year+		
Study	**Study Year**	**Method**	**Resources***	**On-demand**	**Prophylaxis**	**Notes**
Szucs, 1996[163]	Not stated	Cost-effectiveness analysis. 6 month European cross-sectional study on 50 individuals.	1,2,3	£11,400	£17,700 ICER: £800 per joint bleed averted	Secondary prophylaxis. Not all individuals had severe haemophilia. Health care costs accounted for on-demand 94% and prophylaxis 99% of total costs. No sensitivity analysis performed
Smith, 1996[174]	Not stated	Cost-effectiveness analysis. US multi-centre study including 107 individuals followed for median time of 26 months (range: 6.5-72.0 months). Future costs were modelled from baseline data.	1,2,3	£16,650	Model 1: £53,700 Model 1: ICER: £750 per bleed averted Model 2: ICER: £950 per bleed averted	Secondary prophylaxis for individuals with <2 iu/dl haemophilia A under the age of 18 years. Clotting factor use accounted for >93% of total costs. Prophylaxis significantly (P<0.05) more costly than on-demand. Sensitivity analysis performed
Carlsson, 1997[123]	Not stated	Cost analysis. Swedish. Two times 6 months cross over study in 21 individuals with haemophilia A. Study compared prophylaxis 3 times per week compared to a reduced interval between doses based on individual pharmacokinetic data.	1	-	£62,600 and £42,400 for per patient-year for treatments respectively	Only 13 patients finished the reduced dose part of the study. Trough *in vivo* clotting factor level was higher (P<0.005) during reduced dose period. No statistical comparisons for differences in cost were performed. No sensitivity analysis performed

The costs and cost-effectiveness of replacement therapy: results from the literature search (continued)

				Cost per patient-year+		
Study	**Study Year**	**Method**	**Resources***	**On-demand**	**Prophylaxis**	**Notes**
Bohn, 1998[175]	Not stated	Cost analysis. Multi-centre study from US, Japan and Europe. 2,190 patient-years of data.	1,2,3	£13,200	£36,300	On-demand defined as no prophylaxis. Unclear whether prophylaxis was primary or secondary. Prophylaxis defined as treatment for >46 weeks in a year. Costs are per patient-year. Study based on the Orthopaedic Outcomes Study [84]. No sensitivity analysis performed
Carlsson, 1998[124]	Not stated	Cost analysis. Swedish. Two times 2 weeks cross over study in 8 individuals with haemophilia B. Study compared prophylaxis 3 times per week compared to 2 days between doses based on individual pharmacokinetic data.	1	-	£80,600 and £36,300 for per patient-year for treatments respectively	No statistical comparisons for differences in cost were performed. No sensitivity analysis performed

* **(1) clotting factor, (2) other health care resources and (3) indirect resources**

\+ **Costs are displayed in 1998 UK £**

In the most comprehensive study, the costs and effects (the number of bleeds prevented) of treating American individuals with severe haemophilia A with prophylaxis versus treating on-demand was assessed using patient based data and modelling techniques[174]. Data were collected retrospectively from 11 treatment centres on 90 and 27 individuals who had been treated on-demand and with secondary prophylaxis respectively; all individuals were under 19 years of age at the time of the study. However, those receiving prophylactic treatment had a history of frequent haemarthroses, intracranial haemorrhage or low titre inhibitors meaning that the treatment groups were likely to be unrepresentative of the haemophilia community at large. Prophylaxis was defined as treatment with FVIII at least three times per week for a minimum of 6.5 consecutive months; although this did not necessarily mean primary prophylactic therapy. The median observation period was 26 months (range: 6.5-72 months) and all patients were under the age of 18 years at the time the data were collected. Future costs were extrapolated using a model (although no details of this model are provided). Medical resource (clotting factor use, hospital visits) use was abstracted from patient notes but indirect resource use was estimated. Clotting factor was valued at 38 p/iu and charge data were used to value the remaining medical resources. Productivity losses as a result of disability were estimated by means of published data on men with polyarthritis as listed in the 1978 US Social Security Survey of Disability and Work. These data indicated that the earnings differential between affected and unaffected men is approximately 38%. Expected future lifetime earnings were also calculated on the basis of published data. The loss of a school or workday was valued at £33 *per diem*. Future costs and effects were discounted at an annual rate of 5%.

The results from the analysis showed that the annual costs of treating individuals with prophylaxis and on-demand were £53,700 and £16,650 respectively. Similarly to the studies by Szucs *et al.* and Bohn *et al.*, the results from this study showed that clotting factor provision alone accounted for a very high percentage of total costs (93%-97%). The results from this analysis were also extrapolated using modelling techniques. Although no real details of this model were provided, the results from the exercise produced net present costs of £620,000, £900,000 and £1,200,000 for individuals treated on-demand, prophylaxis between the ages of 3-20 years and prophylaxis between the ages of 3-50 years respectively. The two models also produced incremental cost-effectiveness ratios of between £750-£950 per bleed avoided. The authors also noted

that the ICERs were sensitive to the clotting factor cost and the discount rate. Threshold analysis also showed that the total costs of prophylactic care from ages three to 50 years would equal the costs of treating on-demand if the clotting factor cost was less than 3 p/iu.

A number of studies have also attempted to quantify the indirect costs associated with prophylaxis and / or treatment on-demand (Table 2.5). Although they are of unequal design, they suggest that individuals treated on-demand were absent from work or school each year for a mean of between 1.3 and 10.6 days per year whereas individuals who received primary or secondary prophylaxis were absent from work or school for a mean of between 0-22 days per year.

2.4 Summary and general discussion

The aim of this Chapter was to review the existing literature on the costs and effects (or benefits) of treating individuals with severe haemophilia on-demand or with prophylaxis. The results show that there has never been a definitive randomised controlled trial of treatment on-demand compared to prophylaxis that has assessed the comparative costs and / or consequences of both treatments. Moreover, very few uncontrolled data have been reported either on the long-term costs or health consequences of treating individuals with severe haemophilia on-demand. Additionally, the majority of evidence on the ability of primary and secondary prophylaxis to reduce bleeding frequency and its associated sequeale (haemophilic arthritis) is from studies that were small in sample size, uncontrolled and of inadequate duration to capture all outcomes of interest. However, the results from these studies combined with long-term observational data from the Malmö Centre strongly suggest that prophylaxis can modify the frequency of bleeding episodes and consequently the progression of haemophilic arthritis if sufficient amounts of clotting factor are administered at appropriate intervals.

Table 2.5: Studies reporting absenteeism from work or school by method of replacement therapy

Study	Mean annual days absent from work / study Sample size Age at time of study		Notes
	Prophylaxis	On-demand	
Aledort, 1994[84]	-	-	Study doesn't refer to prophylaxis *per se* just annual amounts of clotting factor. Individuals receiving 0-500 iu/kg/year and >2,000 iu/kg/year were absent from work for a mean of 8 and 3 days respectively. Precise group sizes are unclear.
Leisner, 1996[21]	1 day per term at most n=27 median 8.5 (range 2.9-17.7)	-	Mix of primary and secondary prophylaxis. Children of school age followed for a mean of 30 months (range 7-76).
Löfqvist, 1997[114]	0 n=15 7-15 years	-	Primary prophylaxis started between 1.0-2.0 years of age. Patients have received clotting factor infusions of between 4.7-8.9 '000s iu/kg/year. The study possibly duplicates some of the data published in Nilsson, 1992.
Nilsson, 1992[115]	0.9 (range 0.6-7.0) n=20 between 13-17 years	-	Prophylaxis started at a mean of 2.6 (range 1-4.5) years of age. Patients with haemophilia A have received mean clotting factor infusions of 1.5 (range 0.8-6.6) '000s iu/kg/year.
"	5.8 (range 1.0-20.0) n=20 between 24-32 years	-	Secondary prophylaxis started at mean of 7 (range 3-13) years of age. Patients with haemophilia A have received mean clotting factor infusions of 0.4 (range 0.2-6) '000s iu/kg/year.
Smith, 1996[174]	0.9 n=16 all <18 years	1.3 n=42 all <18 years	Secondary prophylaxis. Mean follow-up period of 26 months (range 6.5-72). Group differences were non-significant. Severe haemophilia defined as <2 iu/dl.
Szucs, 1996[163]	2 n=11 -	10.6 n=39 -	Secondary prophylaxis. No P-values quoted for differences between groups. Figures annualised. Not all individuals had severe haemophilia.
Szucs, 1998[173]	8 n=399 mean 35.3 (sd. 14.6)	7.2 n=145 mean 35.3 (sd. 14.7)	Secondary prophylaxis. Includes days off work by a child's carer. No P-values quoted for differences between groups. Figures annualised. Not all individuals had severe haemophilia.
Triemstra, 1995[176]	School 10 / work 22 n=980 mean 32 years	-	No definition of prophylaxis or treatment details provided. Cross-sectional postal study.

Two published studies were found that examined the impact of treatments on health-related quality-of-life (HR-QoL) in individuals with haemophilia. However, neither study adequately adjusted their results for potentially confounding factors such as clinical severity, age, HIV serostatus and previous clinical experiences. Thus, the results from these studies are of limited use. Also in terms of morbidity, only one (US) study was found in which the potential comparative ability of prophylaxis to reduce the need for hospital visits such as inpatient stays or orthopaedic procedures was reported.

A number of studies were found that assessed the costs of treatment: Szucs *et al.*[163] estimated the cost of treating individuals on-demand and with (secondary) prophylaxis to be £11,400 and £17,700 per annum respectively and Smith *et al.*[174] estimated these respective costs to be higher at £16,650 and £53,700 per annum. The literature search also produced three studies that claimed to be cost-effectiveness analyses of prophylaxis. However, one of these studies was found to be a cost analysis and not a cost-effectiveness analysis[175]. One of the remaining two evaluations was limited because few treatment details were provided, results were not adjusted for differences between patient groups, no details were provided as to how individuals were assigned to the two different treatment groups and no sensitivity analysis was performed on the incremental cost-effectiveness ratio[163]. The final study by Smith *et al.*[174] provided the most comprehensive information on cost-effectiveness to date. However, the data used in this study related to individuals who received secondary prophylaxis and no attempt was made to link final intermediate outcomes (joint bleeds) to final health outcomes (eg. the development of haemophilic arthritis). Therefore, although it is relatively clear that primary prophylaxis can prevent bleeding and is more costly than on-demand treatment, it currently remains uncertain whether it is cost-effective.

3 GENERAL METHODS AND SOURCES OF DATA

This chapter describes the general methods used in this research and the sources of data. However, specific details of how these methods were implemented, why particular methods were chosen and, in some instances, how the data were collected and analysed, are presented in the relevant chapter(s).

3.1 Economic Evaluation

Information on efficiency in health care resource use can be generated through '*economic evaluations*'[17,177-180]. To qualify as a *full* health economic evaluation, a comparison is needed between the costs and benefits of two or more health care programmes. An economic evaluation that considers only the costs or benefits of treatment is a *partial* form of evaluation and cannot be used in most instances to assess efficiency of resource allocation[177]. However, despite some agreement about the fundamentals of economic evaluation, no standard design framework exists and there is much disagreement about specific details[181].

3.1.1 The forms of full economic evaluation

There are four full forms of economic evaluation. Each form considers costs in a similar manner but they differ in the way that they measure and value health outcomes and hence in which circumstances each form of evaluation is the most appropriate.

3.1.1.1 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) can be useful when there is one main natural dimension along which to measure changes in health outcome, such as 'years-of-life saved'. The use of 'intermediate' outcome measures should, however, be avoided if possible, as they may be poor surrogates for final outcomes. For example, in evaluating treatment for individuals who are HIV seropositive it would be preferable to express outcomes as years-of-life saved rather than as changes in the CD4 T-cell count.

3.1.1.2 Cost-minimisation analysis

Cost-minimisation analysis (CMA) is a special instance of CEA where there is good evidence to suggest that the health outcomes provided by the treatments under scrutiny are identical hence, the treatment of choice is simply the least costly option.

The major limitation of CEAs / CMAs is that comparing the cost-effectiveness of treatments across different clinical settings is difficult to do when effectiveness has been evaluated using different outcome measures. For example, it would be difficult to compare the cost-effectiveness of providing a hepatitis A vaccine to the cost-effectiveness of providing beta interferon to individuals with multiple sclerosis if the outcome measures used are the number of protected days of exposure to risk and symptom-free-days respectively.

A further limitation of CEA is that uni-dimensional outcome measures such as disease-free-joints and symptom-free-days do not incorporate the full benefits of treatment as no reference is made to health-related quality-of-life (HR-QoL). Although there is no definitive description of HR-QoL, Patrick *et al.*[182] defined it as:

"the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy".

3.1.1.3 Cost-utility analysis

The nineteenth-century political theorist Jeremy Bentham first discussed utility theory and utility scales[183]. Bentham stated that if an individual prefers situation A to situation B, the individual must place a higher value (or utility) on situation A than B. Utility scales are similar to ordinal ranking systems in that the utility placed on a situation or object simply records relative rather than absolute levels of desirability.

In more recent times, utility theory has been developed in accordance with the von Neumann & Morgenstern normative theory of decision making under uncertainty in order to overcome some of the limitations posed by CEAs[184]. *Cost-utility analysis* (CUAs), as this form of evaluation is known, combines evidence on mortality with evidence on morbidity in order to express health outcomes in terms of a single utility figure or preference score. Theoretically, these utility scores can be determined for all existing health care programmes, although in practice they can sometimes prove difficult to calculate. Perhaps the most widely used utility measure is the *Quality-Adjusted Life-Year* (QALY) where a value of 1 QALY is equivalent to a year of perfect health and a value of 0 QALYs is equivalent to death[185]. Values between 0 and 1 relate to a year spent in varying degrees of health relative to these two points. For example, if

an individual valued their current health at 0.8, a year spent in this health state has been valued equivalently to 0.8 of a year in perfect health.

In addition to including issues of HR-QoL, the advantage of this utility-based approach is that using a common measure of health outcome allows for comparisons of cost-effectiveness across different clinical settings. Results from CUAs can also be used to inform the resource allocation of a fixed budget through the principle of QALY maximisation and through the use of QALY league tables, although the use of these league tables is controversial[186].

QALYs are calculated by assigning individuals to '*health states*' using either a specially customised HR-QoL questionnaire or a generic HR-QoL questionnaire such as the EuroQol[187] (EQ-5D) or the Disability / Distress matrix[166]. A set of weights (utilities) is then required with which to value each individual health state; the result being the total number of QALYs.

The advantage of using a generic HR-QoL questionnaire to calculate QALYs is that health states can be valued using pre-calculated utility values that have been derived from the general population. The disadvantage of this approach is, however, that generic questionnaires may not be sensitive to all clinical events, as they have been designed to be used in a number of different clinical settings. A customised questionnaire that contains disease-specific health states is likely to be more sensitive. However, the analyst will also need to ask patients a number of questions based on standard gamble techniques or allied scaling methods[178] to generate a set of utilities; this can often be extremely time consuming.

3.1.1.4 Cost-benefit analysis

Pareto's definition of an efficient allocation of resources is a situation where no one person could be made better off without making a different person worse off. To achieve Pareto efficiency, a necessary precondition is that the allocation of resources is *economically efficient.* That is, that the economy under scrutiny is producing on its production possibility frontier (PPF). This is because if production was inside the PPF, one person could feasibly be made better off without making someone else worse off. Further criteria for Pareto efficiency are that no more resources than necessary are used to produce a given output (*technical efficiency*) and that resources are used to produce

goods that society values most highly (*allocative efficiency*). For example, an economy producing all left shoes on its PPF would not be allocatively efficient because clearly a Pareto improvement could be found that would benefit everyone. CBAs address issues of Pareto efficiency because they seek to address all three notions of efficiency and include all social and private costs of benefits whom so ever they may apply to. However, in the absence of robust effectiveness data, CEAs only address issues of technical and economic efficiency because they do not attempt to value resource allocations. CUAs, on the other hand, only address issues of economic and allocative efficiency because they do not indicate whether minimal resources are being used to produce the output of interest.

The distinguishing feature of a CBA is that health outcomes are expressed in monetary terms, rather than physical units such as disease free days or QALYs. Because a monetary value is placed on benefits, CBAs do not necessarily need to include a comparative programme. Results for treatment A can, therefore, be expressed as *net benefits* using the formula:

$$\text{Net benefit}_A\ (£) = \text{Benefit}_A\ (£) - \text{Cost}_A\ (£)$$

CBAs are often viewed as the theoretically most complete form of economic evaluation as they are the only form of evaluation to incorporate non-health related benefits such as the effects of an intervention that spill over to other people (externalities). However, CBAs are rarely used to evaluate health care technologies because of the ethical concerns of placing a monetary value on human life and because of methodological concerns over the methods used to assign such values[188].

One method of quantifying non-marketed benefits for use in a CBA is to use *'willingness-to-pay' (WTP)* techniques[178]. Using this technique, survey methods are used to ask individuals to consider the contingency of an actual market existing for a programme or health benefit and to reveal the maximum they would be willing-to-pay for such a programme in an attempt to measure underlying consumer demand. However, there is much disagreement concerning how WTP should be measured and how such measures should be incorporated into CBAs. For example, there is

disagreement as to whether scenarios should include certain or uncertain health outcomes.

3.1.2 Costs

Costs are the product of the quantity of resources used multiplied by their value or unit cost. Drummond[178] identifies *health care, patient / family* and *other sectors* as the three categories of cost. *Health care* costs consist of the costs of organising and operating a health care programme including the costs of dealing with adverse clinical events. *Patient / family* costs include those 'out-of-pocket' costs incurred as a direct result of the decision to undergo some form of health care; this includes the value of the patients and their families' time (these are sometimes referred to as indirect costs). *Other sector* costs incorporate those resources consumed by other public agencies or the voluntary sector.

Costs are either *fixed* or *variable*. Costs that do not vary with quantity of output in the short-term (approximately within one year) are *fixed* costs, for example rent, equipment leases and some staff wages. Costs such as drugs and bed days that vary according to the level of output are examples of *variable* costs.

3.1.2.1 Resource valuation

The theoretically correct unit cost for a resource is its' *opportunity cost*. That is, the value of the forgone benefits because the resource is not available for its next best alternative use[178]. However, the pragmatic approach to valuing marketed resources is to use existing market prices, unless there is some reason to do otherwise, for example, if prices are subsidised by a third party. One major non-market resource input into health care programmes is increased productivity due to 'renewed' health. Since increased productivity does not have a readily available market value, one method of valuation is to use the *human capital approach* (HCA). The HCA places monetary weights on healthy time using appropriate gross market wage rates (ie. gross earnings before any deductions plus employer-paid benefits) but there are a number of practical and methodological controversies surrounding this. For example, imperfections in the labour market may mean that market wages do not reflect the marginal productivity of workers. It has also been argued that the HCA overestimates the true cost to society if an individual is unable to participate in the workforce either through ill health or in order to receive health care particularly following short-term absences[189]. The *friction*

cost method, unlike the HCA, states that losses in production could be compensated for by a worker on his \ her return to work or by colleagues covering the usual workload of the worker while he \ she is absent from their usual duties[189,190]. Moreover, for long-term absences, an employer is likely to hire a replacement worker if unemployment exists in the economy. The basic idea is that the amount of production lost due to illness is dependent on the amount of time organisations need to restore the initial production level. Thus, losses in productivity derived using the friction cost method are likely to be much lower than those derived using the more traditional HCA.

It is important that a *perspective* (or viewpoint) is specified in an economic evaluation as this is the major determinant of which categories of cost should be included in an analysis. For example, if a patient perspective is adopted, the analysis need only include the costs that the patient is liable for; all other costs can be excluded. Other possible perspectives include a societal or that of a purchaser (eg. a Health Authority) perspective. A societal perspective is usually preferred by analysts because it includes all costs and benefits irrespective of individual liability[191]. In practice, however, the perspective taken is usually dictated by the specific research question being addressed. It should also be noted that in the instance of CUA, the inclusion of patient and family costs is viewed by some health economists as 'double-counting'; it is believed that the utility score may already incorporate the valuations of time savings to the patient and / or his / her family[178].

3.1.3 Adjustments for differential in timing (discounting)

Neoclassical welfare economics states that society has a *positive rate of time preference.* It is believed that society values an event that happens in the present more than if the same event occurred in the future. The rate at which the value placed on an event declines over future time is known as the *societal rate of time preference.* This process is taken into account in an economic evaluation by *discounting* the value of future costs and benefits (those that accrue at least one year after the programme has begun) using the formula:

$$NPV(£) = \sum_{n}^{i=1} F_n(1+r)^n \qquad \text{(Equation 3.1)}$$

Where NPV is the *net present value*, F_n is the future cost or benefit in year *n* and *r* is the societal rate of time preference. For example, a cost of £1,000 in 10 years time discounted at 6% per annum has a NPV of £558. At a practical level, the *social rate of time preference* is difficult to measure so national governments usually announce an annual discount rate for all public sector projects.

Although in the majority of published studies future costs are discounted, opinion is divided as to the appropriateness of discounting health outcomes. One rationale for discounting costs is that individuals can choose where to invest their resources. For some, however, it is difficult to conceive of individuals investing in flows of health or trading flows of health over time. Additionally, it is argued that discounting the benefits of treatments gives less weight to future generations and there is some limited evidence to suggest that individuals may discount health benefits at a lower rate to costs. Thus, there is no definitive agreement as to the appropriateness of discounting future health benefits.

In the thesis, all baseline costs were discounted at 6% per annum whereas future benefits of treatment were discounted at 0%; the impact of discounting health outcomes was investigated in the sensitivity analysis (see section 3.1.5).

3.1.4 Synthesising the information

The incremental cost-effectiveness ratio (ICER)[17,177-180] is the statistic used to assess relative levels of efficiency and is calculated for treatments A and B as:

$$ICER = [Cost_A - Cost_B] / [Effects_A - Effects_B] \qquad \text{(Equation 3.2)}$$

Where $Cost_A$ and $Cost_B$ are the costs and $Effects_A$ and $Effects_B$ are the effects associated with programmes A and B respectively. For example, if programmes A and B had net present costs of £2,000 and £500 per year respectively and produced net present QALYs of 8 and 2 per year respectively, the ICER would be £250 ([£2,000 - £500]-[8 QALYs - 2 QALYs]) per QALY gained. In other words, compared to programme A, it costs an additional £250 per QALY gained if resources were instead allocated towards programme B. The lower the ICER the more efficient the programme being assessed; but there is no absolute cut-off level as to what does or doesn't constitute a cost-

effective programme. In this instance, it is dependent upon the decision-makers willingness to pay £250 per additional QALY.

In situations where the cost-effectiveness of three or more programmes is being evaluated, the programmes should be ranked in order of increasing effectiveness and incremental analyses then performed. For example, if programme C produced 1 QALY but cost only £100, then programme C should be evaluated relative to B and programme B to A. However, if programme C produced 4 QALYs but still cost £100, it should be evaluated relative to programme A and programme B relative to programme C. In situations where a programme is both more costly and less effective than its' comparitor(s) or vice versa, it isn't necessary to calculate an ICER since in this instance one treatment is clearly superior on monetary and clinical grounds.

3.1.5 Testing for uncertainty

When assumptions are made and when data are collected, uncertainty arises as to the accuracy of values used in an analysis[192]. The impact of these uncertainties on the results can be assessed using sensitivity analysis. Sensitivity analysis involves replacing existing values with alternative (but, in most instances, still plausible) values and examining the affect of making this change on the ICER. Sensitivity analysis can also be used to examine the impact of 'what if' scenarios and, as such, can be used as a method of generalising the results of an evaluation to different settings.

Ideally, the results from a sensitivity analysis will indicate that an ICER is '*robust*'; that is, despite plausible changes to its' composite variables, the ICER does not change too much. In such instances some degree of certainty can be attached to the ICER. However, in situations where the ICER changes a lot under different assumptions, the ICER is said to be '*sensitive*' to change and an element of uncertainty will surround the ratio.

Many different types of sensitivity analysis were used in this thesis ranging from one-way sensitivity analysis (where one baseline value is changed at a time and the other values are held constant) to Monte Carlo simulation analysis using hypothetical cohorts of patients[192]. When cost-effectiveness has been modelled, this latter form of sensitivity analysis is often preferred because all variables contained within a model can be varied randomly and simultaneously subject to imputed constraints[193]. This type of sensitivity

analysis also has the added advantage of generating stochastic data rather than point estimates of costs and effects.

3.1.6 Economic evaluations and modelling

The most preferred approach to generating data for an economic evaluation is alongside a randomised controlled trial (RCT) since it is likely to produce the least biased estimates of efficacy. However, in instances where true experimentation such as an RCT is unfeasible or impractical, models can be constructed to simulate their effects and to explore alternative scenarios by combining data from a number of different sources[194]. Moreover, it has been suggested that pre-trial modelling studies should be performed and their results used to inform the design of clinical trials[195,196]. Models may utilise data derived from secondary sources, such as a systematic review or an *ad hoc* synthesis of several clinical studies. Drummond also states that, in instances where no relevant controlled clinical studies have been performed, the use of expert opinion to estimate the effectiveness of treatment and resource use may be justified[197]. For example, Buxton *et al.* estimated the physical quantities of resources used for AIDS patients with cryptococcal meningitis by asking an expert panel of physicians to specify the normal clinical protocol[198]. However, even the best models have their limitations and they are rarely a substitute for hard data[199] and are rarely seen as a substitute for hard data[199]. Indeed, O'Brien has likened modelling to creating 'a Frankenstein's monster' as information from a number of different sources is necessarily brought together[200].

3.1.6.1 Concerns about modelling

Concerns about modelling usually focus on the inappropriate use of clinical data, the transparency or validity of the model and the ease with which differences between treatment groups can be made to appear statistically significant. By their very nature, models usually consist of data from more than once source. However, it is important to ask how these heterogeneous pieces of information were derived because they might not be accurate estimates of the particular variable in question; a 'good' economic evaluation should at least reference each source. For example, Buxton[194] notes the problem of extrapolating from observational data and the role of potential biases in deriving accurate future projections of outcomes. There is also some concern over the transparency or validity of models. Often due to publication space, models are not

always fully described in a publication thus, it is sometimes difficult to conceptualise exactly how a particular question has been examined. The issue of statistical inference is also an important issue. This is because increasing the number of hypothetical individuals entering a model increases the sample size and narrows the standard error. Thus, it is conceivable that a model could be run purely until differences appeared to be statistically significant and inaccurate conclusions drawn as a result. However, as Buxton rightly says, sometimes modelling appears to be an unavoidable fact of life[194].

Two of the economic evaluations presented in this thesis have been performed using modelling techniques because of the need to combine information from a number of different sources. Both models are based on *decision analytical techniques* as it provides an intuitive framework for evaluation[201]. *Decision trees* are useful in situations where all relevant events happen over a relatively short period of time; otherwise they can become too large to handle efficiently. *Markov models*, however, are perhaps more appropriate in situations which involve a continuous risk over time (although values can be time-dependent if specified), when the timing of events is important or when important events may occur more than once[202-204]. The disadvantage of this approach is, however, that Markov models do not have 'memory' meaning that the probability of moving to a health state in the following cycle is purely dependent on the probability assigned to the current health state; the so-called chain rule.

Both types of modelling combine data on possible outcomes (costs and benefits) with the probability of relevant clinical and economic events occurring to produce *expected values*. For example, if the National Lottery paid out 25% of all wagers in cash prizes, every £1 spent on Lottery tickets has an expected return of £0.25. This does not mean that a holder of a £1 Lottery ticket you will always get a return of £0.25, but that if he / she plays the Lottery many times, there will be a*n average* return of £0.25 per £1 purchased ticket.

3.2 Sources of data

This thesis primarily utilises data collected from patients with clotting factor deficiencies who were registered for treatment at the Katharine Dormandy Haemophilia Centre (KDHC) between 1980 and 1997. However, a number of different sources have also been used to supplement these data, including information from the existing literature and the use of expert opinion from individuals who had direct experience of

the necessary clinical issue(s). The paragraphs below describe the sources of these data. However, more detailed descriptions of the additional collected data and the methods used to collect them are presented in the relevant empirical chapters.

3.2.1 The Royal Free Hampstead NHS Trust

The Katharine Dormandy Haemophilia Centre (KDHC) was established at the Royal Free Hampstead NHS Trust in 1964 for five outpatients under the direction of Dr. Katharine Dormandy. Since this time the centre has seen enormous expansion and now provides treatment for over 1,500 individuals with various congenital clotting factor disorders. The KDHC is one of 26 comprehensive care centres (CCCs) in the UK. To qualify as a CCC, treatment must be provided for 40 or more severely affected individuals with haemophilia per year and access must be provided to other specialist services eg. orthopaedic units, HIV and hepatitis expertise, counselling and physiotherapy[1]. Individuals attend from a variety of geographic areas, including some from outside of the UK, and treatment is provided for patients of all ages, including children. Since the early 1990s it has been policy to place, whenever feasible, all previously untreated patients (PUPs) with severe haemophilia on primary prophylaxis.

In 1980, under the direction of Dr Peter Kernoff, an internal Paradox (Borland software) database was installed at the KDHC. Data that have been recorded on the database since this time include the type and amount of clotting factor concentrate administered, the manufacturer, the reason for treatment (eg. for surgery, prophylaxis or following a bleed), the date treatment was administered and the details of bleeds. Specific details of each bleed include the date of each subsequent clotting factor dose, the number of doses of clotting factor required to treat each bleed and the size (in iu) of each dose, the type of clotting factor used and the location of each bleed. Thus, the number of bleeds an individual expereienced could be calculated by summing the number of 'first' infusions where treatment on-demand was also indicated. Instances where no bleeds were recorded on the database for a particular individual were assumed to indicate that they had not experienced any bleeds over that period of time (ie. from the date of registration at the KDHC to the end of the period under investigation for the particular analysis).

Individuals are required to record details of all infusions of clotting factor administered outside of the hospital onto a specially designed 'home-infusion' record. Patients return these records to the KDHC once a month at which time the information is recorded onto

the database. However, the database was not primarily designed with research in mind, thus initially, considerable time was spent arranging the information on the database into a format that could be imputed into a statistical package.

Data items from this database that have been analysed in this thesis are shown in Table 3.1. Further data related to individuals registered at the KDHC that were also analysed in this thesis were collected directly from the patients' medical notes and from the Royal Free Hampstead NHS Trusts' Patient Admissions System (PAS). The PAS system was used to collect retrospective data on hospital visits for the period 1988 to 1997 inclusive. More specifically, details on the date of attendance, the treatment speciality (eg. haemophilia, orthopaedic, dental etc.), the type of attendance (inpatient, outpatient or day case) and the length of inpatient stays were collected. However, as with the information from the KDHCs internal database, considerable time was spent collecting and manipulating these data into a useful format as individual patient based data could be down-loaded from the PAS system and because patient records can only be searched one at a time.

The remaining data on Health-Related Quality-of-Life (HR-QoL) and the patient / family costs associated with haemophilia were collected cross-sectionally by posting appropriate questionnaires to selected sub-groups of individuals who were registered for treatment at that KDHC. More specific details regarding these data and the methods used to collect them are provided in the appropriate empirical chapters.

Table 3.1: Data collected and analysed from individuals registered at the KDHC

Data type	Variable	Source
Demographic details	Haemophilia type / severity	Database
	Weight (over time)	Medical notes
	Date of birth	Medical notes
Clinical details	HIV status	Medical notes
	HCV status	Medical notes
	Bleeding frequency / location / date	Database
	Cause / date of death	Medical notes
Other	Clotting factor use / date / type / reason	Database
	Outpatient and day case visits / date / reason	PAS*
	Patient / family / friend resource use	Postal survey

	Health-related Quality-of-life	Postal survey
	Inpatient stays /date / reason / length	PAS

Information from the Katharine Dormandy Haemophilia Centres internal database covered the period 1980 to 1997 inclusive

* **PAS – Patients Admissions System**

3.2.2 Other data sources used in this thesis

3.2.2.1 General population HR-QoL data sets

One of the specific aims of this thesis was to compare levels of HR-QoL recorded by individuals with haemophilia to HR-QoL levels recorded by the general population. We made these assessments by comparing our HR-QoL data to two general population HR-QoL data sets that had been collected using the same questionnaires that we had chosen to use in our patient group. However, direct access was gained to the two data sets because provisional analysis of our data showed the HR-QoL scores were predominantly non-normally distributed. Additionally, having access to the data sets allowed adjustments for the effects of other variables (eg. age and HIV serostatus) on the HR-QoL scores to be made.

The two general population HR-QoL data sets used in this thesis were those collected by Jenkinson[205] using the Medical Outcomes Study Short-Form 36 (MOS SF-36) [164,165] and by Kind[206] using the EuroQol (EQ-5D)[187]. The reasons for using them to measure HR-QoL in our patient group are described in more detail in chapter 5. The SF-36 and EQ-5D questionnaires are generic instruments that are used to compare HR-QoL within and between different clinical conditions. The SF-36 questionnaire measures HR-QoL on eight multi-item dimensions: physical functioning, social functioning, physical and mental role limitations, mental health, energy/vitality, pain and general health perception. Results for each dimension are scored and transformed on to a scale from 0 (worst health) to 100 (best health). Results from the SF-36 can also be reported as a physical component summary scale (PCS) and as a mental component summary scale (MCS)[207].

The EQ-5D is a two-part instrument. The first part consists of five 'domains' that are designed to record health status in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is divided into three levels of

severity meaning that a total of 243 (3^5) possible health states are defined. These results can be displayed as an unweighted profile (EQ-$5D_{Profile}$) or as a single index figure (EQ-$5D_{Utility}$) by applying a utility weight to each health state. In this thesis, the EQ-$5D_{Utility}$ was calculated using utility weights derived from a large UK survey[208] using the time-trade off technique[178]. The second part of the questionnaire consists of a visual analogue self-rating scale (EQ-$5D_{VAS}$) on which the best and worst imaginable health states score 100 and 0 respectively. Individuals are asked to indicate on the scale how good or bad they feel their health is on that particular day. Results from the EQ-$5D_{VAS}$ can be used as a measure of the individuals' valuation of their own overall health status. The EQ-5D was included to complement the SF-36; it's advantage being that it generates a single index (or utility) figure that can be used in CUAs.

3.2.2.2 The Royal London Hospital Haemophilia Centre, Whitechapel

In order to increase the sample size for some of the HR-QoL analyses, individuals with moderate or severe haemophilia who were registered for treatment at the Royal London Hospital Haemophilia Centre were also asked to complete the EQ-5D questionnaire (but not the SF-36 questionnaire) when they next attended the Centre. Data on date of birth, haemophilia type, baseline clotting factor level, whether or not individuals refused to complete the questionnaire and HIV status were also collected for these individuals.

3.2.2.3 Resource valuation

RFH NHS Trust acquisition prices were used to value all market health care resources unless stated otherwise. Where appropriate, costs included value added tax (VAT) at 17.5%. Staff costs were valued using midpoints on relevant RFHS NHS Trust salary scales (including London weighting allowance) and by including a further 17% for employers' costs. The unit cost of an inpatient day was set equal to the RFH NHS Trust *per diem* cost of £188 on an orthopaedic ward (this figure was calculated by the finance department). Descriptions of how the remaining resources were valued (eg. changes in productivity) are explained later in the appropriate chapters in more detail. All costs in this thesis are displayed in 1998/1999 prices in pounds sterling.

3.3 Analysis

All the collected patient data were entered onto appropriate tables stored in an Access (Microsoft software) database. Each record was entered next to an individual hospital number (primary key) meaning that different pieces of information for each individual

could be automatically merged together if and when required. The decision analytical models were constructed using TreeAge software (DATA 3.0.18. TreeAge, MA, USA). Information from the Access database and results from the models were downloaded into the Statistical Analysis System (SAS)[209] when the data required analysing. The methods of statistical analysis used in this thesis are varied and are described in more detail in the relevant section of each chapter. However, all confidence intervals quoted in the thesis were calculated using 95% significance levels. Similarly, results from all statistical tests were considered significant if P-values were ≤ 0.05. Costs from published studies were converted into 1998/99 UK pounds sterling using country specific total health expenditure inflaters and a country specific Gross Domestic Product Purchasing Power Parity index so that the results from different studies could be compared[210]. Where studies did not clearly state the relevant price year, the time at which the study started was used as the relevant price year. In instances where this information was also unavailable, the year in which the study was published was used to calculate the relevant price year. Lastly, in most analyses data for individuals with different types of haemophilia were combined because the number of individuals with haemophilia B were too small in most instances to permit separate analysis.

4 ASSESSING THE EFFECTIVENESS AND COST-EFFECTIVENESS OF PROPHYLAXIS AGAINST BLEEDING FOR INDIVIDUALS WITH SEVERE BLEEDING DISORDERS

4.1 Introduction

Individuals with clotting factor deficiencies such as haemophilia or vWD ordinarily receive treatment with clotting factor following a bleed (on-demand) in order to abort it[5]. The alternative to this approach is for individuals to infuse clotting factor prophylactically to prevent bleeds, and hence joint damage, from occurring in the first instance[3,5,84,96,115-119,211]. Available evidence suggests that prophylaxis given at appropriate time intervals and in sufficient quantity can significantly reduce the incidence of bleeding[21,84,96,101,102,104,109,112,114,115]. However, prophylaxis is also thought to be the more costly treatment option, as it requires considerably more clotting factor than treatment on-demand[19,163,174,175].

A form of prophylaxis was first administered at the KDHC in the late 1970s to some individuals with severe haemophilia A and B, although full-time regimes were not introduced until the early 1980s. In the early 1990s it became the policy to treat, whenever feasible, all newly diagnosed children with severe haemophilia and clinically severe vWD with primary prophylaxis. The aims of the analysis presented in this chapter were, therefore, twofold. Firstly, to assess how effective prophylaxis has been at the KDHC in reducing bleeding for individuals with severe haemophilia A, B and clinically severe vWD and secondly, to provide a preliminary assessment of the cost-effectiveness of prophylaxis alsousing data collected at the KDHC.

4.2 Methods

Clotting factor (FVIII and FIX) usage was categorised according to the reason for which it was given, either for on-demand treatment or as prophylaxis. Clotting factor that had been used prior to physiotherapy, surgery or any invasive procedure to prevent any bleeding complications was excluded. An individual who had routinely received prophylaxis for nine months or more during a year was defined as having received prophylaxis in that year; all others were classified as being treated on-demand. Nine months was chosen as a cut-off margin because the prophylaxis was only introduced at the KDHC in the early 1990s on an ad hoc basis, therefore periods greater than nine

months would have excluded many patient and treatment details from the analysis. Moreover, it was felt that this approach would produce a conservative treatment effect given the problems of collecting and analysing retrospective data. Individuals born before 1/1/80 (ie. 18 years old or over) were classified as adults, those born on or after 1/1/80 (ie. under 18 years old) were classified as children.

4.2.1 Effectiveness evaluation

The evaluation of effectiveness was performed in two stages.

4.2.1.1 Evaluation of the annual median number of bleeds and joint bleeds between 1980 and 1995

All individuals with severe haemophilia A, B or severe vWD who were registered at the KDHC were included in this stage of the analysis. Individuals jointly registered with other haemophilia centres were excluded from the analysis, as their treatment records held at the KDHC were only partially complete.

Adjustments to the observed bleeding patterns were also made as it was suspected that those who died during this period might have been amongst the heaviest bleeders. This was suspected because prior to 1985 approximately 60% of individuals with haemophilia were infected with HIV secondary to clotting factor use[42]. Thus, the more frequently individuals bled in the past, the more often they received treatment and thus the more likely they were to have become infected with HIV. The net result of this process might be that individuals who died during this period were amongst the heaviest bleeders. To take account of this possibility, bleeding patterns were adjusted for deaths by recording the number of bleeds for each individual in the last full calendar year prior to death and by repeating this value in the following calendar year (the year of death).

4.2.1.2 Investigation of bleeding patterns and clotting factor use whilst treating on-demand and after switching to prophylaxis

Adults and children included in the first stage of the study who had switched from treatment on-demand to prophylaxis during the 16 year period and who had experienced at least one calendar year of each treatment regime, were selected for further analysis. However, because individuals switched to prophylactic regimes at different time points, follow-up times were standardised relative to the time of switching regimes to adjust for these differences. The median numbers of bleeds and the median amounts of clotting

factor used and reported in the results section, refer to these date-adjusted years. Individuals who fulfilled the criteria but who subsequently reverted back to treatment on-demand were included in the analysis until the point when they reverted back to treatment on-demand.

4.2.2 Cost-effectiveness evaluation

An assessment was made of the cost-effectiveness of prophylaxis compared with treatment on-demand for children up to the age of 9 years. The outcome measure used was the number of bleeds patients experienced; results were expressed as the incremental cost per bleed avoided.

For this cost-effectiveness analysis, however, a number of problems were encountered when attempting to establishing two exclusive patient sets of data that corresponded to the two different treatment options. Firstly, data were only available for this 16 year period; information on clotting factor use for many individuals when they were children was not available. Secondly, unless born after 1990, individuals treated at the KDHC are likely to have switched between methods of replacement therapy at least once ie. from treatment on-demand to prophylaxis. In addition, irrespective of the method of replacement therapy used, it was believed that bleeding patterns might be correlated with age[212]. Therefore, in order to separate individuals into prophylaxis and on-demand treatment groups, comparisons of bleeding patterns and clotting factor usage for the two methods of treatment were made within year age groups. Hence the number of bleeds experienced and the amount of clotting used by, for example, five year old children receiving prophylaxis were compared to the number of bleeds experienced and clotting factor used by five year old children treated on-demand. This method of matching by age meant that only children up to the age of 9 were included in the analysis of cost-effectiveness, as numbers were too small at each age above this.

The only resource to be included in this economic evaluation was clotting factor use; hence a purchasers perspective to the evaluation was adopted. This decision was made because the data referred to patients when they were relatively young; individuals are unlikely to undergo events such as orthopaedic correction until they are much older this. Additionally, because of the method used to generate the two data sets, it was not possible to categorically state that other resources, even if identified, were consumed as a direct result of one particular treatment modality. For example, an individual treating

with prophylaxis at age nine may have required physiotherapy. However, the physiotherapy may have been required because the individual had been treating on-demand for the previous two years rather than as a 'failure' of prophylaxis *per se*.

4.3 Analysis

Linear regression analysis was used to test the statistical significance of the differences in the annual number of bleeds and joint bleeds and the effects of prophylaxis (yes / no) and calendar year on bleeding frequency. In most of the analyses, individuals with different forms of haemophilia were not distinguished between because of the relatively small number of individuals with haemophilia B.

In the economic evaluation, the costs of treatment were discounted at 6% per annum using Equation 3.1 but the number of bleeds was only discounted in the sensitivity analysis. The robustness of the cost-effectiveness result was examined using one-way sensitivity analysis. The sensitivity analysis was performed by varying the unit price of clotting factor, the discount rate, the quantities of clotting factor required and the number of bleeds individuals had experienced for both methods of treatment. In the base scenario a clotting factor price of 22.5 p/iu was used, representing the KDHC purchase cost for a high-purity clotting factor (Replenate). Intermediate purity products are purchased for 18 p/iu and recombinant FVIII for 52.9 p/iu (inc. VAT). These figures were used as the upper and lower parameters for the unit cost of clotting factor in the sensitivity analysis.

At the base scenario, the median amount of clotting factor used in each age-adjusted year was calculated for both methods of treatment. The values for each individual year were then added together in order to calculate a median value for the whole ten year period per method of treatment. The same process was used to calculate the overall median bleeding frequency. The maximum and minimum values of these medians were used as the upper and lower limits in the sensitivity analysis. This process ensured that the maximum feasible ranges of high and low values based on observations were tested.

4.4 Results

4.4.1 Changes in the annual number of bleeds by calendar year

One hundred and seventy-nine individuals met the criteria for inclusion into part one of the effectiveness evaluation, of whom 78% had a diagnosis of severe haemophilia A (Table 4.1). Between 1980 and 1995 these individuals had a total of 38,014 bleeds, 63% of which were joint bleeds. One hundred and sixty-four (92%) of all individuals experienced at least one bleed over this period.

The median numbers of bleeds experienced by individuals in each year are shown in Figure 4.1. In 1980 individuals experienced a median of 23.5 bleeds (range 1-107), but by 1995 this had decreased to 14 (range 0-52). In 1980 there was a median of 21 (range 1-67) joint bleeds per patient but by 1995 this had fallen to 8 (0-45) (Figure 4.2). Both decreases were highly significant ($P<0.0001$). Additionally, when bleeding frequency was stratified by haemophilia type, both trends remained significant ($P<0.05$) for individuals with haemophilia A and B; the sample size was to small to perform the same analysis for individuals with vWD. Although, 36 (20%) of these 179 individuals died during the 16-year period, adjusting these observed bleeding patterns for these deaths had no affect on either level of significance.

Table 4.1: The number and type of bleeds by diagnosis

Diagnosis	No. of patients (%)	No. who bled (%)	No. of bleeds		No. of joint bleeds	
			Total (%)	Median (low / high)	Total (%)	Median (low / high)
Severe Hem. A	139 (78)	129 (79)	31,750 (84)	300 (0 / 1,096)	20,502 (85)	228 (0-/ 34)
Severe Haem. B	31 (17)	29 (18)	5,710 (15)	211 (8 / 538)	3,360 (14)	124 (2 / 507)
Severe vWD	9 (5)	6 (3)	554 (1)	104 (0 / 156)	40 (1)	44 (0 / 111)
Totals	**179 (100)**	**164 (100)**	**38,014 (100)**	-	**24,082 (100)**	-

Figure 4.1: Median number of bleeds per person between 1980 and 1995

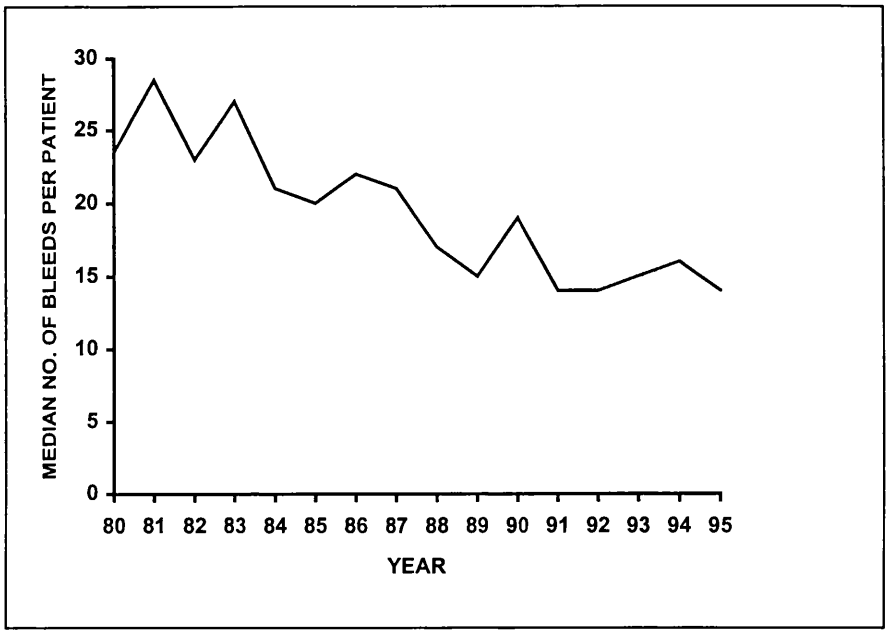
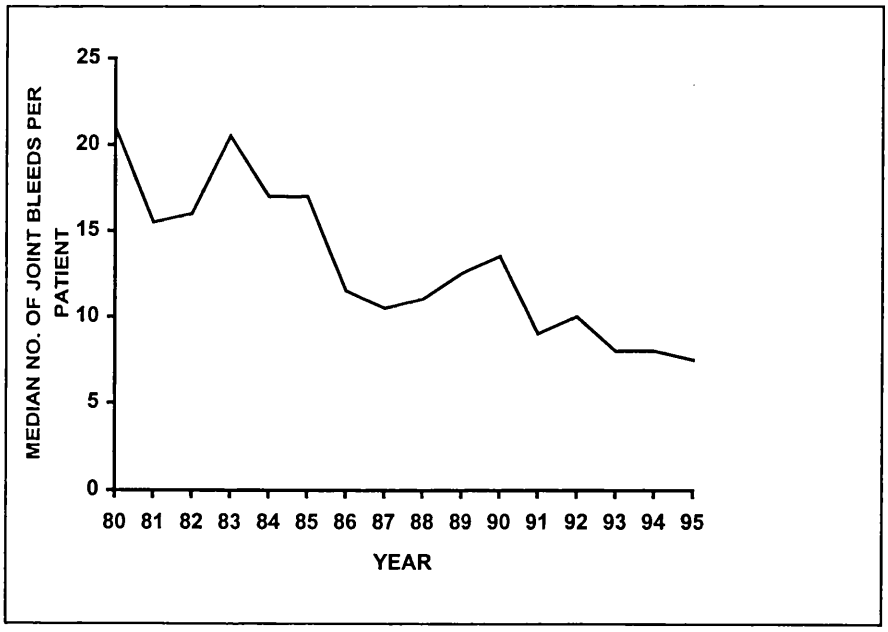


Figure 4.2: Median number of joint bleeds per person between 1980 and 1995



4.4.2 Effect of switching from treatment on-demand to prophylaxis

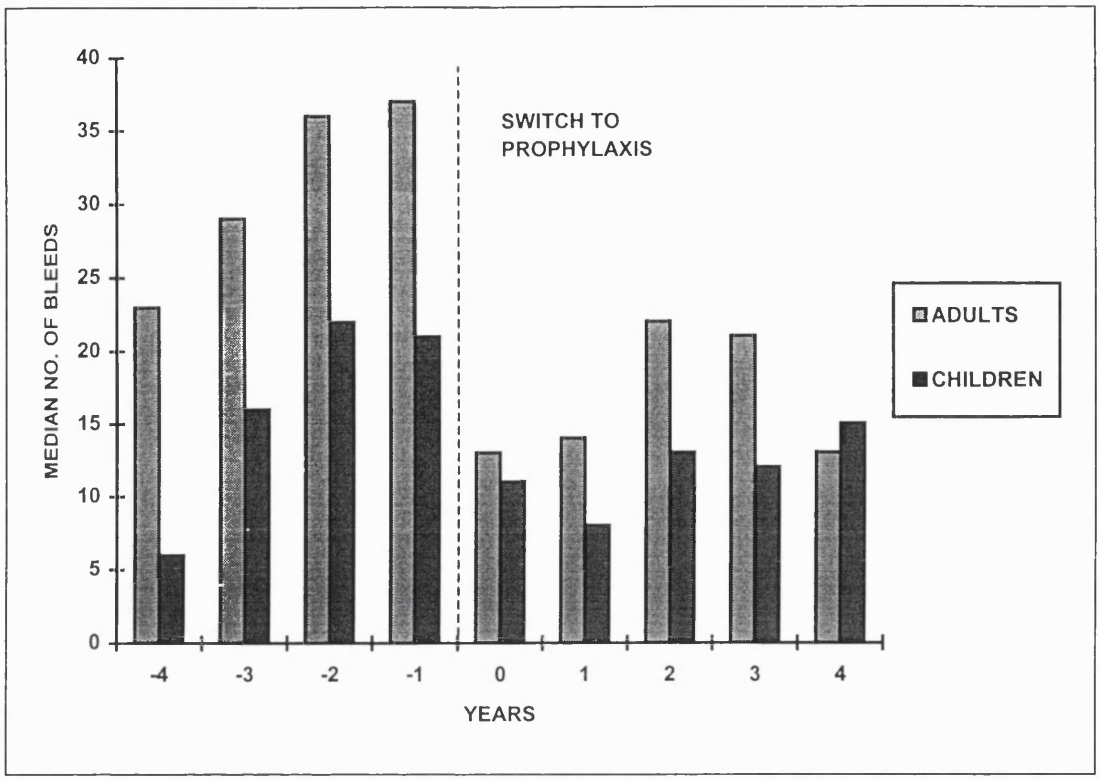
A total of 47 individuals met the inclusion criteria for part two of the evaluation. Twenty-five of these individuals were adults (Table 4.2). In the year prior to prophylaxis (year -1) these 25 adults experienced a median of 37 bleeds (range 11-132) (Figure 4.3) and used a median of 560 (range 196-3,120) iu/kg/year of clotting factor. During the first full calendar year on prophylaxis (year 0) these individuals experienced a median of 13 bleeds (range 0 to 92), representing a 65% reduction. The median level of clotting factor usage was 1,935 (range 592-3,376) iu/kg/year, representing an increase of 350%. Between years -1 and 0 there was a median within-patient decrease of 18 bleeds (range: increase of 22 to a decrease of 112) and a median within-patient increase in clotting factor usage of 411 iu/kg/year (range: decrease of 775 to an increase of 1,263). Five patients increased bleeding after switching methods of treatment.

Table 4.2: Patients details for part 2 of the effectiveness analysis

	Adults	**Children**
No.	25	22
Diagnosis A/B/vWD	19/5/1	14/7/1
Median age at start of prophylaxis in years(range)	30 (4-63)	4 (2-10)
Median follow-up in years (range):		
prior to prophylaxis	7 (1-15)	3 (1-8)
following start of prophylaxis	7 (1-15)	3 (1-11)

In year -1 the 22 children experienced a median of 21 (range 3 to 64) bleeds per year and used a median of 1,974 (range 700-3,750) iu/kg/year of clotting factor. In year 0 the median annual number of bleeds was lower at 11 (range 0-49). Individuals experienced a within patient decrease of 9 (range: increase of 22 to a decrease of 59) bleeds per year. Only one child bled more often after starting prophylaxis. The median level of clotting factor usage increased to 2,967 (range 1,742-5,472) iu/kg/year. The within-patient clotting factor also increased by 865 (range decrease of 322 to an increase of 2,664) iu/kg/year.

Figure 4.3: Median annual number of bleeds per person before and after a switch to prophylaxis



The results from the regression analysis showed that over the nine year period, prophylaxis significantly reduced bleeding frequency for both children (P=0.0037) and adults (P=0.0001). The regression analysis also showed that compared to year 0, children and adults experienced significantly more bleeds in years -2 (P=0.02 \ P=0.001 respectively) and -1 (P=0.004 \ P=0.008). The number of bleeds experienced by children and adults in each of the remaining years were not significantly different to those experienced in year 0 (P>0.05).

When calendar year was combined with prophylaxis (yes / no) in a multivariate regression, prophylaxis remained significantly associates with reduced bleeding for both adults (P=0.004) and children (P=0.0007) but calendar year only predicted bleeding for children. The analysis showed that for children, bleeding frequency increased significantly (P=0.03) by 2.2 (95% CIs 0.25-4.20) bleeds per year irrespective of treatment modality but the same trend was not observed for adults (P=0.50).

4.4.3 Cost-effectiveness analysis

A total of 38 individuals from the original 179 could be included in this section of the analysis, up to the age of 9 years (Table 4.3). Age and treatment adjusted bleeding patterns are shown in Figure 4.4. Apart from when very young, individuals who received prophylaxis at any time until the age of 9 consistently had a lower and a more constant median number of bleeds than those who treated on-demand.

Table 4.3: Patients details for the cost-effectiveness analysis

Total no. of patients	38
Diagnosis A/B/vWD	27/10/1
Total patient years (on-demand/prophylaxis)	216 (132/84)
Median no. of years receiving (range):	
treatment on-demand	3 (0-9)
prophylaxis	2 (0-6)

Whilst treating on-demand and with prophylaxis patients experienced a median of 192.5 and 103 bleeds per patient respectively. However, prophylaxis was the more costly method of treatment. The net discounted costs of treating on-demand and with prophylaxis were £20,813 and £57,512 per patient respectively. The incremental cost-effectiveness ratio (ICER) for prophylaxis compared to treatment on-demand was, therefore, £410 per bleed avoided ([£57,512 - £20,813]/[192.5 - 103]). This figure represents the additional cost associated with every bleed averted by using prophylaxis instead of treating on-demand.

The results of the one-way sensitivity analysis and the range of values used in the analysis are shown in Table 4.4. In two of the scenarios treatment on-demand used less clotting factor and was associated with a lower number of bleeds than prophylaxis. In these conditions, treatment on-demand is considered the more cost-effective option. Conversely, in another two scenarios prophylaxis was associated with a lower quantity of clotting factor and a lower number of bleeds. In these scenarios, prophylaxis is considered the more cost-effective method of treatment. For all other ranges tested in the sensitivity analysis prophylaxis has a higher effectiveness but at higher cost, with an ICER ranging from £328 (low clotting factor price) to £1,250 (high clotting factor use for prophylaxis). The ICER was sensitive to changes in key variables. For example,

varying the unit price of clotting factor from 22.5 p/iu to 52.9 p/iu changed the ICER from £410 to £964 per avoided bleed.

Figure 4.4: Age and treatment-adjusted bleeds per person

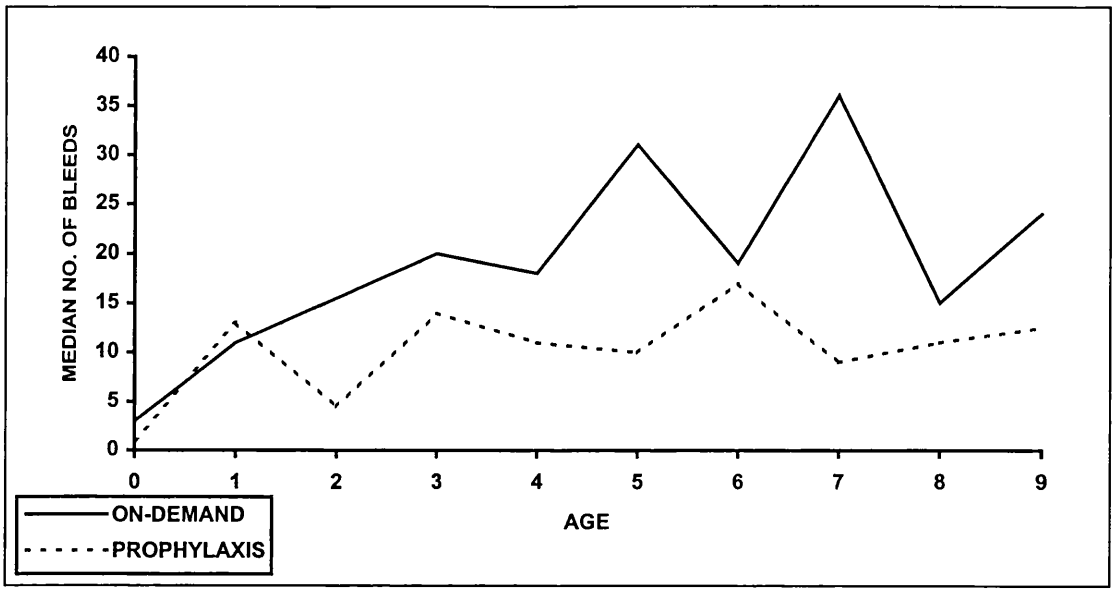


Table 4.4: Results of the sensitivity analysis

Variable	Base Case	Range	ICER (£)	
			Minimum	Maximum
Clotting factor (p/iu)	22.5	18-52.9	328	964
Discount rate - costs (%)	6	0-6	562	-
Discount rate - bleeds (%)	0	0-6	600	-
On-demand (medians)				
no. of bleeds	192.5	34-517	89	dominant+
clotting factor (iu)	135,947	16,092-482,449	dominated†	616
Prophylaxis (medians)				
no. of bleeds	359,565	34-236	232	dominated*
clotting factor (iu)	103	87,548-848,372	dominant‡	1,250

+ **if a patient who treated on-demand had experienced a median of 34 bleeds, prophylaxis would have been less effective and also more costly (ie treatment on-demand is the "dominant" therapy).**

† **if a patient who treated on-demand had used 482,449 iu of clotting factor, prophylaxis would have been less costly and also more effective (ie treatment on-demand is the "dominated" therapy).**

* **if a patient who received prophylaxis had experienced 236 bleeds, treating on-demand would have been less costly and more effective (ie prophylaxis is the "dominated" therapy).**

‡ **if a patient who received prophylaxis had required 87,548 iu of clotting factor, treating on-demand would have been more costly and less effective (ie prophylaxis is the "dominant" therapy).**

4.5 Discussion

There is some evidence to suggest that administering clotting factor to individuals with severe bleeding disorders prophylactically can reduce the incidence of bleeding[21,96,97,101,102,104,106,107,110,112,115,118]. Prophylaxis in varying forms has been used to treat individuals with severe haemophilia who are registered at the KDHC since 1980. Using observational retrospective data for 179 individuals with severe clotting factor deficiencies, we have shown that at the KDHC between the years 1980-1995, the annual median number of bleeds ($P<0.0001$) and joint bleeds ($P<0.0001$) decreased significantly. Moreover, both of these trends remained highly significant irrespective of haemophilia type and after adjusting the data for deaths during this period. In a sub-group of 47 individuals we have also shown that (primary and secondary) prophylaxis reduced but did not eliminate bleeding. However, the cost-effectiveness analysis showed that on average prophylaxis required more clotting factor per annum than treatment on-demand at an additional cost of £410 per avoided bleed.

The data on bleeding patterns is based on individuals recording bleeds as they occur, a potential problem in children. There is a possibility, therefore, that some bleeds are not reported or even identified and as a result the actual number of bleeds that individuals may have experienced could, in reality, have been larger. Additionally, individuals on prophylaxis, conscious of the effort that is being made to reduce bleeding frequency, may actually be more vigilant in identifying and in reporting bleeding episodes, resulting in less 'under-reporting' in this group. Despite this, prophylaxis still resulted in a significantly lower median number of bleeds compared to treatment on-demand. Any adjustment for higher levels of under-reporting in individuals receiving treatment on-demand would only increase the relative effectiveness of prophylaxis.

The 28 adults included in part 2 of the effectiveness analysis may have been amongst the heaviest bleeders registered at the KDHC; those with smaller bleeding frequencies are less likely to have been referred for secondary prophylaxis. However, the switching of children to prophylaxis was the consequence of a policy change at the KDHC. At the time these data were recorded, no such policy had been introduced for adults who could, therefore, have switched to prophylaxis for a variety of reasons including life-style needs that may confound any results. For example, one adult patient switched to using prophylaxis immediately following a successful total joint replacement. Although excluding the patient had little influence on the results, it was impossible to determine whether it was replacing the joint or the switch to prophylaxis, or both, which caused the decrease in the number of bleeds. Interestingly, in the four years prior to switching to prophylaxis, the median annual number of bleeds had steadily risen suggesting that individuals may have changed to prophylaxis to avert a cycle of repeated joint or other bleeds.

The regression analyses conducted in part two of the analysis showed that prophylaxis significantly reduced bleeding frequency for both children (P=0.0037) and adults (P=0.0001) but that bleeding was not fully prevented in either patient group. The analysis also showed that compared to the first year of prophylaxis (year 0), both children and adults experienced significantly more bleeds in the two years prior to this period. However, in the four years following year 0, bleeding frequency did not increase significantly. These results suggest, therefore, that although bleeding was not

fully prevented, prophylaxis consistently maintained bleeding frequency below pre-prophylaxis levels. This said, one explanation for the presence of bleeding in some individuals could be that prophylaxis was defined in this study as treatment for a minimum of nine months. If this period had instead been a whole year, it is possible that the yearly incidence of bleeding would have reduced further than the analyses presented here suggest.

There are perhaps three reasons why prophylaxis did not fully prevent bleeding. Firstly, Nilsson *et al.*[115] reported that 6 children who infused a mean of 4,300 (range 3,000-7,000) iu/kg/year of clotting factor experienced a mean of 0.1 (range 0-0.4) bleeds per year. Similarly, Liesner *et al.*[21] also reported that 27 children who infused a mean of 4,900 (1,900-8,200) iu/kg/year of clotting factor experienced a mean of 1.5 (range 0-12.5) bleeds per year. In the first year of prophylaxis at out treatment centre (year 0), adults and children at our treatment centre received medians of 1,935 (range 592-3,367) iu/kg/year and 2,967 (range 1,742-5,472) iu/kg/year of clotting factor respectively. The higher incidence of bleeding recorded at our treatment centre, could, therefore, be attributable to less intensive treatment regimes. Secondly, it is thought that the majority of adults with severe haemophilia registered at the KDHC have already developed haemophilic arthritis (HA) due to repeated joint bleeding. Evidence that treatment with secondary prophylaxis is unlikely to reverse existing joint damage and that existing damage precipitates further bleeding. Therefore, switching individuals to treatment with (secondary) prophylaxis might be less effective than primary prophylaxis in terms of preventing further bleeding. Lastly, the degree of adherence to prophylaxis as well as prior treatment history is likely to be a strong predictor of bleeding frequency. It is possible, therefore, that individuals continued to bleed despite treating with prophylaxis because they weren't fully adherent to treatment. However, our retrospective data can neither confirm nor deny this assertion.

Further results from part two of the analysis showed that calendar year was a significant (P=0.03) and positive predictor of bleeding irrespective of treatment modality for children but not for adults (P=0.50). Fitting calendar year to the regression equation in this manner is equivalent to including patient age, as the two variables will be highly correlated. These results might suggest, therefore, that as children with severe haemophilia age, their bleeding frequency increases but that it stabilises once they reach

adulthood. Although there are few empirical studies that can support or dispute this possible explanation, it is generally believed that once the musculoskeletal system has finished growing (approximately around the of age 18-20 years), bleeding frequency becomes relatively constant. It also interesting to note that in year 0 adults (1,935 iu/kg) received proportionately less clotting factor than children (2,967 iu/kg) yet they experienced a similar median number of bleeds as the children. These results might suggest that if bleeding is to be fully prevented in individuals, proportionately (ie. in terms of body weight) larger amounts of clotting factor may be required in children than in adults but that doses may be reduced once adulthood is reached. This reason is sometimes used to justify discontinuing prophylaxis once adulthood has been reached. However, further research is required to substantiate these possible hypotheses.

The cost-effectiveness of prophylaxis was estimated using age-adjusted patient treatment data. Our baseline analysis showed that an additional £410 was required to avert each bleed using prophylaxis which is lower than the estimates of DM 2,536 (approximately £1,000) calculated by Szucs *et al.*[163] and $1,380 (approximately £850) calculated by Smith *et al.*[174]. However, there are several possible reasons for these differences. Firstly, we have used total bleeding as our outcome measure whereas the study by Szucs *et al.* focused on joint bleeding and Smith *et al.* defined severe haemophilia as having a clotting factor level of <2 iu/dl rather than <1 iu/dl. Thus, in our analysis, there is more scope for bleeding events to be reduced that has perhaps lead to us producing a lower ICER. Secondly, we have only considered clotting factor costs whereas Szucs *et al.* included reductions in the amount of time absent from work and the amount of schooling missed due to haemophilia related disorders. Smith *et al.* included additional cost categories such as patient travel and laboratory costs. However, if prophylaxis averts these costs, including more resources is likely to reduce, rather than increase, the ICER. Lastly, the results from the sensitivity analysis showed that the ICER was particularly sensitive to changes in clotting factor price. Smith *et al.* used a median charge per iu/dl of clotting factor $0.53 (approximately £0.32 p/iu) and Szucs *et al.* used 1 DM. p/iu (approximately £0.33 p/iu). When these prices were used in place of our baseline price of 22.5 p/iu, our ICER increased to approximately £600 thus reducing the cost differences between the studies.

The finding that the ICER is highly sensitive to the unit price of clotting factor has important implications for the purchase of recombinant clotting factors as they are currently more costly to purchase than their plasma derived alternatives. Indeed, when the unit price of clotting factor was 45 p/iu the ICER increased to £820. The effect of VAT was to increase this by a further £144 to £964 per avoided bleed; a total increase in costs of 235% per avoided bleed. Therefore, despite any other possible benefits of using recombinant clotting factors instead of plasma derived products, their use will have a considerable impact on the cost-effectiveness of prophylaxis due to the higher price faced by purchasers. However, if less clotting factor is needed in the future, perhaps through the use of continuous infusion[133,135,213] or if the unit price of clotting factor decreases, a considerably lower incremental cost per bleed avoided could be expected.

The method that we used to determine the upper and lower limits for the sensitivity analysis was to use the maximum and minimum number of bleeds and amounts of clotting factor used for each treatment regime respectively. This process ensured that the maximum feasible range of high and low values based on observations was tested. However, the limitation of this approach is that this method of sensitivity analysis generates extreme, and therefore unlikely, limits. Additionally, bleeding frequency is likely to be dependent on a number of variables including the amount of clotting factor used. In our one-way sensitivity analyses however, we assumed that the two variables were independent of each other when this is unlikely to be the case. To do a more detailed sensitivity analysis (such as a two-way analysis) more detailed information would be needed on the relationship between bleeding frequency and clotting factor use.

Resource data for the economic evaluation was confined to clotting factor use because of the method that we used to generate the two data sets and because we chose, at this stage in the research, not to complement these data with data from alternative sources. This decision was made because of the inherent limitations of evaluating the cost-effectiveness of (primary) prophylaxis using bleeds as an outcome measure. A complete cost-effectiveness analysis of prophylaxis would need to consider the development of haemophilic arthropathy as the primary measure of effectiveness rather than bleeding *per se*. However, this represents a long-term measure of benefit for which no data is currently available at the KDHC.

One possible method of estimating the cost-effectiveness of primary prophylaxis using these (or similar) data on bleeding frequency would be to develop a model that linked (joint) bleeding with the development of arthropathy. A similar model was developed by Glick *et al.*[214] to link reductions in blood cholesterol with changes in life expectancy. However, the impact of reductions in the number of joint bleeds on the onset and progression of haemophilic arthropathy remains very unclear as do the long-term costs and (dis)-benefits of treatment on-demand. Until these relationships are better understood and quantified, however, it will be difficult to produce an accurate estimate of long-term cost-effectiveness using (joint) bleeds as a marker of disease progression. Despite these concerns, however, the data shown in this Chapter support the growing body of evidence that prophylaxis does reduce bleeding frequency in individuals with severe haemophilia but at a probable increase in the costs of clotting factor provision.

5 ASSESSING HEALTH-RELATED QUALITY-OF-LIFE IN INDIVIDUALS WITH BLEEDING DISORDERS.

5.1 Introduction

There is a growing recognition that health-related quality-of-life (HR-QoL) considerations should play an important role in medical decision-making[215]. HR-QoL is perhaps most relevant in clinical areas such as oncology and rheumatology where treatment may be palliative rather than curative or may moderate the progression of a condition but have little or no effect on more traditional outcome measures such as mortality. Haemophilic arthritis, which resembles progressive osteoarthritis, is thought to be the major cause of morbidity in individuals with severe haemophilia[115,216]. However, the results from the literature review suggest that few HR-QoL data exist for this group of individuals[162,163,217,218].

HR-QoL considerations can also be incorporated into certain types of economic evaluation. Sculpher emphasises that a preliminary economic evaluation of a health care programme should determine the size of the 'effectiveness-gap'[195]. That is, a preliminary economic evaluation should attempt to establish the effectiveness of the orthodox method of patient management so that the scope for improvement can be assessed. The implicit reasoning is that the larger the effectiveness-gap, the greater the chance of a replacement health care technology being cost-effective.

The objectives of the analysis presented in this chapter were, therefore, twofold. Firstly, to determine and to analyse current levels of HR-QoL in individuals with severe haemophilia who were registered at the KDHC. Secondly, because of the difficulties in measuring the impact of primary prophylaxis on HR-QoL, to assess the scope for primary prophylaxis to improve HR-QoL by comparing these levels to those recorded by individuals with moderate / mild haemophilia and by the general population.

5.2 Method

All individuals with mild (>5 iu/dl), moderate (1-5 iu/dl) and severe (<1 iu/dl) haemophilia A and B who were at least 18 years of age and who were solely registered at the KDHC were asked to complete Medical Outcome Study (MOS) Short Form 36 health survey (SF-36)[164,165,207] and EuroQol (EQ-5D) questionnaires[187] (Appendix I).

Questionnaires were sent to individuals by post along with a covering letter; a prepaid envelope with which to reply was also enclosed with the questionnaires. Individuals who did not return the questionnaires within four weeks were sent a reminder and new copies of both questionnaires. No further reminders were sent.

The SF-36 questionnaire was used because there is evidence to suggest that it is of value in assessing in HR-QoL in non-haemophilic patients with osteoarthritis[219,220] and other rheumatoid conditions[221,222] and so would be likely to be useful in measuring HR-QoL in patients with severe haemophilia as HA resembles progressive osteoarthritis[83]. The EQ-5D was included to complement the SF-36; its advantage being that it generates a single index (or utility) figure that can be used to help allocate resources in cost-utility analyses. To date the EQ-5D has never been used to assess HR-QoL in patients with haemophilia. However, available data suggest that the $EQ\text{-}5D_{Profile}$ covers aspects of health that are important to arthritis sufferers[223]. Preliminary evidence also demonstrates the construct validity of the EQ-5D in rheumatoid arthritis[224]. There was reason, therefore, to believe that the EQ-5D would be suitable for measuring HR-QoL in patients with severe haemophilia.

Data also used in the analyses included baseline severity of haemophilia (mild / moderate / severe haemophilia), HIV status (+ve/-ve), patient age (as a continuous variable), history of corrective orthopaedic surgery (yes/no) and the number of bleeds individuals experienced in the previous calendar year (as a continuous variable).

5.2.1 Analysis

The analysis was divided into two separate parts. In the first part it was hypothesised that patient age, HIV status and severity of bleeding disorder, as expressed by previous history of orthopaedic surgery and the number of bleeds experienced in 1996 would all be significant predictors of HR-QoL for individuals with severe haemophilia. The majority of scores from both questionnaires were non-normally distributed so non-parametric tests for significance were used. Chi-squared tests were used to examine the relationship between results from the $EQ\text{-}5D_{Profile}$ and HIV status and orthopaedic history. Mann-Whitney U tests were used to examine the relationship between both patient age, bleeding frequency and the results from the $EQ\text{-}5D_{Profile}$. For the SF-36 scales, $EQ\text{-}5D_{VAS}$ and $EQ\text{-}5D_{Utility}$, regression analysis was used to examine the relationship between computed scores and all four independent variables.

In the second part of the analysis it was hypothesised that, compared to individuals with moderate / mild haemophilia and the general population, individuals with severe haemophilia were experiencing significantly decreased levels of HR-QoL. In order to test this hypothesis, comparisons were made between the completed EQ-5D questionnaires from the severe, moderate / mild individuals and UK EQ-5D normative data (n=1,466) for males only[206]. Statistical differences between the three sets of data were tested for using Chi-squared and Fishers exact tests. In order to compare computed SF-36 scores for both patient groups with the UK normative male population[205], access was also gained to the original male SF-36 normative data set (n=4,229). However, comparisons were initially restricted to a normative data set that consisted of male individuals who were aged between 35-44 years (n=993-1,009 for the ten individual SF-36 scales). Statistical comparisons between the SF-36, EQ-$5D_{VAS}$ and EQ-$5D_{Utility}$ scores for individuals with severe, moderate \ mild haemophilia and the normative male population were tested for using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) in order to ascertain whether any differences could be explained by differences in age. All regression analyses were performed using the PROC GLM procedure contained in the Statistical Analysis System[178,209].

Differences in age between sub-groups of individuals were tested for signifcance using two-tailed unpaired t-tests. Internal consistency for the SF-36 was tested for using Cronbach's alpha statistic and Spearman's rank correlation tests were used to examine correlations between the EQ-$5D_{Utility}$, EQ-$5D_{VAS}$ and SF-36 scales.

5.3 Results

5.3.1 Response rate

A total of 249 individuals with severe haemophilia (n=91) and moderate / mild haemophilia (n=158) were originally posted both HR-QoL questionnaires. One-hundred and sixty-eight (67%) individuals returned their questionnaires of whom 67 and 101 had severe haemophilia and moderate / mild haemophilia respectively (Table 5.1). None of the individuals with severe or moderate / mild haemophilia had received primary prophylaxis with clotting factor. Individuals with severe haemophilia or moderate / mild haemophilia who returned their questionnaires were significantly older than individuals who did not reply; P=0.005 and P=0.002 respectively. Individuals with

moderate / mild haemophilia who did return their questionnaires were also significantly older than severe individuals with haemophilia who also returned their questionnaires (P=0.0006). Three of the returned SF-36 questionnaires and two EQ-5D questionnaires were removed from the analysis as they were too incomplete to be included. One individual with moderate haemophilia completed and returned an EQ-5D questionnaire but not the SF-36 questionnaire hence the final EQ-5D analysis was based on 166 respondents and the SF-36 analysis was based on 164 respondents. Tests for internal consistency showed that the observed coefficients for the SF-36 scales exceeded usual standards for group comparisons; Cronbach's alpha scores ranged between 0.84-0.93 indicating high levels of internal consistency.

5.3.2 Predictors of HR-QoL in individuals with severe haemophilia

Results from the EQ-5D questionnaire are shown in Table 5.2. For the $EQ\text{-}5D_{Profile}$, the majority of individuals with severe haemophilia reported having 'no' or 'some' difficulties for all five domains, few had serious problems. Of the 52 individuals who reported at least 'some' problems with mobility, 47 (90%) also reported having at least 'some' pain.

None of the answers recorded on the $EQ\text{-}5D_{Profile}$, $EQ\text{-}5D_{VAS}$ or $EQ\text{-}5D_{Utility}$ score were found to be significantly associated with HIV status, the number of bleeds patients experienced in 1996 or whether individuals had previously undergone orthopaedic surgery. However, all responses apart from the domain that measured anxiety / depression (P=0.39) and the $EQ\text{-}5D_{VAS}$ (P=0.076) were found to be significantly associated with age; individuals who reported more severe problems tended to be older than those who reported no or some problems with their health (Table 5.3).

Table 5.1: Questionnaire response and non-response rate by demographic and clinical characteristics

	Severe haemophilia (n=91)		Mild or moderate haemophilia (n=158)		P-values
	Responders (%)	Non-responders (%)	Responders (%)	Non-responders (%)	
Total	67 (27)	24 (10)	101 (40)	57 (23)	-
Haemophilia A	56 (83)	18 (75)	75 (74)	46 (81)	-
Haemophilia B	11 (16)	6 (25)	26 (26)	11 (19)	-
HIV +ve*	27 (40)	11 (46)	4 (4)	2 (2)	0.64
Undergone orthopaedic surgery	17 (25)	5 (21)	9 (9)	2 (4)	0.66
Mean age (years)	37.6 (sd. 14.1)	29.4 (sd. 9.4)	46.1 (sd. 17.3)	36.6 (15.0)	0.005
Median clotting factor level (iu/dl)	0	0	9 (1-60)	10 (1-40)	-

* **HIV serostatus for 5 individuals with moderate / mild haemophilia was unknown**
Other than the totals row, percentages relate to the total number of individuals in each column
P-values refer to differences between severe responders and severe non-responders

Table 5.2: EQ-5D questionnaire results and UK EQ-5D general population data from Kind *et al.*, 1998[206]

Domain	Severe haemophilia n=66 (%)	Moderate / mild haemophilia n=100 (%)	General Population n= 1,466 (%)	P-value
Mobility				
-no problems	14 (21.2)	73 (73.0)	1,200 (81.9)	
-some problems	51 (77.3)	26 (26.0)	263 (17.9)	
-confined to bed	1 (1.5)	1 (1.0)	3 (0.2)	<0.001
Self-care				
-no problems	45 (68.2)	92 (92.0)	1,401 (95.6)	
-some problems	21 (31.8)	7 (7.0)	62 (4.2)	
-unable to	0 (0)	1 (1.0)	3 (3.0)	<0.001
Usual activities				
-no problems	27 (40.9)	74 (74.0)	1,233 (83.5)*	
-some problems	37 (56.1)	21 (21.0)	198 (13.5)	
-unable to	2 (3.0)	5 (5.0)	44 (3.0)	<0.001
Pain / discomfort				
-none	11 (16.7)	57 (57.0)	1,002 (68.4)*	
-moderate	52 (78.8)	36 (36.0)	408 (27.8)	
-extreme	3 (4.5)	7 (7.0)	55 (3.8)	<0.001
Anxiety / depression				
-none	44 (66.7)	68 (68.0)	1,207 (82.3)	
-moderate	21 (31.8)	31 (31.0)	226 (15.4)	
-extreme	1 (1.5)	1 (1.0)	33 (2.3)	<0.001
Median EQ-5D$_{Utility}$ (range)	0.66 (-0.48 to 1.00)	0.85 (-0.17 to 1.00)	1.00 (-0.23 to 1.00)	
Median EQ-5D$_{VAS}$ (range)	70 (20 to 98)	80 (23 to 100)	90 (5 to 100)	

* n=1,465

All P-values were calculated using Fishers Exact test and relate to comparisons across all three groups of individuals

The mean SF-36 scores and respective summary statistics for the severe individuals are shown in Table 5.4. Similarly to the results obtained from the EQ-5D, none of the scores on the SF-36 health scales were statistically associated with bleeding history, orthopaedic history or HIV status. However, physical functioning (P=0.0001), physical role limitation (P=0.01) and the PCS (P=0.0001) were all found to be significantly and negatively associated with increasing patient age and patient age-squared (ie. these scores were related to age in a non-linear manner) (Table 5.5). None of the remaining SF-36 scales were found to be significantly associated with age or age-squared. A high degree of correlation (P=0.0001) was also found between the physical functioning and bodily pain scores (Table 5.6). Finally, after adjusting for differences in age and severity, none of the four dependent HR-QoL scores were found to be strongly associated with haemophilia type (ie. A or B) (P>0.05 in all instances).

5.3.3 HR-QoL comparisons between groups

Results from all three sections of the EQ-5D questionnaire showed that compared to the UK general population, individuals with severe haemophilia experienced significantly lower levels of HR-QoL (Table 5.2). Apart from the domain on the EQ-$5D_{Profile}$ that measured anxiety / depression (P=0.95), when compared to individuals with moderate / mild haemophilia, individuals with severe haemophilia again recorded significantly lower scores on all three sections of the EQ-5D questionnaire (P<0.05 in all instances). Noticeably, however, irrespective of haemophilia status (ie. severe, moderate / mild or general population), very few individuals fell into the levels on the EQ-$5D_{Profile}$ that reflected 'most' difficulty.

Table 5.3: Relationship between EQ-$5D_{Profile}$ and age

Domain on EQ-$5D_{Profile}$	Difficulties on domain		P-value
	No difficulties	Some or extreme difficulties	
	Age (range)	Age (range)	
Mobility	27.0 (18-43)	36.0 (18-79)	0.0012
Self-care	33.0 (18-45)	51.0 (18-79)	0.0002
Usual activities	33.0 (18-68)	37.0 (18-79)	0.0314
Pain/discomfort	28.0 (18-68)	35.5 (18-79)	0.0495
Anxiety/depression	36.0 (18-79)	36.0 (25-63)	0.3896

Table 5.4: Haemophilia SF-36 mean scores compared with a male subset from the Oxford Healthy Lifestyles Survey from Jenkinson *et al.*, 1993[205]

	Severe haemophilia (n=65)				Moderate \ mild haemophilia (n=99)				General population		P-Value
SF-36 Scale	Mean (sd.)	95% CI	% Floor	% Ceiling	Mean (sd.)	95% CI	% Floor	% Ceiling	Mean (sd.)	95% CI	
Physical functioning	53.8 (31.1)	(46.2-61.4)	3.1	7.7	67.9 (37.6)	(58.8-77.0)	13.9	25.7	91.9 (14.5)	91.0-92.8	0.0001
Role physical	58.1 (42.6)	(47.7-68.5)	29.2	40.0	81.2 (33.6)	(73.0-89.4)	9.9	70.3	89.5 (25.5)	87.9-91.1	0.0001
Bodily pain	57.7 (21.7)	(52.4-62.9)	0.0	0.0	76.8 (28.5)	(69.9-83.7)	1.0	43.6	85.6 (19.7)	84.4-86.8	0.0001
General health perception	46.8 (24.7)	(40.8-52.8)	0.0	3.1	64.1 (23.6)	(58.4-69.8)	1.0	7.1	74.1 (18.5)	72.6-75.6	0.0001
Energy/vitality	55.0 (20.4)	(50.0-60.0)	0.0	4.6	61.4 (24.8)	(55.4-67.4)	3.0	3.0	63.5 (18.6)	61.9-65.0	0.0004
Social functioning	70.4 (28.0)	(63.6-77.2)	1.5	27.7	79.9 (27.5)	(73.2-86.6)	2.0	49.5	90.5 (17.0)	89.5-91.6	0.0001
Role emotional	74.9 (39.5)	(65.3-84.5)	16.9	67.7	86.1 (31.0)	(78.6-93.6)	8.9	80.2	86.0 (28.6)	84.2-87.8	0.0125
Mental health	72.9 (15.7)	(69.1-76.7)	0.0	1.5	74.0 (18.7)	(69.5-78.5)	0.0	6.1	75.0 (16.1)	74.0-76.0	0.19
PCS	31.9 (14.8)	(28.3-35.3)	-	-	43.2 (13.8)	(39.9-46.6)	-	-	52.0 (8.58)	51.5-52.6	0.0001
MCS	52.5 (11.1)	(49.8-55.2)	-	-	53.2 (11.9)	(50.3-56.1)	-	-	51.4 (9.85)	50.8-52.0	0.62

All P-values were calculated using ANOVAs and relate to comparisons across all three groups of individuals

With the exception of the mental health scale (P=0.20) and the MCS (P=0.11), individuals with severe haemophilia consistently reported significantly lower levels of HR-QoL compared to the UK general male population as measured by the SF-36 (Table 5.4). Multiple regression analysis also revealed that the remaining eight statistically significant relationships were independent of age; differences between in HR-QoL between the two populations could not be explained by age differences alone.

Other than the mental health (P=0.32), emotional role limitation (0.055) and the MCS (P=0.97) scales, individuals with severe haemophilia also recorded significantly lower scores on the SF-36 scales compared to individuals with moderate / mild haemophilia. With the exception of the energy / vitality, social functioning scales and the MCS, multiple regression analysis again revealed that statistically significant differences in scores were independent of age.

Table 5.5: Univariate regression analysis between SF-36 scales, EQ-5D$_{Utility}$, EQ-5D$_{VAS}$ and age

	Age		
Scale	**Reg. coef.**	**95% CI**	**P-value**
Physical functioning	-1.28	(-1.71 to -0.85)	0.0001*
Role physical	-0.94	(-1.65 to -0.23)	0.011*
Bodily pain	-0.20	(-0.57 to 0.17)	0.29
General health perception	-0.42	(-0.83 to -0.01)	0.051
Energy/vitality	-0.27	(-0.62 to 0.08)	0.13
Social functioning	-0.26	(-0.74 to 0.22)	0.29
Role emotional	-0.29	(-0.98 to 0.40)	0.41
Mental health	0.064	(-0.21 to 0.28)	0.65
PCS	-0.50	(-0.72 to -0.28)	0.0001*
MCS	0.094	(0.01 to 0.03)	0.34
EQ-5D$_{Utility}$	-0.005	(-0.002 to -0.009)	0.005
EQ-5D$_{VAS}$	-3.02	(-3.57 to 2.97)	0.076

EQ-5D$_{VAS}$ for individuals with severe haemophilia and age

* **Remained significant in multivariate analysis of age and age^2**

With the exception of the domains on the EQ-5D$_{Profile}$ that measured self-care (P=0.93) and usual activities (P=0.51), the analysis showed that individuals with moderate / mild

haemophilia recorded significantly lower levels of HR-QoL than the general male population. Similarly, other than the scales that measured bodily pain (P=0.45), energy / vitality (P=0.72), emotional role limitation (P=0.43), mental health (P=0.55) and the MCS (P=0.51), the SF-36 scores recorded by individuals with moderate / mild haemophilia were also significantly reduced compared to the general population. However, multiple regression analysis revealed that only the relationships with physical functioning, physical role limitation and the PCS scores were independent of age.

5.3.4 Correlation between EQ-5D and SF-36 results

Both the EQ-$5D_{Utility}$ and EQ-$5D_{VAS}$ showed statistically significant correlations with all the individual SF-36 scales and with each other (Table 5.6 and Table 5.7).

Table 5.6: Assessing the correlation between SF-36 scales, R is the Spearman rank correlation coefficient

	R						
SF-36 scale	**PF**	**RP**	**BP**	**GHP**	**E/V**	**SF**	**RE**
PF	-	-	-	-	-	-	-
RP	0.6	-	-	-	-	-	-
BP	0.46	0.46	-	-	-	-	-
GHP	0.55	0.57	0.31	-	-	-	-
E/V	0.40	0.54	0.47	0.46	-	-	-
SF	0.49	0.63	0.58	0.53	0.47	-	-
RE	0.18*	0.49	0.10*	0.29	0.43	0.46	-
MH	0.26	0.34	0.47	0.54	0.51	0.54	0.43

PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GHP, General Health Perception; E/V, Energy/Vitality; Social Functioning, SF; Role Emotional; Mental Health, MH.

P<0.05 unless *P>0.05

Table 5.7: Correlations between EQ-5D and SF-36 scores in all individuals with haemophilia

SF-36 scale	EQ-5D$_{Utility}$ R	95% CI	P-Value	EQ-5D$_{VAS}$ R	95% CI	P-Value
Physical functioning	0.59	0.48-0.68	0.0001	0.59	0.48-0.68	0.0001
Role physical	0.50	0.38-0.61	0.0001	0.49	0.38-0.61	0.0001
Bodily pain	0.80	0.74-0.85	0.0001	0.80	0.74-0.85	0.0001
General health perception	0.69	0.60-0.77	0.0001	0.77	0.71-0.83	0.0001
Energy/vitality	0.62	0.52-0.71	0.0001	0.63	0.53-0.71	0.0001
Social functioning	0.70	0.61-0.77	0.0001	0.59	0.48-0.69	0.0001
Role emotional	0.33	0.19-0.46	0.0001	0.35	0.21-0.48	0.0001
Mental health	0.44	0.31-0.56	0.0001	0.50	0.38-0.61	0.0001
PCS	0.74	0.67-0.80	0.0001	0.54	0.42-0.64	0.0001
MCS	0.33	0.19-0.46	0.0001	0.27	0.27-0.55	0.0001
EQ-5D$_{Utility}$	-	-	-	0.67	0.58	0.0001

R is the Spearman rank correlation coefficient

5.4 Discussion

The aim of this chapter was to assess HR-QoL in individuals with severe haemophilia who were registered at the KDHC and to assess the scope for these levels to improve. In order to do this, 249 individuals with severe, moderate and mild haemophilia were posted SF-36 and EQ-5D questionnaires. Results from these questionnaires showed that HIV status, history of orthopaedic surgery and bleeding frequency in the previous calendar year were not strong predictors of HR-QoL for individuals with severe haemophilia. However, for the majority of scales, age was found to be a strong predictor of HR-QoL for this patient group. The results from the analysis also showed that compared to individuals with moderate / mild haemophilia and the UK male general population, individuals with severe haemophilia generally recorded poorer levels of HR-QoL. The latter differences were particularly large and would be both subjectively and clinically meaningful[225].

The SF-36 scores recorded by individuals with severe haemophilia were similar to those found by Djulbegovic *et al.* (1996) and Szucs *et al.* (1996). However, in our study, the sample size was larger and we were able to directly control for age and haemophilia status by gaining access to two large normative data sets[205,206].

The mental health scale and the MCS aside, analysis of the results from the SF-36 questionnaire showed that individuals with severe haemophilia recorded significantly lower levels of HR-QoL compared to the general population. The analysis also showed that these differences were significant irrespective of differences in age. The SF-36 results also showed that other than the SF-36 scales that measured energy / vitality, social functioning and the MCS, differences in HR-QoL between individuals with severe and moderate / mild haemophilia could not be explained by age differences alone. These findings suggest that individuals with severe haemophilia will have reduced levels of HR-QoL compared to individuals with moderate / mild haemophilia and the general population irrespective of age.

Of the individuals with severe haemophilia who reported at least 'some' problems with mobility on the $EQ\text{-}5D_{Profile}$ (n=52), 90% also reported at least 'some' level of pain. Moreover, the corresponding SF-36 physical functioning and bodily pain scales were also highly correlated (P=0.0001). Because primary prophylaxis has only recently

become treatment policy at the KDHC, the majority of individuals with severe haemophilia included in this study have already developed haemophilic arthritis (HA). HA is believed to resemble progressive osteoarthritis and is often extremely painful and physically debilitating[82,83]. These results are, therefore, consistent with our prior expectation and with the results of other studies[162,163,217,218]. The finding that individuals with mild / moderate haemophilia also reported decreased physical and pain scores as recorded using the EQ-5D and the SF-36 compared to the general populations is also consistent with the finding that these individuals can also develop HA but at a reduced rate. However, whether or not these HR-QoL scores were decreased purely because of the presence of HA and the extent to which HA affects the intensity of pain and the degree of mobility as recorded by both questionnaires can not be deduced from our data as a clinical patient assessment was not performed.

Results from other studies have previously demonstrated the adverse impact of HIV infection on HR-QoL[226,227]. For example, the study by O'Keefe[226] and colleagues showed that individuals who were HIV seropositive recorded significantly ($P<0.01$) lower scores on all eight SF-36 scales when compared to a control group of HIV seronegative individuals. Similarly, HIV infection was found to be a strong predictor of health perception and pain using the SF-36 in HIV seropositive haemophiliacs as opposed to HIV seronegative haemophiliacs, although these differences were considered to be smaller than expected[217]. We had, therefore, expected to identify some relationships between HR-QoL and HIV serostatus in our haemophilia patients. However, results from both questionnaires showed that HIV status was not a strong predictor of HR-QoL in this patient group. There are several factors that could explain this result. Firstly, the two HR-QoL instruments may not be sufficiently sensitive to detect clinical details that are important to individuals infected with HIV. Although evidence suggests that this is not the case for the SF-36[227], to the best of our knowledge, the sensitivity of the EQ-5D to HIV infection has not been reported. Secondly, it may be the case that that the combined effects of HIV infection and haemophilia on HR-QoL are not purely additive. That is, there may be an interaction between haemophilia status and HIV infection that lessens the influence of haemophilia status on HR-QoL or the influence of HIV infection on HR-QoL[217]. Such interactions may help to explain why in our study differences in HR-QoL as measured using the SF-36 mental health scale between individuals with severe haemophilia who were HIV seropositive and the

general population were non-significant (P=0.20). Thirdly, approximately 60% of haemophiliacs who received products derived from untreated large plasma pools prior to 1985 became infected with HIV[22,42]. At the KDHC 130 such cases were initially identified but since this time approximately half this number have died. It is possible, therefore, that the 27 HIV seropositive individuals with severe haemophilia who were included in the analyses were those who have remained the most asymptomatic and who have derived the most benefit from the comprehensive care offered at the KDHC including full HIV counselling. This may have enabled some individuals to come to terms with their infection and to reduce the impact of HIV infection on HR-QoL. However, without knowing more about the 11 HIV infected patients who did not return their questionnaires, it is difficult to know whether HIV serostatus is truly unrelated to HR-QoL in patients with severe haemophilia because these individuals may not have replied due to acute illness.

Episodes of bleeding are thought to be painful and debilitating but surprisingly on no occasion was bleeding frequency found to be a strong predictor of HR-QoL. Moreover, although the data are not presented here, when specific types of bleeds were considered separately (ie. joint or muscle bleeds), still no statistically significant relationships with HR-QoL were found. There are, however, several factors that could explain these findings. Firstly, the questionnaires were posted between March and April 1997 whereas the bleeding data referred to the total number of bleeds individuals experienced during 1996. The version of the SF-36 questionnaire used in this study asks individuals to consider their health over the previous four weeks whereas the EQ-5D questionnaire asks individuals to consider their health at the moment of responding. It is feasible, therefore, that any short-term effects on HR-QoL that were caused by episodes of bleeding (such as swelling) may have subsided by the time the questionnaires were completed. Thus, no significant relationships were found between bleeding frequency and any of the HR-QoL scales as the data on bleeding frequency did not relate to the appropriate time period. Secondly, it is feasible that through the use of home treatment and the increased availability of clotting factor, individuals are now able to treat episodes of bleeding more quickly and successfully than was once possible, which has in turn reduced any short-term affects of bleeding on HR-QoL.

If individuals with severe haemophilia develop chronic haemophilic arthropathy, they may be offered the option of undergoing corrective orthopaedic surgery such as an arthrodesis or a total joint replacement. As with bleeding history, however, the analysis showed that history of orthopaedic surgery (yes / no) was not a strong a predictor of HR-QoL as measured by any of the SF-36 or EQ-5D scales. However, there are also several factors that might explain these results. Firstly, although surgery may alleviate pain and aid the functioning of one specific joint, it is feasible that individuals may have developed haemophilic arthropathy in other joints concurrently. In instances such as this, any increase in HR-QoL that might have resulted from surgery may have been reduced as the patient was still contending with other health-related issues. Secondly, successful operations might have alleviated much of the pain and immobility caused by the initial joint defect. Thirdly, it might be the case that some individuals declined corrective surgery despite being clinically indicated. If this were indeed true, the value of history of orthopaedic surgery as a predictor of HR-QoL would certainly be reduced.

Although the impact of asymptomatic HCV infection on HR-QoL is unclear[228], there is a strong association between chronic HCV infection, fatal liver diseases such as hepatocellular cancer and decreased levels of HR-QoL[229]. However, it was not possible to directly assess the impact of HCV infection on HR-QoL because all individuals with severe haemophilia who were treated with products derived from untreated large plasma pools prior to 1985 became infected with HCV[22,41]; thus the direct affects of HCV infection could not be isolated. However, irrespective of these problems, the impact of HCV infection on HR-QoL in these individuals is likely to be confounded with age and method of treatment ie. HCV negative individuals are likely to be young, on primary prophylaxis (if severe) or have very mild haemophilia. Additionally, it was not possible to evaluate the effect of secondary prophylaxis on HR-QoL. This was because at the time the questionnaires were posted, nearly all adults registered at the KDHC were receiving secondary prophylaxis.

Twenty-four individuals with severe haemophilia and 57 individuals with moderate / mild haemophilia did not return either HR-QoL questionnaire. In both instances, however, responders were significantly older than non-responders meaning that their inclusion might increase these mean HR-QoL scores; particularly for the variables that were significantly related to age. However, it is equally conceivable that some

individuals did not respond because they were experiencing relatively poor levels of HR-QoL.

In order to evaluate the impact of treatments that may modify the progression of rheumatoid conditions such haemophilic arthritis, HR-QoL instruments are required that are sensitive to clinical change. The results from this analysis provide some evidence for the reliability and validity of the SF-36 as a measure of health status in individuals with severe haemophilia. However, although these data provide some evidence for the concurrent validity of EQ-5D questionnaire, Wolfe *et al.*[230] believe that the scaling on the $EQ\text{-}5D_{Profile}$ fails to capture many important rheumatic changes and that it does not reflect clinical rheumatic data accurately. For cross-sectional studies such as ours this means that many individuals may appear to have similar levels of HR-QoL when compared to each other but are, in reality, clinically diverse. The large grouping of individuals with severe haemophilia in the 'some problems' grouping in our own study and the fact that irrespective of haemophilia status, very few individuals appeared in the 'most severe' health states on any of the domains, goes some way to support this argument. These findings have important implications if the effectiveness of primary prophylaxis relative to treating on-demand with clotting factor is to be assessed using the $EQ\text{-}5D_{Profile}$ or $EQ\text{-}5D_{Utility}$. For example, it is conceivable that individuals who are wheel chair bound, but not confined to bed, will appear to have the same level of mobility and the same level of HR-QoL as those who only have 'some' problems walking about, perhaps as a result of primary prophylaxis. However, studies are needed to substantiate all these hypotheses and it is possible that if the results were normally distributed around the 'some' problems health states overall mean utility values would not be affected. Moreover, both the EQ-5D and the SF-36 questionnaires did discriminate between the three groups of individuals on the domains that are thought to be clinically important to individuals with haemophilia suggesting that both instruments have some degree of discriminative validity of the EQ-5D in this patient group.

The aim of (primary) prophylaxis with clotting factor is to prevent bleeding episodes and their associated sequelae from occurring by converting severe haemophilia into a moderate / mild form of the disease[14,114,115]. A prerequisite for cost-effectiveness is that a treatment is at least as effective as the programme it is ultimately seeking to replace. The results from Chapter 4 and the literature suggest that prophylactic clotting factor

regimes can reduce the number of bleeds experienced by individuals with severe haemophilia. Therefore, this necessary but not sufficient criterion has been satisfied. However, because of the large cost associated with primary prophylaxis, if it is to hold any possibility of being cost-effective, the scope for it to improve effectiveness must also be high. The results from this analysis showed that differences in HR-QoL between individuals with severe and moderate / mild haemophilia were, in the most part, subjectively large and statistically significant meaning that the scope for increasing HR-QoL in individuals with severe haemophilia is high. Therefore, despite the high costs of treatment, the capacity for prophylaxis to be cost-effective does exist.

6 TO WHAT EXTENT COULD PRIMARY PROPHYLAXIS REDUCE THE DEMAND FOR HOSPITAL VISITS AND REDUCE INDIRECT RESOURCE USE?

6.1 Introduction

The rationale for primary prophylactic treatment in haemophilia was the observation that chronic arthropathy was less frequent and less severe in patients with moderate haemophilia than in those with severe haemophilia[86]. When individuals with severe haemophilia do develop chronic haemophilic arthropathy or experience particularly severe episodes of bleeding, in addition to treatment with clotting factor, they may require the input of additional medical resources in an attempt to reduce or correct the problem. These additional resources may include outpatient visits, day-case visits or even inpatient stays. If they occur, these joint and muscle problems might also cause costs to the patient or his family if they reduce an individual's capacity to perform paid work or to independently perform other daily activities such as shopping and cleaning. Potentially, therefore, if primary prophylaxis can reduce the incidence of bleeding and secondary degenerative orthopaedic change, in addition to improving HR-QoL, the demand for some health care and indirect resources might also be reduced[231].

The potential for primary prophylaxis to reduce the consumption of some health care resources is used as an argument to favour its' use in preference to treating individuals on-demand[21]. For example, Szucs *et al.*[163] stated that the 'true' economic benefit of primary prophylaxis lies in the avoidance of inpatient stays. However, very few studies have attempted to quantify the medical resources used by individuals with severe haemophilia other than clotting factor requirements whether treated on-demand or with (primary) prophylaxis[174,175]. Moreover, of the published studies, none have reported UK specific resource data and only Smith *et al.*[174] have reported disaggregated medical resource data in any real detail.

The optimal method of assessing the way in which primary prophylaxis versus treatment on-demand affects resource consumption would be to perform a comparative study. However, primary prophylaxis has only been introduced at the KDHC in more recent years and a prospective study would take several decades to yield any useful

data. Therefore, we indirectly examined the extent to which primary prophylaxis could reduce the frequency of hospital visits and patient / family resources rather than estimating reductions in these resources following the introduction of prophylaxis *per se*.

6.2 Method

The analysis was divided into two parts. In the first part, the potential for reductions in hospital resource use was assessed by comparing rates of inpatient, outpatient and day-case visits per patient-year and patient / family resources for individuals with severe (<1 iu/dl) haemophilia who had never received primary prophylaxis to attendance rates for individuals with mild / moderate (1-50 iu/dl) haemophilia; a similar approach to that used in Chapter 5 to assess the scope for improvements in HR-QoL. Additionally, differences in the rate of orthopaedic procedures and joint replacements were also assessed, as these procedures are possibly the most common and costly sequeale of repeated joint bleeding[87]. Similarly in the second part of the analysis, differences in indirect resource use between the two groups were assessed by examining completed levels of education and how these individuals and their friends and family routinely spent their time. For example, whether individuals were in full or part-time employment or whether they were unemployed. The null hypothesis was that there were no significant differences between individuals with severe haemophilia and mild / moderate haemophilia in terms of these resource requirements.

6.2.1 Data collection

The initial objective was to collect resource data for the same adults (n=249) with mild, moderate and severe haemophilia who had previously been included in the HR-QoL study. However, hospital activity data were only collected for 246 individuals (Table 6.1) on this occasion because it was decided only to include data for individuals who had been registered for treatment at the KDHC for at least one patient-year. Hospital attendance data were collected retrospectively for the period 1988 to 1997 inclusive from PAS and from patients' medical notes. Appointments on the PAS system also include impromptu visits by patients. Appointments where patients failed to attend were not included in the analysis. A day-case episode was defined as a hospital visit where the patient was planned to be, and was, admitted, treated and discharged on the same day.

Table 6.1: Details of patients included in the rates of hospital visit calculations

	Milds / mods.	Severes
N	155	91
Median clotting factor level (iu/dl) (range)	10 (1-60)	0 (0-0)
Age (on 31/12/97)	40 (18-94)	34 (18-80)
HIV+ (%)	4 (3)	38 (42)
Median follow-up period years (range)	10 (1-10)	10 (1-10)

Productivity data were collected cross-sectionally by posting individuals a specially designed 'time-use' questionnaire in October 1998 (see Appendix II). However, since the time of the HR-QoL study, eleven individuals had moved address without notifying the KDHC or had died. Therefore, the time-use questionnaire was only posted to 238 rather than 249 individuals. Individuals who did not return the questionnaire within four weeks were sent a reminder and a new copy of the questionnaire. No further reminders were sent.

The time-use questionnaire was based on an experimental questionnaire designed by researchers at Brunel University (Adam Parnaby and Jackie Brown, Brunel University) to elicit the indirect costs associated with breast cancer. However, the original questionnaire was adapted to only include questions that were pertinent tp individuals with haemophilia. For example, questions that were phrased 'pre or post diagnosis' were removed, as were questions on age and gender, as this information was already known.

Individuals were asked to indicate on the questionnaire which qualifications they had completed, ranging from no qualifications to professional qualifications or post-graduate degrees. Participants were then asked to indicate, from a variety of options including full-time employment, part-time employment, education, housework and sick-leave, how many hours they spent performing these activities over a one week period. Those who indicated that they were presently in full or part-time employment were also asked to indicate how many hours they worked on average each week (including over-time) and whether they had required any time off work in the two weeks prior to completing the questionnaire due to ill health. Individuals who required time off work during this period were also asked to indicate the reason for their absence and if they knew what arrangements had been made by their employer to cover their work while

they absent. All participants were asked to indicate how many hours they spent on unpaid activities including housework, shopping, odd-jobs and chores, voluntary work and educational courses in a typical one week period and, on a corresponding ten-point likert scale, how efficiently they felt they performed each of these tasks. Scores of 1 and 10 on this scale indicating 'very inefficiently' to 'very efficiently' respectively. Finally, individuals were asked to indicate how much help they had received over the past two weeks from family or friends to perform their usual activities due to health-related problems.

6.2.2 Analysis

Attendance rates were calculated for each type of hospital attendance by dividing the number of visits made by patients into the sum of the relevant patient-years of follow-up. Patient follow-up was calculated as the time between the date of registration at the KDHC or January 1st 1988 (whichever occurred last) and December 31st 1997.

Orthopaedic procedures were defined as joint replacements, arthrodeses, synovectomies, O'Donoghues procedures, ulnar nerve decompressions, excision of radial heads and other miscellaneous orthopaedic procedures. Joint replacements included revisionary procedures and age was taken at 31st December 1997. Poisson regression techniques were used to perform significance tests of the differences in hospital attendance rates between subgroups of patients. Categorical productivity data were analysed using Chi-squared tests and logistic regression analysis. Continuous productivity data were analysed using Mann-Whitney U-tests and linear regression analysis.

6.3 Part one results: hospital attendance rates

Over a total of 2,187 patient-years, 246 individuals attended 424 inpatient, 4,091 outpatient, 2,757 day-case appointments and underwent a total of 50 orthopaedic procedures.

Table 6.2: Rates of hospital attendance per patient-year

	No. of episodes	Total patient-years	Rate	95% CI
All patients (n=246)	7,272	2,187	3.30	3.25-3.40
Inpatient	424	"	0.20	0.18-0.21
Outpatient	4,091	"	1.87	1.81-1.93
Day-case	2,757	"	1.26	1.21-1.31
Milds / mods (n=155)	2,916	1,352	2.16	2.07-2.24
Inpatient	204	"	0.15	0.13-0.17
Musculoskeletal op.	16	"	0.012	0.002-0.018
Joint replacements	5	"	0.004	0.001-0.009
Outpatient	1,790	"	1.32	1.26-1.39
Day-case	922	"	0.68	0.64-0.73
Severes (n=91)	4,356	835	5.10	4.90-5.30
Inpatient	220	"	0.26	0.23-0.30
Musculoskeletal op.	34	"	0.04	0.025-0.055
Joint replacements	15	"	0.02	0.01-0.03
Outpatient	2,301	"	2.76	2.64-2.86
Day-case	1,835	"	2.20	2.10-2.30
HIV+ve severes (n=38)	2,072	369	5.60	5.40-5.90
Inpatient	106	"	0.29	0.23-0.34
Outpatient	1,102	"	3.00	2.80-3.20
Day-case	864	"	2.30	2.20-2.50
HIV-ve severes (n=53)	2,284	466	4.90	4.70-5.10
Inpatient	114	"	0.24	0.20-0.29
Outpatient	1,199	"	2.60	2.40-2.70
Day-case	971	"	2.10	1.95-2.21

6.3.1 Inpatient visits

On average, individuals with haemophilia required 0.20 (95% CI 0.18-0.21) inpatient visits per patient-year (Table 6.2) or one inpatient admission once every 5.00 (4.76-5.56) patient-years. Univariate poisson regression analysis revealed that individuals with mild / moderate haemophilia were almost half (rate ratio of 0.54, 95% CI 0.52-0.64) as likely to have required an inpatient visit as individuals with severe haemophilia (P=0.0001) (Table 6.3). Univariate analyses also revealed that both age (P=0.02) and HIV serostatus (P=0.0002) were associated with an increased rate of inpatient admissions. However, when all three independent variables were fitted together, only severity remained an independent predictor of inpatient visits (P=0.0001) (Table 6.4). That is, once differences in the severity of haemophilia were controlled for, age and HIV serostatus no longer remained independently associated with the rate of inpatient stays. Moreover, fitting both age and HIV serostatus separately in bivariate models

with severity made little difference to their predictive values (P=0.46 and P=0.92 respectively).

Similar univariate analyses showed that severity of haemophilia was a significant predictor of the rate of all orthopaedic operations (P=0.0003). Individuals with mild / moderate haemophilia were 0.34 (0.19-0.61) times as likely to have undergone musculoskeletal procedures per patient-year than individuals with severe haemophilia. However, no significant relationships were found between either age (P=0.31) or HIV serostatus (P=0.47) and the rate of orthopaedic operations. Severity of haemophilia (P=0.0001), age (P=0.0001) and HIV serostatus (P=0.0004) all strongly predicted the rate of joint replacements per patient-year in univariate analyses. Severity of haemophilia and age remained associated with joint replacements in a multivariate model however, when simultaneous adjustments were made for severity of haemophilia and ag, HIV serostatus no longer remained a significant predictor of the rate of joint replacements (P=0.49).

6.3.2 Outpatient visits

The analysis showed that individuals with haemophilia required 1.87 (1.81-1.93) outpatient visits per patient-year or once every 0.53 (0.52-0.55) patient-years (Table 6.2). Individuals with mild / moderate haemophilia attended significantly (P=0.0001) fewer outpatient visits per patient-year than individuals with severe haemophilia (rate ratio of 0.56 (0.55-0.59)) (Table 6.3). Univariate analyses also revealed that both age and HIV serostatus were significant predictors of the rate of outpatient visits; P=0.0001 for both comparisons. Indeed, individuals who were HIV seropositive were 1.72 (1.60-1.84) times as likely to have attended an outpatient visit than individuals who were HIV seronegative. Further multivariate poisson analysis revealed that all three variables were independent predictors of the rate of outpatient visits (Table 6.4). Thus, individuals with severe haemophilia attended significantly more outpatient visits per patient-year than individuals with mild / moderate haemophilia irrespective of differences in age and HIV serostatus.

6.3.3 Day-case visits

On average, individuals with haemophilia attended 1.26 (1.21-1.31) day-case visits per patient-year or once every 0.79 (0.76-0.83) patient-years (Table 6.2). Univariate analysis showed that haemophilia severity (P=0.0001) and HIV serostatus (P=0.0001)

were both significant predictors of the rate of day case appointments but age was unrelated (P=0.92) (Table 6.3). For example, individuals who were HIV seropositive were more than twice (rate ratio of 2.18 (2.01-2.36)) as likely to have attended a day-case appointment than individuals who were seronegative. Multivariate analysis revealed that severity of haemophilia, HIV serostatus and age were all significant and independent predictors of the rate of day-case visits (P=0.0001). This apparent anomaly with the age affect in the univariate and multivariate models was examined further by considering the effect of age on the rate of day case visits for individuals with severe and mild / moderate haemophilia separately. When these two analyses were performed individuals with severe haemophilia were found to require progressively more day-case visits per patient-year with increasing age whereas individuals with mild / moderate haemophilia were found to require progressively fewer visits. Thus, age was only found to be a significant predictor of the rate of day-case visits when adjustments for haemophilia severity were also made (Table 6.4).

6.3.4 Effects of haemophilia type (A or B)

Results from multivariate Poisson models showed that individuals with haemophilia A attended significantly more outpatient (P=0.0001) and day-case (P=0.0001) visits per year compared with individuals with haemophilia B after adjustments were made for severity, age and HIV serostatus. However, further analysis using the same model also showed that individuals with haemophilia B attended significantly more inpatient visits per year compared to individuals with haemophilia B (P=0.03).

6.4 Part two results: productivity levels

One hundred and forty-five of the 238 time-use questionnaires were returned (61%). During the study it transpired that a further ten individuals had moved address and could not be contacted. Removing these individuals from the analysis produced an adjusted response rate of 64% (145/228) (Table 6.5). Respondents were found to be significantly older than those who did not reply (P=0.0001) with mean ages of 43.8 years (sd. 16.4) and 35.3 (sd. 13.9) years respectively. Individuals with mild / moderate haemophilia who returned their questionnaire were significantly older than individuals with severe haemophilia who responded (P=0.001).

Table 6.3: Univariate poisson regression analysis on hospital attendances

	Severity (milds / mods. *vs* severes)			Age (per year)			HIV (+ve's *vs* -neg's)		
	R.R.	**CI**	**P-value**	**R.R.**	**CI**	**P-value**	**R.R.**	**CI**	**P-value**
Inpatient	0.54	0.52-0.64	0.0001	0.99	0.99-0.99	0.024	1.52	1.22-1.90	0.0002
Musculoskeketal op.	0.34	0.19-0.61	0.0003	0.99	0.97-1.00	0.31	1.28	0.66-2.51	0.47
Joint replacement	0.70	0.61-0.81	0.0001	0.99	0.98-0.99	0.0001	1.36	1.15-1.62	0.0004
Outpatient	0.56	0.55-0.59	0.0001	0.99	0.98-0.99	0.0001	1.72	1.60-1.84	0.0001
Day-case	0.31	0.28-0.33	0.0001	1.00	0.99-1.00	0.92	2.18	2.01-2.36	0.0001

R.R. – relative rate

Table 6.4: Multivariate poisson regression analysis on hospital attendances

	Severity (milds / mods. *vs* severes)			Age (per year)			HIV (+ve's *vs* -neg's)		
	R.R.	**CI**	**P-value**	**R.R.**	**CI**	**P-value**	**R.R.**	**CI**	**P-value**
Inpatient	0.55	0.44-0.69	0.0001	0.99	0.99-1.00	0.47	0.99	0.77-1.30	0.98
Joint replacement	0.77	0.64-0.92	0.004	0.99	0.99-1.00	0.006	1.07	0.87-1.35	0.49
Outpatient	0.64	0.59-0.69	0.0001	0.99	0.99-0.99	0.0001	1.11	1.21-1.32	0.0001
Day-case	0.30	0.27-0.33	0.0001	1.01	1.01-1.12	0.0001	1.19	0.93-1.31	0.0003

R.R. – relative rate

Table 6.5: Questionnaire response and non-response rate by demographic and clinical characteristics

	Severe haemophilia (n=85)		Mild or moderate haemophilia (n=143)	
	Responders (%)	Non-responders (%)	Responders (%)	Non-responders (%)
Total	54	31	91	52
Mean age (years)	38.3 (sd. 13.9)	31.9 (sd. 11.9)	47.0 (sd. 16.9)	37.5 (15.1)
Median clotting factor level (iu/dl)	0 (0-0)	0 (0-0)	10 (0.1-60)	10 (0.1-60)
HIV +ve*	25	9	1	0

* **HIV serostatus for 5 individuals with moderate / mild haemophilia was unknown**
Other than the totals row, percentages relate to the total number of individuals in each column

6.4.1 Completed qualifications

Chi-squared analysis showed that severity of haemophilia was not associated with completed levels of education (Table 6.6). For example, similar proportions of individuals with severe (33% and 26%) and mild / moderate (28% and 27%) haemophilia reported that they had completed degrees and professional qualifications / post-graduate degrees respectively.

Table 6.6: Levels of education completed according to haemophilia severity

Level of education	Severes (%)	Mild / moderate (%)	P-value
At least O-levels, GCSEs or NVQs			
Yes	46 (85)	66 (73)	
No	8 (15)	25 (27)	0.08
A-levels or BTECs			
Yes	24 (44)	37 (41)	
No	30 (56)	54 (59)	0.66
Degree or HND			
Yes	18 (33)	26 (28)	
No	36 (67)	35 (71)	0.55
Professional qualification / Post-graduate degree			
Yes	14 (26)	25 (27)	
No	40 (74)	66 (73)	0.84

6.4.2 Employment details

The analysis showed that similar proportions of individuals with severe and mild / moderate haemophilia were in either full (P=0.89) or part-time (P=0.48) employment (Table 6.7) and that they worked a similar number of hours per week (medians of 40 [range: 10-67] hours and 40 [range: 7-70]) hours per week respectively, P=0.60). Further analysis showed that severity of haemophilia was not associated with either the work efficiency score (P=0.31), whether or not individuals had been absent from work over the prior two week period (P=0.96) or the median number of days individuals had been absent (median 0 [range: 0-4] days and 0 [range: 0-8] days respectively, P=0.93).

Table 6.7: Use of time in the two week period prior to completing the questionnaire according to severity of haemophilia. Percentages refer to columns.

	Severes n (%)	Mild / moderate n (%)	P-value
Full-time work			
Yes	35 (65)	60 (66)	
No	19 (35)	31 (34)	0.89
Part-time work			
Yes	3 (6)	8 (9)	
No	51 (94)	83 (91)	0.48
Self-employed			
Yes	9 (17)	17 (19)	
No	45 (83)	74 (81)	0.76
Working*			
Yes	35 (85)	61 (98)	
No	6 (15)	1 (2)	0.01
On sick-leave			
Yes	4 (7)	2 (2)	
No	50 (93)	89 (98)	0.13
Retired			
Yes	4 (7)	2 (2)	
No	50 (93)	89 (98)	0.13
Absent from work over the past 2 weeks?**			
Yes	5 (16)	9 (15)	
No	27 (84)	50 (85)	0.96
Help over past 2 weeks from family / friends?			
Yes	10 (32)	7 (13)	
No	21 (68)	49 (87)	0.026

* **those who reported that they were self-employed, in full or part-time employment and removing individuals who were studying or who had retired**

** **those who reported that they were in full or part-time employment only**

Severity of haemophilia was only found to be significantly associated with employment status when individuals who were in full or part-time education or who had retired were removed from the analysis. When these individuals were removed, the analysis showed that individuals with severe haemophilia were significantly more likely not to be working than individuals with more mild / moderate forms of the condition (P=0.01). However, when further adjustments were made for HIV serostatus, the relationship was no longer found to be significant (P=0.42).

6.4.3 How individuals spent their leisure time

Individuals with severe haemophilia spent significantly fewer hours each week performing odd-jobs and chores than individuals with mild / moderate haemophilia; a median of 2 (range: 0-20) and 3 (range: 0-29) hours per week respectively (P=0.01) (Table 6.8). Moreover, individuals with severe haemophilia also reported that they had performed their odd-jobs and chores significantly less efficiently than individuals with mild / moderate haemophilia (P=0.001). Further multivariate analysis revealed, however, that the difference in the number of hours that individuals spent each week performing odd-jobs and chores (P=0.13) could be explained by differences in age between those with severe and mild / moderate haemophilia. In contrast, multivariate analysis showed that the differences in the odd-jobs efficiency score could not be explained by differences in age (P=0.0002) or HIV serostatus (P=0.009). The number of hours individuals spent each week performing housework, voluntary work, going shopping or studying on educational courses or their associated efficiency scores were not associated with severity of haemophilia.

Table 6.8: Severity of haemophilia and how individuals spent their time

	Severes		Mild / moderate		P-value
	n	median (range)	n	median (range)	
Hours spent per week on:					
Housework	54	2 (0-20)	91	2 (0-20)	0.90
Shopping	54	2 (0-29)	91	2 (0-15)	0.73
Odd-jobs and chores	54	2 (0-20)	91	3 (0-29)	0.01
Voluntary work	54	0 (0-24)	91	0 (0-15)	0.17
Educational courses	54	0 (0-21)	91	0 (0-40)	0.24
Efficiency of time spent per week on:					
Housework	42	6.5 (1-10)	68	8 (1-10)	0.10
Shopping	45	8 (1-10)	72	9 (1-10)	0.23
Odd-jobs and chores	46	6 (1-10)	78	9 (1-10)	0.001
Voluntary work	8	7.5 (2-10)	19	9 (6-10)	0.38
Educational courses	8	3 (1-10)	16	8 (1-10)	0.29

6.4.4 Help from family and friends

Over the two week period prior to completing the questionnaire, a significantly larger proportion of individuals with severe haemophilia (32%) reported that they had required help from their family and friends in order to perform routine household tasks than individuals with mild / moderate haemophilia (13%) (P=0.03) (Table 6.7). This difference could not be explained by differences in age or HIV serostatus. However, for individuals who had required help, there was no relationship between severity of haemophilia and the duration (hours) of help although the sample size was very small for this sub-analysis. These individuals with severe and mild / moderate haemophilia reported requiring a median of 5 (range: 2-28) hours and 10 (range: 1-36) hours over the two week period respectively, P=0.26.

6.5 Discussion

Available evidence suggests that primary prophylaxis with clotting factor may prevent episodes of bleeding and, consequently, the onset and development of secondary degenerative orthopaedic change[115]. Therefore, in addition to preserving health-related quality-of-life, primary prophylaxis may also reduce the demand for patient / family resources, inpatient stays, outpatient and day-case visits. As the aim of primary prophylaxis is to 'convert' severe haemophilia into a mild / moderate form of the condition, we examined the scope for primary prophylaxis to reduce the demand for these resources by comparing differences in resource use between these two groups of patients. In order to assess these differences, inpatient, outpatient and day-case attendance data for 246 individuals with haemophilia were collected retrospectively for the period 1988 to 1997 inclusive. Productivity data were collected cross-sectionally by posting 238 of these 246 individuals a specially adapted version of the van Roijen *et al.* 'time-use' questionnaire; an adjusted response of 64% was achieved.

The results from the analysis showed that individuals with mild / moderate haemophilia were 45% (31%-56%), 36% (31%-41%) and 70% (67%-73%) less likely to have required inpatient, outpatient and day-case visits than individuals with severe haemophilia. Moreover, the results also showed that individuals with mild / moderate haemophilia were 66% (39%-81%) and 23% (8%-36%) less likely to have undergone orthopaedic procedures and joint replacements, respectively, compared to individuals with severe haemophilia. HIV serostatus and age were also shown to be significant and

independent predictors of the rate of outpatient and day-case visits but not the rate of inpatient stays. These results suggest, therefore, that individuals with severe haemophilia required significantly higher rates of inpatient visits, outpatient visits, day-case visits, orthopaedic operations and joint replacements than the individuals with mild / moderate haemophilia irrespective of age differences between the two groups and HIV serostatus. Thus, it follows that primary prophylaxis for individuals with severe haemophilia could significantly reduce the demand for these resources.

The results from the 'time-use' questionnaire showed that there were no differences between individuals with severe and mild / moderate haemophilia in terms of completed levels of education, employment status, absenteeism from work, the number of hours each week spent performing unpaid tasks and how efficiently individuals performed these tasks after adjustments for differences in age and HIV serostatus were made; the efficiency score for performing odd-jobs and chores aside. Only the proportion of individuals with severe (32%) and mild / moderate (13%) haemophilia who had required help from family or friends to perform routine household tasks each week differed between the two groups. Individuals with severe haemophilia were significantly more likely to have required help than individuals with mild / moderate haemophilia irrespective of differences in age and HIV serostatus (P=0.03). Thus, the potential for primary prophylaxis to decrease patient / family costs is arguably low.

Evidence suggests that individuals with severe haemophilia experience decreased levels of physical functioning compared to individuals with mild / moderate haemophilia[232,233]. Our finding that hospital attendance rates were significantly lower for individuals with mild / moderate haemophilia compared to individuals with severe haemophilia lends some support to this assertion. We also expected to find that individuals with severe haemophilia were less productive with their time than individuals with mild / moderate haemophilia. However, this expectation was not supported by our data although this finding could simply reflect a number of limitations with our data. Firstly, our data may not be representative of all individuals with severe haemophilia. For example, it is feasible that individuals who missed a large amount of schooling due to haemophilia related problems could not complete their 'time-use' questionnaire because of difficulties with reading and writing. A number of publications and the results from Chapter 4 have demonstrated that secondary prophylaxis with clotting factor can reduce

bleeding frequency[109,234]. At the time of data collection, over 90% of individuals at the KDHC with severe haemophilia were believed to be receiving secondary prophylaxis. Thus, this method of treatment may have already helped to reduce the short-term need for medical resources in the form of outpatient and day-case appointments and already reduced patient / family resource consumption. In the absence of this treatment, we might therefore expect larger reductions in these resource requirements.

The results from Chapter 5 suggest that individuals with severe haemophilia experience decreased levels of physical functioning compared to individuals with more mild / moderate forms of the condition but that levels of mental functioning are comparable between the two groups. It is seems likely that individuals with severe haemophilia are capable of working if they choose jobs that reflect their physical capabilities. Alternatively, the effects of HIV infection aside, it might be the case that individuals with severe haemophilia do have a decreased tendency to work compared to the general population. However, compared to the general population, individuals with mild / moderate haemophilia also have a decreased tendency to work; thus any reduction in levels of productivity between the two groups are not reflected in these data.

In terms of absenteeism from paid work, it is possible that individuals with severe haemophilia are more used to coping with bleeding episodes than individuals with mild / moderate haemophilia and are less likely to take time off work when they experience a bleed. It is also conceivable that, individuals with severe haemophilia do not take time off from paid work even if clinically advisable, because of fears of being absent too often and the possible consequence of being asked to seek alternative employment. It is possible that differences in levels of productivity do exist between the two groups but the study was not sufficiently powered to detect these changes. Finally, although the proportions of individuals in both patient groups who reported that they were retired were small, with hindsight it would have been useful to ask individuals at what age they had retired from paid employment and whether they retired due to ill health.

There were a number of limitations with our hospital activity data. The attendance data included in this analysis do not take into account either length of visit or the quantity of resources consumed during these visits. For example, individuals with severe haemophilia usually require longer inpatient or outpatient visits than individuals with

mild / moderate haemophilia because they had more problems to deal with at each visit. Thus, as well as reducing the rate of inpatient and outpatient visits, it is possible that primary prophylaxis might further reduce resource use by reducing the length of these visits. Additionally, policy at the KDHC is to review individuals with severe haemophilia biannually and mild / moderate haemophilia annually on an outpatient basis. Irrespective of any problems individuals with severe haemophilia may develop, therefore, we would expect them to have attended hospital on an outpatient basis more frequently than individuals with mild / moderate haemophilia. However, the same is not true for day-case and inpatient visits.

There are few other published empirical studies for comparison. However, Smith[174] calculated that individuals in the US with severe haemophilia A (<2 iu/dl) underwent an average of two orthopaedic procedures during a 50 year at risk period or equivalently, once every 0.04 patient-years. Our analysis also showed that individuals with severe haemophilia underwent orthopaedic procedures once every 0.04 (95% CI 0.025-0.055) patient-years. However, in contrast to Smith, we used a much broader definition of surgery and included data for individuals who were older than 18 years of age. Varekamp *et al.* also reported that Dutch individuals with severe (<1 iu/dl) haemophilia were more likely to be in employment than Dutch males from the general population and that completed levels of education were comparable across the two groups. Although we considered individuals with mild / moderate haemophilia as our comparative group, rather than the general population, these findings are similar to our own and also suggest that the scope for primary prophylaxis to reduce productivity losses is limited.

In order to isolate the effects of severity of haemophilia on resource use, it was necessary to remove the potentially confounding effects of HIV infection. In the majority of instances, the analysis showed that HIV serostatus often significantly and independently predicted resource use. However, HIV serostatus was not found to be significantly associated with the rate of inpatient stays although this lack of association was probably because our data were not collected for individuals who had died before 31st December 1997. As with the HR-QoL scores in Chapter 5, it was not possible to directly assess the impact of HCV infection on resource use. This was because all individuals with severe haemophilia and many with mild / moderate haemophilia who

were treated with products derived from untreated large plasma pools prior to 1985 became infected with HCV[41]; thus the effects of HCV infection could not be isolated in this analysis.

The aim of the analyis in this chapter was to assess the extent to which primary prophylaxis could reduce the demand for hospital visits and indirect resource use by comparing resource utilisation rates for individuals with severe haemophilia to similar rates for individuals with mild / moderate forms of the condition. The results from this analysis showed that primary prophylaxis is unlikely to reduce patient / family resource consumption as the scope for improvement was negligible as individuals with severe haemophilia recorded that they were spending their time in a similar manner compared to those with mild / moderate forms of the condition. In contrast, however, the results showed that individuals with severe haemophilia attended significantly more inpatient, outpatient and day-case visits than individuals with mild / moderate haemophilia, irrespective of differences in age and HIV serostatus. Thus, primary prophylaxis could significantly reduce the demand for these hospital visits. However, whether this potential benefit affects the cost-effectiveness of treatment will ultimately depend on the effectiveness of primary prophylaxis in converting haemophilia into mild / moderate haemophilia, the unit cost of each hospital visit and how far into the future they are averted due to the process of discounting[178].

7 A COST-MINIMISATION ANALYSIS OF CONTINUOUS INFUSION DURING SURGERY FOR INDIVIDUALS WITH SEVERE BLEEDING DISORDERS

7.1 Introduction

Repeated bleeding into joints may eventually result in the onset and progression of haemophilic arthropathy (HA)[86,115,211,216]. In severe instances of HA, individuals may be offered the choice of undergoing corrective surgery such as a total joint replacement[81,87,235,236]. Indeed, the results from chapter 6 suggest that individuals with severe haemophilia undergo major orthopaedic surgery once every 25 patient-years (95% CI 18-40 years). Individuals with these clotting factor deficiencies may also require surgery due to co-morbidities and other haemophilia-related sequelae such as muscular atrophy[237]. Excluding dental procedures, the 148 patients registered at the Katharine Dormandy Haemophilia Centre (KDHC) with severe haemophilia and vWD underwent a total of 39 surgical procedures in 1995 alone.

When individuals with clotting factor deficiencies undergo major (eg. orthopaedic, intracranial, abdominal) or minor (eg. arthroscopy, skin excisions) surgical procedures, they must receive adequate haemostatic cover with clotting factor before, during and after the procedure in order to prevent any problematic bleeding occurring. Traditionally, individuals receive clotting factor using a series of appropriately timed intravenous bolus infusions. However, an alternative to bolusing is to infuse clotting factor on a continual basis using an infusion pump. Continuous infusion (CI), as this process is known, has previously been used as a method of supplying clotting factor during a range of different invasive procedures, to treat potentially life threatening bleeds such as cerebral haemorrhages and to supply clotting factor to individuals who have developed inhibitors to treatment. The theoretical advantage of this approach is that, unlike bolusing, CI maintains a constant *in vivo* clotting factor level thus reducing the risk of post-operative bleeding. Additionally, due to the pharmacokinetic properties of clotting factor, studies have also shown that in some circumstances CI for surgery may require between 30-75% less FVIII than bolusing whilst providing a similar haemostatic effect[126,127,132,134,139,140]. However, with the exceptions of the studies by Hay[132] and Hathaway,[139] these studies have used retrospective controls to estimate the

amount of clotting factor required for bolusing, meaning that differences in the study populations (eg. in terms of body weight, pharmacokinetic response) and study objectives (in terms of target *in vivo* clotting factor levels) could account for some or all of the differences in FVIII use between the two modes of treatment. No similar studies could be identified where the differences in FIX consumption were considered or where adequate consideration had been given to the cost-effectiveness of CI. Moreover, because haemophilia is rare, it is difficult to design a randomised trial of CI versus bolusing in individuals with same characteristics undergoing similar types of surgery[133]. Thus, the aim of this chapter was to assess the cost-effectiveness of CI during surgery versus bolus infusions for individuals with clotting factor deficiencies using a decision analytical approach.

7.2 Method

7.2.1 Form of economic analysis and perspective

The analysis was performed from a National Health Service (NHS) perspective meaning that only the direct costs of treatment were included in the analysis. This perspective was chosen as it was thought unlikely that the indirect costs would differ between the two treatment methods. When resources between two (or more) methods of treatment are identical, they can be excluded from an economic evaluation because they will not have an affect on cost differences and hence, will not effect cost-effectiveness.

Similarly, there was no evidence to suggest that the method of clotting factor delivery has an effect on the outcome of treatment *per se*. For example, there was no evidence to suggest that rates of post-operative infection (such as deep vein infection) and post-operative mortality are affected by the method of clotting factor delivery used. Where there is prior knowledge that health outcomes between two methods of treatment are equal, the most cost-effective option is the least costly treatment; this type of evaluation is known as a cost-minimisation analysis.

The economic evaluation took the form of a probabilistic simulation (Monte Carlo) analysis for hypothetical cohorts of individuals with severe haemophilia A and B. This type of analysis was used because the combined effects of uncertainty surrounding the different variables could be examined without the need to resort to the wide range of values generated by optimistic (most cost-effective) / pessimistic (least cost-effective)

scenario analysis. However, a limitation of this approach is that probabilistic simulations can only handle uncertainty in the data requirements of the analysis at hand. If, for example, the effect of using two different priced clotting factors on the cost-effectiveness of CI were required, the model would have to be 'run' twice. For this reason, the model was run several times so that a number of different clinical scenarios could be represented in the analysis. Additionally, where stochastic data were available, variables were specified as distributions rather than point estimates in an attempt to mimic more 'realistic' situations. This approach to variable specification was recently used in a model designed to assess the cost-effectiveness of antiretroviral treatment for individuals with HIV/AIDS[238]. The distributions were specified in the model as the most 'likely' value along with upper and lower limits for each variable. These limits were set equal to the first and third quartiles of the distribution unless stated otherwise. Values outside of these limits were not permitted.

In each scenario a cohort of 100 individuals with severe haemophilia A or B were assumed to require surgery over a one-year period. The model then calculated the expected costs of treating these individuals with CI or with bolus infusions. That is, two costs were calculated per person so that differences in clotting factor use could be attributed to the treatment methods and not to any other factor.

7.2.2 Data source

Parameter estimates were collected from a number of different publications and from patient records. Where data from neither of these sources was available, expert opinion was sought from clinical staff at the RFH NHS Trust who had direct experience of the relevant clinical issues (Dr KJ Pasi consultant in haemophilia and Sister C Harrington, staff nurse).

7.2.3 Resource estimation

7.2.3.1 Treatment protocols

The different target nadir clotting factor levels and the duration of each stage of treatment (defined below) are show in Table 7.1 and Table 7.2 respectively. The target nadir *in vivo* clotting factor levels were based partly on World Federation of Haemophilia (WFH) recommended treatment protocols[239,240] and on clinical practice at the KDHC. Trough *in vivo* clotting factor levels for the two methods of treatment were

equalised to ensure that protocols with identical objectives were compared. The treatment protocols were also divided into separate stages in order to reflect the need for progressively lower trough clotting factor levels over the course of treatment. The duration of each stage (in days) was specified as a distribution rather than a point estimate. The most likely duration of treatment stages were set broadly in accordance with the WFH recommendations but, in the absence of any further information, the upper and lower limits for this variable were estimated.

Table 7.1: Clotting factor treatment protocols

Stage	Peak / trough *in vivo* clotting factor levels (iu/dl)			
	Major surgery		Minor surgery	
	FVIII	FIX	FVIII	FIX
Stage 1*	100	100	60	40
Stage 2**	50	40	25	15
Stage 3**	30	25	15	15
Stage 4**	1	1	-	-
Stage 5*	100	100	50	50

* **clotting factor (peak) level immediately following infusion**
** **clotting factor (trough) level immediately prior to maintenance dose**

Model dependent rather than independent methods were used to estimate clotting factor pharmacokinetics. This model relates time after infusion to factor concentrate whereas the latter method does not. Although the independent method is thought to be more robust than the dependent method, this approach was used because more published data were available with which to populate the model, particularly for individuals receiving FIX and because existing modelling studies have also used this technique to estimate clotting factor use[132]. However, the model could easily be changed to incorporate model independent techniques using an appropriate set of equations.

Table 7.2: Parameter estimates and sources for Monte Carlo analysis of CI

Variable	Low	Most likely	High	Data Source
FVIIII				
FVIII beta half-life (hours)	10	12.2	13.6	Carlsson, 1993[125] and 1997[123,125]
FVIII recovery rate (iu/dl)	-	2	-	Berntop, 1995[5]
FIX				
FIX alpha half-life (hours)	4.53	5.25	5.72	Carlsson, 1998[124]
FIX beta half-life (hours)	26.7	29.8	31.0	Carlsson, 1998[124]
C_1 (iu/dl)	8.70	11.75	14.4	Carlsson, 1998[124]
C_2 (iu/dl)	6.05	6.50	6.70	Carlsson, 1998[124]
Mdose (iu/kg)	13.2	14.5	17.4	Carlsson, 1998[124]
FIX recovery rate (iu/dl)	-	1	-	Berntop, 1995[5]
Duration of each stage (days)				
Major surgery: stage 2*	4	5	6	Rickard, 1995[240], Kobrinsky, 1997[239] and the KDHC
Major surgery: stage 3*	4	5	6	Rickard, 1995[240], Kobrinsky, 1997[239] and the KDHC
Major surgery: stage 4*	4	5	10	Rickard, 1995[240], Kobrinsky, 1997[239] and the KDHC
Minor surgery: stage 2*	2	3	4	Rickard, 1995[240], Kobrinsky, 1997[239] and the KDHC
Minor surgery: stage 3*	4	5	6	Rickard, 1995[240], Kobrinsky, 1997[239] and the KDHC
Patient details				
Patient weight (kg)**	48	69	137	KDHC

Ranges were set equal to first and third quartiles from quoted source(s) unless *estimated, **equal to first and last percentile

7.2.3.2 The treatment stages included in the model

In the first treatment stage **(stage 1)**, *all* individuals received a single initial (loading) bolus dose of clotting factor immediately prior to surgery. For example, individuals with haemophilia A undergoing major and minor surgery received bolus doses of FVIII sufficient to raise their *in vivo* clotting factor levels to 100 iu/dl and 60 iu/dl respectively. No further doses of clotting factor were administered during this stage. Immediately after surgery **(stage 2)**, individuals with haemophilia A \ vWD or B either continued to receive bolus (maintenance) doses of FVIII or FIX every 12 or 24 hours respectively or were treated using CI. In the next stage of treatment **(stage 3)**, the target trough clotting factor levels were lowered in accordance with WFH guidelines to simulate the effects of the wound healing process. At the end of this treatment stage, bolusing and CI were discontinued. All individuals who underwent major surgery switched to a standard prophylactic treatment regime for the remainder of their inpatient stay at this point **(stage 4)**. This prophylactic regime consisted of 30 iu/kg three times a

week for those with severe haemophilia A or vWD and 30 iu/kg twice a week for those with severe haemophilia B. However, to reflect the less invasive treatment, individuals undergoing minor surgery were assumed not to require this prophylactic treatment stage. Finally, *all* individuals were assumed to require a precautionary bolus dose of clotting factor immediately prior to being discharged from hospital **(stage 5)**. For individuals undergoing minor or major surgery, these infusions were sufficient to raise *in vivo* clotting factor levels to 50 iu/dl and 100 iu/dl respectively. Figure 7.1 illustrates the theoretical *in vivo* clotting factor profile by stage of treatment for an individual with haemophilia A or vWD who has undergone major surgery using bolus infusions or CI. For the purposes of this illustration, most likely values have been used for the duration of each treatment stage.

7.2.4 Clotting factor doses

FVIII and FIX are believed to decay exponentially (Figure 7.2) and biexponentially (Figure 7.3) respectively, meaning that their decays are best described using one and two half-lives. For the sake of simplicity, it was assumed that all half-lives remained constant over the treatment course. However, it is acknowledged that half-lives are thought to vary over the course of treatment particularly during the peri-operative period[132].

Figure 7.1: Approximation of the *in vivo* clotting factor level for an individual with severe haemophilia A undergoing major surgery

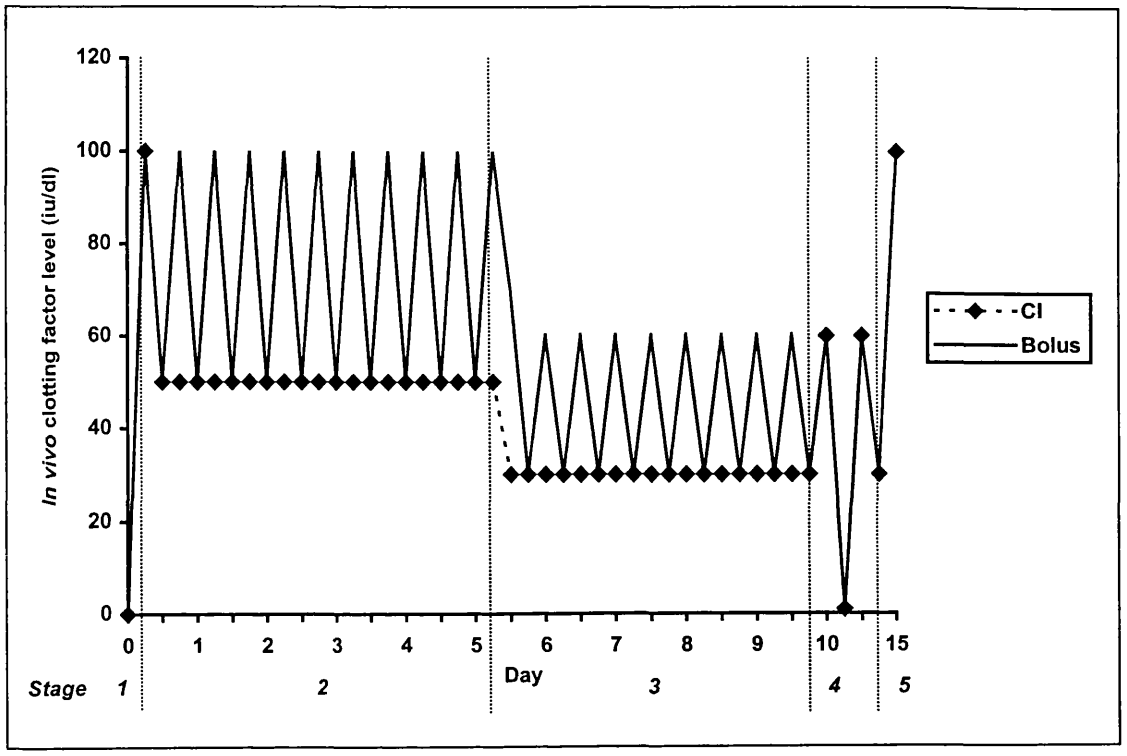


Figure 7.2: FVIII decay curve can be described exponentially by the equation $A_t = A \times e^{-k \cdot t}$

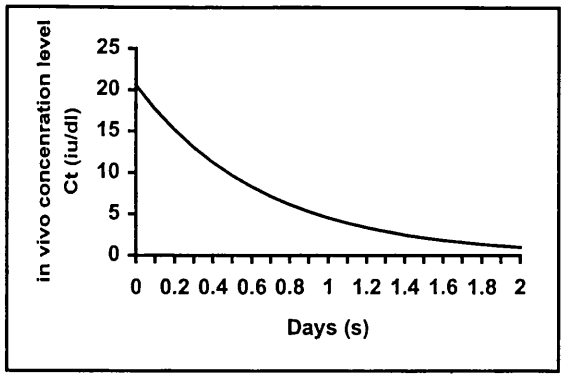
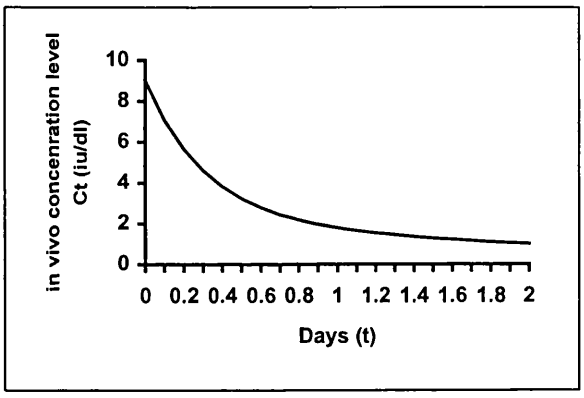


Figure 7.3: FIX decay curve can be described biexponentially by the equation $A_t = A_1 \times e^{-k1 \cdot t} + A_2 \times e^{-k2 \cdot t}$



7.2.4.1 Bolusing - FVIII

The values used to calculate bolus doses and their sources are shown in Table 7.2. Individual bolus doses of FVIII were calculated using the equation:

$$C_t = A \cdot e^{-k \cdot t} \qquad \text{(Equation 7.1)}$$

Where A is the initial *in vivo* concentration level at time 0 (in iu/dl), C_t is the required trough clotting factor level at time t after the infusion (t was fixed at 12 hours for individuals receiving FVIII and 24 hours for individuals receiving FIX) and k is the rate constant of the exponential term (calculated as: ln2 / half-life). Thus, for any patient, A

can be calculated given particular values of C at time t and k. This can be achieved by rearranging Equation 1 to give:

$$A = C_t / e^{-k \cdot t} \qquad \text{(Equation 7.2)}$$

The desired rise in clotting factor concentration in iu/dl is equal to:

$$A - E_0 \qquad \text{(Equation 7.3)}$$

Where E_0 is the *in vivo* clotting factor level just prior to the infusion (ie. just before time 0). The required dose to achieve this rise was then calculated as:

$$Dose(iu) = \frac{A - E_0}{\text{Recovery}} \cdot Weight \qquad \text{(Equation 7.4)}$$

The total number of infusions required over each stage of treatment was calculated by dividing t into the total number of hours in each treatment stage. Finally, the total of amount of clotting factor used per patient was calculated by multiplying the number of infusions in each stage of treatment by the relevant dose and by summing the totals from each stage.

7.2.4.2 Bolusing - FIX

Bolus doses for individuals with haemophilia B were calculated differently in order to reflect the biexponential decay of the FIX molecule. Carlsson *et al.*[124] state that bolus doses of FIX needed to achieve a desired concentration at time t can be calculated using the following equations:

$$C_{total} = C + C_{previous} \qquad \text{(Equation 7.5)}$$

Where C_{total} is the desired trough concentration level, and C and $C_{previous}$ are the concentration levels at t and $t+ t$ (days) respectively. C and $C_{previous}$ were calculated as:

$$C = (dose / Mdose) + (C_1 \cdot e^{-k_1 \cdot t} + C_2 \cdot e^{-k_2 \cdot t}) \qquad \text{(Equation 7.6)}$$

$$C_{previous} = (dose / Mdose) + (C_1 \cdot e^{-k_1 \cdot t+t} + C_2 \cdot e^{-k_2 \cdot t+t}) \qquad \text{(Equation 7.7)}$$

Where dose is the actual bolus dose of clotting factor and Mdose is set equal to 1,000 iu divided by the patients body weight in kg. C_1, C_2 and k_1, k_2 are the *in vivo* concentrations at time 0 normalised to doses of 1,000 iu and the rate constants of the exponential terms for the alpha and beta half-lives respectively. Thus, given pre-specified values for Mdose, C_1, C_2, k_1 and k_2, the size of each bolus dose could be calculated that would result in a specified trough *in vivo* clotting factor level at time *t*. The size of each dose was calculated by adding together equations 6 and 7 and rearranging the result to give:

$$Dose(iu / kg) = \frac{\text{target} \cdot \text{Mdose}}{(C_1 \cdot e^{-k_1 \cdot t} + C_2 \cdot e^{-k_2 \cdot t}) + (C_1 \cdot e^{-k_1 \cdot t+t} + C_2 \cdot e^{-k_2 \cdot t+t})} \qquad \text{(Equation 7.8)}$$

Where target equals target trough *in vivo* level. *T* was fixed at 24 hours for individuals with haemophilia B in order to reflect the FIX molecules longer beta half-life. The total number of doses in each stage and the total amounts of clotting factor used per patient over the course of treatment were then calculated in the same way as for individuals who received bolus doses of FVIII.

7.2.4.3 Unadjusted-dose CI (FVIII and FIX)

Required rates of continuous infusion (iu h^{-1} kg^{-1}) were calculated as:

$$Desired\ steady\ state\ level\ (iu / ml^{-1}) \cdot clearance\ (ml\ h^{-1}\ kg^{-1}) \qquad \text{(Equation 7.9)}$$

Where the desired steady state level was set equal to the trough clotting factor level for individuals undergoing bolusing and clearance (Cl) was equal to:

$$Cl = Dose(iu / dl) / AUC \qquad \text{(Equation 7.10)}$$

where area under the curve (AUC) was equal to:

$$AUC = \sum_{i=1}^{n} (C_i / k_i) \qquad \text{(Equation 7.11)}$$

7.2.4.4 Adjusted-dose CI

Evidence suggests that clearance reduces during the course of treatment in individuals undergoing CI meaning that progressively less clotting factor needs to be infused in order to maintain a given *in vivo* clotting factor level. Martinowitz *et al.*,[133] demonstrated that clearance decreased in individuals with haemophilia A from a median post-operative level of 3.2 ml/kg/hour to 1.7 ml/kg/hour on day 5, after which time clearance levelled off. In a separate study in four individuals with severe and moderate haemophilia B, three individuals experienced the same progressive decrease in clearance[71]. The effect of decreasing clearance on the costs of treatment was investigated in a number of scenarios by assuming that the rate of clearance reduced by 53% during treatment stage 3 (ie. approximately on days 4-5) for the remainder of treatment with CI.

7.2.5 The choice of clotting factor

CI requires clotting factor to remain in solution in plastic containers for periods of time. Efficacy must be established and a license granted before a clotting factor can be stored and used in this manner. At present Monoclate P (a very-high purity FVIII produced by Centeon) and Mononine (a very-high purity FIX produced by Centeon) there is published data for only to be stored and infused in this way. The safety and efficacy of using a recombinant FVIII (Kogenate) for CI is currently undergoing trial in the UK and a similar trial for a recombinant FIX is anticipated in the near future. Therefore, at the baseline scenarios, it was assumed that irrespective of treatment method all individuals with haemophilia A \ vWD and B received Monoclate P or Mononine respectively but the impact of using rDNA FVIII on the cost-effectiveness of treatment was investigated in the one-way sensitivity analysis. Although no rDNA FIXs yet have licences in the UK to be used for CI, the cost-effectiveness of CI with recombinant FIX was also examined to explore the impact of its use on the cost-effectiveness of treatment. The impact of using an intermediate clotting factor on the cost-effectiveness of treatment was not considered in this analysis as these products are thought to be unsuitable for CI.

7.2.6 Remaining resources included in the model

Only the costs of providing the clotting factor, using the infusion pump, normal saline solution (30 iu ml h^{-1} of normal saline for individuals undergoing CI) and inpatient stays were included in the analysis. A number of resources were excluded for the following reasons. Firstly, there was no evidence to suggest that the size of some of the remaining resources were dependent on the method of clotting factor delivery. For example, the time spent in theatre, the volume of analgesics patients receive or the number of outpatient visits individuals require following discharge are unlikely to vary according to the method of clotting factor delivery employed. Thus, similarly to the indirect costs, these resources can be excluded from the analysis because their precise size will not affect the cost-effectiveness of either treatment. Secondly, although CI is likely to require the use of more disposable resources than bolusing (eg. cannulas, giving sets, venflons etc.), these additional costs are unlikely to amount to more than a few pounds per procedure, a very small amount compared to the costs of clotting factor provision. Lastly, when doctors at the KDHC were asked how much time they thought they spent with each inpatient per day, their response suggested that there were no differences between the two treatment groups. When the nursing staff were asked the same question, their response strongly suggested that, if anything, CI reduced the average amount of time per day they spent with each patient mainly because there was no longer a need to measure pre and post bolus infusion clotting factor levels. However, this possible cost difference was not included in the analyses because a conservative approach to estimating cost differences was preferred.

7.2.7 Treatment complications

It was assumed in the model that patients did not experience any peri or post-operative complications. This assumption was made because, apart from some minor episodes of bleeding, infections around the cannula site for individuals undergoing CI and minimal blood loss[132,133,140,241], no major adverse events or treatment complications could be found in the literature that were directly linked to either method of clotting factor delivery. Secondly, it had already been assumed that the two treatments were equally effective in terms of the outcome of surgery *per se*. Thirdly, the design of the model automatically equalised nadir clotting factor levels. Thus, the risk of bleeding was likely to be similar in both treatment groups. Moreover, it was also felt that the risk of

post-operative bleeding was minimal given the relatively high target clotting factor levels specified by the WFH.

7.2.8 Epidemiology

Irrespective of the method of delivery used, clotting factor is always administered according to a function of body weight. In 1994, 348 adults (those over 18 years of age) with severe haemophilia who were registered for treatment at the KDHC had a median weight of 69kg (range: 48-137 kg), the figures used in the analysis. Individuals were also assumed to have baseline clotting factor levels of 0 iu/dl and not to have developed inhibitors to clotting factor at any time.

7.2.9 Resource valuation

Monoclate P, Mononine, recombinant FVIII and recombinant FIX were valued at RFH Trust acquisition prices: 32.5, 32.5, 52.9 (including VAT) and 70 (including VAT) p/iu, respectively. The RFH NHS Trust acquisition price for a (reusable) Walk-Med infusion pump was £1,800 (including VAT). Although these pumps have a life span lasting a number of years, the cost of the pump was conservatively estimated to be £180 per operation (ie. this is likely to be an overestimate of the pump's true cost per procedure). The cost of an inpatient day on an orthopaedic ward at the RFH NHS Trust was calculated (by the finance department) to be £188 *per diem*. However, it is noted that prices do not necessarily reflect costs[242].

7.2.10 The scenarios

Eight (2^3) individual simulations were performed in total in order to allow for the different types of surgery (major \ minor), clotting factor (FVIII \ FIX) and whether or not adjusted-dose CI was assumed (yes \ no).

7.2.11 Additional sensitivity analysis

Although the models were specified as probabilistic simulations, one-way sensitivity analyses were also performed on the costs of major surgery using a basic expected value approach in order to highlight the importance of key variables in determining the cost-effectiveness of treatment. Where variables had previously been specified in the models as distributions, a midpoint based on each variable's range was calculated and held fixed at this value while the parameter under investigation was varied.

The variables subjected to one-way sensitivity analysis were the unit cost of the infusion pump, the unit cost of the clotting factor, patient body weight, alpha and beta half-lives, Mdose, the time between bolus doses and the rate of CI. All variables were varied over a plausible range of estimates.

7.2.12 Model formation and statistical analysis

The decision tree was constructed using TreeAge 3.0.18 software and SAS was used to analyse the results. Paired t-tests were used to analyse the results as all clotting factor use / costs were normally distributed.

7.3 Results

Calculating the mean and standard error of the steady-state clearance rates was a simple method of testing the coherence of the model. On examination, the clearances were considered to be realistic with values of 2.77 (95% CI 2.36-3.18) ml h^{-1} kg^{-1} and 4.27 (95% CI 3.64-4.89) ml h^{-1} kg^{-1} for individuals receiving FVIII and FIX respectively.

7.3.1 Expected clotting factor use

The mean expected clotting factor requirements according to surgery and clotting factor type are shown in Table 7.3 and Table 7.4. Compared to bolusing, unadjusted (ie. no adjustments for decreases in clearance) CI with FVIII or FIX during major surgery required 10,522 iu (22%) and 39,384 iu (44%) less FVIII and FIX respectively. For minor surgery unadjusted CI also resulted in respective FVIII and FIX savings of 3,938 iu (23%) and 13,917 iu (45%). In each scenario the saving in clotting factor use was highly significant ($P<0.0001$). Further analysis showed that compared to unadjusted dose CI, adjusted dose CI resulted in further significant ($P<0.0001$) clotting factor savings in each scenario. Additional savings ranged between 2,026 iu (15%) using FVIII for minor surgery to 5,077 iu (10%) using FIX for major surgery.

7.3.2 Expected costs

The expected costs of treatment with a clotting factor cost of 32.5 p/iu are shown in Table 7.5. In each scenario, unadjusted dose CI was significantly ($P<0.0001$) less costly compared to bolusing and adjusted dose CI (ie. where adjustments were made for decreases in clearance) was significantly ($P<0.0001$) less costly compared to unadjusted dose CI. Unadjusted dose CI during major surgery with FVIII and FIX resulted in mean overall cost savings of £3,419 (95% CI £3,326-£3,512) and £12,800 (95% CI £12,482-

£13,120) per procedure respectively compared to bolusing. For minor surgery the equivalent figures were £1,280 (95% CI £1,244-£1,316) and £4,523 (95% CI £4,414-£4,632) per procedure respectively. Compared to unadjusted dose CI, adjusted dose CI produced additional cost savings per procedure of between £659 (95% CI £643-£675) for treatment with FVIII during minor surgery to £1,650 (95% CI £1,608-£1,692) for treatment with FIX during major surgery. The costs of the inpatient stay and the pump were £3,237 and £1,677 for individuals undergoing major and minor surgery respectively.

7.3.3 One-way sensitivity analysis

When the steady-state rate of CI was varied independently of the half-lives, the analysis showed that unadjusted dose CI remained the least costly method of providing FVIII and FIX unless the infusion rate increased above 0.04 iu/kg/hour and 0.106 iu/kg/hour respectively. That is, if the levels of CI were equivalent to these rates over the entire treatment period, the costs of CI and bolusing were equivalent. Rates of infusion above or below these thresholds would make CI less or more costly compared to bolusing respectively.

Further results from the one-way sensitivity analyses showed that the cost-effectiveness of unadjusted dose CI was extremely sensitive to the clotting factor unit cost. When FVIII cost 18 p/iu, each major procedure cost £11,300 and £13,300 using unadjusted dose CI and bolusing respectively a difference of £2,000 per procedure (Figure 7.4). However, when the unit FVIII cost increased to 52.9 p/iu, the per procedure costs of treatment increased to £27,100 and £33,300 for unadjusted dose CI and bolusing respectively meaning that the overall cost difference increased to £6,200 or by 210%. For FIX, the costs of unadjusted dose CI and bolusing increased from £16,400 and £26,900 respectively when the unit FIX cost was set at 22.5 p/iu, to £44,200 and £77,200 respectively when the unit cost was set at 70 p/iu (Figure 7.5). This is an increase in the difference in cost between the two methods of treatment of £22,800 per procedure or 214%.

Table 7.3: Results from the Monte Carlo analyses: predicted clotting factor use (iu)

Clotting factor	Surgery type	Bolusing (iu) (1)		Unadjusted CI (iu) (2)		Adjusted CI (iu) (3)		P-value	P-value
		mean	Sd.	mean	sd.	mean	sd.	(1) v (2)	(2) v (3)
FVIII	Major	48,340	10,784	37,818	8,137	35,223	7,342	<0.0001	<0.0001
"	Minor	17,041	3,821	13,103	2,803	11,077	2,349	<0.0001	<0.0001
FIX	Major	88,836	21,525	49,452	11,963	44,375	10,749	<0.0001	<0.0001
"	Minor	31,182	7,315	17,265	3,992	14,341	3,308	<0.0001	<0.0001

P-values were calculated using paired t-tests

Table 7.4: Results from the Monte Carlo analyses: predicted clotting factor use (iu/kg)

Clotting factor	Surgery type	Bolusing (iu/kg)		Unadjusted CI (iu/kg)		Adjusted CI (iu/kg)	
		mean	sd.	Mean	sd.	mean	sd.
FVIII	Major	592	48.2	463	29.5	431.7	27.90
"	Minor	208	19.4	160	11.3	135.7	9.7
FIX	Major	1,053	66.5	586	31.3	526	28.2
"	Minor	382	32.0	211	13.8	176	10.2

Table 7.5: Results from the Monte Carlo analyses: predicted costs of treatment (£). All clotting factor at 32.5 p/iu.

Clotting factor	Surgery type	Bolusing (£) (1)		Unadjusted CI (£) (2)		Adjusted CI (£) (3)		P-value	P-value
		Mean	sd.	mean	sd.	mean	sd.	(1) v (2)	(2) v (3)
FVIII	Major	18,948	3,533	15,528	2,681	14,684	2,425	<0.0001	<0.0001
"	Minor	7,213	1,255	5,933	922	5,275	776	<0.0001	<0.0001
FIX	Major	32,107	7,540	19,306	3,942	17,656	3,549	<0.0001	<0.0001
"	Minor	11,810	2,389	7,286	1,310	6,336	1,089	<0.0001	<0.0001

P-values were calculated using paired t-tests

Figure 7.4: Sensitivity analysis on FVIII cost during major surgery

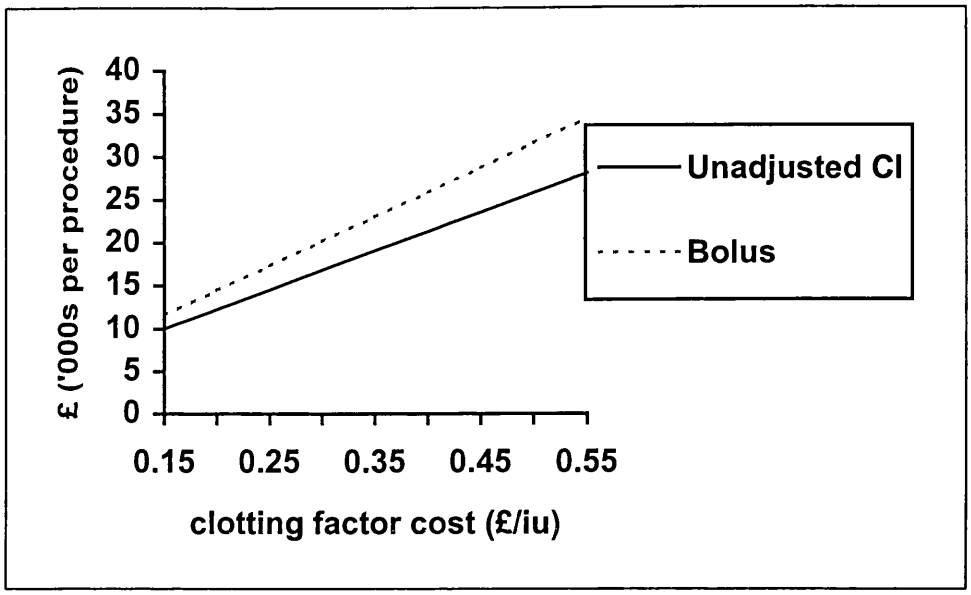
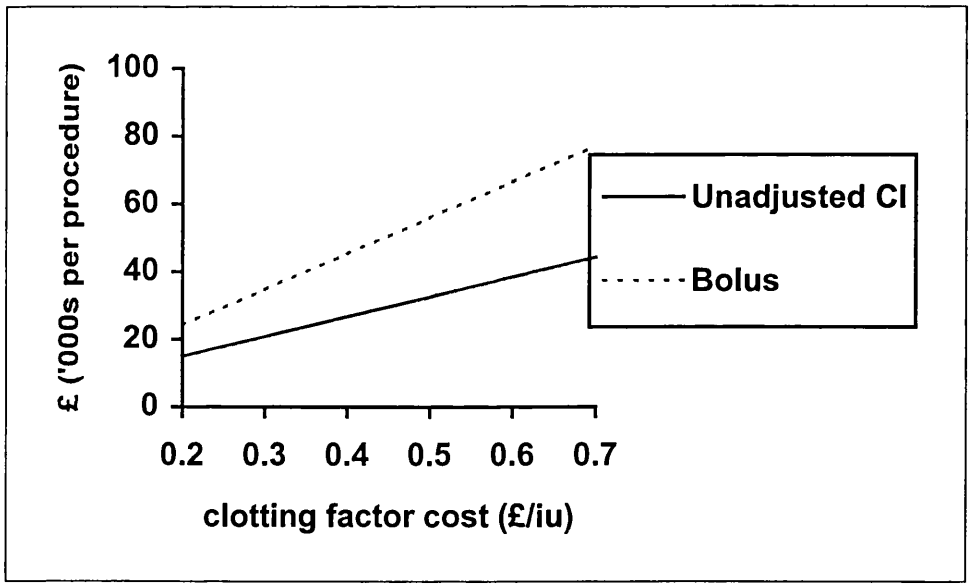


Figure 7.5: Sensitivity analysis on FIX cost during major surgery



The cost-effectiveness of unadjusted dose CI was found to be sensitive to the (beta) FVIII half-life (Figure 7.6) but was not so sensitive to the either the alpha or beta FIX half-life (Figure 7.7-Figure 7.8). When the FVIII half-life was increased from 10 hours to 13.6 hours, the cost difference between the two treatment methods decreased from £5,700 to £2,740 per procedure or equivalently, the cost difference decreased by almost 50%. Similarly, the cost-effectiveness of CI with FVIII was found to decrease markedly when the interval between maintenance doses was shortened (Figure 7.9). However, decreasing the interval between maintenance doses of FIX had little effect on cost-effectiveness unless the interval was less than every 13.5 hours. In this instance however, the cost-effectiveness of CI increased as the decrease in intervals between doses caused the costs of bolusing to increase sharply (Figure 7.10). The analysis also showed that the cost-effectiveness of unadjusted dose CI with FIX was relatively sensitive to the variable Mdose. As Mdose increased from 13.2 iu/dl to 17.4 iu/dl, the difference in cost between the two treatment methods increased from £12,600 per procedure to £16,700 (Figure 7.11). Doubling the cost of the infusion pump from £180 to £360 per procedure had negligible impact on the cost-effectiveness of treatment with either FVIII or FIX.

Figure 7.6: Sensitivity analysis on FVIII beta half-life during major surgery

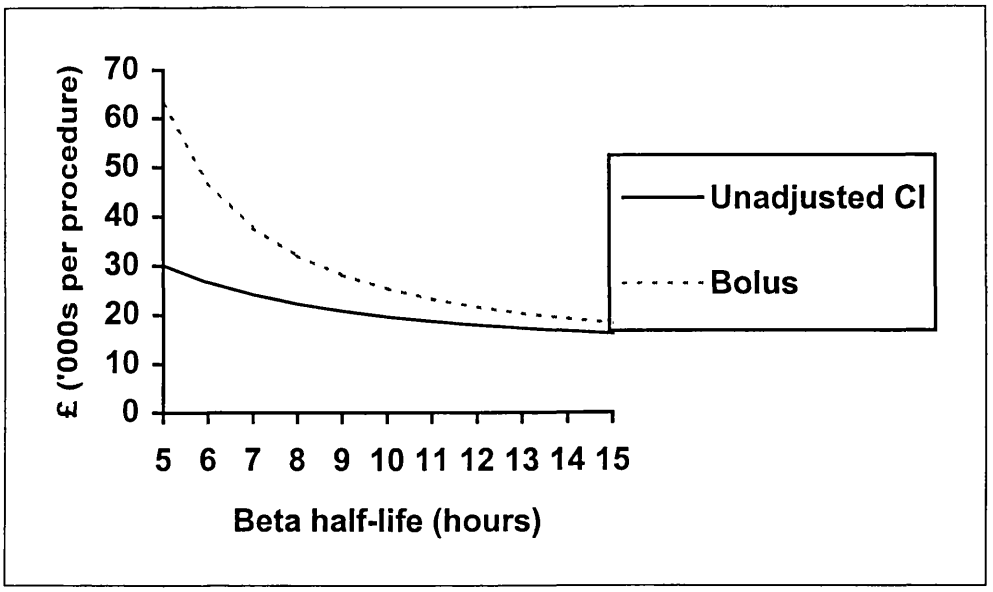


Figure 7.7: Sensitivity analysis on FIX alpha half-life during major surgery

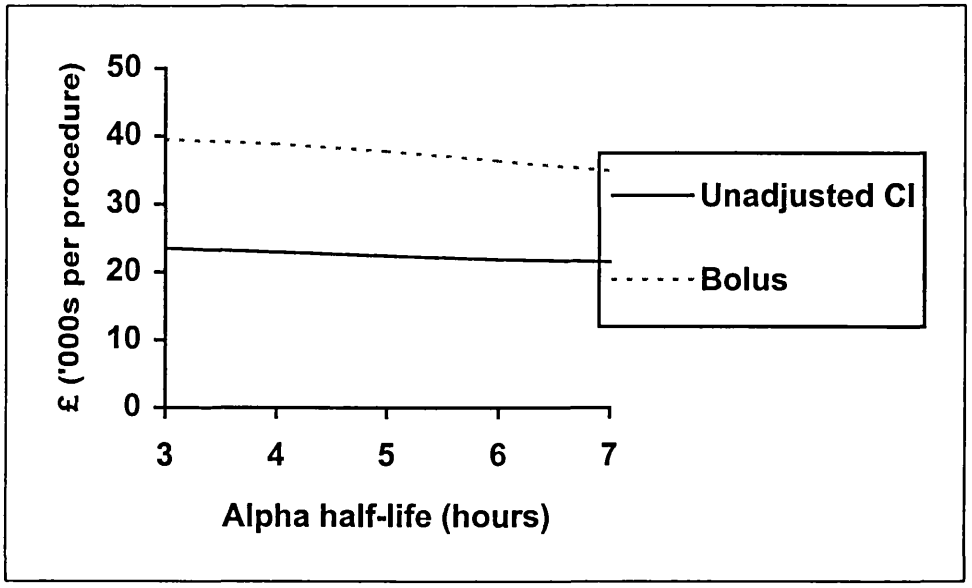


Figure 7.8 Sensitivity analysis on FIX beta half-life during major surgery

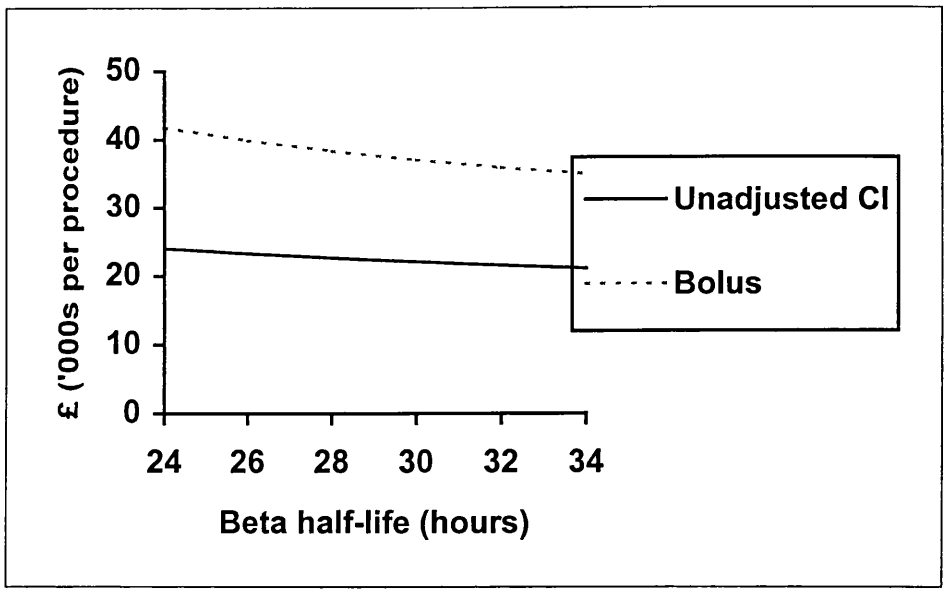


Figure 7.9: Sensitivity analysis on time between bolus doses of FVIII during major surgery

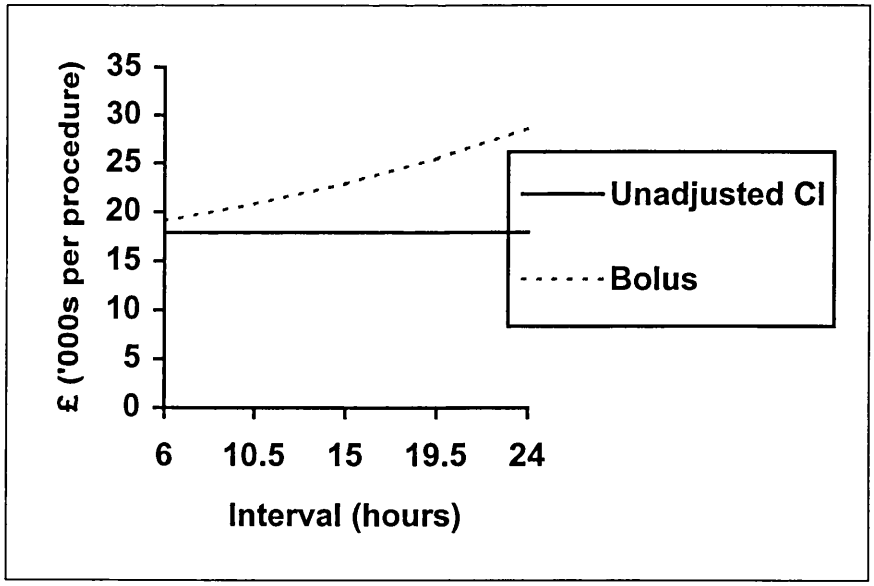


Figure 7.10: Sensitivity analysis on time between bolus doses of FIX during major surgery

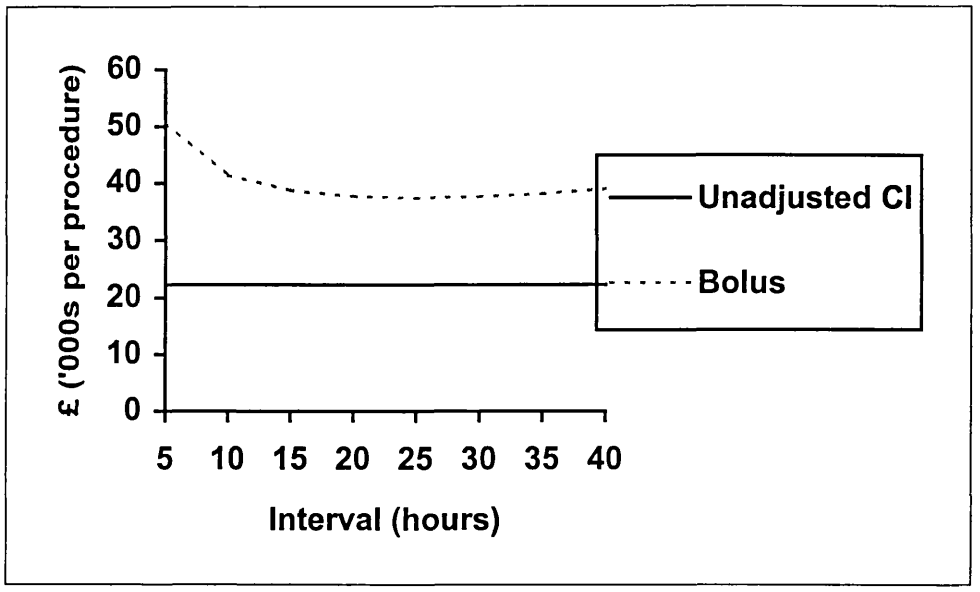
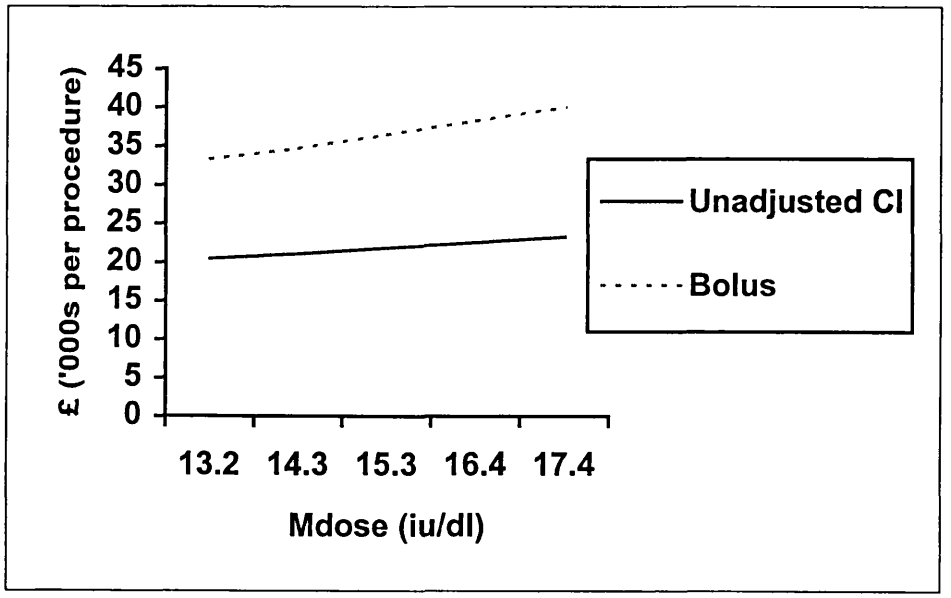


Figure 7.11: Sensitivity analysis on Mdose during major surgery using FIX



7.4 Discussion

There is a growing interest in administering clotting factor to individuals with haemophilia on a continual basis using an infusion pump (CI) rather than intermittently with bolus infusions following serious episodes of bleeding, to manage inhibitors to treatment and to provide post-surgical haemostatic cover. In this analysis, we assessed the cost-effectiveness of CI with clotting factor during surgery for individuals with severe haemophilia under a range of different clinical scenarios by synthesising information from a number of sources using a decision analytical approach.

When the values from Table 7.1 and Table 7.2 were used in the model, unadjusted dose CI for major or minor surgery reduced FVIII and FIX consumption by approximately 22% and 44% respectively compared to intermittent bolusing. When adjusted dose CI was assumed, additional respective clotting factor savings of 15% to 10% were achieved. Using a unit clotting factor cost of 32.5 p/iu, these clotting factor savings translated into cost savings of between £1,280-£12,800 per procedure depending on the remaining underlying assumptions. These reductions occurred even after taking into account the cost of the infusion pump. Indeed, in some instances it is likely that the costs of purchasing the infusion pump required for CI would be more than off-set after a single operation. Moreover, although the overall cost differentials were highly sensitive to a number of variables such as the beta half-life and the interval between doses, under all plausible assumptions unadjusted-dose CI consistently remained the less costly treatment option compared to bolusing. These results suggest, therefore, that unadjusted-dose CI is significantly less costly than bolusing and that further significant cost savings could be achieved if the rate of CI was adjusted for decreasing clearance levels. Alternatively, CI can achieve higher *in vivo* clotting factor levels than bolusing for an equivalent cost.

Existing comparative clinical studies of unadjusted and adjusted-dose CI for surgery have reported reductions in FVIII savings of between 19%-50% per procedure and Hermans[243] has reported theoretical FIX savings of approximately of 40% compared to bolusing. However, with the exception of one study, FVIII consumption for bolusing has been calculated using either retrospective controls or prospectively using a relatively small number of individuals who have not necessarily undergone similar surgical procedures to the cases. Moreover, Hay *et al.* have demonstrated that the costs

of bolusing, and hence the overall cost differential, reduces exponentially when the trough *in vivo* clotting factor level is allowed to decrease below the target concentration level. Thus, differences in treatment protocols over time (eg. duration of treatment, target *in vivo* clotting factor levels, time between bolus doses and trough clotting factor levels), *in vivo* FVIII responses (beta half-life) or differences in patient characteristics such as body-weight could account for overall differences in clotting factor use between the two methods of treatment seen in some of these studies. Unlike these clinical studies however, our model adjusts for differences in these variables by simulating the costs of CI and bolusing with FVIII or FIX for the same individuals under the same conditions.

It was difficult to compare the results from our study to the results from other existing studies because of differences in study design and patient characteristics. However, there are a number of reasons why our predicted FVIII savings of between 22% to 37% per procedure lie within this reported range (19%-50%) but why they might appear at the conservative end of this range. Firstly, in line with recommendations[14], we included a period of standard prophylactic treatment for individuals undergoing major surgery in the treatment algorithm. Thus, the addition of this extra phase of treatment will have reduced the overall clotting factor saving when expressed as a percentage of total clotting factor consumption. Secondly, we assumed that the rate of CI could be adjusted for decreasing clearance on post-operative days 4-6 in order to make the modelling process simpler. Although the precise reason is unknown[132], existing evidence suggests that clearance actually decreases progressively over this period thus the percentage saving from adjusted-dose CI could be higher than our analyses suggest. Lastly, our model did not take into account actual vial sizes which might also account for differences in reported clotting factor consumption and may have an implication for the implementation for the use of CI.

There is also a possibility that we have underestimated the true ability of CI to reduce the costs of treatment. For example, clinical staff at the RFH NHS Trust believed that CI might reduce the amount of time per day that they need to spend with each with each patient as less time is spent preparing the clotting factors for administration. Evidence also suggests that infusions of either high-purity or recombinant FVIII may be cleared much faster in individuals with vWD than in individuals with haemophilia A because

stabilisation of the FVIII is lacking. Thus, in instances where individuals with vWD receive these products, the cost-effectiveness of CI is likely to further increase. Additionally, although there is no evidence to support this claim, Martinowitz *et al.*[133] has suggested that CI facilitates faster wound healing than bolusing. Thus it is feasible that individuals could be discharged from hospital earlier than usual, resulting in further cost savings. Similarly, Varon[244] has demonstrated the feasibility of treating patients who have undergone minor surgery or serious haemorrhaging with CI with a portable infusion pump at home after an initial inpatient stay. It is also technically feasible that a less costly syringe driver could be used instead of the portable infusion pump described here. Indeed, it is likely that many haemophilia centres already own syringe drivers, thus the costs of purchasing the pump could be much less than the values used in these baseline analyses. Lastly, by assuming that there are no major post-operative complications, such as deep vein thrombosis, individuals need not undergo a second surgical procedure to alleviate the problem. However, if this possibility had been included and assuming the second surgical procedure was performed using the same method of replacement therapy as used for the first procedure, CI would have appeared even less costly than bolusing.

The results from the one-way sensitivity analysis also demonstrated how sensitive the costs of treatment were to the unit clotting factor cost. For example, when the unit FVIII cost increased from 18 p/iu to 52.9 p/iu, the cost saving for major surgery increased from approximately £2,000 per procedure to £6,000 when unadjusted-dose CI was used instead of bolusing. The proportion of individuals in the UK with severe haemophilia who receive recombinant clotting factors is increasing[67]. Thus, it is likely that the importance of CI in reducing costs will increase over time as the percentage of operations performed using recombinant clotting factors increases.

Although the model presented in this chapter was constructed to predict the likely difference in costs using CI instead of bolusing to deliver clotting factor to individuals post-surgery, the results from the model can be extrapolated to other clinical contexts. For example, the results from the one-way sensitivity analysis clearly suggested that the overall difference in cost was inversely related to the beta half-life when the clotting factor was assumed to decay exponentially; a finding also reported by Hay *et al.*[132]. That is, the shorter the beta half-life, the greater the overall cost saving. Thus, in

instances where individuals with inhibitors to clotting factor are to receive rDNA VIIa, it is likely that CI would be a highly cost-effective method of replacement therapy because rDNA VIIa has a relatively short beta half-life (approximately 3-7 hours[245]) and because it is currently extremely expensive to purchase. Moreover, there is nothing intrinsically different between this 'surgical analysis' and an analysis involving treatment following an event such as a cerebral bleed, other than the fact that treatment intensity (ie. target *in vivo* clotting factor levels) and duration of treatment might be different to the values used here. Thus, it is likely that CI would also be cost-effective compared to bolusing following a serious bleeding episode.

One of the assumptions in the model was that local infection around the cannula site was prevented using 30 iu ml h^{-1} of normal saline and that all individuals were able to tolerate cannula insertion for the duration of treatment. However, the degree to which infection occurs around the cannula site and issues of tolerance are likely to affect the cost-effectiveness of CI. This will depend on the incidence of local thrombophlebitis, at what stage (day) over the course of treatment the infection occurs and whether the cannula can be relocated to a different peripheral vein. Clearly, if the cannula cannot be relocated any potential cost savings will be jeopardised. In order to simplify the analysis it was also assumed that the half-lives remained static over the period, although there is evidence to suggest that they may decrease substantially during the peri-operative period due to heavy blood loss, and that they may be shorter in children[132,133]. However, incorporating either of these two factors into the model would not have reduced the cost-effectiveness of CI because CI was assumed not to commence until the beginning of the post-operative stage and because decreasing the half-life could only have increased the cost differences. It was also assumed that clearance rates only decreased in the post-operative stage in patients undergoing CI as it was unclear whether or not this phenomena occurs in patients undergoing bolusing[132,246]. However, if clearance rates do decline in individuals undergoing bolusing the size of any cost differential may also decline. Although evidence is limited, it may be the case that patients undergoing CI may be at increased risk of developing inhibitors to treatment[247]. Such an event would seriously jeopardise the potential of CI to be cost-effective even if the incidence of inhibitor development were small, as treating one individual who has developed an inhibitor can be extremely costly[145,147]. Finally, the large number of trials per scenario (n=100) could easily artificially increase the significance of cost

differences. However, when each scenario was re-run using 20 hypothetical trials rather than 100, only negligible changes in the P-values were noted ($P<0.001$ in all instances).

In our model we assumed that FIX decayed biphasically in line with more recent recommendations[248,249]. However, when this assumption was relaxed, and a beta half-life of 30 hours was used in the analysis, the savings in clotting factor use reduced to 4% for major surgery when unadjusted-dose CI was used instead of bolusing compared to the original figure of 44%. This is because the initial and relatively rapid clearance during the alpha-phase is removed from the calculations. Thus, these results suggest that differences in the assumptions regarding FIXs decay can have profound effects on the predicted costs of bolusing.

Evidence is emerging that CI is a safe and efficacious method of delivering some clotting factors during major and minor surgery for patients with severe haemophilia. The results from our model provide preliminary economic evidence to show that CI during surgery for individuals with severe haemophilia may result in significant cost savings to the National Health Service despite the extra costs of using an infusion pump. Moreover, despite the inherent limitations of this model, it is likely that economic decisions regarding the use of CI will have to be based on the results of modelling exercises such as these because of the practical difficulties involved in performing a comparative clinical study. However, the extent to which individuals could undergo CI instead of bolusing is limited at present by the clotting factors individuals receive for routine treatment (eg. prophylaxis) and clinical concerns over switching individuals between different clotting factors (eg. the risk of inhibitor development) and licensing requirements for CI. But as the proportion of individuals who routinely receive treatment with recombinant clotting factors increases over time, it is likely that the economic importance of CI will also increase. Additionally, evidence that patients prefer CI to bolusing or are indifferent between the two methods of treatment is currently limited and a number of patients who have undergone CI for surgery at the RFH NHS Trust have expressed some concerns over being permanently connected to the tubing (personal communication, Riva Miller, KDHC). Thus future studies of the costs and effects of CI should also aim to assess levels of patient acceptability and process disutility.

8 A COST-UTILITY ANALYSIS OF PRIMARY PROPHYLAXIS VERSUS TREATMENT ON-DEMAND FOR INDIVIDUALS WITH SEVERE BLEEDING DISORDERS

8.1 Introduction

The preliminary cost-effectiveness analysis (CEA) in Chapter 4 and the CEAs by Szucs[163], Smith[174] and Butler[167] showed that it costs an additional £350-£1,000 to prevent one (joint) bleed by treating individuals with prophylaxis instead of on-demand. However, there are at least three reasons why the results from these CEAs are of limited use to decision-makers. Firstly, if the results from CEAs are to be used to adequately inform resource allocation decisions, measures of effectiveness should relate to final health outcomes such as 'life-years saved' or 'disease free joints', as 'bleeds' are only an intermediate measure of effectiveness. Secondly, decision-makers may also wish to compare estimates of cost-effectiveness across a range of different clinical settings. This is difficult to do unless incremental cost-effectiveness ratios (ICERs) are expressed using identical measures of clinical effect. For example, it would be difficult to compare the cost-effectiveness of highly active antiretroviral therapy (HAART) for individuals with HIV/AIDS with the cost-effectiveness of (primary) prophylaxis using bleeds avoided as an outcome measure. Lastly, the aim of primary prophylaxis is to modify the progression of HR-QoL in individuals with severe haemophilia[21,115]. Measures of effectiveness such as bleeds, life-years saved or disease-free joints say little, if anything, about the impact of treatment on morbidity. Thus, economic evaluations that use these measures of effectiveness are unlikely to incorporate the main benefit of treatment in the analysis.

One method of including HR-QoL into an economic evaluation is to perform a cost-utility analysis (CUA). Drummond states that CUAs are a particularly useful form of evaluation in situations where HR-QoL is *the* most or *an* important health outcome[178]. CUAs combine evidence on mortality with evidence on morbidity in order to express health outcomes in terms of a single utility figure or preference score. Perhaps the most widely used outcome measure that incorporates utilities measure is the QALY where a value of 1 QALY is equivalent to a year of perfect health and a value of 0 QALYs is equivalent to death[185]. QALY values in-between 0 and 1 relate to a year spent in

varying degrees of health. In theory utility, scores can be determined for any health care programme thus, CUAs permit comparisons of cost-effectiveness across a wider range of clinical settings than CEAs[178].

The aim of the study reported in this Chapter was to perform using a modelling approach a CUA of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia A, B and clinically severe vWD.

8.2 Method

The CUA was performed using information from a number of different sources including the results from Chapters 4-7 of this thesis. The information was combined using a quasi-Markov model[202]. Markov models are a decision analytical technique that are most appropriate in instances where the costs and benefits of treatment accrue over relatively long periods of time, as is the case for most haemophilia treatments. Markov models divide patients' possible prognosis into a series of discrete health states. Costs and benefits are assigned to each health state and transition probabilities define the movement of an individual between these health states over a particular time frame (*cycle length*). The costs and benefits of comparative treatments are then estimated on the basis of the length of time individuals spend in each health state.

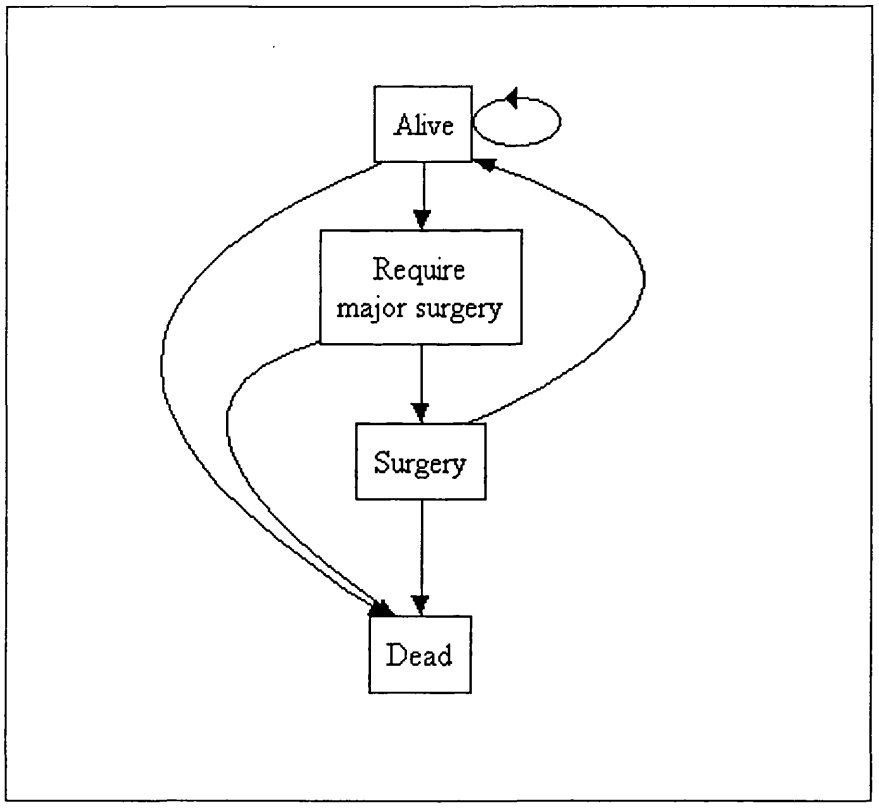
The Markov model was 'run' using the same Monte Carlo simulation technique used to evaluate the cost-effectiveness of continuous infusion with clotting factor during surgery in the previous Chapter. In a similar manner to this model, variables in this CUA were specified as a most likely value with a range where stochastic data were available. Mean values and 95% confidence intervals (CIs) were used to approximate these values respectively unless otherwise stated and values outside these ranges were not permitted. All variables quoted in the methods section along with 95% CIs or ranges were imputed in the model as distributions accordingly. All the remaining variables were specified in the model as point estimates and were not allowed to vary.

The CUA was performed from a societal perspective meaning that both the direct and indirect costs of treatment were included in most analyses. However, the indirect costs were excluded in some of the analyses on the grounds that their inclusion in a CUA might represent 'double counting'[178]. Additionally, authors such as Gerard and Mooney argue that in cost-utility analyses the opportunity cost of scarce health care resources

should be defined only in terms of health care forgone, thus it would be incorrect to include indirect costs in the cost function[186].

The model was run several times so that a number of different clinical scenarios could be represented in the analysis. For example, the model was run with and without the indirect costs and to reflect different assumptions regarding utility measurement. Each run of the model consisted of a hypothetical cohort of 100 individuals moving between the health states according to sets of transition probabilities. All transition probabilities, utilities and costs were assumed to be independent of haemophilia type (ie. A \ B \ vWD) unless otherwise stated.

Figure 8.1: Health state transition diagram for the Markov model



8.2.1 The Markov model

The health states included in the Markov model are shown in Figure 8.1. All individuals entered the model at birth in the health state *alive*. After the first cycle, individuals remained in the health state *alive*, *require major (corrective) surgery* or entered the health state *dead*. At the beginning of the next cycle, individuals who entered the health state *require major surgery* then either entered the health state *surgery* (at which time they underwent the necessary procedure) or the health state *dead*. Those who underwent *surgery* then moved directly to the health state *alive* or *dead* at the beginning of the next cycle. A one year cycle length was used in the model and treatment for each individual either terminated when the individual died or when they reached 70 years of age, which ever occurred first. However, for individuals who died before reaching 65 years of age, it was necesary to run the model to the end of the 65^{th} cycle in order to estimate the indirect costs associated with their death.

8.2.2 The transition probabilities

Table 8.1: One-year transition probability matrix

	To state:			
	Alive	**Require surgery**	**Surgery**	**Dead**
From state:				
Alive	$1-(Prob_{death}+Prob_{surg})$	$Prob_{surg}$	0	$Prob_{death}$
Require surgery	0	0	$1-Prob_{death}$	$Prob_{death}$
Surgery	$1-(Prob_{death}+0.01)$	0	0	$Prob_{death}+0.01$

$Prob_{surg}$ =probability of requiring major surgery
$Prob_{death}$ = life-table probability of death
All row probabilities sum to one

8.2.2.1 The probability of death

The one-year transition probability matrix is shown in Table 8.1. The risk of death was considered both for the underlying mortality level and for the risk of death following major surgery. The available evidence suggests that individuals with severe haemophilia have a life expectancy equivalent to that of the general North European male population once the effects of HIV and HCV infection are removed[9]. Moreover, there was no evidence to suggest that the method of replacement therapy predicts mortality *per se*[9]. Thus, a single UK male life-table was used to calculate the

probability of death in each year for individuals treated on-demand and with primary prophylaxis thus the probability of death increased with age in a non-linear manner[250]. The probability of death in the year following major surgery was taken to equal the appropriate life-table figure plus an additional 1%[251] as there was no evidence to suggest that post-operative mortality levels were higher in individuals with haemophilia than the general population.

8.2.2.2 The probability of requiring major surgery

The probability of an individual requiring major surgery (defined as an O'Donoghues procedure, synovectomy, total joint replacement, excision of a radial head or an arthrodesis) in each year was calculated using the data presented Chapter 6. Univariate regression analysis of this data showed that neither HIV status (P=0.14) or age (P=0.73) were significant determinants of the rate of major surgery in this cohort of individuals. Thus, the effect of HIV infection on the rate of major surgery was not accounted for in the analysis and the rate of surgery was assumed to be the same for individuals of all ages. The analysis in Chapter 6 also showed that severity of haemophilia (ie. mild / moderate or severe haemophilia) was found to be a significant (P=0.0001) predictor of the rate of major surgery. Univariate poisson regression analysis revealed that these probabilities were 0.023 (95% CI 0.014-0.036) and 0.007 (95% CI 0.004-0.015) for individuals with severe and mild / moderate haemophilia respectively. These values were used as estimates for the probability of individuals undergoing treatment on-demand and primary prophylaxis requiring major surgery in each year respectively. Individuals who entered the health state *require major surgery* automatically progressed to the health state *surgery* or *dead* in the following year.

8.2.3 Patient Benefits

The traditional method of incorporating QALYs into a Markov model is to assign an appropriate utility weight to each health state. Total QALYs are then calculated by multiplying these weights by the amount of time individuals spend in each health state and by summing the results. However, because of the model structure, utility weights were expressed as functions of treatment modality and age in this model and were not health state specific except for the utility weight for the health state *require major surgery* and *dead.*

8.2.3.1 Utility weights for health states alive *and* surgery

Annual utility weights for the health states alive and surgery were calculated using the utility data collected and presented in Chapter 5 for individuals with severe and mild / moderate haemophilia combined with similar additional data for 50 patients from the Royal London Hospital, Whitechapel, London. The utility weights for individuals with severe and mild / moderate haemophilia were used to approximate utility weights for individuals who had been treated on-demand ($Utility_{On\text{-}demand}$) and with primary prophylaxis ($Utility_{Prophylaxis1}$) respectively. However, in an additional scenario, it was assumed that individuals undergoing primary prophylaxis experienced levels of health equivalent to that of the general UK male population ($Utility_{Prophylaxis2}$). These utility weights were estimated using linear regression analysis on the general population utility data collected by Kind *et al.* using the EQ-5D questionnaire (n=1,466)[206].

Univariate regression analysis of the HR-QoL data presented in Chapter 5 showed that HIV serostatus did not significantly predict utility ($EQ\text{-}5D_{Utility}$) (P=0.60) meaning that there was no need to adjust the utility scores for the presence of HIV infection in this analysis. Multivariate analysis of these data did show, however, that age (P=0.0001) and severity (P=0.0001) of haemophilia both significantly and independently predicted utility but that there was no signifcant interaction between these factors (P=0.88). Univariate linear regression of Kind *et al*'s. data also showed that age significantly predicted utility in the general male population (P=0.0001). The yearly utility values for the health states *alive* and *surgery* were, therefore, defined as:

$$Utility_{On\text{-}demand} = 0.84\ (95\%\ CI\ 0.74\text{-}0.94) + (-0.006\ (95\%\ CI\ -0.008\ to\ -0.004) \cdot age)$$

$$Utility_{prophylaxis1} = 1.05\ (95\%\ CI\ 0.94\text{-}1.16) + (-0.006\ (95\%\ CI\ -0.008\ to\ -0.004) \cdot age)$$

$$Utility_{prophylaxis2} = 1.03\ (95\%\ CI\ 1.00\text{-}1.06) + (-0.003 \cdot age)$$

Where $Utility_{On\text{-}demand}$ is the utility experienced by individuals receiving treatment on-demand, $Utility_{prophylaxis1}$ is the utility experienced by individuals receiving primary prophylaxis calculated using data from individuals with mild / moderate haemophilia, $Utility_{prophylaxis2}$ is the utility experienced by individuals receiving primary prophylaxis calculated using UK male general population data and age where age is equivalent to the cycle number. The age effect on $Utility_{prophylaxis2}$ was not specified as a distribution because the confidence interval around this variable was extremely small owing to the

large sample size used to estimate this parameter. One problem of using linear regression analysis to estimate the utility functions, $Utility_{prophylaxis1}$ and $Utility_{prophylaxis2}$, was that annual utility values were sometimes found to exceed 1 (perfect health) when individuals were very young. Since annual utilities above perfect health are not permitted they were set equal to 1 in these instances.

It was felt justified not to include a further health state post surgery because a large UK study showed following total hip replacement, which is arguably one of the most invasive forms of corrective orthopaedic surgery individuals with haemophilia will undergo, 80% of patients felt no further pain[252]. Moreover, the remaining 20% of patients reported mild pain scores and associated utility values that were very similar to the scores predicted by our utility functions.

8.2.3.2 Utility weights for the health state require major surgery

It was assumed that all individuals who were in the health state *require major surgery* were in severe pain as this is typically one of the prerequisites for this type of surgical intervention. Laupacis *et al.* derived a utility value using time trade-off techniques of 0.19 in 188 individuals with osteoarthritis who reported that they were in severe pain[253]. Although this study was Canadian, and it was recognised that there might be problems of generalising its' results to this setting, this was the most appropriate utility value that could be identified as haemophilic arthritis is though to resemble progressive osteoarthritis[83].

8.2.4 Resource Use

8.2.4.1 Clotting factor use

8.2.4.1.1 Treatment on-demand

It was assumed that a single bolus dose of 31 iu/kg body weight of FVIII was sufficient to stop all episodes of bleeding in individuals with severe haemophilia A[68]. However, no published data could be found on which to base bolus doses per bleeding episode for individuals with severe haemophilia B. It was assumed, therefore, that individuals with severe haemophilia B also required a single dose of 31 iu/kg of FIX to stop each bleed; the importance of this assumption was examined in the sensitivity analysis.

8.2.4.1.2 Primary Prophylaxis

It was assumed that the aim of primary prophylactic treatment was to prevent trough *in vivo* clotting factor activity levels from falling below 1 iu/dl at all times, in line with the Malmö protocol[114,115] and World Federation of Haemophilia treatment guidelines[14]. The size of each bolus dose of clotting factor was, therefore, calculated with regard to this assumption and also using a specified time in-between maintenance infusions of clotting factor.

The size of each bolus dose of clotting factor was calculated by applying the same set of equations, pharmacokinetic parameters and assumptions used in the previous Chapter to calculate bolus doses of clotting factor for individuals undergoing major surgery (Equations 7.1-7.8). Clearance rates for individuals undergoing long-term continuous infusion (CI) were also calculated using Equations 7.9 and 7.10. The same FVIII beta half-life, recovery values and ranges used in Chapter 7 (Table 7.2) were also used in this analysis whereas for FIX, the same alpha half-life, beta half-life, C1, C2 and Mdose values were used.

The annual number of bolus doses required in each year was calculated by dividing the time between doses of clotting factor into the total number of hours in each year (8,760 hours). Annual amounts of clotting factor were calculated by multiplying the number of doses in each year by the required dose. Finally, total clotting factor use was calculated by summing these annual amounts over all years of follow-up.

8.2.4.2 Major surgery

To cost a major surgical event, estimates were needed of the type and quantity of resources consumed during the various types of surgery. However, no detailed studies assessing resource use during these procedures by individuals with haemophilia on which to base these cost estimates could be found in the literature. It was also difficult to assess resource use by undertaking either retrospective or prospective studies because of the relative rarity of these surgical events. For example, only 44 total joint replacements were performed between 1966 and 1999 in individuals with haemophilia at the RFH NHS Trust. Given these considerations, a single set of resources consumed 'during major surgery' was estimated and no cost distinction was made between the various types of major surgery. This approach to costing explains why the probability of undergoing surgery was expressed as an aggregate probability rather than individually for each separate type of surgical procedure.

Resource requirements for major surgery were based on the likely resources consumed during total hip replacements (THRs). This procedure was chosen because THRs are arguably one of the most invasive form of major surgery, require the most resources and are likely therefore, to be one of the most costly procedures.

The amount of clotting factor required during surgery and the length of each inpatient stay were estimated using the same treatment algorithms and values used in the previous Chapter to estimate the costs of bolusing with clotting factor during major surgery. Quantities of the remaining resources (eg. the prosthesis) were estimated using the results of a recent primary THR costing exercise for non-haemophilic individuals (Table 8.2)[254].

8.2.4.3 Rates of remaining hospital visits

The model also allowed for the possibility that individuals might require outpatient visits (OPV), day-case visits (DCV) and additional inpatient visits (Additional Inpatient Visits or AIPVs) for reasons in addition to major surgery in recognition that individuals with haemophilia might attend hospital for other disease related or co-morbid conditions.

Similarly to the approach taken throughout this Chapter, the annual rates of OPVs, DCVs and AIPVs for individuals receiving treatment on-demand and primary prophylaxis were calculated using the data presented in Chapter 6 for individuals with severe and mild / moderate haemophilia. However, these annual rates were not health state specific meaning that the probability of requiring a hospital visit was the same in each year a patient remained alive after adjusting for the effects of treatment and age.

The results from the poisson regression analysis in Chapter 6 suggested that age, severity of haemophilia and HIV serostatus all significantly predicted the rate of OPVs and DCVs. For DCVs, the analysis also showed that an interaction term between age and severity improved the model fit (P=0.01). Removing the effects of HIV infection, the annual rate of OPVs was predicted by:

$$OPV_{On\text{-}demand} = exp((-5.00\ (95\%\ CI\ -5.08\ to\ -4.09) + (-0.006 \cdot age))) \cdot 365$$

$$OPV_{Prophylaxis} = exp((-5.40\ (95\%\ CI\ -5.50\ to\ -5.3) + (-0.006 \cdot age))) \cdot 365$$

And the annual rate of DCVs was predicted by:

$$DCV_{On\text{-}demand} = exp((-5.90\ (95\%\ CI\ -6.00\ to\ -5.80) + (-0.023 \cdot (age \cdot severity)))) \cdot 365$$

$$DCV_{Prophylaxis} = exp((-6.40\ (95\%\ CI\ -6.50\ to\ -6.30) + (0.02 \cdot age) + (-0.023 \cdot (age \cdot severity)))) \cdot 365$$

Where 365 was the number of days in a year; 95% CI's for the age variable have been excluded, as they were extremely small. For example, these equations predict 2.3 and 1.5 OPVs per year for individuals receiving treatment on-demand and primary prophylaxis for a 20 year-old individual respectively. Poisson regression analysis also showed that the annual rate of AIPVs per year was predicted by:

$$AIPV_{On\text{-}demand} = exp((-4.90\ (95\%\ CI\ -5.00\ to\ -4.80) + (0.01 \cdot age))) \cdot 365$$

$$AIPV_{Prophylaxis} = exp((-5.40\ (95\%\ CI\ -5.50\ to\ -5.30) + (0.01 \cdot age))) \cdot 365$$

Further regression analysis showed that neither HIV status (P=0.23) and age (P=0.53) nor severity of haemophilia (P=0.59) predicted the length of these AIPVs. The mean length of stay of 7.4 days (95% CI 6.4-8.4 days) was, therefore, not adjusted for the affects of these variables.

8.2.4.4 Clotting factor consumed during OPVs, DCVs and AIPVs

Individuals with severe haemophilia are likely to require AIPVs for minor surgery or in the event of a serious bleed. However, to simplify the model, the treatment algorithm used to estimate the daily costs of bolusing with clotting factor for minor surgery in Chapter 7 was also used in this analysis to estimate the daily costs of clotting factor provision for individuals requiring AIPVs. It was further assumed that individuals with haemophilia A or vWD and haemophilia B required two infusions of 31 iu/kg of FVIII and FIX respectively during each DCV. For outpatient visits, it was assumed that no further clotting factor was required as the majority of visits are thought likely to consist of consultations with staff rather than treatments. It was assumed that no other medical resources were consumed during either of these types of hospital visit.

8.2.5 Indirect costs

The results from existing studies suggest that individuals treated on-demand are absent from work or school each year for a mean of between 1.3 and 10.6 days per year (Table

2.5). Studies have shown that individuals treated with primary or secondary prophylaxis were absent from work or school for a mean of between 0-22 days per year. It was assumed in the baseline analysis, therefore, that individuals receiving treatment on-demand and primary prophylaxis were absent from school or work for 10.6 and 0 days each year, respectively, as the chosen objective was to maximise and minmise the number of days individuals treated on-demand and with prophylaxis were absent from their usual activities.

8.2.6 Patient characteristics and epidemiological estimations

All individuals in the hypothetical cohort were assumed to have baseline clotting factor levels of 0 iu/dl. It was also assumed individuals were and remained free of inhibitors to clotting factor at all times as there was no evidence to suggest that primary prophylaxis increases the risk of inhibitor development *per se*. Clotting factor is always administered as a function of body weight irrespective of the method of replacement therapy used to treat individuals. Male age-specific body weights were, therefore, incorporated into the model using values from an appropriate reference table[255].

8.2.6.1 Bleeding frequency

The required estimates of annual bleeding frequency for individuals who were treated on-demand were taken from the results of Chapter 4. For individuals aged <9 years of age, the median number of bleeds per year of age as shown in Figure 4 were used to estimate the annual incidence of bleeding. It was assumed that individuals treated on-demand aged 18 years or above experienced an average of 37 bleeds per year; this was the median number of bleeds experienced by these individuals in the year prior to starting secondary prophylaxis. However, this figure varied between 9 and 55 bleeds per year (values for the first and third quartiles). Finally, the average annual number of bleeds for an individual aged between 10-17 years of age was calculated by interpolating between the median number of bleeds for individuals aged 9 and 18 years of age. Although a few similar studies exist in the literature, we chose to estimate bleeding frequency using our data because it allowed adjustments for the effects of age on bleeding frequency to be made. However, it should be noted that other studies have reported the frequency of bleeding to be similar for children and adults. In addition, it is generally accepted that adults with severe haemophilia who are treated on-demand experience a mean of 30-35 bleeds per year[5].

For the sake of simplicity it was assumed that individuals receiving prophylaxis did not require the use of indwelling venous access devices such as port-o-caths. It was also assumed that individuals fully adhered to their prescribed treatments and viral transmissions were assumed not to occur.

8.2.7 Resource valuation

8.2.7.1 Direct unit costs

The clotting factor unit costs were valued as per Chapter 7, using RFH NHS purchase prices for intermediate purity, high purity and recombinant clotting factors of 22, 32.5, and 52.9 (including VAT) p/iu respectively. Unit costs for the THR were taken from the same HTA report used to derive the resource estimates and also from information provided by the RFH NHS Trust finance department (Table 8.2). As in Chapter 7, an inpatient day was valued at £188 *per diem*.

It proved very difficult to derive an accurate estimate of the unit cost of outpatient and day-case visits because very little information regarding the specific resources consumed during these visits were known. Moreover, the RFH NHS finance department does not collect any of these activity data because the costs associated with the hospital visits are traditionally incorporated into block contracts. Additionally, the decision was made not to embark on a detailed microeconomic costing project because one of the secondary aims of this analysis was to identify needs for a more detailed study to assess cost-effectiveness.

Table 8.2: THR cost estimate for individuals with severe haemophilia weighing 70kg with a clotting factor cost of 32.5 p/iu

Resource	No. of units	Unit cost (£)	Total Cost (£)
Theatre overheads (mins)	134	4.89*	655
Theatre staff (mins)			
Consultant surgeon	134	0.52+	70
Consultant anaesthetist	"	0.52+	70
Registrar	"	0.26+	35
Grade F nurse (x2)	"	0.20+	54
Grade E nurse	"	0.18+	24
X-rays (days)	6	25+	150
Prosthesis	1	306*	306
Cement	2	31*	62
Sub-total			**1,426**
Clotting factor and inpatient costs			
Haemophilia A \ vWD**	-	-	16,449
Haemophilia B**	-	-	27,987
Totals			
Haemophilia A \ vWD	**-**	**-**	**17,875**
Haemophilia B	**-**	**-**	**29,413**

* **values taken from HTA report by Fitzpatrick *et al.*[254]**

** **clotting factor pharmacokinetic parameters, the length of inpatient stays and body-weight were allowed to vary according to pre-specified parameters.**

\+ **values taken from RFH NHS Trust finance department**

Because of these difficulties unit costs for these two types of hospital visit were estimated as follows:

It was estimated that the majority of outpatient appointments for individuals who are HIV and HCV negative are purely consultative and are unlikely to consist of any direct diagnostic procedure or treatment. Moreover, the majority of outpatient visits are likely to be for patients' annual reviews where, for the majority of time, dialogue between the doctor and patient will be the main activity. The unit cost for this type of visit was therefore estimated to be £80 on this basis allowing for administrative costs. Outpatient visits for orthopaedic reasons were, however, initially assigned a higher unit cost because they are likely to require additional resources such as X-rays and staff time; in

addition to a consultant haematologist, a consultant orthopaedic surgeon, registrar, physiotherapist and social worker usually attend this type of outpatient visit. Further analysis of the data presented in Chapter 6 suggested, however, that only approximately 4% of all outpatient visits were for orthopaedic outpatient clinics. Thus, a single unit cost for an outpatient visit of £80 was used in the model. An assumption was made that the unit cost of day-case visit was equivalent to 80% of the costs of an inpatient stay plus the additional clotting factor costs. The importance of these three unit cost estimates in determining cost-effectiveness was examined in the sensitivity analysis.

8.2.7.2 Indirect unit costs

The human capital approach (HCA) is the traditional method used to value productivity losses. Using the HCA, the potential value of lost production to society (ie. the indirect cost) is estimated by multiplying the amount of time individuals are unable to work due to the presence of a condition by an appropriate unit cost (usually a set of wage rates). However, some authors have suggested that societies' true productivity loss is much smaller than estimates derived using the HCA. This is because for short-term absences from work, existing employees might cover their colleagues' work or non-urgent work might be cancelled with little or no cost to the employer[189,190]. Additionally, in instances of long term absence from work, the worker might be replaced by someone who was previously unemployed thus the reduction in productivity is only for a limited amount of time (*friction period*) and does not persist until retirement age as implied by the HCA.

An alternative method of assessing indirect costs to the HCA is the friction cost approach (FCA)[190]. Using the FCA, productivity losses are likely to be smaller than those estimated using the HCA as losses are confined to the time it takes employers to restore production to its initial (pre-disease) level, or friction period. Under the FCA, absenteeism from work in excess of this friction period does not constitute a loss in production because the employee can be replaced if unemployment in the economy is above the level of frictional unemployment. In this instance, however, an employer does face the additional cost of filling the vacancy and training the new personnel. The FCA, unlike the HCA, also emphasises that reduced time at work causes a less than proportional decrease in labour productivity and that the relationship between these two variables can be expressed as a ratio (elasticity).

Given these methodological considerations, maximum and minimum indirect cost valuations were generated using the HCA and FCA respectively so that the impact of the methodological differences on the cost-effectiveness of treatment could be assessed. The values in the following costing algorithms have, therefore, been chosen with these extreme scenarios in mind but in both scenarios it was assumed that losses in production due to absenteeism were equivalent for children and adults bar differences in the wage rate.

8.2.7.2.1 The human capital approach (maximum valuation method)

It was assumed in the model that every individual was in full-time employment or education up to retirement age (set equal to 65 years of age) and each that each day absent from either of these activities due to illness or death prior to retirement age resulted in production losses equivalent to a daily average UK gender and age-adjusted gross wage rate[256].

8.2.7.2.2 The frictional cost approach (minimum valuation method)

Using the FCA, indirect productivity losses were calculated by multiplying the number of days individuals were absent from work or school by the same gross wage rate used in the HCA for all individuals below retirement age. The product of this step was then multiplied by the annual labour time versus labour productivity elasticity, which Koopmanschap estimated to be 0.8 in the Dutch economy. The friction period of unemployment was also assumed to be 3.2 months[190]. The costs of recruiting and training new personnel were not included in any of the analyses.

8.2.8 Remaining resources

It was assumed that resources such as KDHC staff time and building overheads were fixed as in the short to middle-term at least, they are likely to be similar across both methods of clotting factor delivery. Thus, the method of clotting factor delivery chosen is unlikely to have a positive or negative affect on the size of these costs and cannot therefore, affect cost-effectiveness. Smaller cost items, such as the cost of cannula and needle provision were also excluded from the analysis, as they are likely to be negligible in proportion to the total costs of clotting factor provision.

8.2.9 Analysis

The Markov model was constructed using TreeAge 3.0.18 software and SAS was used to analyse the results. Paired t-tests were used to analyse the results as they were

normally distributed except for the indirect costs which were non-normally distributed and therefore analysed using Wilcoxon signed rank paired tests.

8.2.9.1 Baseline scenarios

In the baseline scenarios it was assumed that individuals with severe haemophilia A / vWD and severe haemophilia B received doses of clotting factor every 56 hours (three times per week) and every 84 hours (twice per week) respectively with a clotting factor costing 32.5 p/iu. In the baseline analysis only the costs of treatment were discounted (at 6% per annum using Equation 3.1).

8.2.9.2 Sensitivity analysis

Although the scenarios were specified as probabilistic simulations, one-way sensitivity analysis was also performed using an expected value approach in order to highlight the importance of key variables in determining the cost-effectiveness of treatment. Where variables had previously been specified in the models as distributions, a midpoint based on each variable's range was calculated and held fixed at this value while the parameter under investigation was varied. Elasticities, that measure the impact of a change in the parameter in question on the incremental cost-effectiveness ratio (ICER), were also calculated for some variables. The elasticities were calculated as the percentage change in the ICER over the percentage change in the input parameter. Elasticities greater than one indicate that a percentage change in the input variable results in a greater percentage change in the ICER. Positive elasticities indicate that increases in the input parameter have caused the ICER to increase whereas negative elasticities indicate that the ICER has decreased following increases in the input parameter. Finally, in one separate scenario, a 250 iu vial size constraint was added to the model meaning that each bolus infusion of clotting factor was rounded up to the nearest value perfectly divisible by 250.

8.3 Results

In the baseline analysis, treating individuals on-demand or with primary prophylaxis produced a mean of 44.1 QALYs and 55.9 QALYs respectively giving a mean difference of 11.8 QALYs (Tables 8.4 to 8.5). This mean difference increased to 17.5 QALYs when it was assumed that primary prophylaxis enabled individuals with severe haemophilia to achieve comparable levels of health to the general male population.

The results from the baseline analysis showed that the mean lifetime net present discounted health care costs of treatment on-demand were approximately £272,000 per person irrespective of haemophilia type. However, the mean lifetime cost of providing primary prophylaxis was dependent on haemophilia type and also on the interval between prophylactic doses of clotting factor. For example, the mean expected lifetime health care cost of bolusing with FVIII every 56 hours including the costs of all hospital visits was £966,078; 3.5 times greater than treating individuals on-demand (Figure 8.2). Similarly, the mean net present lifetime cost of providing primary prophylaxis with FIX every 84 hours for individuals with haemophilia B was £406,539; 1.5 times greater than the cost of treating individuals with haemophilia B on-demand. However, when the interval between prophylactic doses of FVIII and FIX was decreased to 24 hours, the mean costs of treatment decreased to £213,658 and £249,180 respectively and in both instances, the health care costs of primary prophylaxis were lower than those associated with treating on-demand. Indeed, primary prophylaxis was less costly than treating individuals on-demand when the time between doses was less than 32 hours and between 17 to 50 hours respectively (Figures 8.3-8.6).

Table 8.3: The estimated mean net present lifetime costs and benefits of treating individuals with severe haemophilia on-demand or with primary prophylaxis using a clotting factor cost of 32.5 p/iu.

Variable	Primary Prophylaxis	On-demand	Difference	P-value
Patient Benefits				
Not discounted				
QALYs ($Utility_{Prophylaxis1}$)	**55.89**	**41.10**	**11.79**	**<0.0001**
QALYs ($Utility_{Prophylaxis2}$)*	61.62	"	17.52	<0.0001
Discounted at 6% per annum				
QALYs ($Utility_{Prophylaxis1}$)	15.11	11.77	3.34	<0.0001
QALYs ($Utility_{Prophylaxis2}$)*	15.86	"	4.09	<0.0001
Productivity Losses (£)				
Discounted at 6% per annum				
Human capital approach	**1,007#**	**7,167#**	**(6,160)**	**<0.001$**
Friction cost approach	43	4,377	(4,334)	<0.001$
Total Health Care Costs (£)				
Not discounted				
Haemophilia A / vWD	5,980,000	1,780,000	4,200,000	<0.0001
Haemophilia B	2,470,000	1,780,000	690,000	<0.0001
Discounted at 6% per annum				
Haemophilia A / vWD				
Infusing every 56 hours	**966,078**	**272,008**	**694,070**	**<0.0001**
Infusing every 48 hours	636,290	"	364,282	<0.0001
Infusing every 24 hours	213,658	"	(58,350)	<0.0001
Continuous infusion	97,184	"	(174,824)	<0.0001
Haemophilia B				
Infusing every 84 hours	**406,539**	**272,721**	**133,818**	**<0.0001**
Infusing every 56 hours	291,134	"	18,413	0.0003
Infusing every 48 hours	271,044	"	(1,677)	0.70
Infusing every 24 hours	249,180	"	(23,541)	<0.0001
Continuous infusion	122,351	"	(150,370)	<0.0001

Baseline results are in bold type

P-values were calculated using paired t-tests unless $ Wilcoxon Signed Rank Paired Test. Values refer to differences between treatment groups

* **Utility values for individuals receiving primary prophylaxis calculated using male UK general population data**

The figures in parenthesis denote cost savings when primary prophylaxis is used instead of treatment on-demand

\# **Costs were significantly higher than costs produced using the frictional cost approach using the same method of treatment, P<0.001**

Table 8.4: The total net present costs of treatment and percentages of total net present costs attributable to clotting factor (C. factor) provision, outpatient \ day-case visits (Out \ day), major surgery (Surgery) and productivity losses (Prod. loss).

	Primary Prophylaxis (£'000s)					On-demand (£'000s)				
Scenario	**Total**	**C. factor**	**Out / day+**	**Surgery+**	**Prod. loss***	**Total**	**C. factor**	**Out / day+**	**Surgery+**	**Prod. Loss***
Haemophilia A / vWD										
infusing every 56 hours	**967**	**931 (96%)**	**31 (3%)**	**4 (<1%)**	**1 (<1%)**	**279**	**226 (81%)**	**38 (14%)**	**8 (3%)**	**7 (2%)**
infusing every 48 hours	637	601 (94%)	31 (5%)	4 (<1%)	1 (<1%)	"	"	"	"	"
infusing every 24 hours	215	179 (83%)	31 (14%)	4 (2%)	1 (<1%)	"	"	"	"	"
continuous infusion	98	62 (63%)	31 (32%)	4 (4%)	1 (1%)	"	"	"	"	"
Haemophilia B										
infusing every 84 hours	**408**	**356 (63%)**	**46 (11%)**	**5 (1%)**	**1 (<1%)**	**280**	**209 (75%)**	**50 (18%)**	**14 (5%)**	**7 (2%)**
infusing every 56 hours	292	240 (82%)	46 (16%)	5 (2%)	1 (<1%)	"	"	"	"	"
infusing every 48 hours	272	220 (81%)	46 (17%)	5 (2%)	1 (<1%)	"	"	"	"	"
infusing every 24 hours	250	79 (63%)	46 (18%)	5 (2%)	1 (<1%)	"	"	"	"	"
continuous infusion	123	71 (58%)	46 (37%)	5 (4%)	1 (<1%)	"	"	"	"	"

Baseline results are in bold type

* **Calculated using the human capital approach**

\+ **Costs include clotting factor consumed during these visits**

Figure 8.2: Mean lifetime costs of treating individuals with haemophilia A \ vWD with primary prophylaxis or treatment on-demand using a clotting factor costing 32.5 p/iu and discounting the costs at 6% per annum.

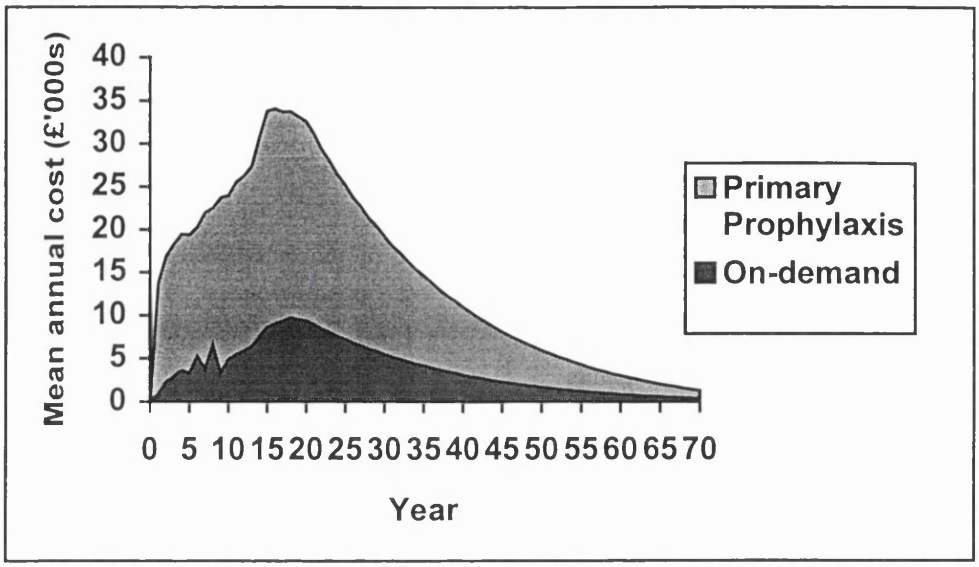


Figure 8.3: The relationship between timing of FVIII doses and total cost using a unit clotting factor cost of 32.5 p/iu

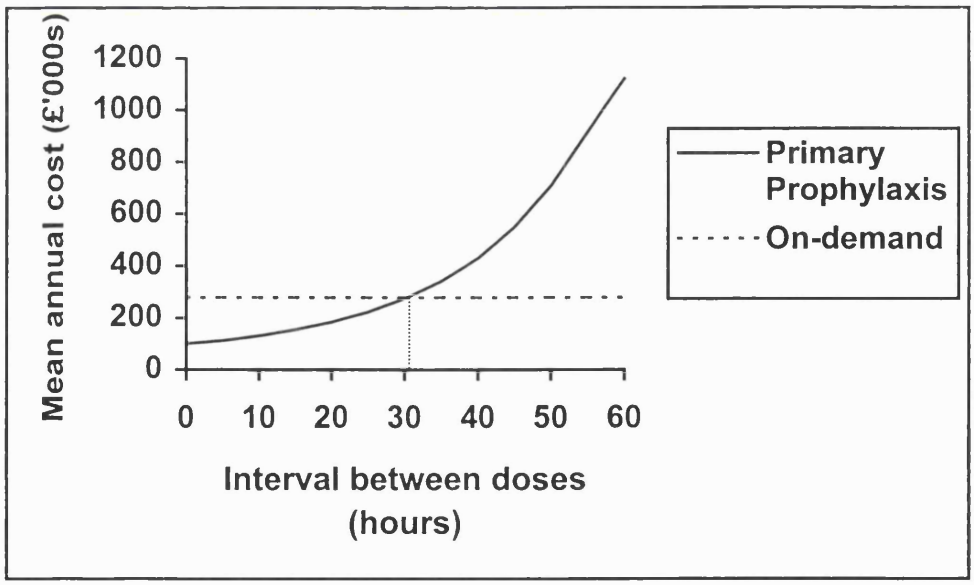


Figure 8.4: The relationship between timing of FIX doses and total cost using a unit clotting factor cost of 32.5p/iu

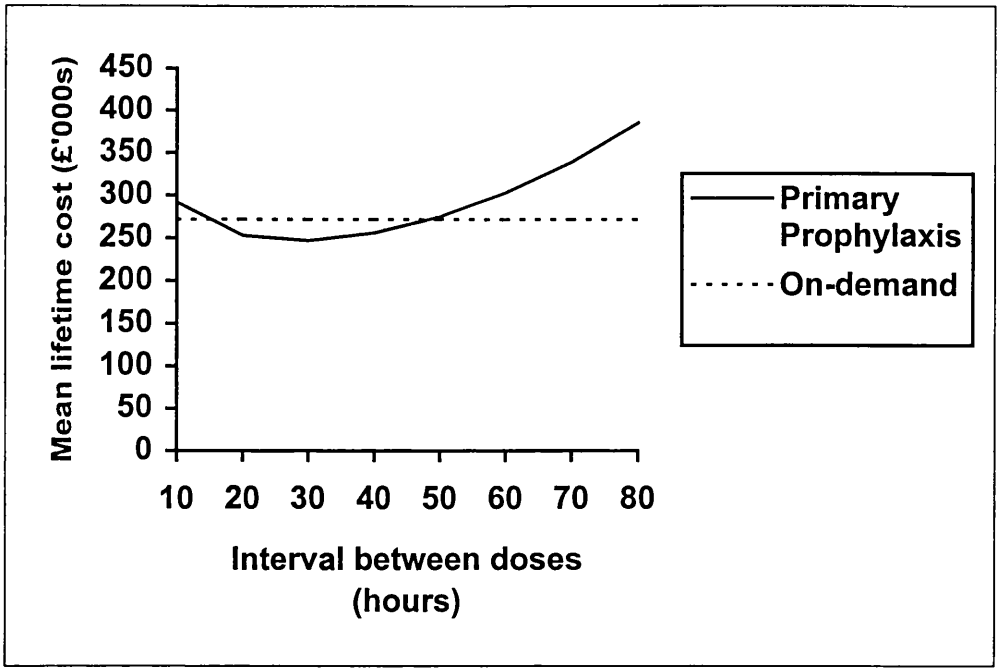


Figure 8.5: The relationship between time between prophylactic doses of FVIII, clotting factor unit cost and cost-effectiveness

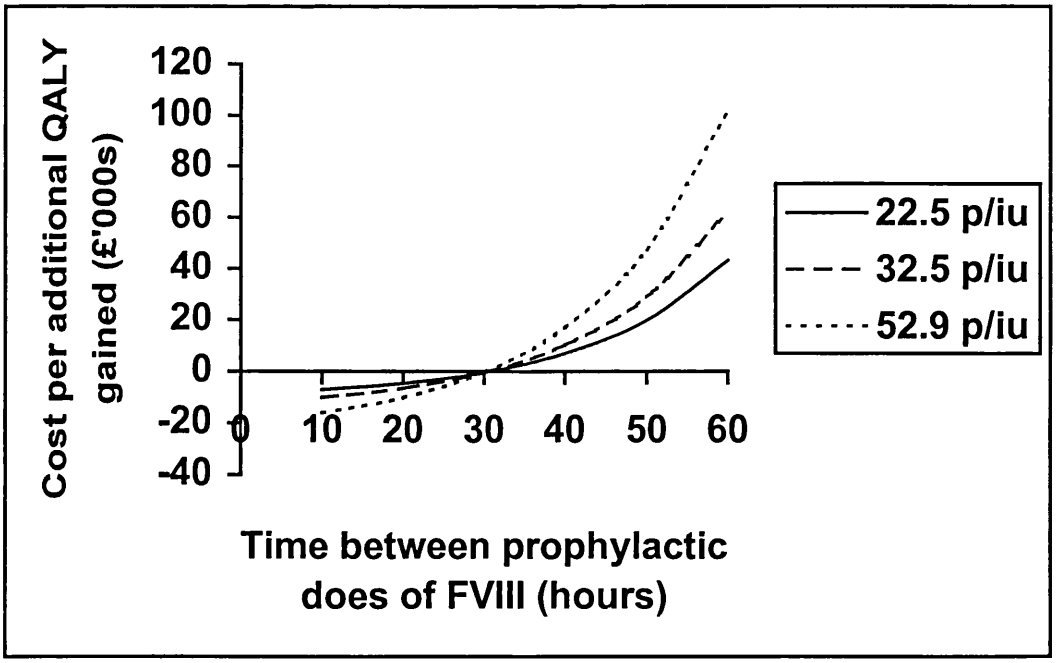
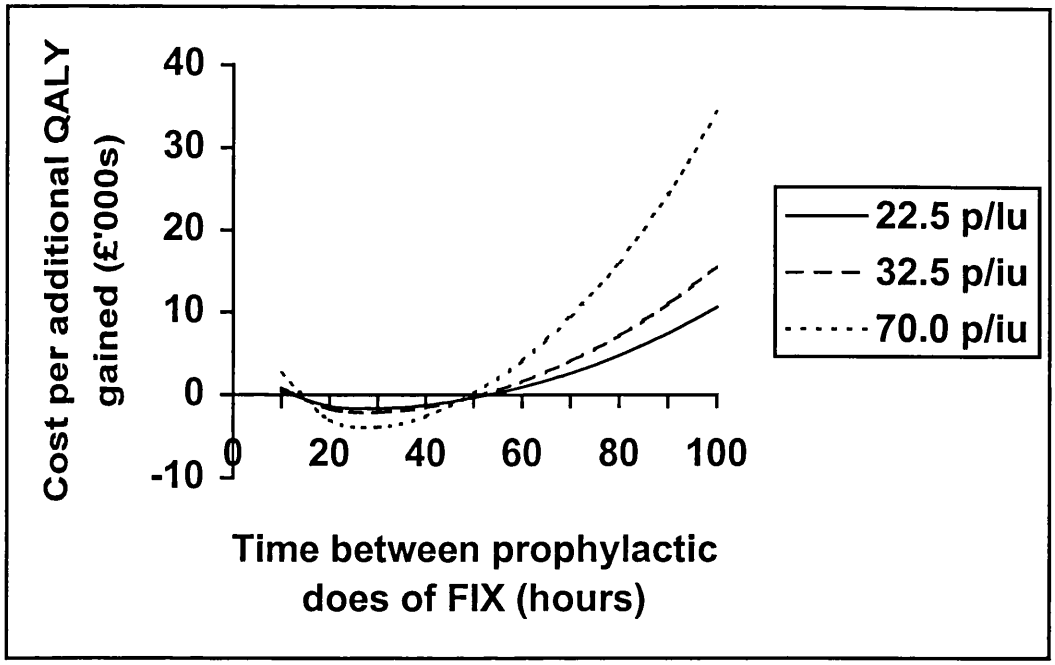


Figure 8.6: The relationship between time between prophylactic doses of FIX, clotting factor unit cost and cost-effectiveness



Clotting factor provision alone accounted for by far the largest proportion of total costs; 58%-96% depending on the clotting factor type (FVIII or FIX) and the time between prophylactic doses of clotting factor. The mean net present costs for major surgery for individuals receiving primary prophylaxis were £4,000-£5,000 per patient or 1%-4% of the total cost, whereas the mean costs of major surgery for individuals receiving treatment on-demand were £8,000-£14,000 or 3%-5% of the total cost. The indirect cost estimated produced using the HCA were significantly ($P<0.001$) higher estimates produced using the FCA (Table 8.4). However, the productivity losses associated with either treatment method accounted for no more than 2% of the total costs in any scenario. Thus, it is unlikely that methodological considerations surrounding the measurement and valuation of indirect costs will have a large bearing on determining the cost-effectiveness of primary prophylaxis.

8.3.1 Incremental analysis

The baseline analysis produced incremental cost-effectiveness ratios (ICERs) for individuals receiving FVIII and FIX of £46,500 per QALY gained and £8,600 per QALY gained respectively (Table 8.6). This means, for example, that it costs an

additional £46,000 to produce health gains equivalent to one year of perfect health if individuals with severe haemophilia A or vWD are treated with primary prophylaxis instead of treatment on-demand.

8.3.2 Sensitivity analysis

The results from Table 8.6 show how the ICER changed with different assumptions regarding utility estimation, the interval between prophylactic doses and the unit cost of clotting factor. For example, when it was assumed that individuals with severe haemophilia A experienced levels of health similar to the general male population rather than individuals with mild / moderate forms of the condition, the ICER decreased by £13,000 per QALY gained to £33,500 per QALY gained; a decrease of 28% per QALY. Conversely, however, when it was assumed that individuals received treatment with a FVIII costing 52.9 p/iu rather than 32.5 p/iu, the baseline ICER increased by £29,600 per QALY gained to £76,100 per QALY gained; an increase of 39% per QALY gained. The relationship with the interval between prophylactic doses of FVIII and FIX, the unit clotting factor cost and the incremental cost per QALY gained are demonstrated in more detail in Figures 8.5 to 8.6. Negative costs per QALY gained on these two Figures represent points where primary prophylaxis was both less costly and more effective (ie. 'dominant') than treatment on-demand.

Table 8.5: The incremental cost-effectiveness ratios (ICERs) for primary prophylaxis expressed as cost per additional (undiscounted) QALY gained

	ICER - cost per QALY gained*				ICER - cost per QALYgained**			
Clotting factor (p/iu)	**22.5**	**32.5**	**52.9**	**70.0**	**22.5**	**32.5**	**52.9**	**70.0**
Haemophilia A / vWD								
infusing every 56 hours	32,000	**46,500**	76,100	-	23,000	33,500	54,800	-
infusing every 48 hours	29,500	42,600	69,300	-	21,300	30,700	50,000	-
infusing every 24 hours	dominant	dominant	dominant	-	dominant	dominant	dominant	-
continuous infusion	dominant	dominant	dominant	-	dominant	dominant	dominant	-
Haemophilia B								
infusing every 84 hours	5,800	**8,600**	-	19,500	4,200	6,200	-	14,000
infusing every 56 hours	385	829	-	2,704	300	600	-	2,000
infusing every 48 hours	dominant	dominant	-	dominant	dominant	dominant	-	dominant
infusing every 24 hours	dominant	dominant	-	dominant	dominant	dominant	-	dominant
continuous infusion	dominant	dominant	-	dominant	dominant	dominant	-	dominant

Baseline values are in bold type

Primary prophylaxis is a dominant strategy when it is both more effective and less costly than treatment on-demand
Productivity losses calculated using the HCA are included in the derivation of all these ICERs

*** Utility values calculated using $Utility_{On\text{-}demand}$ and $Utility_{Prophylaxis1}$ for individuals receiving treatment on-demand and primary prophylaxis respectively**
**** Utility values calculated using $Utility_{On\text{-}demand}$ and $Utility_{Prophylaxis2}$ for individuals receiving treatment on-demand and primary prophylaxis respectively**

It is clear from the results provided in Table 8.6 that the cost-effectiveness of treatment with FVIII was most reliant on the unit clotting factor cost, the time between prophylactic doses of clotting factor, the utility gain, the trough *in vivo* concentration, the beta half-life, the rates at which future costs and benefits were discounted and the vial size constraint. In addition to these variables, the size of bleeding frequency, the amount of clotting factor required to treat each bleed, Mdose and C2 were also shown to be important predictors of the cost-effectiveness of primary prophylaxis for individuals receiving treatment with FIX. Most of the remaining variables, such as the outpatient / day case visit unit costs, have relatively low elasticities indicating that they are unlikely to be key variables in determining cost-effectiveness.

Table 8.6: Examining the sensitivity of the ICER for primary prophylaxis

	Elasticity*	
Parameter description (unit)	**Haemophilia A \ vWD**	**Haemophilia B**
clotting factor unit cost (p/iu)	1.45	1.76
time between prophylactic doses (hours)**	4.28	13.48
unit cost of surgery (£)	negligible	-0.75
unit cost of outpatient / day-case visits (£)	negligible	-0.09
utility values for primary prophylaxis[+]	-3.03	-3.03
beta half-life (hours)[$]	-1.88	-13.47
absenteeism from work / school (days)	-0.01	-0.44
wage rate (£/day)	-0.01	-0.47
discount rate (increase for costs only) (%)	-1.31	-0.06
discount rate (increase for QALYs only[++]) (%)	40.17	40.17
size of bolus infusion following a bleed (iu/dl)	-0.37	-19.34
annual number of bleeds	-0.35	-19.34
probability of major surgery on-demand	-0.01	-1.32
body weight (kg)	1.11	1.25
probability of death on-demand	negligible	negligible
trough *in vivo* concentration (iu/dl)	1.41	21.70
alpha half-life (hours)[$]	-	-0.11
Mdose[$]	-	-2.68
C1[$]	-	0.01
C2[$]	-	-6.80
vial size of 250 iu (cost per QALY gained)	£52,700	£4,000

* **Quoted figures are based on a 1% increase in the input variable. The baseline ICER was calculated using a clotting factor cost of 32.5 p/iu and bolusing every 56 hours for individuals receiving primary prophylaxis and discounting the treatment costs at 6% per annum**

** **Because the relationship between dosing interval and the cost of prophylaxis is exponential, the elasticity changes with changes in the baseline assumptions**

\+ **Except in the year prior to surgery**

++ **Calculated using an interest rate of 1%**

$ **Increase in most likely value only**

8.4 Discussion

The aim of this Chapter was to assess the cost-effectiveness of primary prophylaxis versus treatment on-demand using a cost-utility framework. In order to do this, information from a number of different sources including the preceding Chapters were collected and synthesised using a quasi Markov model. The costs and benefits of treatment were estimated for individuals up to a maximum age of 70 years and patient benefits were expressed using Quality-Adjusted Life-Years (QALYs).

Table 8.7: The Wessex Institute for Public Health Medicine decision matrix[257]

	Cost per QALY gained			
Quality of the evidence	**<£3,000**	**£3,000-£20,000**	**£20,000+**	**Negative**
I	++	++	-	x
II	++	+	-	x
III	+	-	-	x
IV	o	o	o	o

Key

++	**strongly recommended**
+	**recommended**
-	**beneficial but high cost**
x	**not recommended**
o	**not proven**

I **Strong evidence obtained from at least one properly designed randomised controlled trial of appropriate size**

II **Evidence from well designed controlled trials without randomisation / controlled case or cohort studies preferably from more than one centre or research group / evidence from multiple time series or from dramatic results in uncontrolled experiments**

III **Opinions of respected authorities based on clinical evidence, descriptive studies or reports of expert committees**

IV **Evidence inadequate owing to problems with methodology (eg. sample size, length or comprehensiveness of follow-up) or conflicts of evidence**

The results from the baseline analyses showed that the mean baseline costs of primary prophylaxis and treatment on-demand for individuals with severe haemophilia A or clinically severe vWD were £967,000 and £279,000 respectively whereas the mean respective costs for individuals with severe haemophilia B were £408,000 and £280,000. The model also estimated baseline lifetime patient benefits to be 55.9 QALYs and 44.1 QALYs for individuals undergoing primary prophylaxis and treatment on-demand respectively. Synthesising these parameters produced ICERs of £46,500 per additional

QALY for individuals with severe haemophilia A and manifestly severe vWD and £8,600 for individuals with haemophilia B although subsequent sensitivity analysis showed that both baseline ICERs were extremely sensitive to a number of parameters.

Although cost-effectiveness comparisons should be performed with caution, one of the main uses of CUAs is to allow cost-effectiveness comparisons across different clinical settings to be made. For example, a recent Health Technology Assessment exercise concluded that the most optimistic ICER for treatment with interferon beta for individuals with multiple sclerosis compared to a 'do nothing' policy was approximately £75,000 per QALY[258]. Similarly, studies that discounted both future costs and benefits at 5% per annum have reported cost per QALYs of approximately £1,500 and £2,200 for radiotherapy for Hodgkins Disease compared to a do nothing policy[259] and maintenance treatment of with sertraline instead of episodic treatment with dothiepin for individuals with recurrent depression[260] respectively. Therefore, using primary prophylaxis with clotting factor instead of treatment on-demand to treat individuals with severe clotting factor disorders might not be cost-effective compared to sertraline instead of episodic treatment with dothiepin for individuals with recurrent depression but it might be more cost-effective than radiotherapy compared to a do nothing policy for individuals with Hodgkin's Disease.

The Wessex Institute of Public Health Medicine has devised a matrix for deciding whether a health care programme should be implemented on economic grounds (Table 8.7)[257]; although the authors note that the process is not immutable. Possible conclusions from the matrix range from cost-effectiveness 'not proven' or 'not recommended' through to 'strongly recommended' depending on the ICER and on the quality of the evidence used in its' construction. The lower the ICER and the stronger the quality of the evidence, the more likely it is that a health care programme will be recommended. The quality of the evidence used in our model varies by parameter but an overall quality score would arguably be no higher than III using the provided scale, as the model contains no RCT data. Thus, the best recommendation for primary prophylaxis with FVIII or FIX using these criteria would be 'beneficial but high cost'. In the past, the Institute has recommended that high-purity FVIII for HIV seronegative individuals with haemophilia, Ceredase for individuals with Gaucher's Disease and Adagen for Adenosine Deaminase Deficiency were 'beneficial

but high cost', but in each instance has suggested that formal reviews of the decisions were necessary in the future.

It is difficult to compare the results from this CUA analysis to the results from other full economic evaluations of primary prophylaxis because no CUAs of primary prophylaxis with clotting factor have been published. Moreover, the results from existing CEAs of prophylaxis are all expressed in terms of cost per (joint) bleed prevented. However, one US modelling study[174] estimated the discounted costs of treating individuals with severe haemophilia A on-demand up to the age of 50 years to be £617,000 and the costs of treating individuals with primary prophylaxis between the ages of 3-50 years to be £1,178,000. While these cost estimates are arguably much larger than our own, the results from the sensitivity clearly showed that the baseline ICERs were highly sensitive to the unit clotting factor cost and the discount rate. Smith *et al.* used a higher clotting factor cost (36.6 p/iu) and a lower discount rate (5% per annum) meaning that the present value of future costs would appear much larger than those derived from our study although these factors are not sufficient to explain the entire cost difference. This said, however, Smith *et al.*[174] also showed that FVIII provision alone accounted for 89%-99% the total costs and that productivity losses associated with either method of treatment only represented 6% of total costs at most. Thus, although the overall costs of treatment differ between the two studies, the proportions of the cost components to total cost were relatively similar.

Szucs has stated that the true economic benefit of (secondary) prophylaxis lies in its' ability to avert the costs of hospitalisations and physician visits[163,173]. Other authors have also concluded or implied that the costs of primary prophylaxis will, to a large extent, be offset by reductions in productivity losses as more individuals with severe haemophilia either enter the labour market, do not leave the labour market on grounds of ill health or a combination of both. However, despite their intuitive appeal and the high cost of surgery in individuals with severe haemophilia, the results from our baseline analysis and sensitivity analysis do not support either of these assertions primarily because the cost of providing the additional clotting factor is so high but also because the effect of discounting reduces the size of any future cost savings. For example, the net present value of a £100,000 surgical cost discounted at 6% per annum in 30 and 50 years time is only £17,400 and £5,400

respectively. Moreover, in the baseline analysis we used the maximum indirect cost estimates produced in Chapter 7 using the HCA rather than the minimum cost estimates produced using the FCA, which further suggests that productivity losses are unlikely to influence cost-effectiveness. Additionally, although we assumed that primary prophylaxis would reduce rates of absence from school or work, the results from Chapter 7 strongly suggested that there is already little room for these rates to improve. Indeed, if primary prophylaxis is to be cost-effective it is more likely to be as a consequence of improvements in HR-QoL given the sensitivity of the ICER to the utility estimates than as a result of any cost savings.

Much has been written in the last two decades over the feasibility of short-term continuous infusion and the possibility of it being performed on a long-term basis using an implantable micro-system[71,113,122,126-140,213,231,241,244,261-264]. Although our analysis does not include the purchasing and maintenance costs of such a system, the results clearly show that continuous infusion could reduce the lifetime net present baseline costs of clotting factor provision by 1000% and 350% for individuals with severe haemophilia A / vWD and severe haemophilia B respectively. However, if the objective were simply to equate the costs of treating on-demand and with primary prophylaxis, there is no need to perform continuous infusion as costs were equated when prophylactic infusions of FVIII and FIX were administered approximately every 30 and 50 hours respectively.

There are a number of limitations with our model due to its' structure, the quality of the evidence for some of the parameters and because of the need to make some assumptions. The available information that could be collected over a reasonable time period determined the health states included in the final model to a large extent. Ideally the model would have consisted of five health states: no, mild, moderate, severe joint problems and dead rather than the four health sates included in Figure 8.1. However, it proved impossible to derive the required transition probabilities needed for this model for individuals who had been treated on-demand either from the literature or by performing a suitable primary study. It was suspected that the ICER would be highly sensitive to these probabilities. 'Expert opinion' data were collected from consultant haematologists around the world in order to estimate these transition probabilities. However, concern was raised that these data were

simply reinforcing existing prejudices regarding the effectiveness of both treatments and that they were unlikely to be based on actual clinical observations. Another possible method of estimating the cost-effectiveness of primary prophylaxis was to quantify the relationship between (joint) bleeding and changes in orthopaedic status. However, as noted in Chapter 4, the impact of reductions in the number of joint bleeds on the onset and progression of haemophilic arthropathy remains very unclear. Thus, this method of model specification was not viewed as a realistic option.

A further limitation of the model was that the relative hospital attendance rates and particularly the utility estimates were based on differences observed between individuals with severe and mild / moderate haemophilia rather than the effects of the specific treatments. While the latter data were clearly preferable, they were unavailable at the time of analysis and are unlikely to be available in the short to medium term hence we used the observed differences in these parameters between individuals with severe and mild / moderate haemophilia to estimate these effects. However, one possible concern regarding the suitably of these proxy data is that primary prophylaxis with a trough *in vivo* level of 1 iu/dl was more likely to convert severe haemophilia into moderate haemophilia rather than a mild / moderate form of the condition. Thus, we might have over estimated the ability of primary prophylaxis to reduce both hospital attendance rates and to modify the progression of morbidity. Although the results from the sensitivity analysis showed that the ICER was not sensitive to the probability of requiring major surgery for individuals receiving FVIII, the ICER was sensitive to this probability for individuals receiving treatment with FIX. Moreover, both baseline ICERs were extremely sensitive to changes in the utility estimates which might ultimately mean that we have overestimated the cost-effectiveness of primary prophylaxis. Conversely, the majority of the individuals with severe haemophilia included in the calculations of hospital attendance rates and the utility estimates were being treated with secondary prophylaxis at the time of assessment. Thus, the relative parameters for both variables might be larger than those used in our baseline analysis meaning that we might equally have underestimated cost-effectiveness. Regression analysis also showed that age and severity of haemophilia significantly predicted utility but that an interaction term (between age and severity) did not significantly predict utility. Thus, the relative undiscounted utility score for individuals with severe and mild / moderate haemophilia

aged five years was equal to the relative utility score for individuals with severe and mild / moderate haemophilia aged 70 years. But it is intuitive to believe that the observed relative difference in morbidity is more likely to be similar for individuals with severe and mild / moderate haemophilia when they are young than when they are older. However, it is difficult to estimate how such a relationship between age and severity of haemophilia (or method of treating individuals with severe haemophilia) would alter our cost-effectiveness estimates. Finally on this issue of utility estimation, although primary prophylaxis may provide individuals with severe haemophilia with trough *in vivo* clotting factor levels similar to those for individuals with moderate haemophilia, for most of the time circulating clotting factor levels are much higher than the trough level. Thus, although this point is theoretical, it might be that primary prophylaxis decreases morbidity more than our baseline data suggest and that actual levels lie somewhere between those currently experienced by individuals with moderate / mild haemophilia and the general male population. However, further research is needed to examine all of these issues.

An important issue in the valuation of health is the effect that the time spent in a health state might have on the way that health state is perceived. The utility scores used in this analysis were mean values derived using the time trade-off technique for health states lasting 10 years. However, evidence suggests that poor states of health become increasingly intolerable the longer they last meaning that if primary prophylaxis prevents individuals from being in poor states of health for periods greater than 10 years, the overall utility gain from this treatment might be greater than this analysis suggests.

The model assumed that children who received primary prophylaxis did not experience any difficulties during infusions. However, current policy at some treatment centres is to fit children with indwelling venous access devices if they or their carers are having problems infusing the necessary clotting factor[121,152-156,161,265]. This possibility was not included in the model because very few children registered at the KDHC have required or been fitted with such a device for the purposes of prophylactic treatment and because of the difficulty in estimating the impact of the device on utility levels. If either the proportion of children fitted with indwelling venous access devices is large, the procedure is costly or its' impact on morbidity is high fitting these devices could markedly decrease the cost-effectiveness of

primary prophylaxis because these outcomes would occur relatively early before discounting could reduce their effect. Similarly, although the model does not include the possibility that carers might attend hospital as outpatients more frequently whilst learning to treat their child with prophylaxis compared to treating on-demand, the effect of including these expected costs could also decrease cost-effectiveness.

Three further important assumptions in the model were that the rates of developing inhibitors to clotting factor were independent of treatment method, individuals adhered to treatments at all times and that precise amounts of clotting factor were always infused. With regard to inhibitor development, nothing could be found in the literature to suggest that primary prophylaxis increases the rate of inhibitor development *per se*. However, if it were to increase this rate, even by a small amount, this could seriously affect cost-effectiveness as inhibitors tend to develop when individuals are relatively young and treatment can be extremely costly. It is also acknowledged that adherence to treatments is likely to affect cost-effectiveness but this variable wasn't included in the model because virtually nothing is known regarding predictors of adherence, the costs or the dis-benefits of non-adherence in this patient group. However, in one study that examined the efficacy of administering clotting factor prophylactically to individuals with haemophilia every 48 hours for 6 months, 7 out of 21 (33%) of individuals did not finish protocol and reverted back to a standard dosing regime[123]. Moreover, in one further individual, no realistic dose could be achieved that maintained a desirable trough level with a dosing interval of every 48 hours. Thus although decreasing the interval between prophylactic doses could in theory increase cost-effectiveness, clinical practice might prove otherwise (a study is currently underway at the KDHC to try to determine some of the predictors of adherence to treatment). Lastly, clotting factor vials usually contain 250 iu, 500 iu or 1,000 iu of clotting factor and treatment is usually rounded up to the nearest vial size because it is recommended that the vials are not stored once opened. The results from the sensitivity analysis showed that rounding up bolus doses of clotting factor to the nearest 250 iu markedly decreased cost-effectiveness because more clotting factor was consumed. However, it is also feasible that such 'over infusing' might also raise an individuals trough *in vivo* clotting factor level meaning that morbidity is also affected in addition to treatment costs. Whatever the precise outcome of this 'rounding up' process, the analysis clearly

suggests that either a method of withdrawing only the required amount of clotting factor from a vial or a safe means of storing vials once opened, could greatly improve the cost-effectiveness of prophylaxis. Similarly, given that the baseline cost-effectiveness estimates were highly sensitive to the beta half-lives, scope also exists for synthetic clotting factors with much longer half-lives to also dramatically increase cost-effectiveness.

A number of possible events (pathways) were deliberately excluded from the model in order to simplify the analysis but their inclusion could alter our baseline cost-effectiveness estimates. Firstly, it is understood that a small percentage of individuals with severe haemophilia do not bleed as frequently as clinically predicted. Thus, some clinicians advocate waiting until individuals have had three joint bleeds or two successive bleeds into the same joint before starting prophylaxis[21,111]. However, whether such a policy would increase the cost-effectiveness of primary prophylaxis ultimately depends on the *a priori* probability of an individual with severe haemophilia behaving as if they had a moderate form of the condition and the cost and dis-benefits of allowing all individuals to experience 2-3 joint bleeds. Secondly, it is also sometimes argued that primary prophylaxis can be discontinued after an individual's musculoskeletal system has finished growing (at approximately 20 years of age) but there are no data to suggest how costly or effective such a policy would be or whether it would be ethically acceptable. Lastly, the possibility of viral infections secondary to clotting factor infusion was not included in the model as the precise clinical benefits of increasing clotting factor purity in terms of reduced rates of viral transmission and their subsequent clinical and economic impact remains the matter of some debate. Thus in this analysis, the effects of infusing with clotting factors of increasing purity and of increasing cost were simply to decrease the cost-effectiveness of primary prophylaxis.

The aim of this analysis was to assess the cost-effectiveness of primary prophylaxis versus treatment on-demand for individuals with severe clotting factor disorders. The results from the baseline analysis suggest that primary prophylaxis for individuals with haemophilia B is likely to be considerably more cost-effective than primary prophylaxis for individuals with severe haemophilia A or clinically severe vWD. However, in both circumstances primary prophylaxis was extremely costly thus irrespective of cost-effectiveness, another possible

barrier to its' use is the issue of 'affordability' and the decision makers ability / willingness to pay for treatment.

The sensitivity analysis showed that the cost-effectiveness estimates were extremely insensitive to changes in the unit cost of outpatient, day-case or hospital visits or the probability of individuals requiring major surgery. Conversely however, the sensitivity analysis showed that changes in the assumptions regarding utility weights had a more than proportional effect on cost-effectiveness. Thus, future research should focus on establishing a more accurate set of utility weights rather than establishing more accurate estimates of hospital attendance data and accompanying information on unit costs if tighter estimates of the cost-utility of primary prophylaxis are required. Indeed, until appropriate (longitudinal) utility data are collected, it is likely that an accurate estimate of cost-effectiveness will prove difficult to derive. The value of this model is in identifying the variables where better quality data are required and to suggest how measures may be taken to improve cost-effectiveness. Moreover, as the proportion of individuals receiving more costly recombinant clotting factors continues to grow, the importance of implementing these measures will increase.

9 GENERAL DISCUSSION AND CONCLUDING REMARKS

Ever increasing pressures on health care budgets has made it important for health care programmes not only to demonstrate their safety and efficacy but also to show that they represent an efficient (or cost-effective) use of resources. To increase efficiency in resource allocation, scarce health care resources should be allocated towards programmes that are considered cost-effective and away from programmes that are considered less cost-effective. Where true market mechanisms are not in operation, as is the case within the National Health Service (NHS), economic evaluations can provide information on the cost-effectiveness of health care programmes. Economic evaluations such as cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analysis are a set of formal quantitative methods used to inform, but not to make, resource allocation decisions[17].

The primary aim of this thesis was to assess the costs, effects and cost-effectiveness of primary prophylaxis for individuals with severe clotting factor deficiencies relative to treatment following a bleed (on-demand). Perhaps the most preferable method of making this assessment would be to use data collected alongside a suitable randomised trial as they produce the least biased estimates of efficacy. However, there has never been a randomised controlled trial (RCT) of primary prophylaxis versus treatment on-demand, primarily because of the difficulty in recruiting sufficient numbers of patients to detect significant differences in outcomes between treatment groups. For ethical reasons, it is also now unlikely that such a trial would ever proceed in the UK[21]. In this thesis, therefore, effectiveness was assessed using retrospective data collected between 1980 and 1994 on bleeding frequency (Chapter 4). A preliminary cost-effectiveness analysis (CEA) of prophylaxis was also performed in this Chapter. However, a number of problems were encountered when performing this analysis. For example, in order to separate individuals into prophylaxis and on-demand treatment groups, comparisons of bleeding patterns and clotting factor usage for the two methods of treatment had to made within year age groups and costs were confined to clotting factor provision because of the difficulties of attributing to outcomes to inputs retrospectively. Moreover, data for individuals who had received primary or secondary prophylaxis were combined in this analysis in order to maximise the

sample size meaning that the cost-effectiveness of primary prophylaxis was not directly assessed in this analysis.

9.1 The need for modelling

Given the problems encountered when performing and interpreting the results from the CEA in Chapter 4, it was decided to assess the cost-effectiveness of primary prophylaxis by synthesising information from a number of different sources using modelling techniques. In the absence of suitable RCT data, two approaches to estimating cost-effectiveness using these techniques were initially considered. The first approach was to use data from a number of uncontrolled long-term prospective studies and to combine this information using decision analytical techniques to produce an overall cost-effectiveness estimate. However, at time of starting this thesis, too few suitable studies had been published to enable cost-effectiveness to be estimated in this manner. The second possible approach was to assess the effectiveness of treatment by developing a model that linked uncontrolled short-term data on joint bleeding frequency to the development of arthropathy and the progression of health-related quality-of-life (HR-QoL), such has been developed by Glick *et al.*[214] to link reductions in blood cholesterol with changes in life expectancy. However, as with the former approach, no useful studies that examined the relationship between these variables could be found in the literature and treatment records for individuals with haemophilia registered at the KHDC did not extend far back enough for such an association to be made in a primary study. Moreover, a prospective study was not feasible given time and financial constraints.

Given these further difficulties, an alternative approach to modelling was required. The method chosen aimed to undertake, where feasible, primary analyses where gaps in current knowledge could be identified. A decision analytical model was then designed to combine the results from these analyses with those from other sources to assess the cost-utility of primary prophylaxis. The model was designed to allow extensive sensitivity analysis to be undertaken so that the robustness of the model could be rigorously tested, the cost-effectiveness of a number of different treatment scenarios could be examined and priorities for future data collection could be determined.

The main purpose of primary prophylaxis with clotting factor is to prevent the onset and development of haemophilic arthropathy and hence, to modify the progression of health-related quality-of-life (HR-QoL). However, the literature review produced no suitable information on HR-QoL that could be used to adjust for changes in HR-QoL in the model. This issue was addressed by collecting information on HR-QoL from individuals with mild, moderate and severe haemophilia registered for treatment at the KDHC and the Royal London Hospital. A number of analyses were performed on these data to ascertain whether variables including age and HIV serostatus independently predicted HR-QoL so that the effects of these variables could, if necessary, be isolated for the purposes of the final modelling exercise. It was also evident that assessing the direct impact of primary prophylaxis or treatment on-demand on HR-QoL would be extremely difficult given that haemophilia is a rare condition requiring lifelong treatment. Therefore, an indirect assessment based on the extent to which primary prophylaxis could change HR-QoL was used in the model rather than observed changes in HR-QoL following the introduction of prophylaxis *per se*.

The literature review also produced little information on the health care (other than clotting factor use) and indirect costs associated with treating individuals with severe haemophilia although the ability of primary prophylaxis to reduce these costs is often used as a reason to justify its use instead of treatment on-demand. Therefore, hospital visit and indirect resource data were collected and analysed in Chapter 6 and, in a similar manner to the HR-QoL analysis contained in Chapter 5, the results from these analyses were incorporated into the CUA. A separate model was constructed in Chapter 7 not only to assess the cost-effectiveness of continuous infusion during surgery for individuals with severe clotting factor disorders, but also to provide estimates of clotting factor usage for individuals undergoing surgery for the CUA as this information was not available from other sources.

The results from this series of analyses suggests that prophylaxis significantly reduced the incidence of (joint) bleeding at the KDHC between 1980 and 1995 ($P<0.0001$) but that bleeding was not eliminated. Further analysis showed that increasing severity of haemophilia was significantly associated with decreased HR-QoL on the domains on the MOS SF-36 and EuroQol questionnaires that measured 'physical health' and 'pain' despite

adjusting for differences in age. However, the analysis also showed that the scores on the domains that measured 'mental health' were similar to those recorded by the general population. These findings suggest, therefore, that the scope for primary prophylaxis to improve HR-QoL, and thus to be cost-effective, is high despite its large costs, as the treatment is designed to modify the progression of physical functional and pain but that treatments designed to improve mental health in this population are unlikely to increase HR-QoL.

Multivariate analysis showed that significant scope existed for primary prophylaxis to reduce the number of hospital visits required by individuals with severe haemophilia. This was because the rates of inpatient, outpatient and day-case visits between 1980 and 1997 for individuals with severe haemophilia were significantly higher than the rates recorded by individuals with mild / moderate haemophilia, despite adjusting for differences in HIV serostatus and age. For example, individuals with severe haemophilia received joint replacements on average once every 25 (95% CI 18-40) patient-years whereas individuals with mild / moderate haemophilia received joint replacements on average once every 250 (95% CI 111-1000) patient-years. However, an assessment of the indirect costs associated with severe haemophilia revealed that the scope for primary prophylaxis to reduce these costs was minimal as the resources consumed by individuals with severe haemophilia registered at the KDHC were similar to those consumed by individuals with mild / moderate forms of the condition. Alternatively, if the aim of treatment is to significantly reduce the indirect costs associated with severe haemophilia, primary prophylaxis with a trough *in vivo* clotting factor level much greater than 1 iu/dl would be required.

The results from the model in Chapter 7 showed that under most plausible assumptions, unadjusted-dose CI was significantly less costly than bolusing and that further cost savings could be achieved if the rate of infusion was adjusted for decreases in clearance. Conversely, CI could be performed with FVIII or FIX for the same cost as bolusing but with concomitant increases in *in vivo* clotting factor levels.

Combining the information from Chapters 4-7 with information from other sources produced baseline cost-effectiveness estimates for primary prophylaxis with FVIII and FIX of £46,500 and £8,600 per QALY gained respectively. However, extensive sensitivity analysis showed that these incremental cost-effectiveness estimates (ICERs) were highly sensitive to a number of factors including the unit clotting factor cost, the decision to discount health benefits, the utility weights and the timing between prophylactic doses of clotting factor. Indeed, in the most optimistic scenario shown in Table 8.6 primary prophylaxis with FVIII was dominant (ie. less costly and more beneficial) compared to treatment on-demand but in the most pessimistic scenario it cost an additional £54,800 per QALY gained.

9.2 Issues in contracting for haemophilia care

Traditionally, the Royal Free Hampstead NHS Trust has offered purchasers of haemophilia care the option of a fully inclusive block contract, where a specified amount of activity is provided for an agreed amount of money. This approach, however, is no longer sustainable. The rapidly escalating and unpredictable level of costs has meant that expenditure on haemophilia treatment is often not covered within the block contract sum and as a result the Trust, under current arrangements, is faced with an unacceptable level of financial risk (this is despite significant and successive annual uplifts to budget). It has, therefore, become increasingly difficult for the Trust and its purchasers to ensure that haemophilia patients receive the appropriate care, while at the same time, sustaining the level of service provision in other specialities. Additionally, purchasers of haemophilia care are divided over the decision to purchase plasma derived clotting factors or the new recombinant clotting factors; presumably because they are uncertain whether recombinant products represent value for money and because of issues of affordability. Purchasers have so far found themselves able to decline funding for recombinant products and some have chosen to do so. Therefore, whether patients receive primary or secondary prophylaxis varies according to their place of residence. However, there is considerable pressure on the Trust, from patients and doctors, to treat patients according to clinical diagnosis and in accordance with clinical guidelines rather than specific contractual arrangements but compliance with these demands has a large financial implication for the Trust.

Different contract formats have been explored in order to try to identify a mechanism which ensures the desired clinical treatment and at the same time manages the very high levels of financial risk in particular, central funding. It is likely, therefore, that this may be a better way of commissioning haemophilia services, particularly in respect of severe haemophilia. However, such adjustments to contractual arrangements will shift the burden of cost elsewhere but unless there are agreed care plans negotiated and adhered to by all haemophilia treatment centres, central funding on its own is unlikely to stop the costs of treatment from increasing.

Useful information on the cost-effectiveness of prophylaxis is beginning to emerge but there is no hard information available as yet as to the cost-benefit of using recombinant clotting factors. Purchasers are not, therefore, able to compare the true costs and benefits of newer treatment options and interventions with those that have been evaluated in the past. Purchasers and providers should be encouraged to perform complete economic evaluations of prophylaxis and the use of recombinant clotting factors so that the costs and benefits of improving haemophilia care and the priority setting of clinical interventions can be rationalised. Whether it is economically desirable to increase spending now is open to argument but what is true is that within the constraints and pressures of an annual contracting round, the adoption of a longer perspective is often difficult.

In the short-run we are left with new contractual arrangements between purchasers and providers to prevent haemophilia services being a drain on their own hospital budgets. In the long-run it may be necessary to revert to central funding for this and other rare, expensive, unpredictable and lifelong conditions.

9.3 Implications of the findings

While there is a large amount of uncertainty surrounding the results due to the sensitivity of the baseline incremental cost-effectiveness ratios, the results show that practical steps could be taken that might improve the cost-effectiveness of primary prophylaxis. For example, when it was assumed that maintenance doses of FVIII and FIX were administered approximately every 30 and 50 hours respectively, the lifetime costs of primary prophylaxis and treatment on-demand were equated. Thus, reducing the time between prophylactic

doses of clotting factor, if feasible and acceptable to patients, would lead to a more cost-effective allocation of resources. However, even under objectively cost-effective circumstances, primary prophylaxis is extremely costly thus another possible barrier to its' use is the issue of 'affordability' and decision makers ability / willingness to pay for treatment.

All individuals with severe haemophilia A and B in England, Scotland and Wales under the age of 16 years and previously untreated individuals with severe haemophilia are offered treatment with more costly recombinant clotting factors. When a unit cost of 52.9 p/iu of FVIII was assumed instead of 32.5 p/iu and the interval between maintenance doses was decreased from every 56 hours to every 48 hours, the incremental cost-effectiveness ratio still increased from £46,500 per QALY gained to almost £70,000 per QALY gained. Thus, the results from the CUA showed that the implication of purchasing more costly clotting factors was a dramatic decrease in the cost-effectiveness of primary prophylaxis. Clearly, some purchasers of health care might conclude that this is an inefficient use of resources[257,266] therefore it becomes even more important to find ways of increasing cost-effectiveness.

With regards to present decision making, the results from this thesis show that primary prophylaxis for individuals receiving treatment with FIX is likely to be considerably more cost-effective than for individuals receiving treatment with FVIII. However, as the sensitivity analysis showed that both baseline estimates were highly sensitive to a number of variables, little certainty can be attached to them. Moreover, a number of parameter estimates included in the CUA model, including the impact of treatment on HR-QoL and hospital attendance rates, were, through necessity, indirectly estimated and were not based on actual observations of the impact of treatments on these outcomes. Any limitations that weaken the assessment of effectiveness inevitably weaken the results of an economic evaluation based on it.

9.4 Future research

Although this thesis provides some evidence on the potential cost-effectiveness of primary prophylaxis, further research is required to establish tighter cost-effectiveness estimates

because of the sensitivity of the results to particular variables and because the resource implications to the NHS of providing primary prophylaxis are extremely large. Additionally, health technology assessment should be viewed as an iterative process where increasingly more reliable cost-effectiveness estimates are produced through a series of evaluations and not just as a 'one-off' process[195,196].

The results from this analysis suggest that evidence on the ability of primary prophylaxis to modify the progression of HR-QoL relative to treatment on-demand is crucial to establishing cost-effectiveness. Thus, further long-term observational studies are required to establish the size of these variables and to see whether it is possible to remove the confounding effects of hepatitis C (HCV) infection on HR-QoL. One possible method of isolating the effects of HCV infection on HR-QoL would be to compare the data presented here to HR-QoL data collected in non-haemophilic individuals infected with HCV and to adjust these figures for differences in age, gender and clinical stage of infection[267]. Additionally, in our baseline CUA analyses we assumed that there were no additional health-related benefits to 'peaks' in *in vivo* clotting factor levels for individuals receiving primary prophylaxis. A possible means of addressing this issue in the future could be to compare HR-QoL in individuals with severe haemophilia who had received primary prophylaxis 2-3 times per week to HR-QoL in individuals with mild / moderate forms of the condition who had never received primary prophylaxis.

Ideally, future research could examine the impact of different target *in vivo* trough levels for individuals receiving primary prophylaxis on HR-QoL. This would allow assessments of 'intensifying' the treatment programme to be made. For example, such research could address the question, is it cost-effective to increase the target trough *in vivo* clotting factor from 1 iu/dl to 2 iu/dl? Moreover, such research could also examine under which circumstances it would be cost-effective to provide primary prophylaxis to individuals with moderate haemophilia. Research that focused on establishing a link between joint bleeding, the development of haemophilic arthropathy and HR-QoL would also aid future modelling studies of cost-effectiveness. Efforts are also required to estimate the costs and effects on HR-QoL of fitting individuals with indwelling venous access devices to aid prophylaxis as this factor might also influence cost-effectiveness. As is the case in this thesis, traditional

utility assessment has focused upon health outcomes therefore future research could also examine the (process) utility of non-health outcomes, including factors such as the continuity of staff and treatments because these factors could also effect cost-effectiveness[268]. Research is also required into the acceptability to patients and the practicality of shortening the time between prophylactic infusions of clotting factor because this too could considerably enhance cost-effectiveness. The results from the CUA also suggest that cost-effectiveness could be improved considerably if individuals did not have to round up clotting factor doses to the nearest vial size or if the clotting factor half-lives could be improved. Thus, future R&D programmes could focus on producing vials where clotting factor could be withdrawn in required amounts and then resealed rather than permanently opened. R&D efforts could also focus on producing recombinant clotting factors with longer half-lives than are presently available. Finally, little has been said in this thesis regarding the cost-effectiveness of secondary prophylaxis and little work on this subject has been published. Thus, future research is also needed to address this issue.

Very few studies have examined the indirect costs associated with haemophilia or the extent to which prophylaxis could reduce these costs. Although the results in this thesis suggest that prophylaxis is unlikely to significantly reduce the size of these costs and that they are unlikely to affect cost-effectiveness if prophylaxis is administered 2-3 times per week, indirect costs could strongly affect cost-effectiveness if the interval between maintenance doses of clotting factor were reduced. Thus, if the cost of collecting these data were acceptable, studies that collected observational data on indirect costs to aid future economic analyses of primary prophylaxis should be encouraged.

On a methodological note, more research is required into the appropriateness of discounting future health benefits because at present it is conceivable that this decision alone could be the difference between primary prophylaxis appearing to be cost-effective or not. More research is also required into the relationship between health state valuation (utility weights in this instance) and the effects of duration in severe health states. This is because individuals with severe haemophilia might experience these relatively poor states of health, the cost-effectiveness ratios were sensitive to this parameter and there is evidence to suggest that the duration of time spent in severe health states effects the value individuals

place on being in these health states. However, available evidence on the direction of this relationship is conflicting as there is evidence suggesting that the value individuals place on being in severe levels of health both increases and decreases with increasing time. Moreover, studies reporting relationships between health state valuation and the effects of duration provide little guidance on how to adjust for these factors in routine economic analysis.

In conclusion, therefore, this thesis contains research that has been combined with existing evidence to estimate the cost-effectiveness of primary prophylaxis versus treatment on-demand for individuals with severe clotting factor disorders. While there are large amounts of uncertainty surrounding these estimates, it is clear that measures could be made to improve the cost-effectiveness of primary prophylaxis particularly for individuals receiving treatment with FVIII. It is hoped that future research planned at the KDHC will help to provide more insight into the cost-effectiveness of primary prophylaxis and other forms of replacement therapy for individuals with lifelong inherited bleeding disorders.

Appendix I: The Medical Outcomes Study Short Form-36 (questions 1-10) and the Euroqol (questions 11-17) health-related quality-of-life questionnaires

☐☐☐☐

The Royal Free Hospital Health Survey Questionnaire

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any questions please give the best answer you can and make any of your own comments if you like. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

1. **In general**, would you say your health is:

*(Please tick **one** box)*

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. **Compared to one year ago,** how would you rate your health in general now?

*(Please tick **one** box)*

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

Please Turn Over

3. **Health and Daily Activities**

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

*(Please tick **one** box)*

		Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
a)	**Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities,** such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐
h)	Walking **half a mile**	☐	☐	☐
i)	Walking **100** yards	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

*(Please tick **one** box)*

		Yes	**No**
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐
b)	**Accomplished less** than you would like	☐	☐
c)	Were limited in the **kind** of work or other activities	☐	☐
d)	Had **difficulty** performing the work or other activities (eg. it took more effort)	☐	☐

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

*(Please tick **one** box)*

		Yes	No
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐
b)	**Accomplished less** than you would like	☐	☐
c)	Didn't do work or other activities as **carefully** as usual	☐	☐

6. During the **past 4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

*(Please tick **one** box)*

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much **bodily pain** have you had during the **past 4 weeks**?

*(Please tick **one** box)*

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

8. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including work both outside the home and housework)?

*(Please tick **one** box)*

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

Please Turn Over

9. **Your Feelings**

These questions are about how you feel and how things have been with you **during the past month**. (For each question, please indicate the one answer that comes closest to the way you have been feeling).

*(Please tick **one** box)*

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a)	Did you feel full of life?	☐	☐	☐	☐	☐	☐
b)	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c)	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d)	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e)	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f)	Have you felt down hearted and low?	☐	☐	☐	☐	☐	☐
g)	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h)	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i)	Did you feel tired?	☐	☐	☐	☐	☐	☐
j)	Has your **health limited your social activities** (like visiting friends or relatives)?	☐	☐	☐	☐	☐	☐

10. **Health in General**

Please choose the answer that best describes how **true** or **false** each of the following statements is for you.

*(Please tick **one** box)*

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

For each of the following questions please place a tick in the box that closest describes your state of health.

11. Please indicate your level of mobility (*Please tick one box*).

- ☐ I have no problem walking
- ☐ I have some problems walking about
- ☐ I am confined to bed

12. Please indicate your level of self-care (*Please tick one box*).

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

13. Please indicate your ability to perform your usual activities eg. work, study, housework, family or leisure activities (*Please tick one box*).

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems performing my usual activities
- ☐ I am unable to perform my usual activities

14. Please indicate your level of pain (*Please tick one box*).

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

15. Please indicate your level of anxiety or depression (*Please tick one box*).

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

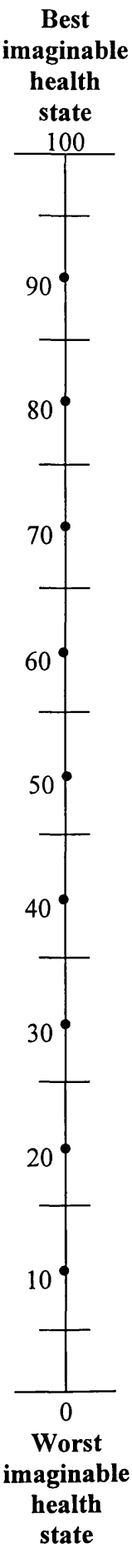
16. Compared with my general level of health over the past 12 months, my health state today is. (*Please tick one box*).

- ☐ Better
- ☐ Much the same
- ☐ Worse

Please Turn Over

17. To help people say how good or bad a health state is we have drawn a scale rather like a thermometer. The best health state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad you feel your state of health is today. Please do this by placing a cross on the scale at the point that indicates how good or bad your current health is.



Thank you for answering this questionnaire

Appendix II: Patient time use questionnaire

RFHHC questionnaire on time use ☐☐☐☐

Thank you for completing this questionnaire. It would help us if you could provide some information about yourself, which will be treated in the strictest confidence.

1. Which of the following levels of education have you completed?
(you may tick more than one box if applicable)

None	☐
O-Level / GCSE / NVQ	☐
A-level / BTEC	☐
Degree / HND	☐
Professional qualification (eg. Accountancy)	☐
Post-graduate degree	☐

2. Which of the following best describes your day to day activities?
You may tick more than one box.

Full-time employment	Part-time employment	Self-employed	Voluntary work	Household work
☐	☐	☐	☐	☐

Seeking work	Part-time student	Full-time student	Retired	Sick-leave	Other
☐	☐	☐	☐	☐	☐

<u>If you DID NOT tick full-time or part-time employment, then go to question 8</u>

3. How many hours a week do you work on average (including any over-time)?
☐☐ hours per week.

4. *Over the past two weeks*, have you taken any time off work due to your health?
☐ Yes ☐ No

if yes, for how many days ☐☐ and for what reason(s) (eg. a headache, cold, following a bleed).....
.....

5. *On the days that you did go to work over the past two weeks*, on a scale of 1 to 10, how much do you think your ability to work efficiently has been affected by your health? Please place a circle around the most appropriate level.

1	2	3	4	5	6	7	8	9	10
Not affected at all									**Very affected**

6. Did your employer make arrangements to cover for you whilst you were or are unable to work?

☐ Yes ☐ No

☐ Don't know ☐ Not applicable

7. *If you answered yes to question 6*, please tick any of the following that best describes the arrangements your employer made or you made if you are self-employed. You may tick more than one box if applicable.

Employed temporary workers ☐

Hired new workers ☐

Made up by you on return to work (during normal working hours) ☐

Made up by you on return to work (during extra working hours) ☐

Covered by other existing employees (during normal working hours) ☐

Covered by other existing employees (during extra working hours) ☐

Nothing ☐

Don't Know ☐

Other ☐

please specify.....

The following questions concern <u>unpaid work</u>, i.e. activities that involve your time but for which you do not receive payment.

8. *On average over a one week period*, how much time do you spend on the following activities:

a.	housework (eg. cleaning)	☐☐ hours
b.	shopping	☐☐ hours
c.	odd-jobs and chores	☐☐ hours
d.	voluntary work	☐☐ hours
e.	educational courses	☐☐ hours

9. The scale below measures the degree of efficiency with which you consider yourself to have performed each of the above tasks *over the past two weeks*. Please place a circle around the most appropriate level if you have spent anytime doing them.

a. **<u>Household work</u>**

1	2	3	4	5	6	7	8	9	10
Very inefficiently									**Very efficiently**

b.**<u>Shopping</u>**

1	2	3	4	5	6	7	8	9	10
Very inefficiently									**Very efficiently**

c.**<u>Odd-jobs</u>**

1	2	3	4	5	6	7	8	9	10
Very inefficiently									**Very efficiently**

d.**<u>Voluntary work</u>**

1	2	3	4	5	6	7	8	9	10
Very inefficiently									**Very efficiently**

e.**Educational courses**

1	2	3	4	5	6	7	8	9	10
Very inefficiently									**Very efficiently**

10. *Over the past two weeks*, have others (eg. family, neighbours or friends) taken over any of your household tasks because of any problems with your health?

☐☐ Yes ☐☐ No

if yes, for approximately how many hours in total? ☐☐ hours.

Thank you for completing this questionnaire.

Appendix III: Recent published papers arising from this research

	Full Reference	Page
1997		
1.	Lee, C., Sabin., C. and Miners, A. High cost, low volume care: the case of haemophilia. *BMJ* 1997; **315**: 962-963.	
2.	Miners, A.H., Sabin, C.A., Stevens, A.J., Tolley, K.H. and Lee, C.A. Financing the rising cost of haemophilia care at a large comprehensive care centre. *Journal of the Royal College of Physicians of London* 1997; **31**: 640-644.	
1998		
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4.	Miners, A.H., Sabin, C.A., Tolley, K.H. and Lee, C.A. Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's Disease. *Journal of Internal Medicine* 1998; **244**: 515-522.	
1999		
5.	Miners, A.H., Sabin, C.A., Tolley, K.H. Jenkinson, C., Ebrahim, S. and Lee, C.A. Assessing health-related quality-of-life in patients with severe haemophilia. *Psychology, Health & Medicine* 1998; **4**: 4-15.	
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2000		
7.	Miners, A.H., Sabin, C.A., Tolley, K.H. and Lee, C.A. Primary prophylaxis for individuals with severe haemophilia: how many hospital visits could treatment prevent. *Journal of Internal Medicine* 1998; **247**: 493-499.	

clear that exposure to environmental tobacco smoke is a cause of lung cancer, heart disease, and other serious illnesses. In the United States alone, it is responsible each year for 3000 deaths from lung cancer, 35 000 to 62 000 deaths from ischaemic heart disease, 150 000 to 300 000 cases of bronchitis or pneumonia in infants and children aged 18 months and younger (causing 136 to 212 deaths), 8000 to 26 000 new cases of asthma, exacerbation of asthma in 400 000 to 1 million children, 700 000 to 1.6 million visits to physician offices for middle ear infection, 9700 to 18 600 cases of low birth weight, and 1900 to 2700 sudden infant deaths.[12] Those figures make passive smoking one of the leading preventable causes of premature death in the United States.[13]

History repeats itself not only in research on active and passive smoking, but in the actions of the tobacco industry to deny and obfuscate the findings of that research. The latest example, which compares the hazards of second-hand smoke with the "risks" of drinking milk and eating biscuits,[16] is as inane as were the industry's denials of the hazards of active smoking in past decades. Their public pronouncements are particularly cynical in the light of contradictory statements in their internal documents,[17] and their recent settlement (for $300 m) of the class action lawsuit in Florida on behalf of flight attendants harmed by second-hand smoke (p 968).

Public health action to eliminate exposure to environmental tobacco smoke is long overdue. The minimum acceptable standard for indoor facilities is to allow smoking only in physically separated and separately ventilated areas.[18,19] A total ban on smoking is preferred on three grounds: it provides maximum protection of non-smokers, it avoids exposing smokers to extremely high levels of environmental tobacco smoke in designated smoking areas,[20] and it avoids the costs of constructing separately ventilated smoking areas. Health advocates should pursue all strategies that would help accomplish that goal, including education, legislation, regulation, and litigation.

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High cost, low volume care: the case of haemophilia

Reverting to central funding might be the only option

Haemophilia is a rare and expensive condition. In Britain it affects 5418 males with factor VII deficiency and 1109 with factor IX deficiency, and in 1994 they used 158 million units of factor VIII and 9 million of factor IX at an average cost of 30p per unit. Over the past 20 years the amount of clotting factor used per patient has increased, and both the quality of the clotting factors and methods of administration have improved.

In theory the nature and level of treatment is specified in contracts between purchasers and providers, but at our centre, which cares for 14% of the haemophilic population of England and Wales, contract revenue is regularly outweighed by the cost of care. Our cost pressures are similar to those of any high cost, low volume clinical service in any general trust. Accumulating experience suggests that the present funding arrangements are failing; the danger is that such services will become a liability and be eliminated by both providers and purchasers.

Clotting factor concentrate represents 50-80% of the total direct cost of haemophilia care.[1] Over the past

15 years the use of concentrate in Britain has risen threefold. For reasons of viral safety recombinant factor VIII is the treatment of choice[2]; recombinant factor IX is also likely to become so once it is licensed. However, while intermediate purity plasma derived clotting factor costs 32p per unit and is exempt from value added tax, recombinant factor VIII costs 52p per unit and is liable to 17.5% VAT. Thus in our centre, where the median annual use of concentrate for an adult is 72 000 units, the annual cost per patient would be £23 000 for intermediate purity plasma derived concentrate but £44 000 (including VAT) for recombinant factor VIII.

A further cost pressure has been changes in treatment strategy, particularly the introduction of prophylaxis for children. Traditionally a patient with severe haemophilia received clotting factor concentrate (30 IU/kg) after a bleed and could expect 30-35 bleeds per year.[3] Long term prophylactic regimens, introduced before any sign of joint damage, have benefited patients by preventing joint damage and improving the quality of life.[4] These regimens, however, require a fourfold increase in clotting factor use. Although in Britain the number of boys aged under 10 with severe haemophilia is small (only 385 in 1994), for our trust the cost of giving 31 of them prophylaxis with recombinant concentrate is about £2m. Furthermore, contracts for this care have to be negotiated with 16 health authorities. Perhaps the greatest difficulty, however, is the unpredictability of individual clotting factor requirements. For example, the concentrate required for a total knee replacement for haemophilic arthropathy could double the annual cost of treatment for a single patient.

Although information on the cost effectiveness of prophylaxis is beginning to emerge,[5] there is no hard information on the benefits of using recombinant factors over plasma derived concentrate. Currently we rely on the biological plausibility that recombinant factors are likely to prove beneficial in the long term. Whether it is economically desirable to increase spending on patients now is open to argument, but within the constraints of an annual contracting round adopting a longer perspective is clearly difficult. Should we be investing in alternative ways of reducing costs, such as gene therapy and continuous infusion? What are the costs and benefits of liver transplantation, which can cure haemophilia?[6]

Additional costs of iatrogenic infections

Iatrogenic problems add to the cost pressures. In 1979-86, 1321 individuals with haemophilia in Britain were infected with HIV from clotting factor concentrate, and 560 are currently alive. Our centre looks after 70 of them. All concentrates are now sterilised and no new transmissions have occurred since 1986.[7] Such processes have added considerably to the cost of treatment, but there is good evidence that monoclonally purified products slow the deterioration of the immune system in HIV positive patients.[8] Although additional funding was provided to pay for placing patients on these high purity products, patients with end stage AIDS consume upwards of 50% more clotting factor than when they are asymptomatic.[9] It has been estimated that 25 years from seroconversion—that is, around the year 2008 for the haemophilic community—20% will still remain AIDS free.[10] With the advent of triple antiviral therapy, the cost of drug treatment as well as a longer duration of life will add to the costs of caring for these patients.

Most patients treated with large pool clotting factor concentrates between 1965 and 1985 were infected with hepatitis C virus. A fifth are coinfected with HIV, which accelerates the progression of the liver disease.[11] Many are treated with interferon, calculated at a lifetime cost of £70 555-£195 407.[12] In addition, since coagulation factors are synthesised in the liver, increased amounts of factors VII, VIII, and IX are required when the liver fails. These deaths are largely unpredictable but occur at a rate of two a year in our centre. There is no additional funding for concentrate in these circumstances.

Contracting for this high cost service is made harder by the uneven geographical spread of patients. In 1994, 42 of 85 haemophilia centres treated fewer than 10 patients with severe disease; only three centres, including our own, treated more than 110. These three centres treated over half the 2368 patients needing clotting factor concentrates in 1994 in England and Wales.

These escalating and unpredictable costs mean that expenditure on haemophilia treatment is often not covered within a block contract. As a result the trust and purchasers find it increasingly difficult to ensure that patients with haemophilia receive appropriate care while sustaining the level of service in other specialities. In the long term it may be necessary to revert to central funding for this rare, expensive, unpredictable, and lifelong condition and others like it.

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Financing the rising cost of haemophilia care at a large comprehensive care centre

A leader based on this paper appeared in the *British Medical Journal*. Lee C, Sabin C, Miners A. High cost, low volume care: the case of haemophilia. *Br Med J* 1997;315:962-3.

ABSTRACT – Haemophilia affects 1 in every 6,000 males. Patients with haemophilia A receive treatment with factor VIII (FVIII) and those with haemophilia B receive factor IX (FIX). In the UK, patients receive their treatment from comprehensive care centres (CCCs) or haemophilia centres. Over the last two decades the amount of clotting factor used per patient has increased; the quality of the clotting factors available and the methods of administration have also improved. As a consequence, the cost of providing care has increased substantially. In theory, the nature and level of haemophilia treatment is specified in contracts between purchasers and providers, ensuring that the costs of treating patients are fully recovered. However, at our large CCC, which has 1,700 registered patients with inherited bleeding disorders, the costs of care regularly exceed contract revenue. This paper describes the cost pressures and difficulties faced by a North London Trust in an attempt to maintain, and in some instances improve, the services provided within its CCC.

Haemophilia affects 1 in every 6,000 men[1]. A patient has either mild, moderate or severe haemophilia. Those with mild haemophilia will experience few problems. However, those with severe haemophilia may spontaneously bleed. In 1994 in the UK 2,300 patients were registered as severe[2]. Patients receive treatment from comprehensive care centres (CCCs) or haemophilia centres. To qualify as a CCC, a centre must provide treatment for 40 or more severely affected patients per year and offer other specialist services, eg orthopaedic units, HIV and hepatitis expertise, counselling and physiotherapy[3]. In most cases treatment is used to abort a bleed once it has occurred (on-demand therapy) although in children and adults there is increasing interest in giving clotting factor prophylactically to prevent bleeds from occurring.

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The cost pressures

New clotting factors

The provision of clotting factors is believed to account for up to 93% of the total cost of care[4]. As a result, total costs are sensitive to the unit price of clotting factors, and to the amount of clotting factor used. Because plasma-derived products continue to transmit hepatitis A[5–7] and B19 parvovirus[7–9], and because of concern over as yet unknown viruses[8], most haemophilia treating specialists consider recombinant (synthetic) clotting factors as the treatment of choice[10]. A recombinant FVIII was first licensed in the UK in 1994. Recombinant FIX is currently under clinical trial and, once licensed, is likely to become the recommended treatment for patients with haemophilia B. Whilst increased purity probably reduces the risk of viral transmissions, it is more expensive. For example, one particular clotting factor of intermediate purity currently costs 18 pence per iu to purchase and, because it is derived from human plasma, it is exempt from VAT. However, recombinant FVIII is currently purchased at 48 p/iu and *is* subject to VAT (these acquisition prices are lower than corresponding list prices[10]). In 1994, 146 severe patients at our CCC required a median of 72,000 (range 20,000–640,000) iu of clotting factor. Table 1 demonstrates the effects of variations in the amount of clotting factor used and the price of clotting factor on the costs of acquisition

Patients with von Willebrand's disease (vWD) may also need treatment with FVIII. Previously, they were treated with desmopressin or cryoprecipitate. However, the early 1990s saw the introduction of high purity FVIII concentrates containing large quantities of von Willebrand factor (vWF)[11]. Concentrates that are rich in vWF, along with pure vWF, are now purchased regularly. In 1980, six patients with vWD were treated with clotting factor, but by 1994 this number had increased to 28. Total clotting factor usage in these patients had increased from 0.08 million iu in 1980 to 2.35 million iu by 1994 (Fig 1). Additionally, whilst no pure vWF had been purchased before 1993, in 1995 0.25 million iu were used.

Table 1. Clotting factor cost (£) per patient per year by units required and product type.

Clotting factor usage (iu)	Intermediate purity	Recombinant excl. VAT	Recombinant incl. VAT*
20,000	3,600	9,600	11,280
72,000	12,960	34,560	40,600
640,000	115,200	307,200	361,000

*at current level of 17.5%

Different treatment strategies

After a bleed, patients used to receive clotting factor at a dose of 30 iu per kg body weight, and they could expect to need treatment for 30-35 bleeds per year[12]. However, spontaneous bleeding and chronic joint arthropathy seldom occur in patients with mild or moderate haemophilia. Thus prophylactic regimes have been introduced in an attempt to convert severe haemophilia A and B to a milder form. A prophylactic regime will typically comprise 25–40 iu per kg body weight of the appropriate clotting factor three times a week[13]. Long-term results have been at their best when prophylaxis is started before any signs of joint damage[13,14]. Therefore, since the early 1990s it has been policy to place, whenever feasible, all previously untreated patients with severe haemophilia on prophylaxis. For the most part they will be young children. Assuming the above treatment protocols, a change to prophylaxis for a patient would require a four-fold increase in clotting factor.

Antibodies (inhibitors)

The development of antibodies that inactivate FVIII remains a serious and continuing complication in the management of haemophilia A. Treatment involves achieving immune tolerance with massive doses of clotting factor and is therefore extremely expensive[15]. In the UK the incidence of inhibitors developing in previously untreated patients with severe haemophilia is 20–25%[16]. However, in our experience with a cohort of boys exposed to a single FVIII concentrate (BPL SY) since 1985, there have been no high titre inhibitors[17] and thus no additional costs.

Unpredictability

Haemophilia is a highly unpredictable disorder[3]. Individual clotting factor requirements can vary dramatically from year to year and from patient to patient. This complicates the contracting process, as is shown in Fig 2 which illustrates yearly FVIII usage in a typical patient.

Human immunodeficiency virus (HIV)

In the early 1980s, many patients became infected with HIV through the use of plasma-derived clotting factor[18]. The CCC has provided care for approximately 130 HIV infected patients. There have been no new HIV transmissions secondary to clotting factor since 1986[19], as all products are now sterilised. Patients who are known to be HIV positive receive monoclonally purified products as there is reason to believe that this slows the deterioration of the immune system[20,21].

Fig 1. Total FVIII usage 1980–94 by patients with vWD at the CCC.

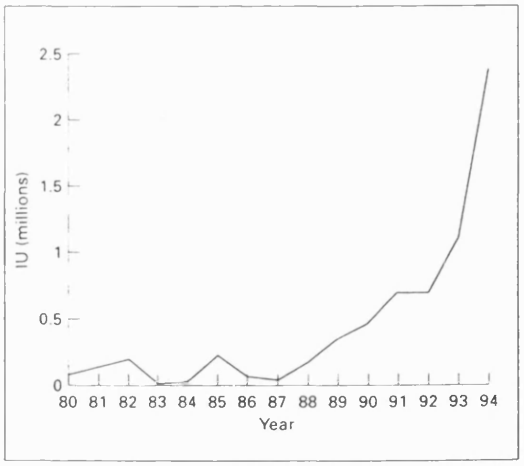
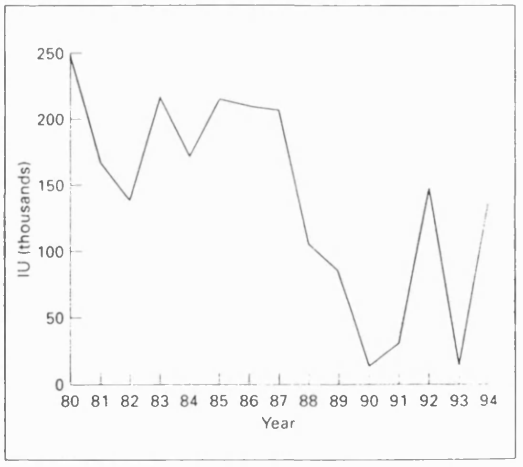


Fig 2. Total amount of FVIII needed by a 27 year old patient with severe (<2 u/dl) haemophilia A during period 1980–94.



Patients who are HIV negative are placed on standard intermediate products. In 1993 it was estimated that the additional hospital costs attributable to HIV infection amounted to £6,050 per patient year[22], although treatment protocols have since been revised and average treatment costs are likely to be higher. Although additional AIDS funding provides financial cover for placing patients on high purity products, there is evidence to suggest that patients with end stage AIDS need upwards of 50% more clotting factor than when they were asymptomatic[22].

Hepatitis C virus (HCV)

The majority of patients with severe haemophilia who received untreated, large pool blood products in the years 1965–85 became infected with HCV[23]. The CCC has identified 255 patients infected with this virus. Over 100 of these patients are co-infected with HIV which can accelerate the rate of progression of HCV[24]. Studies indicate that 20% of patients infected with chronic HCV have a prolonged response to treatment with interferon alpha[25]. A six month course of treatment with 6 million units of interferon alpha three times per week costs £6,000; however, responsiveness to treatment remains unpredictable[26]. After 20 years' infection with HCV, it is calculated that 10% of these co-infected patients will have progressed to chronic liver failure. As they reach a terminal phase, patients are likely to be admitted to hospital. They may also need increased amounts of the clotting factors normally made by the liver (including FVII, FVIII and FIX). It is expected that there will be at least two patients with HCV-related liver failure per year at the CCC for the foreseeable future. No additional funding for this group of patients is available.

An increase in the numbers of patients

The CCC has witnessed a steady increase in the number of registered patients and the percentage of patients who are treated with clotting factor in each year. In 1980, 30% of patients received at least one iu of clotting factor; by 1994 this had increased to 60%. This may be the result of a combination of the introduction of prophylaxis, the incidence of AIDS- and HCV-related illnesses, and the availability and use of more appropriate clotting factors.

Confounding issues

Patient base and size

In 1994 (Fig 3) 42 out of the 85 haemophilia centres sending information to the United Kingdom Haemophilia Centres Directors Organisation treated fewer than 10 patients with severe haemophilia A, B and severe vWD[2]. Only three centres treated more than 110 such patients: the CCC treated 153 [haemophilia A 112, haemophilia B 34 and vWD 7]. This group represents the largest drain on resources. In the UK in 1994, 2,855 patients with haemophilia A, B or vWD of all grades of severity received clotting factor; almost 8.5% of them were treated at this North London Trust. The remainder were treated at one of 92 other centres in the UK.

Contracting

The Trust has contracts with several different purchasers to treat haemophilic patients. At present, they are divided over the decision to purchase plasma-derived clotting factors or the new recombinant

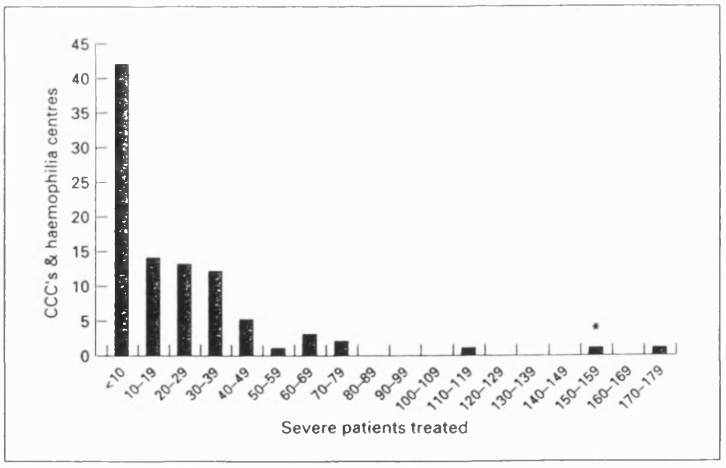


Fig 3. The number of severe patients treated in CCCs and haemophilia centres in 1994 (*Royal Free Hospital). (Reproduced from reference 2 by permission of the UK Haemophilia Centres Directors Organisation).

clotting factors, presumably because they are uncertain whether recombinant products represent value for money and whether they can afford them. Purchasers can decline to pay for recombinant products, and some have chosen to do so. Therefore, whether a patient at the CCC receives recombinant FVIII depends upon their place of residence. However, there is considerable pressure on the Trust, from patients and doctors, to treat patients according to clinical diagnosis and in accordance with new guidelines[10] rather than specific contractual arrangements. Compliance with these demands has a large financial implication for the Trust.

The current situation

In the past, the Trust has offered purchasers the option of a fully inclusive block contract, where a specified amount of activity is provided for an agreed amount of money. This approach, however, is no longer sustainable. The rapidly escalating and unpredictable level of costs has meant that expenditure on haemophilia treatment is often not covered within the block contract sum and as a result, the Trust is faced with an unacceptable level of financial risk (even in light of significant and successive annual uplifts to the CCC's budget). It has, therefore, become increasingly difficult for the Trust and its purchasers to ensure that haemophilia patients receive the appropriate care, while at the same time sustaining the level of service provision in other specialties.

Discussion

This paper has demonstrated the serious problems that haemophilia and its treatment pose for both the purchasers and providers of a large CCC. These pressures derive from a number of different sources but the order of magnitude of these pressures on a Trust's financial position increases dramatically in relation to the number of cases of severe haemophilia. The same difficulties apply for other rare and expensive disorders that are disproportionately spread around the country.

Different contract formats have been explored in order to identify a mechanism that ensures the desired clinical treatment and at the same time manages the very high levels of financial risk. Central funding[37] may be a better way of commissioning haemophilia services, particularly in respect of severe haemophilia. However, such adjustments to contractual arrangements simply shift the burden of cost elsewhere, and unless agreed care plans are negotiated and adhered to by all CCCs, central funding alone is unlikely to stop the costs of treatment from increasing. We believe these conclusions can be generalised beyond haemophilia care to all other rare and expensive conditions.

Useful information on the cost-effectiveness of prophylaxis[1,25] is beginning to emerge but no hard information is as yet available on the cost-benefit of using recombinant clotting factors. Purchasers are, therefore, unable to compare the true costs and benefits of newer treatment options and interventions with those that have been evaluated in the past. Purchasers and providers should be encouraged to perform complete economic evaluations of prophylaxis and the use of recombinant clotting factors so that the costs and benefits of improving haemophilia care and the priority setting of clinical interventions can be rationalised.

Whether it is economically desirable to increase spending now is open to argument, but adopting a longer perspective within the constraints and pressures of an annual contracting round is often difficult. Should we be looking for alternative ways of reducing costs by evaluating new approaches to the management of haemophilia care[29,30] such as continuous infusion[31-33] and gene therapy[34,35]? What are the costs and benefits associated with liver transplantation which can cure haemophilia[36]?

In the short run we are left with new contractual arrangements between purchasers and providers to prevent haemophilia services being a drain on their own hospital budgets. In the long run it may be necessary to revert to central funding for this and other rare, expensive, unpredictable and lifelong conditions.

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The changing patterns of factor VIII (FVIII) and factor IX (FIX) clotting factor usage in a comprehensive care centre between 1980 and 1994

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Summary. The annual amount of clotting factor used by patients at the Royal Free Haemophilia Centre increased significantly from 4 million iu in 1980 to over 15 million iu by 1994 ($P < 0.0001$). In order to assess the reasons for this increase, data on concentrate usage over this period were retrospectively collected for patients who had haemophilia or von Willebrand's disease. Only patients who were registered exclusively at the Centre were included in the study. In total, 498 patients met the inclusion criterion. The median age of the cohort on 1 January 1980 was 21 (range < 1–69) years. During the period there were 88 births and 45 deaths. The majority of patients had haemophilia A (55%). The median follow-up period per patient was 2.1 (range 0–14.8) years. Despite adjusting for increases in the number of patients and changes in body weight, statistically significant increases in clotting factor usage were detected for some subgroups of patients, in particularly for those with severe haemophilia A and B and from the late 1980s onwards, for patients with von Willebrand's disease. Two reasons for this increase in clotting factor usage were identified as being the introduction of improved products and prophylaxis. However, the increased cost of clotting factor provision that has resulted from these changes in treatment policy should not be analysed in isolation but should be balanced off against cost decreases in other areas and against increases in the effectiveness of treatment.

Keywords: clotting factor, costs, economics, haemophilia, prophylaxis, von Willebrand's disease.

Replacement therapy with clotting factor is the single most expensive direct cost component associated with haemophilia care, particularly for those with the severe form of the condition. It is estimated that the provision of replacement products for children accounts for 50–85% of the total costs of haemophilia care, although this figure is higher in those who have developed inhibitors secondary to treatment [1].

In 1994 160 million international units (iu) of FVIII were used in the UK to treat patients with haemophilia A and von Willebrand's disease (vWD) compared with 60 million iu in 1980 [2]. The Royal Free Haemophilia Centre (RFHC), a comprehensive care centre in London, used 4 million iu in 1980 and 15 million iu in 1994, an increase in annual FVIII usage of 11 million iu or 375%. Some reasons for increased usage, such as the introduction of prophylaxis in the late 1970s and the use of virally safer products since the mid 1980s, may explain why patients now receive more clotting factor. Several observational studies have since demonstrated the effectiveness of prophylaxis [3, 4]. It is believed that clotting factor administered at levels of 25–40 iu kg^{-1} three times a week for those with haemophilia A and 25–40 iu kg^{-1} twice a week for those with haemophilia B may prevent the onset of haemophilic arthropathy [3]. Hence prophylaxis has become the preferred method of patient management, particularly for children. However, Savidge [5] estimated that the additional clotting factor required for a patient with severe haemophilia A weighing 30 kg to switch from treatment on-demand to a full-time prophylactic regime cost between £10 560 and £29 700 per annum depending on the purity of clotting factor used.

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In the UK, patients with haemophilia who were treated prior to 1985 [6] with plasma-derived large pool clotting factor concentrates were infected with HCV. It is further estimated that 60% were co-infected with HIV [7]. Previous work has demonstrated an increase in clotting factor usage associated with a decrease in CD4+ count in those infected with HIV [8].

Assessing the increase in clotting factor usage is necessary in order that future resources are appropriately allocated. Therefore, the aim of this study is to assess the changing patterns of factor VIII (FVIII) and factor IX (FIX) clotting factor usage in a comprehensive care centre between 1980 and 1994.

Methods

Study design and population

Changes in FVIII and FIX usage were investigated using a retrospective cohort study of patients with haemophilia A, B and vWD. Levels of severity for patients with haemophilia A and B were defined as: severe < 1 u dL^{-1}, moderate 1–5 u dL^{-1} and mild > 5 u dL^{-1}.

Data collection

Yearly total treatment figures were used in the analysis. These are recorded by patients on home-treatment records which are returned monthly to the RFHC and stored on its internal database. The information collected from these returned records includes the type and amount of treatment administered, the manufacturer, the medical reason for treatment, the day and time, and the number and location of bleeds. The number of days between the first and last recorded dose of clotting factor for each patient was used to calculate individual follow-up periods. Causes and dates of death, and the HIV and HCV status of each patient were recorded from medical records. The clotting factor usage each year was calculated, adjusted to the weight abstracted from the medical notes. Concentrate usage was categorized as either on-demand, preventative (treatment given prior to an invasive procedure or physiotherapy) or prophylaxis (including all clotting factors other than those given for preventative reasons that had been administered whilst a patient had been on a full-time prophylactic regime).

Patient inclusion criteria

A patient receiving 1 iu or more of FVIII or FIX during a year was classified as being 'active' and included in the analysis for that year. Patients jointly registered with other haemophilia centres were excluded as treatment records held for them at the RFHC were only partially complete. Those born or who registered at the RFHC during the period who met the criteria were automatically entered into the cohort in the following full calendar year, e.g. a new patient who registered in June 1988 would enter the cohort in 1989.

Statistics

P values for the changes in median yearly usage over time were calculated using linear regression analysis.

Results

Patient details

Details of 498 patients who met the inclusion criteria are shown in Table 1. The majority of patients had haemophilia A. Eighty-nine patients were infected with HIV. The median follow-up period was 2.1 (range 0–14.8) years per patient. During the 15-year period there were 88 births and 45 deaths; causes of death for those 45 patients are shown in Table 2. Four hundred and six of these patients were registered at the RFHC in 1980; by 1994 this had increased to 449. Ninety-nine patients received at least 1 iu of clotting factor in 1980 but by 1994 this had increased to 202 patients, an increase of 104%. The median age of the cohort on 1 January 1980 was 21 (range < 1–69) years. By 31 December 1994 this had increased to 32 (range < 1–84) years. The median patient body weight in 1980 was 63 (range 20–87) kg but by 1994 this had

Table 1. Cohort statistics.

Diagnosis	No. (%)	Births	Deaths	HIV
Severe haem. A	139 (28)	24	34	75
Moderate/mild haem. A	134 (27)	21	7	10
Severe haem. B	31 (6)	11	2	0
Moderate/mild haem. B	45 (9)	8	1	1
Severe vWD	9 (2)	3	0	1
Moderate/mild vWD	140 (28)	21	1	2
Totals	498 (100)	88	45	89

Table 2. Cause of death.

Cause	No. (%)
HIV/AIDS	23 (51)
HCV-related	6 (13)
MI/stroke	2 (4.6)
Carcinomatosis	2 (4.6)
Respiratory failure	2 (4.6)
Haemorrhage	1 (2)
Operative	1 (2)
Other	4 (9)
Unknown	4 (9)
Total	45 (100)

fallen slightly to 60 (range 4–99) kg. When patients with HIV/AIDS were excluded, the median weight in 1994 still decreased to 62 (range 4–99) kg.

FVIII usage

The total amount of FVIII used between 1980 and 1994 is shown in Fig. 1. In 1980 a total of 2.5 million iu of FVIII were used. By 1994 this had increased to 12.1 million iu, an increase in FVIII usage of 470%. Figure 2 shows the median FVIII usage according to clotting factor disorder. Increases in FVIII usage were seen irrespective of diagnoses.

Haemophilia A

In 1980 patients with haemophilia A used 2.5 million iu of FVIII; by 1994 this had increased to 9.8 million iu, an increase of 390%. The median level of FVIII usage increased irrespective of the severity of the disorder (Fig. 3). However, only those patients with severe and moderate haemophilia A experienced significant increases in FVIII usage ($P < 0.0001$ and $P = 0.04$, respectively). After adjusting treatment usage for changes in body weight, for those with moderate and severe haemophilia A, both increases remained highly significant ($P < 0.0001$).

vWD

Figure 4 shows the total FVIII usage by year for patients with vWD. Patients with severe vWD did not experience a significant increase in the median level of FVIII usage ($P = 0.16$). However, in 1980 patients with moderate and mild vWD used a median of 8000 (range 1000–10 000) iu and 250 (range 100–500) iu, respectively. By 1994 both

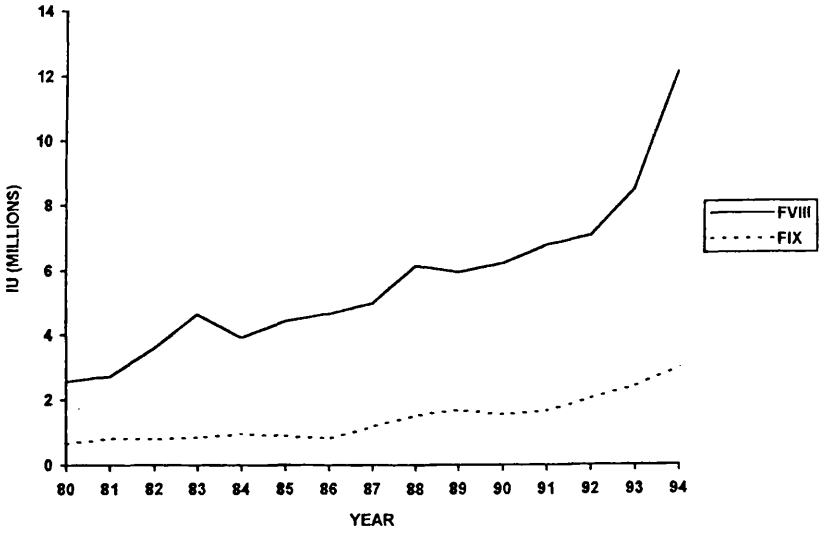

Fig. 1. Total FVIII and FIX usage between 1980 and 1994.

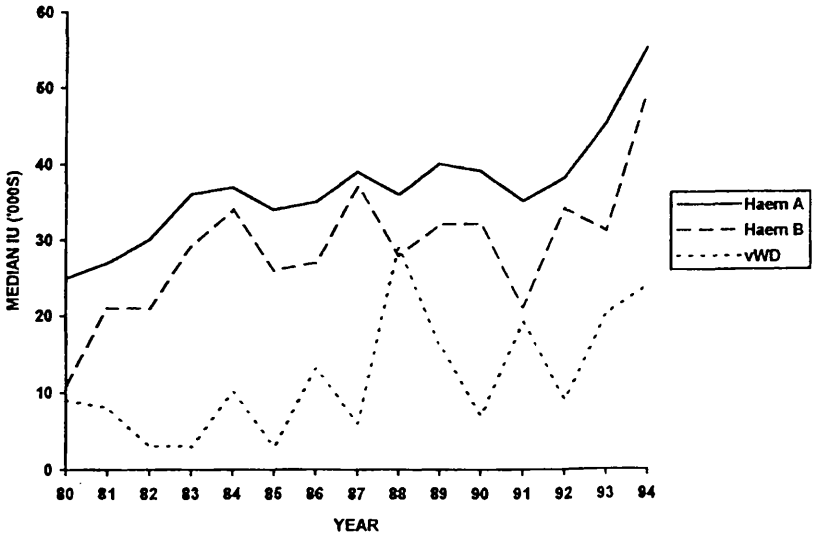

Fig. 2. Median clotting factor usage by diagnosis between 1980 and 1994.

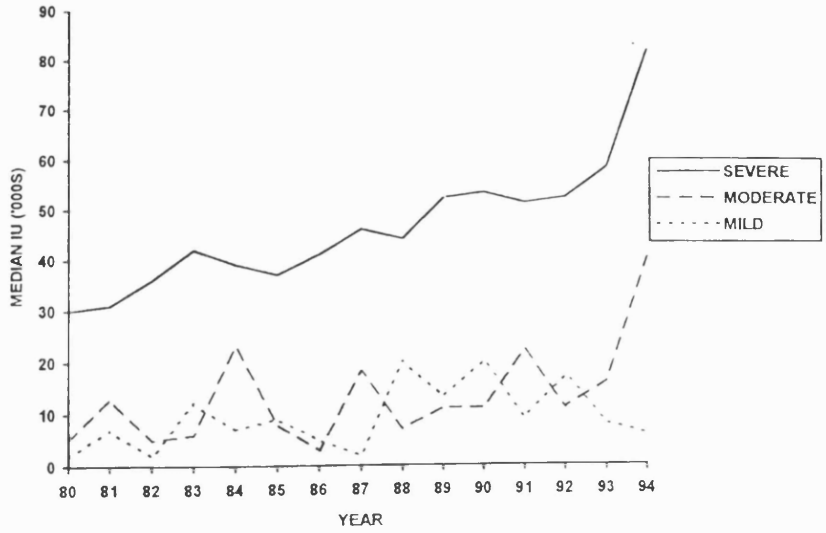

Fig. 3. Haemophilia A. Median clotting factor usage by severity between 1980 and 1994.

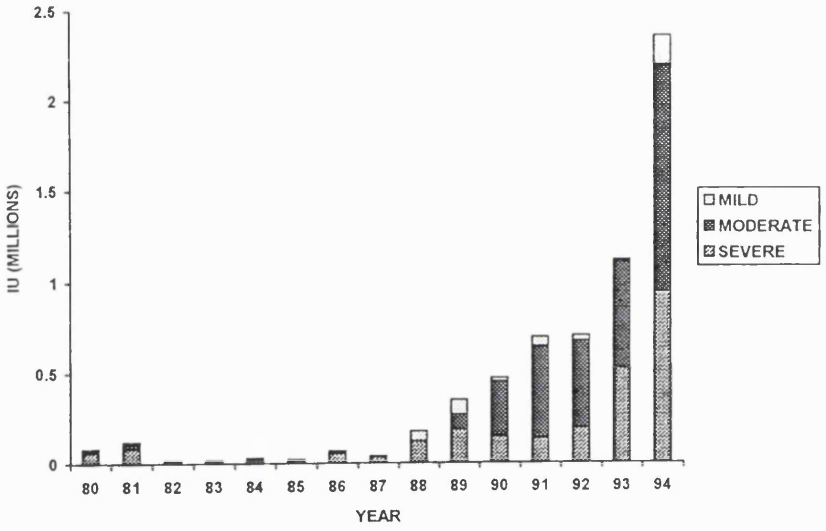

Fig. 4. vWD. Total clotting factor usage by severity between 1980 and 1994.

medians had increased significantly to 28 000 (range 2000–540 000) iu and 13 000 (range 3000–54 000) iu ($P = 0.03$ and $P = 0.02$, respectively). These increases remained significant after adjusting for changes in body weight ($P = 0.006$ and $P = 0.02$).

Haemophilia B

Over the total period there had been a 340% increase in the annual quantity of FIX used (Fig. 1). Patients with mild and moderate haemophilia B did not experience a significant increase in usage ($P = 0.50$ and $P = 0.28$). However, patients with severe haemophilia B experienced an increase in median levels of FIX usage from 22 000 (range 350–99 000) iu in 1980 to 59 000 (range 4000–232 000) iu by 1994 ($P < 0.0001$). After adjusting these treatment levels for changes in body weight, patients with severe haemophilia B still experienced a significant ($P = 0.02$) increase in FIX usage.

Method of treatment

The total amount of clotting factor used for prophylaxis between 1980 and 1994 had increased by over 900% ($P < 0.0001$) (Fig. 5). In 1980 prophylaxis accounted for 16% of the total amount used but by 1994 this had increased to 37%. The amount of clotting factor administered on-demand had also increased significantly ($P = 0.0003$) but when calculated as a proportion of the total amount of clotting factor used, treatment on-demand had declined from 59% in 1980 to 50% by 1994. The total amount of clotting factor used for preventative purposes had also increased significantly from 0.8 million iu in 1980 to 2.1 million iu by 1994

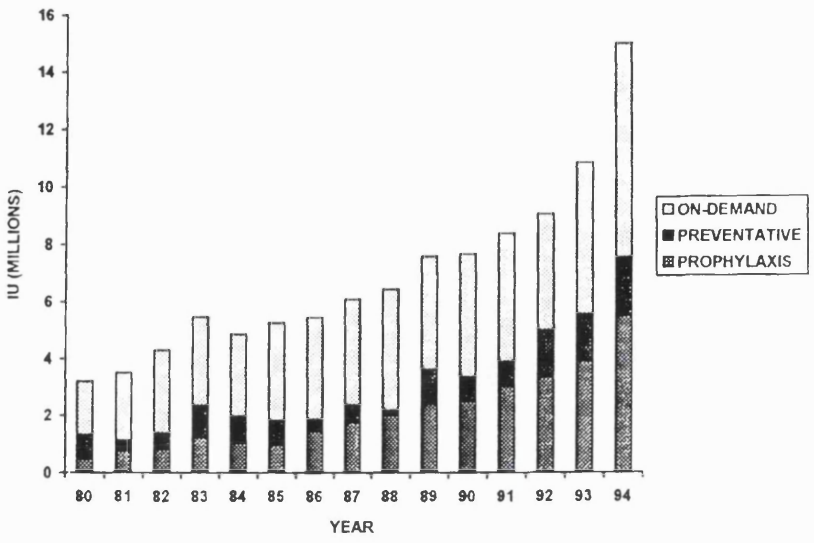

Fig. 5. Total clotting factor usage by reason for treatment between 1980 and 1994.

($P < 0.01$). In 1980 patients with vWD were responsible for 17 000 iu of this total compared to 614 000 iu in 1994 ($P < 0.004$).

Discussion

Patients with severe haemophilia and severe vWD can receive their clotting factor on-demand or prophylactically. Patients treated on-demand can expect to treat 30–35 [9] bleeds per year using 30–35 iu kg^{-1} of clotting factor per acute bleeding episode [10]. However, it is believed that by administering 24–40 iu kg^{-1} of clotting factor prophylactically three times a week for those with haemophilia A or 25–40 iu kg^{-1} twice a week for those with haemophilia B on an indefinite basis, it is possible to prevent acute bleeding, thus preventing haemophilic arthropathy [3]. Since the early 1990s policy at the RFHC has been to treat children newly diagnosed with severe haemophilia and severe vWD with primary prophylaxis. However, it has been suggested that prophylaxis requires an increase in clotting factor usage [3, 10]. Thus, as expected, we have seen a large increase in the median annual levels of FVIII and FIX used by patients with severe haemophilia A and B at the RFHC between 1980 and 1994 (provisional analysis of 1995 data shows a slight decline in total usage). However, because only patients with severe haemophilia and vWD are referred for treatment with prophylaxis, this does not explain the increase in the median or weight-adjusted amounts of clotting factor used in those with moderate haemophilia. These patients have probably contributed to the significant increase in clotting factor used on-demand, but it is unclear from these data why this has happened, particularly as treatment policy for a haemorrhage has remained unchanged over the period.

Because clotting factor is administered according to body weight it might be speculated that total body weight had increased with age, contributing to the increase in usage. However, this is not the case because those groups who experienced significant increases in the annual median level of clotting factor maintained their significant increases in clotting factor usage despite adjusting for weight. Further, 89 of the patients in the cohort have HIV, 23 of whom died during the 15-year period from AIDS-related illnesses. Patients with HIV/AIDS often experience weight loss as the disease progresses [11]. Possibly as a result the median patient weight for the cohort decreased by 3 kg over the 15-year period. However, despite excluding these patients from the analysis the median patient weight still decreased by 1 kg. If anything, and assuming that treatment schedules were regularly revised, one would have expected average usage to have decreased over time.

Despite often experiencing chronic bleeds that require prolonged treatment [12], patients with vWD used only small quantities of clotting factor in 1980. However, by 1994 patients with vWD had increased their usage of clotting factor; those with mild and moderate haemophilia used significantly more FVIII than in 1980. FVIII usage for those with severe vWD did not increase significantly ($P = 0.16$) but, given the range of treatments they now require, they had still used a lot more FVIII in the 1990s than they had previously used in the early to mid 1980s. Moreover, patients with severe vWD are now amongst the heaviest users of clotting factor registered at the RFHC. Indeed, even we incorporate other blood products such as cryoprecipitate into the analysis these conclusions still hold. Of particular interest is the timing of the increase in clotting factor usage (Fig. 5): Haemate P (Behring, now Centeon) and 8Y (BPL) were first marketed in the late 1980s/early 1990s and were amongst the first clotting factors to contain native von Willebrand factor, especially suitable for treating patients with vWD [13]. It is likely

therefore that part of this increase is attributable to the availability of these improved products for routine replacement purposes and for cover during invasive medical procedures.

Other potential reasons for the increase in clotting factor use include the problems of patients 'leaking' clotting factor to relatives abroad and vial size. Despite recently suspecting a family of exporting some of their clotting factor to the Yemen to treat a baby, we believe 'leaking' to be a rare problem in the UK. Since 1980, patients have received their clotting factor in variable size vials (500 or 1000 iu) and have been taught to 'round up' their treatment to the nearest vial. However, although it is a potential cause of some of the increase its precise impact is difficult to assess.

Patients with haemophilia and vWD have become extremely expensive to treat partly because they are now requiring more clotting factor than in the early 1980s. However, cost increases that result from a change in treatment policy should not be analysed in isolation, but should be balanced against increases in the effectiveness of treatment for which the new policy is responsible [14]. For example, prophylaxis is thought to be more expensive than treatment on-demand but it is also believed that it can prevent arthropathy. If a full analysis of the changing costs of haemophilia care is to be performed, then other cost categories, including the costs of joint replacements for patients with arthropathy, must also be examined. However, only when all appropriate costs and benefits are examined will an idea of an intervention's true 'worth' be obtained.

In conclusion, we have shown that the usage of clotting factor concentrates has dramatically increased over the past 15 years in our large comprehensive care centre. This has largely been due to the introduction of prophylactic treatment regimes. Whether resulting cost increases will ultimately be offset by reductions in costly orthopaedic procedures will only be known in many years time. However, it is clear that, in the short term, increased resources are essential to fund this expensive intervention.

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Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease

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Abstract. Miners AH, Sabin CA, Tolley KH, Lee CA (Royal Free Hospital School of Medicine, London; University Hospital Queen's Medical Centre, Nottingham; and Royal Free Hampstead NHS Trust, London, UK). Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease. *J Intern Med* 1998; **244**: 515–22.

Objectives. To assess the effectiveness and cost-effectiveness of prophylaxis with clotting factor against bleeding in patients with severe haemophilia and von Willebrand's disease (vWD).

Design. Treatment details that related to 179 patients with severe (< 1 u dL^{-1}) haemophilia A, B and vWD were retrospectively examined for the period 1980–95. A subgroup of these patients, 25 adults and 22 children, who had previously received treatment on demand and who had switched to treating with prophylaxis, were studied in order to examine the effects of the change. The cost-effectiveness of prophylaxis was also analysed using another subgroup of 38 patients and by adjusting their treatment details by age and method of treatment.

Setting. Data were obtained on patients who were solely registered at the Royal Free Hospital Haemophilia Centre (RFHHC), London, UK.

Outcome measure. Bleeds.

Results. The median annual number of bleeds decreased from 23.5 (range 1–107) in 1980, to 14 (range 0–45) in 1995 ($P < 0.0001$). Switching from treating on demand to prophylaxis reduced bleeding frequency in 41 out of 47 patients within the period of 1 year. At the base scenario, switching to prophylaxis cost an additional £547 per averted bleed; however, this figure was highly sensitive to certain variables.

Conclusion. Prophylaxis can reduce bleeding frequency but requires more clotting factor than treatment on demand. More detailed proof of cost-effectiveness is likely to require the use of modelling techniques.

Keywords: bleeds, clotting factor, cost, economics, haemophilia, prophylaxis.

Introduction

Patients with haemophilia and von Willebrand's disease (vWD) are deficient in clotting factor VIII (haemophilia A), factor IX (haemophilia B) and von Willebrand factor (vWF). These deficiencies can result in painful [1] and sometimes fatal bleeding. More commonly, repeated bleeds into joints may cause arthritis. As few as 10 bleeds into a single joint may cause a change in joint status [2]. If joints are to remain fully functional, it is important that these bleeds are prevented [3].

Those with severe forms of haemophilia (< 1 u dL^{-1}) are treated with clotting factor either on demand following a bleed, or prophylactically to prevent bleeds from occurring in the first instance. On demand, patients can expect to treat 30–35 bleeds per year with 30 IU kg^{-1} per bleed of clotting factor

[4]. However, studies in the 1960s [5, 6] showed that haemophilia patients with base line activity levels of 1 u dL^{-1} or above rarely developed disabling arthropathy. It was hypothesized that by keeping trough levels above 1 u dL^{-1} arthropathy would be prevented. This was the rationale behind long-term prophylaxis. By administering concentrate at 24–40 IU kg^{-1} three times a week for those with severe haemophilia A and 25–40 IU kg^{-1} twice a week for those with severe haemophilia B on an indefinite basis, it has proved possible to prevent bleeding and the development of arthropathy [7, 8]. Prophylaxis is currently the preferred method of patient management [9] but, as it requires more clotting factor than treatment on demand, the direct cost of purchasing the additional clotting factor can prove inhibitive [10].

Prophylaxis of limited duration was first administered at the Royal Free Hospital Haemophilia Centre (RFHHC) in the late 1970s to patients with severe haemophilia A and B, although full-time regimes were not introduced until the early 1980s. In the early 1990s, it became the comprehensive policy to treat, whenever feasible, all newly diagnosed children with severe haemophilia and severe vWD with primary prophylaxis.

This paper presents an assessment of the effectiveness and cost-effectiveness of prophylaxis in reducing the number of bleeds in patients with severe haemophilia A and B, and severe vWD registered at the RFHHC between 1980 and 1995.

Methods

This paper uses retrospective data available for a cohort of patients treated at the RFHHC during the period 1980–95. Patient-specific data on the type and amount of treatment administered, the manufacturer, the medical reason for treatment, the day and time, and the number and location of bleeds (reported by patients) are all recorded on an internal database. Clotting factor (factors VIII and IX) usage was grouped according to the reason for which it was given, either on demand or for prophylaxis. Clotting factor that had been used prior to physiotherapy, surgery or any invasive procedure was excluded. Treatment method and dates relating to changes in treatment method were identified using patient treatment records. A patient who had routinely received prophylaxis for 9 months or more during a year was defined as having received prophylaxis in that year. Patients born before 1 January 1980 were classified as adults, and those born on or after this date were classified as children.

Effectiveness evaluation

This involved two parts.

Part 1: Evaluation of the annual median number of bleeds between 1980 and 1995. All patients with severe (< 1 u dL^{-1}) haemophilia A, B or severe vWD who were registered at the RFHHC were included in this part of the analysis. Patients jointly registered with other haemophilia centres were excluded, as their treatment records held at the RFHHC were only partially complete. *P*-values for the changing number of bleeds over time were calculated using linear regression analysis.

Part 2: Investigation of bleeding patterns whilst treating on demand and after switching to prophylaxis. Patients included in part 1 of the study who had switched from treatment on demand to prophylaxis during the 16-year period and who had experienced at least one calendar year of each treatment regime were selected for this part of the analysis. However, because patients switched to prophylactic regimes at different time points, follow-up times were standardized to adjust for these differences.

Cost-effectiveness evaluation

An assessment was made of the cost-effectiveness [11] (or value for money) of prophylaxis compared with treatment on demand. The primary outcome measure used was the number of bleeds experienced by patients; results were expressed as costs per bleed avoided.

For the cost-effectiveness analysis there were a number of problems in using the retrospective data to establish two exclusive patient sets that corresponded to the two different treatment options. Firstly, data was only available for this 16-year period. Secondly, patients treated at the RFHHC are likely to have switched between methods of treatment at least once. In addition, irrespective of the method of treatment used, clotting factor is administered according to body weight, and it was also believed that bleeding patterns would be correlated with age [12]. Therefore, in order to separate patients into prophylaxis and on-demand treatment groups, bleeding

patterns and clotting factor usage were studied according to age of the patient and method of treatment. Hence the number of bleeds experienced and the amount of clotting used by, for example, 5-year-old children receiving prophylaxis were compared with the number of bleeds experienced by 5-year-old children treated on demand. This method of matching by age meant that only children up to the age of 9 years were included in the analysis of cost-effectiveness as numbers were too small at each age above this.

Because the data were gathered retrospectively, the only resource to be included in the analysis was the amount of clotting factor used. Costs that accrued after the first year of treatment were discounted at 6% per annum. There is a lack of empirical evidence supporting the discounting of health-related outcomes such as bleeds reduced, so these were not discounted in the base analysis [13, 14].

The robustness of the cost-effectiveness result was examined using one-way sensitivity analysis [15]. The sensitivity analysis was performed by varying the unit price of clotting factor, the discount rate, the quantities of clotting factor required and the number of bleeds patients had experienced for both methods of treatment. In the base scenario, a clotting factor price of 30p IU^{-1} was used, representing the RFHHC purchase cost for a high-purity clotting factor. Intermediate purity products are purchased for 18p IU^{-1} and recombinant FVIII for 48p IU^{-1} + value added tax (VAT) at 17.5%. These figures were used as the upper and lower parameters for the unit cost of clotting factor in the sensitivity analysis (it was assumed that the choice of clotting factor does not influence the amount that is administered to patients).

At the base scenario, median clotting factor usage was calculated for each year and for both methods of treatment. These values were then added together in order to calculate total clotting factor use. The parameters used in the sensitivity analysis for these variables were based on the highest and lowest possible totals. This ensures that the maximum feasible range of high and low values based on observation are tested. The same process was used to calculate total bleeding frequency and the parameters for the sensitivity analysis.

Results

Changes in the annual number of bleeds by calendar year

A total of 179 patients met the criteria for inclusion in part 1 of the effectiveness evaluation, of whom 78% had a diagnosis of severe haemophilia A (Table 1). Between 1980 and 1995, these patients had a total of 38 014 bleeds, 63% of which were joint bleeds; 164 (92%) of all patients experienced one or more bleed. The overall median number of bleeds per patient for the 16-year period was 162 (range 1–1096).

The median numbers of bleeds experienced by patients each year are shown in Fig. 1. In 1980, patients had a median of 23.5 bleeds (range 1–107), but by 1995 this had dropped to 14 (range 0–52). In 1980 there was a median of 20 (range 1–67) joint bleeds per patient, but by 1995 this had fallen to 8 (0–45) (Fig. 2). Both decreases were highly significant ($P < 0.0001$).

Effect of switching from treatment on demand to prophylaxis

A total of 47 patients met the inclusion criteria for part 2 of the evaluation; 25 of these patients were adults (Table 2). In the year prior to prophylaxis (year −1), these 25 adults experienced a median of 37 bleeds (range 11–132) per year (Fig. 3) and used a median of 560 (range 196–3120) IU kg^{-1} $year^{-1}$ of clotting factor. During the first full calendar year on prophylaxis (year 0), patients experienced a median of 13 bleeds (range 0–92), representing a 65% reduction. The median level of clotting factor usage

Table 1 The number and type of bleeds by diagnosis

Diagnosis	No. of patients (%)	Patients who bled (%)	No. of bleeds (%)	No. of joint bleeds (%)
Severe haemophilia A	139 (78)	129 (79)	31 750 (84)	20 502 (85)
Severe haemophilia B	31 (17)	29 (18)	5710 (15)	3360 (14)
Severe vWD	9 (5)	6 (3)	554 (1)	40 (1)
Totals	179 (100)	164 (100)	38 014 (100)	24 082 (100)

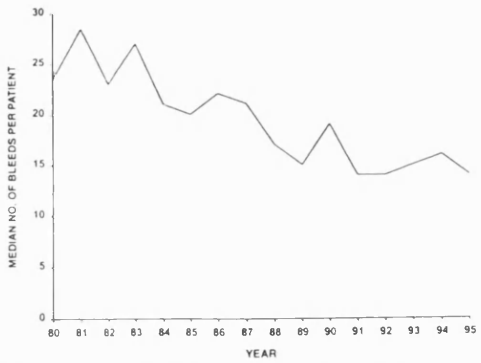

Fig. 1 Median number of bleeds per patient between 1980 and 1995.

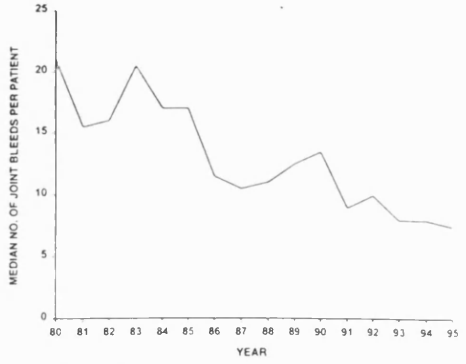

Fig. 2 Median number of joint bleeds per patient between 1980 and 1995.

was 1935 (range 592–3376) IU kg^{-1} $year^{-1}$, representing an increase of 350%. Between years −1 and 0, there was a median within-patient decrease of 18 bleeds (range: increase of 22 to a decrease of 112) and a median within-patient increase in clotting factor usage of 411 IU kg^{-1} $year^{-1}$ (range: decrease of 775 to an increase of 1263). Five patients increased bleeding after switching methods of treatment.

In year −1, the 22 children experienced a median of 21 (range 3–64) bleeds per year and used a median of 1974 (range 700–3750) IU kg^{-1} $year^{-1}$ of clotting factor. In year 0 the median annual number of bleeds was lower at 11 (range 0–49), a decrease of 10 bleeds per year. Patients experienced a within patient-decrease of 9 (range: increase of 22 to a decrease of 59) bleeds per year. Only one child bled more often after starting prophylaxis. The median level of clotting factor usage increased to 2967 (range 1,742–5472) IU kg^{-1} $year^{-1}$. The within-patient clotting factor also increased by 865 (range decrease of 322 to an increase of 2664) IU kg^{-1} $year^{-1}$.

Table 2 Patient details for part 2 of the effectiveness analysis

	Adults	Children
No.	25	22
Diagnosis A/B/vWD	19/5/1	14/7/1
Median age at start of prophylaxis in years (range)	30 (4–63)	4 (2–10)
Median follow-up in years (range)		
Prior to prophylaxis	7 (1–15)	3 (1–8)
Following start of prophylaxis	7 (1–15)	3 (1–11)

Cost-effectiveness analysis

A total of 38 patients from the original 179 could be matched by age and method of treatment up to the age of 9 years (Table 3). Age- and treatment-adjusted bleeding patterns are shown in Fig. 4. Apart from when very young, patients who received prophylaxis at any time until the age of 9 years consistently had a lower and a more constant median number of bleeds than those who were treated on demand.

Whilst treating on demand and with prophylaxis, patients experienced a median of 192.5 and 103 bleeds per patient, respectively. However, prophylaxis was the more costly method of treatment. The net discounted costs of treating on demand and with prophylaxis were £27 751 and £76 863 per patient.

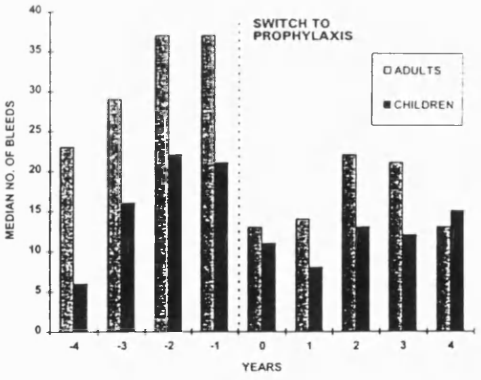

Fig. 3 Median annual number of bleeds per patient before and after a switch to prophylaxis.

Table 3 Patient details for the cost-effectiveness analysis

Total no. of patients	38
Diagnosis A/B/vWD	27/10/1
Total patient years (on demand/prophylaxis)	216 (132/84)
Median no. of years receiving (range):	
Treatment on demand	3 (0–9)
Prophylaxis	2 (0–6)

respectively. The incremental cost-effectiveness ratio (ICER) for prophylaxis compared with treatment on demand was therefore £547 per bleed avoided ([£76 683 − £27,751]/[192.5–103]). This figure represents the additional cost associated with every bleed averted by using prophylaxis instead of treating on demand.

The results of the one-way sensitivity analysis and the range of values used in the analysis are shown in Table 4. In two of the scenarios, treatment on demand used less clotting factor and was associated with a lower number of bleeds than prophylaxis. In these conditions, treatment on demand is considered the more cost-effective option. Conversely, in another two scenarios, prophylaxis was associated with a lower quantity of clotting factor and a lower number of bleeds. In these scenarios, prophylaxis is considered the more cost-effective method of treatment. For all other ranges tested in the sensitivity analysis, prophylaxis has a higher effectiveness but at higher cost, with an ICER ranging from £328 (low clotting factor price) to £1667 (high clotting factor use for prophylaxis). The ICER was sensitive to changes in key variables. For example, varying the unit price of clotting factor from 30p IU^{-1} to 56.4p IU^{-1} changed the ICER from £547 to £1028 per avoided bleed.

Discussion

Over the period 1980–95 there has been a steady decrease in the median annual number of bleeds ($P < 0.0001$) in patients with severe haemophilia and severe vWD registered at the RFHHC. Switching from treatment on demand to prophylaxis has reduced the median annual number of bleeds for both adults and children who are registered at our centre. The age adjustment for the annual number of bleeds conducted as part of the cost-effectiveness analysis showed that, apart from when very young, prophylaxis was consistently associated with fewer bleeds than treatment on demand.

The data on bleeding patterns is based on patients recording bleeds as they occur. There is a possibility that some bleeds are not reported or even identified and as a result the actual number of bleeds that patients may have experienced could, in reality, have been larger. Patients on prophylaxis, conscious of the effort that is being made to reduce bleeding frequency, may actually be more vigilant in identifying and reporting bleeding episodes, resulting in less 'under-reporting' in this group. Despite this, prophylaxis still

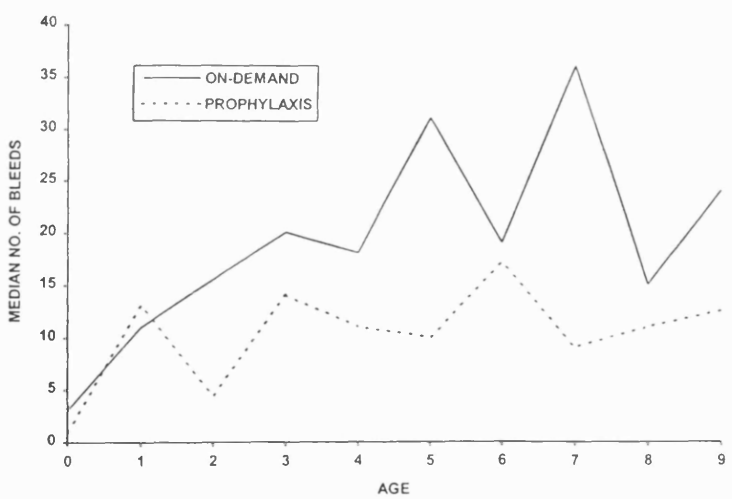

Fig. 4 Age- and treatment-adjusted bleeds per patient.

Table 4 Results of the sensitivity analysis

Variable	Base case	Range	ICER (£)	
			Minimum	Maximum
Clotting factor (p IU^{-1})	30	18–56.4	328	1028
Discount rate				
Costs (%)	6	0	750	—
Outcomes (%)	0	6	800	—
On demand (medians)				
No. of bleeds	192.5	34–517	118	Dominant*
Clotting factor (IU)	135 947	16 092–482 449	Dominated†	821
Prophylaxis (medians)	359 565			
No. of bleeds	103	34–236	309	Dominated ‡
Clotting factor (IU)		87 548–848 372	Dominant§	1667

*If a patient who treated on demand had experienced a median of 34 bleeds, prophylaxis would have been less effective and also more costly (i.e. treatment on demand is the 'dominant' therapy).

†If a patient who treated on demand had used 482 449 IU of clotting factor, prophylaxis would have been less costly and also more effective (i.e. treatment on demand is the 'dominated' therapy).

‡If a patient who received prophylaxis had experienced 236 bleeds, treating on demand would have been less costly and more effective (i.e. prophylaxis is the 'dominated' therapy).

§If a patient who received prophylaxis had required 87 548 IU of clotting factor, treating on demand would have been more costly and less effective (i.e. prophylaxis is the 'dominant' therapy).

resulted in a significantly lower median number of bleeds compared with treatment on demand. Any adjustment for higher levels of under-reporting in patients receiving treatment on demand would only further increase the relative effectiveness of prophylaxis.

The 47 patients included in part 2 of the analysis were amongst the heaviest bleeders registered at the RFHHC: those with smaller bleeding frequencies are less likely to have been referred for prophylaxis. However, the switching of children to prophylaxis was the consequence of a policy change at the RFHHC. No such policy had been introduced for adult patients, who could therefore have switched to prophylaxis for a variety of reasons, including lifestyle needs, which may confound any results. Interestingly, in the 4 years prior to switching to prophylaxis, the median annual number of bleeds had steadily risen, suggesting a change to prophylaxis to avert a cycle of repeated joint or other bleeds (Fig. 3).

The cost-effectiveness of prophylaxis was estimated using age-adjusted patient treatment data. Our baseline analysis showed that an additional £547 was required to avert each bleed using prophylaxis. Whilst avoiding bleeds could lead to a reduction in future health care costs, the decision-maker needs to decide whether the expected benefits can justify the immediate extra treatment costs they will face. A sensitivity analysis can help in this decision-making process. The most pessimistic ICER indicated in our sensitivity analysis (based on an extreme estimate of the amount of clotting factor used whilst treating prophylactically) was £1667. If the decision-maker is willing to pay this amount to avert each additional bleed then the use of prophylaxis can be considered a worthwhile use of resources, as in practice the incremental cost-effectiveness will be more favourable than this.

The sensitivity analysis is also important for indicating key variables to which the ICER is most sensitive. The incremental cost-effectiveness of prophylaxis was highly sensitive to the unit price of clotting factor. This has important implications for the imposition of VAT on the purchase of recombinant clotting factor. When the unit price of clotting factor was 48p IU^{-1}, the ICER increased to £875. The effect of VAT was to increase this by a further £153 to £1028. Therefore, despite any other benefits of using a recombinant clotting factor, its use has a considerable impact on the cost-effectiveness of prophylaxis due to the higher price faced by purchasers [16]. However, if less clotting factor is needed in the future, perhaps through the use of continuous infusion [17–19], or if the unit price of clotting factor decreases, a considerably lower incremental cost per bleed avoided could be expected.

Our baseline estimate of incremental cost-effectiveness is lower than the estimates of DM2536

(approximately £1000) calculated by Szucs *et al.* [20] and $1380 (approximately £850) calculated by Smith *et al.* [21]. There are several possible reasons for these differences. Firstly, we have used total bleeding as our outcome measure whereas the study by Szucs *et al.* focuses on joint bleeding. Thus, in our analysis more bleeds are prevented, leading to a lower ICER. Secondly, we have only considered clotting factor costs, whereas both other studies included additional cost categories, such as the amount of time absent from work, amount of schooling missed, patient travel and laboratory costs.

The cost-effectiveness analysis we have performed represents a preliminary evaluation. It does, however, provide purchasers and providers of haemophilia care with an indication of the potential extra costs and benefits of a policy of administering clotting factor prophylactically, instead of treatment on demand, for patients with severe haemophilia. Whilst a full prospective economic evaluation is likely to provide more robust evidence, such an evaluation takes time to complete, is expensive and may not be feasible [8]. An alternative would be to pool data from previous randomized controlled trials in a meta-analysis, but unfortunately insufficient data exist to allow this to be done.

There are clear limitations to using retrospective data in economic evaluations of health care technologies. Resource data were confined to clotting factor use, although such provision is believed to account for up to 93% of the total cost of care [21]. Similarly, outcomes data were only available for the number of bleeds which represent an intermediate outcome measure. A complete cost-effectiveness analysis would consider the development of arthropathy as the primary measure of effectiveness. However, this represents a long-term measure of benefit for which no data are available at the RFHHC and no data exist from randomized controlled studies on the ability of prophylaxis to reduce such long-term disability. Therefore, in order to establish the cost-effectiveness of prophylaxis, a model is required which links the information relating to joint bleeds with the development of arthropathy; i.e. similar to that described by Glick *et al.* [22] who modelled the link between reductions in blood cholesterol and changes in life expectancy. Currently the impact of reductions in the number of joint bleeds on the onset and progression of arthropathy remains unclear. Until this relationship is better understood and quantified, it will be difficult to produce an accurate estimate of long-term cost-effectiveness in this manner. Nonetheless, based on evidence from this retrospective data and from other studies, prophylaxis appears successful in reducing bleeding in severe haemophilia, so there is certainly scope for it to represent a cost-effective use of resources.

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Assessing health-related quality-of-life in patients with severe haemophilia A and B

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Abstract *Severe haemophilia is a chronically disabling and painful condition but treatment may modify progression of the disease and consequently health-related quality-of-life (HR-QoL). In order to assess HR-QoL in patients with severe haemophilia A and B, 99 patients received MOS Short Form 36 (SF-36) and EuroQol (EQ-5D) questionnaires. The relationships between responses from both questionnaires, HIV status, age, orthopaedic history and the number of bleeds patients had experienced in the previous year were examined. Scores from both questionnaires were also compared to appropriate UK normative data. The final analysis was based on 70 and 71 SF-36 and Euroqol questionnaires, respectively. Age aside, none of the clinical variables were found to be statistically significant predictors of health-related quality-of-life (HR-QoL). However, results from both questionnaires clearly showed that compared to the general population these patients with severe haemophilia are experiencing significantly lower levels of HR-QoL irrespective of differences in age.*

Introduction

Haemophilia is a condition that affects 1 in every 6,000 males (Nilsson, 1994) in the general population but is passed on by females. Individuals with haemophilia are deficient in essential clotting factors resulting in a tendency to bleed. The majority of normal individuals have clotting factor levels of between 50–200 iu/dl, but patients with severe haemophilia have levels of less than 2 iu/dl. Patients with haemophilia A are deficient in clotting factor VIII (FVIII), whereas those with haemophilia B are deficient in clotting factor IX (FIX). When these individuals experience bleeding it is often painful (Janco *et al.*, 1996) and can occasionally be life threatening in the absence of treatment (Aronstam *et al.*, 1979; Doughty *et al.*, 1995). However, with the exception of viral complications, the major cause of morbidity in patients with severe haemophilia is haemophilic arthritis (HA) due to repeated joint bleeding (Brettler *et al.*, 1985). HA is a chronically disabling and painful condition that is thought to resemble progressive osteoarthritis (Pettersson *et al.*, 1981). HA is usually found in the knees, ankles and elbows of patients but can affect any joint (Heim *et al.*, 1994). As

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few as ten bleeds into a single joint may cause clinically significant deterioration (Soreff & Blomback, 1980).

It is known that the majority of adults with severe haemophilia who are registered at the Royal Free Hospital Haemophilia Centre (RFHHC) have started to develop or have already developed HA. During the 1960s and 1970s a number of small studies showed that the prophylactic use of clotting factor could prevent often painful bleeding episodes in patients with haemophilia A (Hirschman *et al.*, 1970; Kasper *et al.*, 1970; Robinson *et al.*, 1967). More recent research has demonstrated that it is possible to prevent the onset of HA in the first instance in patients with severe haemophilia A and B by administering clotting factor at an early age prior to any signs of joint bleeding; a process known as primary prophylaxis (Nilsson *et al.*, 1992). Primary prophylaxis is now regularly used at the RFHHC (one of 102 treatment centres in the UK (UK Haemophilia Centre Directors, 1994)) to treat previously untreated patients with severe haemophilia A and B. The difficulty when evaluating the effectiveness of primary prophylaxis is that it has only recently been introduced and because haemophilia is a life-long condition the full impact of treatment on health-related quality-of-life (HR-QoL) will take many years to be established.

The aims of this study were twofold. To assess the major determinants of HR-QoL in patients with severe haemophilia A and B who were registered at the RFHHC and to compare these levels of HR-QoL to those reported by the general population.

Method

All patients with severe (< 2 iu/dl) haemophilia A and B who were at least 18 years of age and who were registered at the RFHHC were asked to complete Medical Outcome Study (MOS) Short Form 36 health survey (SF-36) (Ware & Sherborne, 1992) and EuroQol (EQ-5D) questionnaires (EuroQol Group, 1994). Questionnaires were sent to patients by post along with a covering letter; a prepaid envelope with which to reply was also enclosed with the questionnaires. Patients who did not return the questionnaires within four weeks were sent a reminder and new copies of both questionnaires. No further reminders were sent.

The choice of instruments

The SF-36 and EQ-5D questionnaires are generic instruments that are used to compare HR-QoL within and between different clinical conditions. The SF-36 questionnaire was used because there is evidence to suggest that it is of value in assessing HR-QoL in non-haemophilic patients with osteoarthritis (Hawker *et al.*, 1995; Stucki *et al.*, 1995) and other rheumatoid conditions (Lyons *et al.*, 1994; Talamo *et al.*, 1997) and so would be likely to be useful in measuring HR-QoL in patients with severe haemophilia as HA resembles progressive osteoarthritis (Pettersson *et al.*, 1981). The SF-36 questionnaire measures HR-QoL on eight multi-item dimensions: physical functioning, social functioning, physical and mental role limitations, mental health, energy/vitality, pain and general health perception. Results for each dimension are scored and transformed on to a scale from 0 (worst health) to 100 (best health). Results from the SF-36 can also be reported as a physical component summary scale (PCS) and as a mental component summary scale (MCS) (Ware *et al.*, 1994). Both summary scales were calculated by multiplying each of the eight individual SF-36 scores by their respective factor score coefficients, previously calculated from a large UK normative data set (Jenkinson *et al.*, 1997). Finally, scores were standardized to a t score with a mean of 50 and a standard deviation of 10. The advantage of reporting the SF-36 as two summary component scores lies in their greater precision and their ability to remove floor and ceiling effects.

However, their disadvantage lies in the necessary aggregation of scores and the subsequent blurring of results (Jenkinson *et al.*, 1997).

The EQ-5D is a two-part instrument. The first part consists of five 'domains' that are designed to record health status in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is divided into three levels of severity meaning that a total of 243 (3^5) possible health states are defined. These results can be displayed as an unweighted profile ($EQ\text{-}5D_{Profile}$) or as a single index ($EQ\text{-}5D_{Utility}$) by applying a suitable utility to each health state. In this analysis, the $EQ\text{-}5D_{Utility}$ was calculated using utilities obtained from a large UK survey (Williams, 1995). The second part of the questionnaire consists of a visual analogue self-rating scale ($EQ\text{-}5D_{VAS}$) on which the best and worst imaginable health states score 100 and 0 respectively. Results from the $EQ\text{-}5D_{VAS}$ can be used as a measure of the patient's valuation of their own overall health status. The EQ-5D was included to complement the SF-36; its advantage being that it generates a single index (or utility) figure that can be used to help allocate resources in cost–utility analyses. To date the EQ-5D has never been used to assess HR-QoL in patients with haemophilia. However, available data suggest that the $EQ\text{-}5D_{Profile}$ covers aspects of health that are important to arthritis sufferers (Hurst *et al.*, 1997). Preliminary evidence also demonstrates the construct validity of the EQ-5D in rheumatoid arthritis (Hurst *et al.*, 1994). There was reason, therefore, to believe that the EQ-5D would be suitable for measuring HR-QoL in patients with severe haemophilia.

All remaining patient data including history of corrective orthopaedic surgery (yes/no), the number of bleeds patients experienced in the previous calendar year, HIV status (positive/negative) and patient age (as a continuous variable) were collected from the RFHHC's internal database and from patient's medical records.

Missing data

Where data were missing from the returned SF-36 questionnaires, average scores were calculated using completed items in the same scale. However, if 50% or more of the answers were missing on a particular questionnaire the SF-36 for that individual was removed from the analysis; both procedures are recommended in the SF-36 user guide (Ware *et al.*, 1993). For the $EQ\text{-}5D_{Profile}$, if one dimension was left unanswered the modal answer from the remaining dimensions was inserted. If two or more dimensions were left unanswered the questionnaire was excluded from the analysis.

Analysis

The analysis was divided into two separate parts. In the first part of the analysis it was hypothesized that patient age, HIV status and severity of bleeding disorder, as expressed by previous orthopaedic surgery and the number of bleeds patients had experienced in 1996, would all be significant predictors of HR-QoL in patients with severe haemophilia. The majority of scores from both questionnaires were non-normally distributed so non-parametric tests for significance were used. Chi-squared tests were used to examine the relationship between results from the $EQ\text{-}5D_{Profile}$ and HIV status and orthopaedic history. Mann-Whitney U tests were used to examine the relationship between the $EQ\text{-}5D_{Profile}$ and patient age and the number of bleeds they had experienced in 1996. For the SF-36, $EQ\text{-}5D_{Profile}$ and $EQ\text{-}5D_{Utility}$, regression analysis was used to examine the relationship between computed scores and all four independent variables. Internal consistency was tested for using Cronbach's alpha statistic.

Table 1. *Questionnaire response and non-response rate by demographic and clinical characteristics*

	Responders ($n = 72$)	Non-responders ($n = 27$)
Haemophilia A	60	20
Haemophilia B	12	7
HIV-positive	28	12
Mean age (years)	37.8 (SD 14.1)	28.7 (SD 9.3)
Median clotting factor level (iu/dl)	0 (0–1.6)	0 (0–1.7)

In the second part of the analysis it was hypothesized that irrespective of patient age, compared to the general population these patients with severe haemophilia were currently experiencing significantly decreased levels of HR-QoL. In order to test this hypothesis the completed EQ-5D questionnaires were compared to published UK EQ-5D normative summary statistics ($n = 3{,}995$) (Kind *et al.*, 1998). Statistical differences between the two sets of data were tested for using Chi-squared and Fishers exact tests.

Computed SF-36 scores were also compared to UK normative data (Jenkinson *et al.*, 1993). Comparisons were initially restricted to a normative data set that consisted of male individuals who were aged between 35–44 years ($n = 993$–$1{,}009$ for the ten individual SF-36 scales). However, access was also gained to the original male normative data set ($n = 4{,}229$). Statistical comparisons were made using Mann-Whitney U tests and linear regression methods were used to assess whether HR-QoL scores on each scale were associated with haemophilia status (i.e. haemophilia/normative patient) after adjusting for age differences between the two groups. All regression analyses were performed using the PROC GLM procedure contained in the Statistical Analysis System (SAS Inst., 1992). Spearman's rank correlation tests were used to examine correlations between the $EQ\text{-}5D_{Utility}$, $EQ\text{-}5D_{VAS}$ and SF-36 scales.

Results

Ninety-nine patients with severe haemophilia A ($n = 80$) and B ($n = 19$) were originally posted both questionnaires, of whom 40 were known to be infected with HIV (all 99 were known to be infected with Hepatitis C (HCV)). Seventy-two (73%) patients returned their questionnaires of whom 60 and 12 had severe haemophilia A and B, respectively (Table 1). All of the patients who returned their questionnaires who were HIV-positive had haemophilia A. The 72 patients who responded were significantly older than non-responders ($p < 0.001$). Of the returned SF-36 questionnaires, two contained less than 18 answers and were removed from the analysis. One patient completed and returned an EQ-5D questionnaire but not the SF-36 questionnaire, hence the final SF-36 analysis was based on 70 respondents and the EQ-5D analysis was based on 71 respondents.

Results from the EQ-5D questionnaire are shown in Table 2. For the $EQ\text{-}5D_{Profile}$, the majority of haemophilic patients reported having 'no' or 'some' difficulties for all five domains; very few patients reported their health to be in any of the most severe states. Of the 54 patients who reported 'some problems' with mobility, 45 (83%) also reported having at least 'some' pain. The mean SF-36 scores and respective 95% confidence intervals for the haemophilia patients are shown in Table 3. Tests for internal consistency showed that the observed coefficients for the SF-36 scales exceeded usual standards for group comparisons; Cronbach's alpha scores ranged between 0.84–0.93.

Table 2. *EQ-5D questionnaire results and UK EQ-5D normative data (Kind, 1998)*

Domain	Haemophilia $n = 71$ (%)	General population $n = 3,395$ (%)	p value
Mobility			
No problems	16 (22.5)	2,772 (81.6)	
Some problems	54 (76.1)	620 (18.3)	
Confined to bed	1 (1.4)	3 (0.1)	< 0.001
Self-care			
No problems	50 (70.4)	3,251 (95.8)	
Some problems	21 (29.6)	139 (4.1)	
Unable to	0 (0)	5 (0.1)	< 0.001
Usual activities			
No problems	29 (41)	2,844 (83.7)	
Some problems	40 (56.0)	481 (14.2)	
Unable to	2 (3.0)	70 (2.1)	0.001
Pain/discomfort			
None	12 (17.0)	2,278 (67)	
Moderate	55 (77.0)	988 (29.2)	
Extreme	4 (6.0)	129 (3.8)	0.001
Anxiety/depression			
None	46 (64.8)	2,685 (79.1)	
Moderate	24 (33.8)	648 (19.1)	
Extreme	1 (1.4)	62 (1.8)	0.006
$EQ\text{-}5D_{Utility}$ (SD)	0.64 (0.23)	–	
$EQ\text{-}5D_{VAS}$ (SD)	65.8 (18.9)	85.3 (8.3)	< 0.001

None of the answers recorded on the $EQ\text{-}5D_{Profile}$, $EQ\text{-}5D_{VAS}$ or $EQ\text{-}5D_{Utility}$ scores were found to be significantly associated with HIV status, the number of bleeds patients experienced in 1996 or whether patients had previously undergone orthopaedic surgery. However, all responses apart from the domain that measured anxiety/depression ($p = 0.27$) and the $EQ\text{-}5D_{VAS}$ ($p = 0.12$) were found to be significantly associated with age (Table 4); older individuals tended to be report more severe problems than younger individuals. The most significant relationship was between age and self-care ($p = 0.0004$), with older individuals tending to report more difficulties with self-care than younger individuals.

Table 3. *Haemophilia SF-36 mean scores compared with a male sub-set from the Oxford Healthy Lifestyles Survey (Jenkinson et al., 1993)*

	Haemophilia patients				Normative individuals		
SF-36 scale	Mean (SD)	95% CI	% floor	% ceiling	Mean (SD)	95% CI	p value
Physical functioning	53.7 (30.9)	46.5–60.9	2.9	7.1	91.9 (14.5)	91.0–92.8	0.0001
Role physical	55.7 (43.2)	45.6–65.8	31.4	38.6	89.5 (25.5)	87.9–91.1	0.0001
Bodily pain	56.6 (21.8)	51.5–61.7	5.7	7.1	85.6 (19.7)	84.4–86.8	0.0001
General health perception	46.6 (24.4)	40.9–52.3	0.0	2.9	74.1 (18.5)	72.6–75.6	0.0001
Energy/vitality	54.1 (21.1)	48.2–59.0	1.4	4.3	63.5 (18.6)	61.9–65.0	0.0001
Social functioning	69.1 (28.1)	62.5–76.2	1.4	25.7	90.5 (17.0)	89.5–91.6	0.0001
Role emotional	74.3 (38.9)	65.2–83.4	15.7	65.7	86.0 (28.6)	84.2–87.8	0.0090
Mental health	72.6 (15.3)	69.0–76.2	0.0	1.4	75.0 (16.1)	74.0–76.0	0.1270
PCS	30.7 (15.9)	27.0–34.4	–	–	52.0 (8.58)	51.5–52.6	0.0001
MCS	51.5 (12.3)	48.6–54.4	–	–	51.4 (9.85)	50.8–52.0	0.1980

Table 4. *Relationship of EQ-5D$_{Profile}$ to age*

Domain on EQ-5D$_{Profile}$	Median age (range)		
	No difficulties	Some or extreme difficulties	*p* value
Mobility	27.0 (18–43)	36.0 (18–79)	0.0006
Self-care	33.5 (18–65)	51.0 (18–79)	0.0004
Usual activities	33.0 (18–68)	39.5 (18–79)	0.018
Pain/discomfort	28.0 (18–68)	36.0 (18–79)	0.016
Anxiety/depression	25.5 (18–33)	36.0 (18–79)	0.27

Note: Tests for statistical significance were performed using Mann-Whitney U tests.

None of the SF-36 health scales were statistically associated with bleeding history, orthopaedic history or HIV status. However, physical functioning ($p = 0.002$), general perception of health ($p = 0.02$) scores and the PCS ($p = 0.001$) were all found to be significantly and negatively associated with increasing patient age and patient age^2 (Table 5). None of the remaining SF-36 scales were found to be significantly associated with age or age^2.

General population comparisons

Results from all three sections of the EQ-5D questionnaire showed that compared to the UK general population, these patients with severe haemophilia experienced significantly lower levels of HR-QoL (Table 2). Patients with severe haemophilia were more likely to have experienced some problems for all five domains on the EQ-5D$_{Profile}$ than the general population. However, all responders were equally likely to fall into the levels that reflected 'most' difficulty.

With the exception of the mental health scale ($p = 0.13$) and the MCS ($p = 0.20$), patients with severe haemophilia consistently reported significantly lower levels of HR-QoL compared to the general population as measured by the SF-36 (Table 3). These differences are large and would be both subjectively and clinically meaningful (Jenkinson & Zeibland, in press).

Combining the SF-36 data from both the haemophilia and the normative populations, all scales, with the exception of the mental role limitation score ($p = 0.83$), were significantly

Table 5. *Relationship of HR-QoL, as measured by the SF-36 in patients with severe haemophilia, and age*

Scale	Age			Age^2		
	Reg. coef.	95% CI	*p* value	Reg. coef.	95% CI	*p* value
Physical functioning	−3.67	−5.90–−1.44	0.0019	0.026	0.011–0.059	0.035
Role physical	−3.38	−7.03–−0.015	0.074	0.025	−0.37–−0.065	0.21
Bodily pain	−1.88	−3.78–0.018	0.056	0.048	−0.002–−0.038	0.085
General health perception	−2.48	−4.50–−0.46	0.018	0.022	0.00–−0.044	0.046
Energy/vitality	0.38	−3.59–3.66	0.84	−0.008	−0.047–0.012	0.68
Social functioning	−0.18	−4.26–0.66	0.15	0.017	−0.026–0.042	0.22
Role emotional	−1.15	−2.99–0.69	0.23	0.009	−0.75–0.77	0.38
Mental health	0.45	−1.11–2.00	0.57	−0.0046	−0.021–0.012	0.59
PCS	−1.98	−3.96–−0.85	0.001	0.016	0.0042–0.028	0.011
MCS	0.436	−0.58–1.46	0.40	−0.004	−0.015–0.007	0.46

Statistical tests were performed using regression analysis.

Table 6. *Correlations between EQ-5D and SF-36 scores*

SF-36 scale	EQ-5D$_{Utility}$ *R*	95% CI	*p* Value	EQ-5D$_{VAS}$ *R*	95% CI	*p* Value
Physical functioning	0.69	0.54–0.80	0.0001	0.60	0.43–0.73	0.0001
Role physical	0.56	0.37–0.70	0.0001	0.48	0.28–0.64	0.0001
Bodily pain	0.55	0.36–0.70	0.0001	0.39	0.17–0.57	0.0009
General health perception	0.55	0.36–0.70	0.0001	0.74	0.61–0.83	0.0001
Energy/vitality	0.47	0.26–0.64	0.0001	0.46	0.25–0.63	0.0001
Social functioning	0.57	0.39–0.71	0.0001	0.49	0.29–0.65	0.0001
Role emotional	0.35	0.13–0.54	0.003	0.22	−0.02–0.43	0.07
Mental health	0.25	0.02–0.46	0.04	0.42	0.21–0.61	0.0004
PCS	0.71	0.57–0.81	0.0001	0.61	0.44–0.74	0.0001
MCS	0.24	0.005–0.45	0.049	0.28	0.05–0.28	0.018
EQ-5D$_{Utility}$	–	–	–	0.49	0.29–0.65	0.0001

R is the Spearman rank correlation coefficient.

related to age. Similarly, with the exception of the mental health score ($p = 0.10$), all scales were significantly related to haemophilia status. Multiple regression analysis revealed that these relationships were independent, i.e. the differences between the two populations could not be fully explained by age differences between the groups.

Correlation between EQ-5D and SF-36

With the exception of the EQ-5D$_{VAS}$ and mental role limitation scale, both the EQ-5D$_{Utility}$ and EQ-5D$_{VAS}$ showed statistically significant correlations with the individual SF-36 scales and with each other (Table 6).

Discussion

The aim of this study was to assess HR-QoL in patients with severe haemophilia who were registered at the RFHHC. In order to do this, 99 patients with severe haemophilia were posted SF-36 and EQ-5D questionnaires. Results from the SF-36 ($n = 70$) and EQ-5D ($n = 71$) questionnaires showed that these patients had generally poor HR-QoL when compared to the general population. These results are similar to those found by Djulbegovic *et al.* (1996) and Szucs *et al.* (1996), although in our study we were able to directly control for age and haemophilia status by making comparisons with a large normative data set (Jenkinson *et al.*, 1993).

The two domains contained in the EQ-5D$_{Profile}$ that were most frequently reduced relative to normative population data were those that measured mobility and pain. The majority (77%) of patients reported having 'some' pain and 76% of patients reported having 'some' problems in terms of mobility. With the exception of the mental health scale and the MCS, SF-36 scores were significantly lower compared to the general population. Because primary prophylaxis has only recently become treatment policy at the RFHHC the majority of patients included in this study have already developed haemophilic arthritis (HA). HA is often extremely painful and physically debilitating. These results are, therefore, consistent with our prior expectation and with the results of other studies (Djulbegovic *et al.*, 1996; Szucs *et al.*, 1996; Triemstra *et al.*, 1996). However, the extent to which joint damage affects

the intensity of pain and the degree of mobility as recorded by both questionnaires can not be deduced from our data.

With the exception of mental role limitation and anxiety/depression, age was found to be an important predictor of HR-QoL in all patients. However, our results showed that the differences in HR-QoL between patients with severe haemophilia and the general population could not be explained by differences in age alone. Patients with severe haemophilia will therefore have reduced levels of HR-QoL compared to the general population irrespective of age.

Results from other studies have previously demonstrated that HR-QoL in non-haemophilia patients is significantly lowered by the presence of HIV infection (Burgess *et al.*, 1993; Carretero *et al.*, 1996; Copfer *et al.*, 1996; Hughes *et al.*, 1997; Murri *et al.*, 1997; O'Keefe *et al.*, 1996; Revicki *et al.*, 1995; Smith *et al.*, 1996; 1997; Wachtel *et al.*, 1991; Wu *et al.*, 1991). Similarly, HIV infection was found to be a strong predictor of health perception and pain in haemophilia patients infected with HIV as opposed to haemophilia patients who were HIV-negative, although these differences were considered to be smaller than expected (Djulbegovic *et al.*, 1996). We had expected to identify some relationships between HR-QoL and HIV status in our haemophilia patients but results from both questionnaires showed that HIV status was not a predictor of HR-QoL in this patient group. There are, however, several factors that could explain this result. Firstly, the two instruments may not be sufficiently sensitive to detect clinically important details that are important to patients infected with HIV. Although evidence suggests that this is not the case for the SF-36 (Wu *et al.*, 1991; 1997), to the best of our knowledge, the sensitivity of the EQ-5D to HIV infection has not been reported. Secondly, there may be an interaction between haemophilia status and HIV infection that lessens the influence of haemophilia status on HR-QoL or the influence of HIV infection on HR-QoL (Djulbegovic *et al.*, 1996). For example, HIV-seropositive haemophilia patients may get more counselling which might improve certain aspects of HR-QoL. Thirdly, approximately 60% of patients who received products derived from untreated large plasma pools prior to 1985 became infected with HIV (Mannucci, 1996). At the RFHHC 130 such cases were initially identified, but since this time approximately half this number have died. It is possible, therefore, that the 28 HIV-seropositive patients included in this analysis were those who have remained the most asymptomatic and who have derived the most benefit from the comprehensive care offered at our treatment centre, including full HIV counselling. This may have enabled many patients to come to terms with their infection and to reduce the impact of HIV infection on HR-QoL. However, and lastly, without knowing more about the HIV-infected patients who did not return their questionnaires it is difficult to know whether HIV serostatus is truly unrelated to HR-QoL in patients with severe haemophilia, because these patients may not have replied due to acute illness and our sample may thus be biased.

It was not possible to directly assess the impact of non-A non-B hepatitis (later known as HCV) infection on HR-QoL because all patients with severe haemophilia who were treated with products derived from untreated large plasma pools prior to 1985 became infected with HCV (Kernoff *et al.*, 1985). The effects of HCV infection could not, therefore, be isolated in this study. Moreover, it is likely that the impact of HCV infection on HR-QoL is likely to be confounded with age and treatment of patients, i.e. HCV-negative patients are likely to be young, on primary prophylaxis (if severe) or have very mild haemophilia.

In order to evaluate the impact of primary prophylaxis on HR-QoL, instruments are required that are sensitive to clinical change. The results from this analysis provide some evidence for the reliability and validity of the SF-36 as a measure of health status in patients with severe haemophilia. However, although results from the EQ-5D questionnaire were strongly correlated with results from the SF-36 questionnaire, Wolfe *et al.* (1997) believe that

the scaling on the EQ-5D$_{Profile}$ fails to capture many important rheumatic changes and that it does not reflect clinical rheumatic data accurately. These findings have important implications if the effectiveness of giving clotting factor prior to any signs of joint damage (primary prophylaxis) relative to treating on-demand is to be assessed using the EQ-5D$_{Profile}$ or the EQ-5D$_{Utility}$. For example, if a patient who has been treated on-demand develops a degree of knee damage he may state that he is currently experiencing 'some' problems walking about. However, if the knee continues to deteriorate but not sufficiently to confine the patient to bed, the most likely answer would again be in the 'some problems' check box. If this were the case, the effectiveness of treating on-demand would have been over stated. Similar permutations that would make primary prophylaxis appear less effective than it is likely to be can also be envisaged. The large grouping of patients in the 'some problems' grouping in our own study and the fact that haemophilia and normative patients were equally likely to fall into the 'worst' groupings goes some way to support this argument. For cross-sectional studies such as ours this means that many patients may appear to have similar levels of HR-QoL when compared to each other but are, in reality, clinically diverse. However, further research is needed to substantiate all these hypotheses.

With the use of the EQ-5D and SF-36 questionnaires we have shown that compared to the general population, patients with severe haemophilia A and B who were registered at the RFHHC experienced lower levels of HR-QoL; particularly in terms of decreased levels of mobility and increased levels of pain. This difference could not be explained by differences in age. However, because these data are cross-sectional they are currently limited in their use and further prospective analysis is needed to examine the effects of new methods of treatment on HR-QoL. Nevertheless, although these results show that these patients currently experience significantly decreased levels of HR-QoL, it is hoped that significant improvements in HR-QoL will be detected over time as the effects of (primary) prophylaxis begin to emerge.

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Assessing health-related quality-of-life in individuals with haemophilia

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Summary. The objectives of this study were to analyse current levels of health-related quality-of-life (HR-QoL) in individuals with severe haemophilia and to assess the scope for these levels to improve. To do this, 249 individuals with severe, moderate and mild haemophilia were asked to complete Medical Outcomes Study (MOS) Short-Form 36 (SF-36) and EuroQol (EQ-5D) questionnaires. Access was also gained to two appropriate normative data sets. The results from these questionnaires showed that HIV status, history of orthopaedic surgery and bleeding frequency in the previous calendar year were not strong predictors of HR-QoL for individuals with severe haemophilia. However, for the majority of scales, age was found to be a strong predictor of HR-QoL for this patient group. The results from the analysis also showed that compared to individuals with moderate/mild haemophilia and the UK male normative population, individuals with severe haemophilia generally recorded poorer levels of HR-QoL. These results suggest, therefore, that individuals with severe haemophilia have reduced levels of HR-QoL compared to individuals with moderate/mild haemophilia and the general population, irrespective of differences in age. The results also suggest that the scope for primary prophylaxis to increase HR-QoL in individuals with severe haemophilia is significant.

Keywords: quality-of-life, economics, primary prophylaxis.

There is a growing recognition that health-related quality-of-life (HR-QoL) considerations should play an important role in medical decision making. HR-QoL considerations are perhaps most relevant in clinical areas such as oncology and rheumatology where treatment may be palliative rather than curative, or may moderate the progression of a condition but have little or no effect on more traditional outcome measures such as mortality. Haemophilic arthritis (HA), which resembles progressive osteoarthritis [1], is thought to be the major cause of morbidity in individuals with severe haemophilia. However, very few HR-QoL data exist for this group of individuals [2, 3].

HR-QoL considerations can also be incorporated into certain types of economic evaluation [4]. Sculpher *et al.* emphasize that a preliminary economic evaluation of a health care programme should determine the size of the 'effectiveness-gap' [5]. That is, a preliminary economic evaluation should attempt to establish the effectiveness of the orthodox method of patient management so that the scope for improvement can be assessed. The implicit reasoning is the larger the effectiveness-gap, the greater is the likelihood that a replacement health care technology will prove to be cost-effective. The objectives of this study were therefore twofold. Firstly, to determine and to analyse current levels of HR-QoL in individuals with severe haemophilia who were registered at the Katharine Dormandy Haemophilia Centre (KDHC). Secondly, to assess the scope for primary prophylaxis to improve HR-QoL by comparing these

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levels to those recorded by individuals with moderate/mild haemophilia and by the general population.

Method

All individuals with mild (>5 IU dL^{-1}), moderate (1–5 IU dL^{-1}) and severe (<1 IU dL^{-1}) haemophilia A and B who were at least 18 years of age and who were solely registered at the KDHC were asked to complete Medical Outcome Study (MOS) Short Form 36 health survey (SF-36) [6] and EuroQol (EQ-5D) questionnaires [7]. Questionnaires were sent to individuals by post along with a covering letter; a prepaid envelope with which to reply was also enclosed with the questionnaires. Individuals who did not return the questionnaires within 4 weeks were sent a reminder and new copies of both questionnaires. No further reminders were sent.

The SF-36 and EQ-5D questionnaires are generic instruments that are used to compare HR-QoL within and between different clinical conditions. The SF-36 questionnaire was used because there is evidence to suggest that it is of value in assessing HR-QoL in nonhaemophilic patients with osteoarthritis [8, 9] and other rheumatoid conditions [10, 11]. The SF-36 questionnaire measures HR-QoL on eight multi-item dimensions: physical functioning, social functioning, physical and mental role limitations, mental health, energy/vitality, pain and general health perception. Results for each dimension are scored and transformed on to a scale from 0 (worst health) to 100 (best health). Results from the SF-36 can also be reported as a physical component summary scale (PCS) and as a mental component summary scale (MCS) [12]. Both summary scales were calculated by multiplying each of the eight individual SF-36 scores by their respective factor score coefficients, previously calculated from a large UK normative data set [13]. Finally, scores were standardized to a *t* score with a mean of 50 and a standard deviation of 10.

The EQ-5D health status questionnaire was used because it produces a HR-QoL utility score that can be used directly in economic evaluations. The results from the EQ-5D can either be displayed as an unweighted profile ($EQ\text{-}5D_{profile}$) or a single index ($EQ\text{-}5D_{utility}$) by applying a suitable weight to each health state. The EQ-5D also includes a visual analogue scale ($EQ\text{-}5D_{VAS}$) scored from 0 (worst imaginable health state) to 100 (best imaginable health state).

Data also used in the analyses included severity of haemophilia (severe, mild/moderate, no haemophilia), HIV status (+ve or −ve), patient age (as a continuous variable), history of corrective orthopaedic surgery (yes or no) and the number of bleeds individuals experienced in the previous calendar year (as a continuous variable). These data were collected from patients' treatment records.

Analysis

The analysis was divided into two separate parts. In the first part it was hypothesized that patient age, HIV status and severity of bleeding disorder, as expressed by previous history of orthopaedic surgery and the number of bleeds experienced in 1996 would all be significant predictors of HR-QoL for individuals with severe haemophilia. The majority of scores from both questionnaires were non-normally distributed so nonparametric tests for significance were used. Chi-squared tests were used to examine the relationship between results from the $EQ\text{-}5D_{Profile}$ and HIV status and orthopaedic history. Mann–Whitney *U*-tests were used to examine the relationship between both patient age, bleeding frequency and the results from the $EQ\text{-}5D_{Profile}$. For the SF-36 scales, $EQ\text{-}5D_{VAS}$ and $EQ\text{-}5D_{Utility}$, regression analysis was used to examine the relationship between computed scores and all four independent variables.

In the second part of the analysis it was hypothesized that compared to individuals with moderate/mild haemophilia and the general population, individuals with severe haemophilia were experiencing significantly decreased levels of HR-QoL. In order to test this hypothesis, comparisons were made between the completed EQ-5D questionnaires from the severe, moderate/mild individuals and UK EQ-5D normative data ($n = 1466$) for males only [14]. Statistical differences between the three sets of data were tested using Chi-squared and Fishers exact tests. In order to compare computed SF-36 scores for both patient groups with the UK normative male population [14], access was also gained to the original male normative data set ($n = 4229$). However, comparisons were initially restricted to a normative data set that consisted of male individuals who were aged between 35 and 44 years ($n = 993$–1009 for the 10 individual SF-36 scales). Statistical comparisons between the SF-36, $EQ\text{-}5D_{VAS}$ and $EQ\text{-}5D_{Utility}$ scores for individuals with severe, moderate\ mild haemophilia and the normative male population were tested for using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) in order to ascertain whether any differences could be explained by differences in age. All regression analyses were performed using the PROC GLM procedure contained in the Statistical Analysis System [15].

Differences in age between subgroups of individuals were tested for using two-tailed independent *t*-tests. Internal consistency for the SF-36 was tested for using Cronbach's alpha statistic and Spearman's rank correlation tests were used to examine correlation's between the EQ-$5D_{Utility}$, EQ-$5D_{VAS}$ and SF-36 scales.

Results

Response rate

Ninety-one individuals with severe haemophilia and 158 individuals with moderate/mild haemophilia were originally posted both HR-QoL questionnaires (total $n = 249$). One-hundred and sixty-eight (67%) individuals returned their questionnaires of whom 67 and 101 had severe haemophilia and moderate/mild haemophilia, respectively (Table 1). None of the individuals with severe or moderate/mild haemophilia had received primary prophylaxis with clotting factor. Individuals with severe haemophilia or moderate/mild haemophilia who returned their questionnaires were significantly older than individuals who did not reply; $P = 0.005$ and $P = 0.002$, respectively. Individuals with moderate/mild haemophilia who did return their questionnaires were also significantly older than individuals with severe haemophilia who returned their questionnaires ($P = 0.0006$). Three of the returned SF-36 questionnaires and two EQ-5D questionnaires were removed from the analysis because they were too incomplete. One individual with moderate haemophilia completed and returned the EQ-5D questionnaire but not the SF-36 questionnaire, hence the final EQ-5D analysis was based on 166 respondents and the SF-36 analysis was based on 164 respondents. Tests for internal consistency showed that the observed coefficients for the SF-36 scales exceeded usual standards for group comparisons; Cronbach's alpha scores ranged between 0.84 and 0.93.

Predictors of HR-QoL in individuals with severe haemophilia

Results from the EQ-5D questionnaire are shown in Table 2. For the EQ-$5D_{Profile}$, the majority of individuals with severe haemophilia reported having 'no' or 'some' difficulties for all five domains. Of the 52 individuals who reported at least 'some' problems with mobility, 47 (90%) also reported having at least 'some' pain.

None of the answers recorded on the EQ-$5D_{Profile}$, EQ-$5D_{VAS}$ or EQ-$5D_{Utility}$ was found to be significantly associated with HIV status, the number of bleeds patients experienced in 1996 or whether individuals had previously undergone orthopaedic surgery, in patients with severe haemophilia. However, all responses apart from the domain on the EQ-$5D_{Profile}$ that measured anxiety/depression ($P = 0.39$) and the EQ-$5D_{VAS}$ ($P = 0.076$), were found to be significantly associated with age; individuals who reported more severe problems tended to be older than those who reported no or some problems with their health.

The mean SF-36 scores and respective summary statistics for the severe individuals are shown in Table 3. Similar to the results obtained from the EQ-5D, none of the scores on the SF-36 health scales was statistically associated with bleeding history, orthopaedic history or HIV status. However, physical functioning ($P = 0.0001$), physical role limitation ($P = 0.01$) and the PCS ($P = 0.0001$) were all found to be significantly and negatively associated with increasing patient age (Table 4). None of the remaining SF-36 scales was found to be significantly

Table 1. Questionnaire response and nonresponse rate by demographic and clinical characteristics.

	Severe haemophilia (n = 91)		Mild or moderate haemophilia (n = 158)		
	Responders (%)	Nonrepsonders (%)	Responders (%)	Nonrepsonders (%)	*P*-values
Total	67 (27)	24 (10)	101 (40)	57 (23)	–
Haemophilia A	56 (83)	18 (75)	75 (74)	46 (81)	–
Haemophilia B	11 (16)	6 (25)	26 (26)	11 (19)	0.64
HIV +ve*	27 (40)	11 (46)	4 (4)	2 (2)	0.66
Undergone orthopaedic surgery	17 (25)	5 (21)	9 (9)	2 (4)	0.005
Mean age (years)	37.6 (SD 14.1)	29.4 (SD 9.4)	46.1 (SD 17.3)	36.6 (SD 15.0)	–
Median clotting factor level (IU dL^{-1})	0	0	9 (1–60)	10 (1–40)	

* HIV serostatus for five individuals with moderate/mild haemophilia was unknown.
Other than the totals row, percentages relate to the total number of individuals in each column.
P-values refer to differences between severe responders and severe nonresponders.

Table 2. EQ-5D questionnaire results and UK EQ-5D normative data [14].

Domain	Severe haemophilia n = 66 (%)	Moderate/mild haemophilia n = 100 (%)	General population n = 1466 (%)	P-value
Mobility				
No problems	14 (21.2)	73 (73.0)	1200 (81.9)	
Some problems	51 (77.3)	26 (26.0)	263 (17.9)	
Confined to bed	1 (1.5)	1 (1.0)	3 (0.2)	< 0.001
Self-care				
No problems	45 (68.2)	92 (92.0)	1401 (95.6)	
Some problems	21 (31.8)	7 (7.0)	62 (4.2)	
Unable to	0 (0)	1 (1.0)	3 (3.0)	< 0.001
Usual activities				
No problems	27 (40.9)	74 (74.0)	1233 (83.5)*	
Some problems	37 (56.1)	21 (21.0)	198 (13.5)	
Unable to	2 (3.0)	5 (5.0)	44 (3.0)	< 0.001
Pain/discomfort				
None	11 (16.7)	57 (57.0)	1002 (68.4)*	
Moderate	52 (78.8)	36 (36.0)	408 (27.8)	
Extreme	3 (4.5)	7 (7.0)	55 (3.8)	< 0.001
Anxiety/depression				
None	44 (66.7)	68 (68.0)	1207 (82.3)	
Moderate	21 (31.8)	31 (31.0)	226 (15.4)	
Extreme	1 (1.5)	1 (1.0)	33 (2.3)	< 0.001
Median EQ-$5D_{Utility}$ (range)	0.66 (–0.48–1.00)	0.85 (–0.17–1.00)	1.00 (–0.23–1.00)	
Median EQ-$5D_{VAS}$ (range)	70 (20–98)	80 (23–100)	90 (5–100)	

*n = 1465.

All P-values were calculated using Fishers Exact test and relate to comparisons across all three groups of individuals.

associated with age. A high degree of correlation (P = 0.0001) was also found between the physical functioning and bodily pain scores.

HR-QoL comparisons between groups

Results from all three sections of the EQ-5D questionnaire showed that compared to the UK general population, individuals with severe haemophilia experienced significantly lower levels of HR-QoL (Table 2). Apart from the domain on the EQ-$5D_{Profile}$ that measured anxiety/depression (P = 0.95), when compared to individuals with moderate/mild haemophilia, individuals with severe haemophilia again recorded significantly lower scores on all three sections of the EQ-5D questionnaire. Noticeably, however, irrespective of haemophilia status (i.e. severe, moderate/mild or normative), very few individuals scored the levels on the EQ-$5D_{Profile}$ that reflected 'most' difficulty.

With the exception of the mental health scale (P = 0.20) and the MCS (P = 0.11), individuals

Table 3. Haemophilia SF-36 mean scores compared with a male subset from the Oxford Healthy Lifestyles Survey [13].

	Severe haemophilia (n = 65)			Moderate \ mild haemophilia (n = 99)				
SF-36 Scale	Mean (SD)	% Floor	% Ceiling	Mean (SD)	% Floor	% Ceiling	Normative Mean (SD)	P-value
Physical functioning	53.8 (31.1)	3.1	7.7	67.9 (37.6)	13.9	25.7	91.9 (14.5)	0.0001
Role physical	58.1 (42.6)	29.2	40.0	81.2 (33.6)	9.9	70.3	89.5 (25.5)	0.0001
Bodily pain	57.7 (21.7)	0.0	0.0	76.8 (28.5)	1.0	43.6	85.6 (19.7)	0.0001
General health perception	46.8 (24.7)	0.0	3.1	64.1 (23.6)	1.0	7.1	74.1 (18.5)	0.0001
Energy/vitality	55.0 (20.4)	0.0	4.6	61.4 (24.8)	3.0	3.0	63.5 (18.6)	0.0004
Social functioning	70.4 (28.0)	1.5	27.7	79.9 (27.5)	2.0	49.5	90.5 (17.0)	0.0001
Role emotional	74.9 (39.5)	16.9	67.7	86.1 (31.0)	8.9	80.2	86.0 (28.6)	0.0125
Mental health	72.9 (15.7)	0.0	1.5	74.0 (18.7)	0.0	6.1	75.0 (16.1)	0.19
PCS	31.9 (14.8)	–	–	43.2 (13.8)	–	–	52.0 (8.58)	0.0001
MCS	52.5 (11.1)	–	–	53.2 (11.9)	–	–	51.4 (9.85)	0.62

All P-values were calculated using ANOVAS and relate to comparisons across all three groups of individuals.

Table 4. Univariate regression analysis between SF-36 scales, EQ-$5D_{Utility}$ and EQ-$5D_{VAS}$ for individuals with severe haemophilia, with regard to age.

Scale	Reg. coef.	95% CI	*P*-value
Physical functioning	− 1.28	(−1.71 to −0.85)	0.0001
Role physical	− 0.94	(−1.65 to −0.23)	0.011
Bodily pain	− 0.20	(−0.57 to 0.17)	0.29
General health perception	− 0.42	(−0.83 to −0.01)	0.051
Energy/vitality	− 0.27	(−0.62 to 0.08)	0.13
Social functioning	− 0.26	(−0.74 to 0.22)	0.29
Role emotional	− 0.29	(−0.98 to 0.40)	0.41
Mental health	0.064	(−0.21 to 0.28)	0.65
PCS	− 0.50	(−0.72 to −0.28)	0.0001
MCS	0.094	(0.01 to 0.03)	0.34
EQ-$5D_{Utility}$	− 0.005	(−0.002 to −0.009)	0.005
EQ-$5D_{VAS}$	− 3.02	(−3.57 to 2.97)	0.076

with severe haemophilia consistently reported significantly lower levels of HR-QoL compared to the UK general male population as measured by the SF-36 (Table 3). Multiple regression analysis also revealed that the remaining eight statistically significant relationships were independent of age; differences in HR-QoL between the two populations could not be explained by differences in age alone.

Other than the mental health ($P = 0.32$), emotional role limitation (0.055) and the MCS ($P = 0.97$) scales, individuals with severe haemophilia also recorded significantly lower scores on the SF-36 scales compared to individuals with moderate/mild haemophilia. With the exception of the energy/vitality, social functioning scales and the MCS, multiple regression analysis again revealed that statistically significant differences in scores were independent of age.

The domains on the EQ-$5D_{Profile}$ that measured self-care ($P = 0.93$) and usual activities ($P = 0.51$) aside, the analysis showed that individuals with moderate/mild haemophilia recorded significantly lower levels of HR-QoL than the general male population. Similarly, other than the scales that measured bodily pain ($P = 0.45$), energy/vitality ($P = 0.72$), emotional role limitation ($P = 0.43$), mental health ($P = 0.55$) and the MCS ($P = 0.51$), the SF-36 scores recorded by individuals with moderate/mild haemophilia were also significantly reduced compared to the normative population. However, multiple regression analysis revealed that only the relationships with physical functioning, physical role limitation and the PCS scores were independent of age.

Correlation between EQ-5D and SF-36 results

Both the EQ-$5D_{Utility}$ and EQ-$5D_{VAS}$ showed statistically significant correlations with all the individual SF-36 scales and with each other (Table 5).

Discussion

The aim of this study was to assess HR-QoL in individuals with haemophilia who were registered at the KDHC and to assess the scope for these levels to improve. In order to do this, 249 individuals with severe, moderate and mild haemophilia were posted SF-36 and EQ-5D questionnaires. Results from these questionnaires showed that HIV status, history of orthopaedic surgery and bleeding frequency in the previous calendar year were not strong predictors of HR-QoL for individuals with severe haemophilia. However, for the majority of scales, age was found to be a strong predictor of HR-QoL for this patient group. The results from the analysis also showed that

Table 5 Correlations between EQ-5D and SF-36 scores in all individuals with haemophilia.

SF-36 scale	EQ-$5D_{Utility}$ *R*	95% CI	*P*-value	EQ-$5D_{VAS}$ *R*	95% CI	*P*-value
Physical functioning	0.59	0.48–0.68	0.0001	0.59	0.48–0.68	0.0001
Role physical	0.50	0.38–0.61	0.0001	0.49	0.38–0.61	0.0001
Bodily pain	0.80	0.74–0.85	0.0001	0.80	0.74–0.85	0.0001
General health perception	0.69	0.60–0.77	0.0001	0.77	0.71–0.83	0.0001
Energy/vitality	0.62	0.52–0.71	0.0001	0.63	0.53–0.71	0.0001
Social functioning	0.70	0.61–0.77	0.0001	0.59	0.48–0.69	0.0001
Role emotional	0.33	0.19–0.46	0.0001	0.35	0.21–0.48	0.0001
Mental health	0.44	0.31–0.56	0.0001	0.50	0.38–0.61	0.0001
PCS	0.74	0.67–0.80	0.0001	0.54	0.42–0.64	0.0001
MCS	0.33	0.19–0.46	0.0001	0.27	0.27–0.55	0.0001
EQ-$5D_{Utility}$	–	–	–	0.67	0.58	0.0001

R is the Spearman rank correlation coefficient.

compared to individuals with moderate/mild haemophilia and the UK male normative population, individuals with severe haemophilia generally recorded poorer levels of HR-QoL irrespective of age differences. The latter comparisons were particularly large and would be both subjectively and clinically meaningful [16].

The SF-36 scores recorded by individuals with severe haemophilia were similar to those found by Djulbegovic *et al.* [2] and Szucs *et al.* [17]. However, in our study we were able to directly control for age and haemophilia status by gaining access to two large normative data sets.

Primary prophylaxis has only recently become treatment policy at the KDHC, therefore the majority of individuals with severe haemophilia included in this study are likely to have already developed HA. These results are therefore consistent with our prior expectation and with the results of other studies [2, 17, 18]. However, the extent to which joint damage affects the intensity of pain and the degree of mobility as recorded by both questionnaires can not be deduced from our data because a clinical patient assessment was not performed.

Results from other studies have previously demonstrated that HR-QoL in nonhaemophilia patients is significantly lowered by the presence of HIV infection [19–21]. For example, the study by O'Keefe and colleagues showed that individuals who were HIV seropositive recorded significantly ($P < 0.01$) lower scores on all eight SF-36 scales when compared to a control group of HIV seronegative individuals [19]. Similarly, HIV infection was found to be a strong predictor of health perception and pain using the SF-36 in HIV seropositive haemophiliacs as opposed to HIV seronegative haemophiliacs, although these differences were considered to be smaller than expected [2]. We had therefore expected to identify some relationships between HR-QoL and HIV serostatus in our haemophilia patients. However, results from both questionnaires showed that HIV status was not a strong predictor of HR-QoL in this patient group. There are several factors that could explain this result. Firstly, the two HR-QoL instruments may not be sufficiently sensitive to detect clinical details that are important to individuals infected with HIV. Although evidence suggests that this is not the case for the SF-36 [21], to the best of our knowledge the sensitivity of the EQ-5D to HIV infection has not been reported. Secondly, it may be the case that the summed effects of HIV infection and haemophilia on HR-QoL are not purely additive. That is, there may be an interaction between haemophilia status and HIV infection that lessens the influence of haemophilia status on HR-QoL or the influence of HIV infection on HR-QoL [2]. Such interactions may help to explain why in our study differences in HR-QoL, as measured using the mental health scale of the SF-36, between individuals with severe haemophilia who were HIV seropositive and the general population were insignificant ($P = 0.20$). Thirdly, approximately 60% of haemophiliacs who received products derived from untreated large plasma pools prior to 1985 became infected with HIV [22]. At the KDHC 130 such cases were initially identified, but since this time approximately half this number have died. It is possible therefore that the 27 HIV seropositive individuals with severe haemophilia who were included in the analyses were those who have remained the most asymptomatic and who have derived the most benefit from the comprehensive care offered at the KDHC, including full HIV counselling. This may have enabled some individuals to come to terms with their infection and to reduce the impact of HIV infection on HR-QoL. However, and lastly, without knowing more about the 11 HIV infected patients who did not return their questionnaires, it is difficult to know whether HIV serostatus is truly unrelated to HR-QoL in patients with severe haemophilia because these individuals may not have replied due to acute illness.

Episodes of bleeding are thought to be painful and debilitating but surprisingly on no occasion was bleeding frequency found to be a strong predictor of HR-QoL. Moreover, although the data are not presented here, when specific types of bleeds were considered separately (i.e. joint or muscle bleeds), still no statistically significant relationships with HR-QoL were found. There are, however, several factors that could explain these findings. Firstly, the questionnaires were posted between March and April 1997 whereas the bleeding data referred to the total number of bleeds individuals experienced during 1996. The version of the SF-36 questionnaire used in this study asks individuals to consider their health over the previous 4 weeks whereas the EQ-5D questionnaire asks individuals to consider their health at the moment of responding. It is feasible therefore that any short-term effects on HR-QoL that were caused by episodes of bleeding (such as swelling) may have subsided by the time the questionnaires were completed. Thus, no significant relationships were found between bleeding frequency and any of the HR-QoL scales because the data on bleeding frequency did not relate to an appropriate time period. Secondly, it is feasible that through the use of home treatment and the increased availability of clotting factor, individuals are now able to treat

episodes of bleeding more quickly and successfully than was once possible, which may have in turn reduced any short-term effects of bleeding on HR-QoL. Arguably a better method of assessing the relationship between disease progression and HR-QoL would be to correlate HR-QoL scores with the results from a clinical assessment of patients' joints rather than bleeding frequency.

If individuals with severe haemophilia develop chronic haemophilic arthropathy, they may be offered the option of undergoing corrective orthopaedic surgery such as an arthrodesis or a total joint replacement. As with bleeding history however, the analysis showed that history of orthopaedic surgery (yes/no) was not a strong a predictor of HR-QoL as measured by any of the SF-36 or EQ-5D scales. There are several factors that might explain these results. Firstly, although surgery may alleviate pain and aid the functioning of one specific joint, it is feasible that individuals may have developed haemophilic arthropathy in other joints concurrently. In such instances, any increase in HR-QoL that might have resulted from surgery may have been reduced as the patient was still contending with other health-related issues. Secondly, successful operations might have alleviated much of the pain and immobility caused by the initial joint defect. Thirdly, it might be the case that some individuals declined corrective surgery despite being clinically indicated. If this were indeed true, the value of history of orthopaedic surgery as a predictor of HR-QoL would certainly be reduced. Lastly, no account was made for the reason for surgery because this was difficult to do accurately in retrospect. Individuals may therefore have undergone orthopaedic surgery due to a nonhaemophilia related event, which may again account for the lack of statistical relationship between history of orthopaedic surgery and HR-QoL.

Although the impact of asymptomatic HCV infection on HR-QoL is unclear, there is a strong association between chronic HCV infection, fatal liver diseases such as hepatocellular cancer and decreased levels of HR-QoL. However, it was not possible to directly assess the impact of HCV infection on HR-QoL because all individuals with severe haemophilia who were treated with products derived from untreated large plasma pools prior to 1985 became infected with HCV [23]; thus the direct affects of HCV infection could not be isolated. Irrespective of this problem, the impact of HCV infection on HR-QoL in these individuals is likely to be confounded with age and method of treatment, i.e. HCV negative individuals are likely to be young, on primary prophylaxis (if severe) or have very mild haemophilia. Additionally, it was not possible to evaluate the affect of secondary prophylaxis on HR-QoL because nearly all adults registered at the KDHC were receiving secondary prophylaxis as at the time the questionnaires were posted.

The aim of (primary) prophylaxis with clotting factor is to prevent bleeding episodes and their associated sequelae from occurring by converting severe haemophilia into a moderate/mild form of the disease. A prerequisite for cost-effectiveness is that a treatment is at least as effective as the programme it is ultimately seeking to replace. The results from other studies suggest that prophylactic clotting factor regimes can reduce the number of bleeds experienced by individuals with severe haemophilia, thus this necessary but not sufficient criteria for cost-effectiveness has been satisfied. However, because of the large cost associated with primary prophylaxis, if it is to hold any possibility of being cost-effective, the scope for treatment to improve effectiveness must also be high. The results from this analysis showed that differences in HR-QoL between individuals with severe and moderate/mild haemophilia were, in the most part, subjectively large and statistically significant, meaning that the scope for increasing HR-QoL in individuals with severe haemophilia is indeed high. Therefore, the capacity for prophylaxis to be a cost-effective use of resources does exist despite its high cost.

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Primary prophylaxis for individuals with severe haemophilia: how many hospital visits could treatment prevent?

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Abstract. Miners AH, Sabin CA, Tolley KH, Lee CA (Royal Free Hospital School of Medicine, London; University of Nottingham, Nottingham; and Royal Free Hampstead NHS Trust, London, UK). Primary prophylaxis for individuals with severe haemophilia: how many hospital visits could treatment prevent? *J Intern Med* 2000; **247**: 000–000.

Objectives. To assess how many hospital visits primary prophylaxis with clotting factor could prevent.

Design. The potential for reducing hospital visits was assessed by comparing rates of in-patient, Out-patient and day-case visits per patient-year for individuals with severe (< 1 IU dL^{-1}) haemophilia who had never received primary prophylaxis with attendance rates for individuals with mild/moderate (1–50 IU dL^{-1}) haemophilia. Hospital attendance data were collected retrospectively for the period 1988–97 inclusive for individuals who were aged 18 years or over.

Setting. Data were obtained on patients who were registered at the Katharine Dormandy Haemophilia Centre (KDHC), London, UK.

Outcome measures. In-patient stays, Out-patient and day-case visits.

Results. Individuals with mild/moderate haemophilia were 45 (31–56), 36 (30–41) and 70% (68–73) less likely to have required in-patient, Out-patient and day-case visits than were individuals with severe haemophilia. HIV serostatus and age were also shown to be significant and independent predictors of the rate of Out-patient and day-case visits, but not the rate of in-patient stays.

Conclusion. These results suggest that primary prophylaxis for individuals with severe haemophilia could significantly reduce the demand for in-patient stays, and Out-patient and day-case visits.

Keywords: day case, haemophilia, in-patient, Out-patient, prophylaxis.

Introduction

The rationale for primary prophylactic treatment in haemophilia was the observation that chronic arthropathy was less frequent and less severe in patients with moderate haemophilia (i.e. factor VIII or IX concentrations between 1 and 4% of normal) than in those with severe haemophilia (i.e. factor VIII/IX concentrations < 1% of normal) [1]. When individuals with severe haemophilia develop chronic haemophilic arthropathy or experience particularly severe episodes of bleeding, in addition to treatment with clotting factor, they may require the input of additional medical resources in an attempt to reduce or correct the problem. These additional resources may include Out-patient visits, day-case visits or even in-patient stays. It is conceivable therefore that if primary prophylaxis can reduce the incidence of bleeding and secondary degenerative orthopaedic change, in addition to improving HR-QoL [2], the demand for some health care resources might also be reduced [3].

The ability of primary prophylaxis to reduce the consumption of some health care resources is used as an argument to favour its use in preference to treating individuals on demand [4]. For example, Szucs *et al.* [5] stated that the 'true' economic benefit of primary prophylaxis lies in the avoidance of in-

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patient stays. However, very few studies have attempted to quantify the medical resources used by individuals with severe haemophilia other than clotting factor requirements whether treated on demand or with (primary) prophylaxis [6, 7]. Moreover, of the published studies, none has reported UK-specific resource data and only Smith *et al.* [7] have reported disaggregated medical resource data in any real detail.

The optimal method of assessing the way in which primary prophylaxis versus treatment on demand affects resource consumption would be to perform a comparative study. However, primary prophylaxis has only been introduced at the Katharine Dormandy Haemophilia Centre (KDHC) in more recent years and a prospective study would take several decades to yield any useful data. Therefore, we examined the extent to which primary prophylaxis could reduce the frequency of hospital visits rather than reductions in hospital visits following the introduction of prophylaxis *per se*.

Methods

Medical resource use was assessed by comparing rates of in-patient, Out-patient (clinic) and day-case visits per patient-year for individuals with severe (< 1 IU dL^{-1}) haemophilia who had never received primary prophylaxis with attendance rates for individuals with mild/moderate (1–50 IU dL^{-1}) haemophilia. A day-case episode is a hospital visit where the patient is planned to be, and is, admitted, treated and discharged on the same day. Additionally, differences in the rate of orthopaedic procedures and joint replacements were also assessed, as these procedures are arguably the most common and costly sequelae of repeated joint bleeding [8]. The null hypothesis was that there were no significant differences between individuals with severe haemophilia and mild/moderate haemophilia in terms of these resource requirements.

Data collection

In-patient, Out-patient and day-case data were collected for all individuals who were aged 18 years or over who had been registered for treatment at the KDHC for at least 1 patient-year and who were alive on 31 December 1997 ($n = 246$, Table 1). The data were collected retrospectively for the period 1988–97 inclusive from the patient admissions system (PAS) and from patients' medical notes.

Analysis

Attendance rates were calculated for each type of hospital attendance by dividing the number of visits made by patients into the sum of the relevant patient-years of follow-up. Patient follow-up was calculated as the time between the date of registration at the KDHC or 1 January 1988 (whichever occurred last) and 31 December 1997.

Orthopaedic procedures were defined as joint replacements, arthrodeses, synovectomies, O'Donoghue's procedures, ulnar nerve decompressions, excision of radial heads and other miscellaneous orthopaedic procedures. Joint replacements included revisionary procedures and age was taken at 31 December 1997. Poisson regression techniques were used to perform significance tests of the differences in hospital attendance rates between subgroups of patients. Regression analysis was used to examine the relationships between severity of haemophilia, age and HIV serostatus on the length of in-patient stays (LOIS).

Results

Over a total of 2187 patient-years, 246 individuals attended 424 in-patient, 4091 Out-patient and 2757 day-case appointments, and underwent a total of 50 orthopaedic procedures. These individuals also required a total over 3500 days as in-patients over this period (Table 2).

In-patient visits

On average, individuals with haemophilia required 0.20 (95% CI = 0.18–0.21) in-patient visits per patient-year (Table 2) or one in-patient admission once every 5.00 (4.76–5.56) patient-years. Univariate Poisson regression analysis revealed that individuals with mild/moderate haemophilia were almost half (rate ratio of 0.54, 95% CI = 0.52–0.64) as likely to have required an in-patient visit as individuals with severe haemophilia ($P = 0.0001$) (Table 3). Univariate analyses also revealed that both age ($P = 0.02$) and HIV serostatus ($P = 0.0002$) were associated with an increased rate of in-patient admissions. However, when all

Table 1 Patient details

	Haemophilia	
	Mild/moderate	Severe
n	155	91
Median clotting factor level (range) [IU dL^{-1}]	10 (1–50)	0 (0–0)
Age (on 31/12/97)	40 (18–94)	34 (18–80)
HIV+ (%)	4 (3)	38 (42)
Median follow-up period (range) [years]	10 (1–10)	10 (1–10)

three independent variables were fitted together, only severity remained an independent predictor of in-patient visits ($P = 0.0001$) (Table 4). That is, once differences in the severity of haemophilia were controlled for, age and HIV serostatus no longer remained independently associated with the rate of in-patient stays. Moreover, fitting both age and HIV serostatus separately in bivariate models with severity made little difference to their predictive values ($P = 0.46$ and 0.92, respectively).

Similarly, results from the multivariate analysis showed that severity, age and HIV serostatus were all independent predictors of the LOIS ($P = 0.0001$ for all three independent variables). However, individuals who were HIV-seropositive required significantly fewer in-patient days than individuals who were HIV-seronegative.

Univariate analyses showed that severity of haemophilia was a significant predictor of the rate of orthopaedic operations ($P = 0.00011$). Individuals

Table 2 Rates of hospital attendance

	Total events	Total patient-years	Rate	95% CI
All patients (n = 246)	7272	2187	3.30	3.25–3.40
In-patient	424	2187	0.20	0.18–0.21
LOIS (days)	3690	2187	1.69	1.51–1.87
Out-patient	4091	2187	1.87	1.81–1.93
Day case	2757	2187	1.26	1.21–1.31
Mild/moderate haemophilia (n = 155)	2916	1352	2.16	2.07–2.24
In-patient	204	1352	0.15	0.13–0.17
LOIS (days)	1723	1352	1.27	1.22–1.32
Orthopaedic operations	16	1352	0.012	0.002–0.018
Joint replacements	5	1352	0.004	0.001–0.009
Out-patient	1790	1352	1.32	1.26–1.39
Day case	922	1352	0.68	0.64–0.73
Severe haemophilia (n = 91)	4356	835	5.10	4.90–5.30
In-patient	220	835	0.26	0.23–0.30
LOIS (days)	1967	835	2.36	2.32–2.40
Orthopaedic operations	34	835	0.04	0.025–0.055
Joint replacements	15	835	0.02	0.01–0.03
Out-patient	2301	835	2.76	2.64–2.86
Day case	1835	835	2.20	2.10–2.30
HIV + severe haemophilia (n = 38)	2072	369	5.60	5.40–5.90
In-patient	106	369	0.29	0.23–0.34
Out-patient	1102	369	3.00	2.80–3.20
Day case	864	369	2.30	2.20–2.50
HIV-severe haemophilia (n = 53)	2284	466	4.90	4.70–5.10
In-patient	114	466	0.24	0.20–0.29
Out-patient	1199	466	2.60	2.40–2.70
Day case	971	466	2.10	1.95–2.21

LOIS, length of in-patient stay.

Table 3 Univariate Poisson regression analysis on hospital attendances

	Severity (mild/moderate versus severe)[a]			Age (per year)			HIV (positive versus negative)[b]		
	RR	CI	*P*-value	RR	CI	*P*-value	RR	CI	*P*-value
In-patient	0.54	0.52–0.64	0.0001	0.99	0.99–0.99	0.024	1.52	1.22–1.90	0.0002
LOIS (days)	0.50	0.48–0.52	0.0001	0.99	0.99–0.99	0.0001	1.22	1.17–1.55	0.0001
Orthopaedic operations	0.34	0.19–0.61	0.0003	0.99	0.97–1.00	0.31	1.28	0.66–2.51	0.47
Joint replacement	0.70	0.61–0.81	0.0001	0.99	0.98–0.99	0.0001	1.36	1.15–1.62	0.0004
Out-patient	0.56	0.55–0.59	0.0001	0.99	0.98–0.99	0.0001	1.72	1.60–1.84	0.0001
Day case	0.31	0.28–0.33	0.0001	1.00	0.99–1.00	0.92	2.18	2.01–2.36	0.0001

RR, relative rate; LOIS, length of in-patient stay.
[a]Figures relate to the RR of a hospital visit for individuals with mild/moderate haemophilia compared with individuals with severe haemophilia.
[b]Figures relate to the RR of a hospital visit for individuals who are HIV-seronegative compared with individuals who are HIV-seropositive.

with mild/moderate haemophilia were 0.34 (0.19–0.61) times as likely to have undergone musculoskeletal procedures per patient-year than were individuals with severe haemophilia. However, multivariate regression analysis showed that once admitted for surgery, there were no significant differences in the LOIS between individuals with severe haemophilia and those with mild/moderate haemophilia despite differences in age and HIV serostatus.

No significant relationships were found between either age ($P = 0.31$) or HIV serostatus ($P = 0.47$) and the rate of orthopaedic operations. Severity of haemophilia ($P = 0.0001$), age ($P = 0.0001$) and HIV serostatus ($P = 0.0004$) all strongly predicted the rate of joint replacements per patient-year in univariate analyses. Severity of haemophilia and age remained associated with joint replacements in a multivariate model, however, when simultaneous adjustments were made for severity of haemophilia and age, HIV serostatus no longer remained a significant predictor of the rate of joint replacements ($P = 0.49$).

Out-patient visits

The analysis showed that individuals with haemophilia required 1.87 (1.81–1.93) Out-patient visits per patient-year or once every 0.53 (0.52–0.55) patient-years (Table 2). Individuals with mild/moderate haemophilia attended significantly ($P = 0.0001$) fewer Out-patient visits per patient-year than individuals with severe haemophilia (rate ratio of 0.56 [0.55–0.59]) (Table 3). Univariate analyses also revealed that both age and HIV serostatus were significant predictors of the rate of Out-patient visits ($P = 0.0001$ for both comparisons). Indeed, individuals who were HIV-seropositive were 1.72 (1.60–1.84) times more likely to have attended an Out-patient visit than individuals who were HIV-seronegative. Further multivariate Poisson analysis revealed that all three variables

Table 4 Multivariate Poisson regression analysis on hospital attendances

	Severity (mild/moderate versus severe)[a]			Age (per year)			HIV (positive versus negative)[b]		
	RR	CI	*P*-value	RR	CI	*P*-value	RR	CI	*P*-value
In-patient	0.55	0.44–0.69	0.0001	0.99	0.99–1.00	0.47	0.99	0.77–1.30	0.98
LOIS (days)	0.48	0.45–0.49	0.0001	0.99	0.99–0.99	0.0001	0.70	0.67–0.74	0.0001
Joint replacement	0.77	0.64–0.92	0.004	0.99	0.99–1.00	0.006	1.07	0.87–1.35	0.49
Out-patient	0.64	0.59–0.69	0.0001	0.99	0.99–0.99	0.0001	1.11	1.21–1.32	0.0001
Day case	0.30	0.27–0.33	0.0001	1.01	1.01–1.12	0.0001	1.19	0.93–1.31	0.0003

RR, relative rate; LOIS, length of in-patient stay.
[a]Figures relate to the RR of a hospital visit for individuals with mild/moderate haemophilia compared with individuals with severe haemophilia.
[b]Figures relate to the RR of a hospital visit for individuals who are HIV-seronegative compared with individuals who are HIV-seropositive.

were independent predictors of the rate of Out-patient visits (Table 4). Thus, individuals with severe haemophilia attended significantly more Out-patient visits per patient-year than did individuals with mild/moderate haemophilia irrespective of differences in age and HIV serostatus.

Day-case visits

On average, individuals with haemophilia attended 1.26 (1.21–1.31) day-case visits per patient-year or once every 0.79 (0.76–0.83) patient-years (Table 2). Univariate analysis showed that haemophilia severity ($P = 0.0001$) and HIV serostatus ($P = 0.0001$) were both significant predictors of the rate of day-case appointments but that age was unrelated ($P = 0.92$) (Table 3). For example, individuals who were HIV-seropositive were more than twice (rate ratio of 2.20 [2.00–2.36]) as likely to have attended a day-case appointment as individuals who were seronegative. Multivariate analysis revealed that severity of haemophilia, HIV serostatus and age were all significant and independent predictors of the rate of day-case visits ($P = 0.0001$). This apparent anomaly with the age effect in the univariate and multivariate models was examined further by considering the effect of age on the rate of day-case visits for individuals with severe and mild/moderate haemophilia separately. When these two analyses were performed, individuals with severe haemophilia were found to require progressively more day-case visits per patient-year with increasing age, whereas individuals with mild/moderate haemophilia were found to require progressively fewer visits. Thus, age was only found to be a significant predictor of the rate of day-case visits when adjustments for haemophilia severity were also made (Table 4).

Discussion

Available evidence suggests that primary prophylaxis with clotting factor may prevent episodes of bleeding and, consequently, the onset and development of secondary degenerative orthopaedic change [9]. Therefore, in addition to preserving health-related quality of life, primary prophylaxis may also reduce the demand for medical resources such as in-patient stays, and Out-patient and day-case visits. As the aim of primary prophylaxis is to 'convert' severe haemophilia into a mild/moderate form of the condition, we examined the extent to which primary prophylaxis could reduce the frequency of hospital visits by comparing differences in hospital attendance rates between these two groups of patients.

The results from the analysis showed that individuals with mild/moderate haemophilia were 45 (31–56), 36 (30–41) and 70% (68–73) less likely to have required in-patient, Out-patient and day-case visits than individuals with severe haemophilia. Moreover, the results also showed that individuals with mild/moderate haemophilia were 66 (39–81) and 23% (8–36) less likely to have undergone orthopaedic procedures and joint replacements, respectively, compared with individuals with severe haemophilia. HIV serostatus and age were also shown to be significant and independent predictors of the rate of Out-patient and day-case visits, but not the rate of in-patient stays. These results suggest, therefore, that individuals with severe haemophilia required significantly higher rates of in-patient visits, Out-patient visits, day-case visits, orthopaedic operations and joint replacements than the individuals with mild/moderate haemophilia irrespective of age differences between the two groups and HIV serostatus. Thus, it follows that primary prophylaxis for individuals with severe haemophilia could significantly reduce the demand for these resources. However, although individuals with severe haemophilia required longer in-patient stays than individuals with mild/moderate haemophilia per patient-year, once admitted, the LOIS did not differ significantly between the two patient groups despite adjusting for differences in age and HIV serostatus. Thus, although primary prophylaxis may reduce the frequency of in-patient visits, these data suggest that it is unlikely to affect the length of each visit should such a visit be required.

It is generally believed that individuals with severe haemophilia experience decreased levels of physical functioning compared with individuals with mild/moderate haemophilia [2, 10]. This belief is supported by our finding that hospital attendance rates were significantly lower for individuals with mild/moderate haemophilia than for individuals with severe haemophilia. There are, however, a number of limitations to our data. Firstly, secondary prophylaxis denotes prophylaxis with clotting factor started after the onset of serial bleeding when joint damage is already manifest. A number of publica-

tions have demonstrated that this form of prophylaxis with clotting factor can reduce bleeding frequency [11, 12]. At the time of data collection, over 90% of individuals at the KDHC with severe haemophilia were known to be receiving secondary prophylaxis. Thus, it is possible that this method of treatment has already helped to reduce the short-term need for medical resources in the form of Out-patient and day-case appointments. In the absence of this treatment, we might expect even larger reductions in these attendance rates. Additionally, policy at the KDHC is to review individuals with severe haemophilia and mild/moderate haemophilia biannually and annually, respectively, on an Out-patient basis. Therefore, irrespective of any problems individuals with severe haemophilia may develop, we would expect them to have attended hospital on an Out-patient basis more frequently than individuals with mild/moderate haemophilia. Lastly, it is probable that, for the majority of the time, primary prophylaxis 'converts' severe haemophilia into a moderate form of the condition rather than a mild form. However, the number of individuals with moderate haemophilia who were included in our study was too small for these individuals to be included in the analyses as a separate patient group. Our results might therefore overstate the potential for primary prophylaxis to reduce hospital visits.

There were also a number of limitations to our attendance data. The attendance data only included booked hospital visits and may not have included informal or impromptu visits by patients. Thus, total hospital attendance rates and differences in hospital attendance rates between subgroups of individuals might be larger than these data suggest. The data also do not take into account the quantity of resources consumed during these visits. For example, individuals with severe haemophilia might consume larger volumes of clotting factor than individuals with mild/moderate haemophilia per in-patient stay. Lastly, the timing of Out-patient and day-case visits is likely to be determined by members of staff at the KDHC. It is feasible therefore that differences in these rates of hospital visits between the two patient groups were due to the medical staff's views that individuals with severe haemophilia *should* be seen more often rather than on the basis of clinical need.

There are few other published empirical studies for comparison. However, Smith *et al.* [7] calculated that individuals in the US with severe haemophilia (< 2 IU dL^{-1}) underwent an average of two orthopaedic procedures during a 50-year at-risk period or, equivalently, once every 0.04 patient years. Our analysis also showed that individuals with severe haemophilia underwent orthopaedic procedures once every 0.04 (0.025–0.055) patient-years. However, in contrast to Smith *et al.* we used a much broader definition of surgery and included data for individuals who were more than 18 years old.

In order to isolate the effects of severity of haemophilia on resource use, it was necessary to remove the potentially confounding effects of HIV infection. In the majority of instances, the analysis showed that HIV serostatus often significantly and independently predicted resource use. However, HIV serostatus was not found to be significantly associated with the rate of in-patient stays, although this lack of association was probably because our data were not collected for individuals who had died before 31 December 1997. The omission of this patient group from the analysis may also explain why the LOIS in this analysis was significantly shorter for individuals who were HIV-seropositive than for individuals who were HIV-seronegative. It was not possible to directly assess the impact of HCV infection on resource use because all individuals with severe haemophilia and many with mild/moderate haemophilia who were treated with products derived from untreated large plasma pools prior to 1985 became infected with HCV [13]; thus the effects of HCV infection could not be isolated in this analysis.

The aim of this study was to assess the extent to which primary prophylaxis could reduce the demand for hospital visits by comparing resource utilization rates for individuals with severe haemophilia with similar rates for individuals with mild/moderate forms of the condition. The results from this analysis clearly show that irrespective of differences in age and HIV serostatus, individuals with severe haemophilia attended significantly more hospital visits than individuals with mild/moderate haemophilia. Thus, we can conclude that primary prophylaxis for individuals with severe haemophilia could significantly reduce the demand for these resources. However, whether this potential benefit affects the cost-effectiveness of treatment will ultimately depend on the probability of primary

prophylaxis working to convert severe haemophilia into mild/moderate haemophilia, the unit cost of each hospital visit and how far into the future these resources are averted [14].

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