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WORKING GROUP ON ACUTE PURCHASING

Recombinant Factor VIII Versus Plasma Derived Factor VIII in the Management of Haemophilia A: An Examination of the Costs and Consequences

June 1997

GUIDANCE NOTE FOR PURCHASERS 97/04

Trent Development and Evaluation Committee

RECOMBINANT FACTOR VIII VERSUS PLASMA DERIVED FACTOR VIII IN THE MANAGEMENT OF HAEMOPHILIA A : AN EXAMINATION OF THE COSTS AND CONSEQUENCES (22.07.97)

AUTHORS: Green C and Akehurst RL. Sheffield : Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1997. Guidance Note for Purchasers: 97/04.

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SUMMARY:

Haemophilia A is one of the most common of the severe coagulation disorders. There are approximately 5,400 people in the UK with haemophilia A. Severe (Classical) haemophilia A occurs in 40% of cases. Haemophilia A is managed through FVIII replacement therapy. A major complication is the development of FVIII IgG antibodies (inhibitors) to FVIII therapy.

Prior to the development of recombinant technology, all FVIII was derived from human plasma fractionation. High purity pdFVIII became the standard treatment of choice for haemophilia A. The rFVIII products use mammalian cell expression systems in manufacture, and some but not all of the products are stabilised using human albumin. The biological and haemostatic characteristics of rFVIII have been found to be comparable to pdFVIII products. It has been suggested, but not established, that rFVIII may be responsible for a greater level of inhibitor development.

Following the effect of HIV on the haemophilic population up to the mid-1980s, the potential of new, as yet unknown, viruses and other agents being inadvertently transmitted to haemophiliacs through FVIII concentrates has been of concern. The known risks associated with the currently produced pdVIII concentrates are very small with respect to AIDS and Hepatitis B and C, but these products are known to transmit other viruses such as parvovirus and Hepatitis A. The risk of Hepatitis A infection is very low. With rFVIII there should be no risk of transmitting known blood borne viruses.

The aggregate financial impact of a switch from pdFVIII to rFVIII, with marginal (extra) cost per district (population 500,000) per year is in excess of £250,000. It is not possible to quantify benefits in terms of direct income, e.g. cost per QALY or life year saved. Indeed, it is difficult to establish any tangible benefit from a product switch. However, Haemophilia Centre Directors believe that rFVIII may be better placed to contend with the 'next' or 'unknown' virus, and see in the use of rFVIII the further reduction of risk of viral infection in what has been a long and troubled history. What may be obtained from rFVIII is an intangible benefit to patients and their families surrounding perceived risk.

DECISION: The Committee's decision was not unanimous but a majority supported the view that recombinant factor VIII should be used only for newly diagnosed haemophiliac patients (that is those who have not previously been exposed to plasma derived factor VIII). Some of the Committee, however, felt that recombinant factor VIII should not be used at all. The Committee agreed that its decision should be reviewed when the price differential between the two products is less. The Committee was not convinced that one product is more likely to produce antibodies than the other, and the recommendation was made knowing that there is little evidence to suggest that the current pdFVIII is responsible for transmitting infections more than the rFVIII product.

June 1997

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- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
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FOREWORD

Individuals or small groups in each District Health Authority in Trent have historically considered evidence on the likely effectiveness of new procedures or therapies in conjunction with their cost, making judgements on whether these should be supported. Since all or most Health Authorities face the same issues, there tends to be repetition in analysis and this can be wasteful of scarce professional expertise.

There are national attempts to remedy this situation by providing information on the effectiveness of interventions and these are welcomed. There remains, however, a significant gap between the results of research undertaken and their incorporation into contracts.

Following a request from purchasers, a network has been established in the Trent Region to allow purchasers to share research knowledge about the effectiveness of acute service interventions and to determine collectively their purchasing stance.

ScHARR, which houses the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A project team is assembled to undertake each review. This team is typically led by a Public Health consultant, includes leading clinicians in the field and a support team from ScHARR which provides help including literature searching, health economics and modelling. A seminar is then held on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes.

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EXECUTIVE SUMMARY

The availability of a recombinant alternative to plasma derived factor VIII (pdFVIII), for the management of haemophilia A, has focused attention on the potential costs and consequences of the recombinant product. This paper considers the issues associated with a switch from pdFVIII to recombinant FVIII (rFVIII).

In assessing the available evidence we find that it is not possible to quantify marginal benefits resulting from the use of rFVIII. Much of the perceived benefit available through the use of rFVIII, albeit unquantifiable, surrounds the potential for protection against future, as yet unknown, viruses/agents. The haemophilic population has suffered greatly from previous blood borne viruses (e.g. HIV) and this adds weight to concerns over future viruses/agents. Such issues go beyond the traditional cost and benefit approach of the Trent Working Group on Acute Purchasing topics which have focused on health gain.

Given present market prices, supporting the use of rFVIII in the management of haemophilia A would involve a substantial increase in funding. It is estimated that a typical purchaser district with a population of approximately 500,000 would expect to have 20 cases of severe haemophilia A and, switching these patients from high purity pdFVIII to rFVIII, would involve a marginal (extra) cost in excess of £250,000 per year per purchaser district.

Recombinant FVIII is a therapeutic product which involves the subjective assessment of unknown risk and, as such, it is not possible to be conclusive in terms of policy recommendations. Therefore, cost analyses are presented which give an insight into the opportunity costs associated with the funding of rFVIII across different patient groups, in accordance with guidelines recently published by the UK Haemophilia Centre Directors Organisation (UKHCDO). Cost analyses are presented which offer some guidance on the time effects, years one to five, of introducing rFVIII across either all haemophilia A patients or across the specific patient categories used in the UKHCDO guidelines.

1. INTRODUCTION

1.1 General

Haemophilia A is an X-linked recessive genetic disorder[a] of blood coagulation caused by diminished or abnormal production of factor VIII (FVIII), a protein present in plasma. It occurs as symptomatic disease in males and can be present in a carrier state in females.[b] Haemophilia A can cause prolonged bleeding, either spontaneously or due to a knock or fall. Bleeding is typically internal into joint spaces (haemarthroses) and muscles (muscle haematoma) throughout the body. The most common sites of joint and muscle bleeds are elbow, knee and ankle. Although the condition can be disabling and life threatening, with treatment most haemophiliacs can lead a relatively normal life.

Treatment of haemophilia A has been managed through FVIII replacement therapy with the infusion of plasma derived FVIII (pdFVIII). The availability (and increased public awareness) of a recombinant alternative to pdFVIII for the management of haemophilia A has focused attention on the potential costs and consequences of the recombinant product.

This paper considers the issues associated with any switch from pdFVIII to recombinant FVIII (rFVIII). The aim of the investigation is to make those responsible for spending decisions concerning the treatment of haemophilia A aware of the cost and benefit implications of a switch from plasma derived to recombinant FVIII.

The Guidance Note addresses the issues from the perspective of an NHS purchaser and begins with an outline of the epidemiology of haemophilia A (Section 1.2). Section 1.3 considers the medical management of FVIII treatment in haemophilia A, giving a general description of the categories of FVIII product available to manage the condition. Section 2 offers a summary of the evidence relating to the effectiveness of rFVIII as an alternative to pdFVIII and highlights important treatment issues. Section 3 discusses the expected costs and expected benefits of rFVIII and an economic assessment of the use of rFVIII as an alternative to pdFVIII. Policy options are discussed in Section 3 with further discussion in Section 4.

[a] Although a number of cases are caused by spontaneous mutation with no familial link.
[b] It is theoretically possible for a woman to have haemophilia A, however, it is a very rare occurrence.

1.2 Haemophilia A : Epidemiology

Haemophilia A is one of the most common of the severe coagulation disorders. There are approximately 5,400 people in the UK with haemophilia A.[1] Reported prevalence figures for haemophilia A vary between 1-20 per 100,000 of the population,[2,3,4,5] with 10 cases per 100,000 being a widely used prevalence marker. Severe (Classical) haemophilia A occurs in 40% of cases.[4] Table 1 details the expected number of haemophilia A cases, both nationally and for a 'typical' district purchaser community of 500,000 population. Table 1 also indicates the number of subsequently expected severe cases of haemophilia A in the relevant populations.

Severity of the clinical course of the disease depends upon the percentage of plasma factor VIII activity present compared with normal levels.

- Severe haemophilia A occurs where there is less than 1% of normal FVIII levels,[a] and is associated with spontaneous bleeding into joints and muscles.
- Moderate haemophilia A occurs where FVIII activity is between 1% and 5% of normal levels, and is associated with occasional spontaneous bleeding and severe bleeding after minor injury.
- Mild haemophilia A occurs where FVIII is between 5% and 25% of normal FVIII levels, and is associated with only severe bleeding after major injury.

(Hoyer 1994). [4]

Incidence figures for haemophilia A are more difficult to determine. New cases of haemophilia A are categorised as 'previously untreated patients' (PUPs) and are generally children or newly identified haemophiliacs. Incidence can only be calculated from the Haemophilia Centre Directors (HCD) Annual Returns, which are not widely available in the public domain. On average, it is expected that between 55 and 65 new cases of haemophilia A (PUPs) present nationally each year.

[a] Severe disease is sometimes defined as < 2% of normal coagulation factor activity (Introduction to haemophilia, 5th Ed, The Haemophilia Society 1995).

Table 1: Prevalence of Haemophilia A

PREVALENCE RATE PER HEAD OF POPULATION	NUMBER OF CASES - U.K. (POP. 58.7 M)	NUMBER OF CASES - DISTRICT COMMUNITY [a] (POP. 500,000)	NUMBER OF SEVERE CASES - U.K. (POP. 58.7 M)	NUMBER OF SEVERE CASES - DISTRICT COMMUNITY (POP. 500,000)
5 per 100,000	2,935	25	1,174	10
7 per 100,000	4,109	35	1,644	14
10 per 100,000	5,870	50	2,348	20
20 per 100,000	11,740	100	4,696	40

[a] Note: It may be that the distribution of haemophilia A patients across the geographical areas is variable due to a tendency for such patients to locate themselves near a specialist haemophilia care centre.

1.3 Medical Management of Haemophilia A

1.3.1 Treatment

(i) Treatment Regimen

Haemophilia A is managed through FVIII replacement therapy. FVIII concentrate is supplied as a freeze dried product and it is reconstituted with a small volume of sterile water before intravenous injection. Treatment can be through designated care centres or home therapy.

'On demand' FVIII replacement, at home at the time of haemorrhage, is the most common treatment regimen. FVIII prophylaxis, to prevent bleeding episodes and the long-term damage that bleeding episodes can cause, can be undertaken in a number of treatment regimens. Prophylaxis can be short-term to prevent bleeding when a patient is intending to participate in an activity which involves some risk e.g. some sports. Alternatively, for patients undergoing invasive procedures, prophylaxis involves the correction of FVIII levels prior to such procedures. Continual and longer-term prophylactic treatment is mostly administered over the period of musculo-skeletal development to prevent muscle and joint damage. Prophylaxis has become the standard treatment of choice for children with severe haemophilia A.

(ii) Frequency and Dose

For 'on demand' therapy, patients with severe haemophilia A will have between 30 and 50 treatments per year,[6] whilst those patients with mild to moderate haemophilia A will have one to two treatments per year.[7] The level of FVIII used per treatment is based on iu per kg (body weight) with treatments generally ranging from 500 to 1000 iu of FVIII.[7] One injection of FVIII is usually effective in treating minor bleeding episodes, although more severe bleeds usually need further treatment.

Longer-term FVIII prophylaxis generally involves FVIII replacement therapy three times per week, at a dose of 20-24 iu/kg.[8]

(iii) Inhibitor Formation

A major complication in the management of haemophilia A is the development of FVIII IgG antibodies (inhibitors) to FVIII therapy. Inhibitor formation can impact upon the degree of effectiveness/efficacy of FVIII treatment or render it ineffective. The extent of the 'inhibitor problem' is dependent upon antibody titre, i.e. the level of antibody activity. Patients with a low antibody titre can continue to benefit from FVIII therapy but at higher doses. Only those patients with a high antibody titre, of 10 BU/ml or more,[1,9] are resistant to human FVIII concentrates. In such circumstances alternative treatment of bleeding episodes is required. The highest risk of inhibitor formation occurs in previously untreated patients with severe haemophilia,[10] whilst in those with mild and moderate disease the incidence of inhibitor formation is much lower.

(iv) Treatment of Cases with Significant Factor VIII Inhibitor Formation

Treatment of those patients with high inhibitor levels can take different forms. Treatment options include: (a) the use of high doses of FVIII to swamp the inhibitors and stop the bleed; (b) the use of porcine FVIII; and (c) the use of other coagulation factors e.g. FVIIa. The treatment of bleeding episodes in patients with inhibitors is a complex, uncertain and costly exercise.

1.4 Factor VIII Products

FVIII is used predominantly for the treatment of haemophilia A, a small amount is used for the treatment of von Willebrand's disease. FVIII can be derived from human plasma through fractionation, or can be derived from recombinant gene technology.

1.4.1 Plasma Derived Factor VIII

Prior to the development of recombinant technology, all FVIII was derived from human plasma fractionation. The plasma fractionation process manufactures FVIII concentrates from cryoprecipitate, (prepared from fresh frozen plasma) and is able to produce FVIII products differing in purity, dependent upon the production process. In our discussion of FVIII concentrates, the two categories of pdFVIII product of interest are termed 'intermediate purity product' and 'high purity product'. High purity pdFVIII has become the standard treatment of choice for haemophilia A. Although intermediate purity pdFVIII is still used in some cases of haemophilia A, it is most commonly used in the treatment of von Willebrand's Disease.

(a) Intermediate Purity Plasma Derived Factor VIII

Conventionally prepared material with heat treatment methods of viral inactivation.

(b) High Purity Plasma Derived Factor VIII

These products are treated with a combination of viral inactivation and purification processes i.e. solvent detergent treatments followed by chromatographic purification techniques. The two major chromatographic techniques are monoclonal antibody chromatography and ion-exchange (or heparin affinity) chromatography.

1.4.2 Recombinant Factor VIII

Developments from the mid-1980s have enabled the production of human plasma proteins through recombinant DNA technology. A number of techniques have been developed to enable the production of recombinant blood products for medical therapy. The available (licensed) recombinant FVIII products use mammalian cell expression systems[a] in the manufacture of FVIII and the final product is stabilised using human albumin. Currently licensed recombinant products undergo chromatographic purification techniques during the production process.

1.5 Viral Inactivation / Transmission

[a] Baxter: *Recombinate* & Centeon: *Bioclate* both use Chinese Hamster Ovarian cells, whilst Bayer: *Kogenate* & Centeon: *Helixate* both use Baby Hamster Kidney cells.

Up to the early 1980s concerns regarding viral transmission through the infusion of blood products mainly surrounded the transmission of hepatitis. The arrival of HIV in the 1980s raised the profile of the issue of viral transmission and its prevention quite dramatically. HIV has had a very significant impact on the haemophilic population.[11] Processes of viral inactivation, introduced since the mid-1980s, have proved successful in reducing the risk of viral transmission from lipid-enveloped viruses (e.g. HIV, HBV & HCV). However, the risk of viral transmission through non-lipid-enveloped viruses (e.g. HAV & human parvovirus B19) has proved more difficult to manage/reduce.

The potential for viral transmission through the infusion of blood products is a major concern with any new product of this nature. The current concerns within the treatment of haemophiliacs surround the viruses shown in Table 2. HIV, HBV and HCV are those with major known clinical significance. Whilst HAV and human parvovirus B19 prove troublesome and raise concerns over future viruses, which may be more damaging, they themselves can be managed (in the case of HAV), or generally prove to be of little clinical significance (in the case of human parvovirus B19).[12,13,14] Although the clinical significance of human parvovirus B19 is an arguable point, in most cases it causes only mild illness, see Section 2.4 for further discussion.

Table 2 : Current Viruses Giving Rise to Particular Concern in the Treatment of Haemophilia A.

TRANSMITTABLE DISEASE	STRUCTURE
Human Immunodeficiency Virus (HIV)	lipid-enveloped virus
Hepatitis B Virus (HBV)	lipid-enveloped virus
Hepatitis C Virus (HCV)	lipid-enveloped virus
Hepatitis A Virus (HAV)	non-lipid enveloped virus
Human Parvovirus (B19)	non-lipid enveloped virus
Unknown virus/agent	virus/agent of unknown make-up

Following the effect of HIV on the haemophilic population up to the mid-1980s, the potential of new, as yet unknown viruses and other transmittable agents, being inadvertently transmitted to haemophiliacs through FVIII concentrates has been of increasing concern.

Viral inactivation processes are now able to reduce the known risks to low level and these are discussed further in Section 2 below.

2. RECOMBINANT FACTOR VIII : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Treatment Effects: Effectiveness

The effectiveness of FVIII products in the treatment of bleeding disorders is associated with the biological and haemostatic characteristics of the products in practice.

The biological and haemostatic characteristics of rFVIII have been found to be comparable to pdFVIII products.[15,16,17,18,19] Bray et al,[16] after 33 months of clinical experience, put forward evidence to support the hypothesis that rFVIII and pdFVIII are biologically identical. Bray et al remark that 'rFVIII is safe and effective in the treatment of haemophilia A related bleeding' (op. cit. p2428). Schwartz et al[15] in a study involving a total of 107 subjects, found rFVIII to be safe and efficacious for the treatment of haemophilia A, with rFVIII having excellent haemostasis qualities and biological activity (half-life) comparable to pdFVIII. Lusher et al,[17] in a multi-centre trial involving 95 previously untreated patients (treatment period 2.4 months to 3.5 years; median of 1.5 years), found all patients responded well with no treatment failures. White et al [19] found pdFVIII and rFVIII to be structurally similar and found rFVIII to be an effective therapeutic agent for the treatment of haemophilia A.

Other studies supporting the efficacy and effectiveness of rFVIII are cited within the literature, however, in the current debate surrounding the switch from pdFVIII to rFVIII, the effectiveness of rFVIII is generally accepted as given.

2.2 Inhibitor Formation

The development of inhibitors to rFVIII compared with pdFVIII is a contentious issue. It has been suggested that rFVIII may be responsible for a greater level of inhibitor development within haemophilia A patients than would be expected through the use of conventional pdFVIII.[10]

Factors exist which make the comparison of inhibitor formation resulting from rFVIII and pdFVIII a complex task. The importance of previously untreated patients within studies, [17,20] retrospective versus prospective trial designs,[1] the differing severity of haemophiliacs evaluated, and the concentration of inhibitors (i.e. low or high responders) all impact upon the interpretation of studies and the clinical significance of the extent of inhibitor formation.

Although the development of inhibitors can prove fatal in cases of high inhibitor concentration, it is also the case that inhibitor development in a low concentration can prove to be of little significance and in some cases transient.

Comment regarding inhibitor formation within haemophilia A has been clouded through the use of studies involving patients with a long record of exposure to various FVIII products. The relative risk of inhibitor formation is very strongly related to the length of exposure to FVIII replacement therapy.[10,20,21] The relative risk of inhibitor formation is about four times higher for patients under the age of five years than for older patients.[20] It is only through studies based on previously untreated patients (calculations based on incidence rather than prevalence) that true information on the frequency of inhibitor development within haemophilia A can be judged (op. cit. p596).

The risk of inhibitor development in patients treated with intermediate purity pdFVIII and high purity pdFVIII products has been shown to be similar.[1,20,22]

With respect to rFVIII, Lusher et al[17] examined inhibitor development in a multi-centre trial involving 95 previously untreated children, (2.4 months to 3.5 years; median of 1.5 years). Of 81 patients tested for antibodies 16 (14 severe and two moderate haemophilia) were shown to have formed antibodies to rFVIII. However, in nine of the 16 patients developing antibodies the concentration of antibodies was low (<10 BU), or disappeared with time. Bray et al[16] considering rFVIII in 71 PUPs (severe haemophilia), found 17 developed inhibitors; five with a high concentration (>10 BU), and 12 with low concentrations (≤10BU). Schwartz et al[15] conducted a study of rFVIII treatment in 107 haemophiliacs, including 20 previously untreated patients. Five of the 20 PUPs developed antibodies, with all inhibitor concentrations except one being low or declining to a low level.

In considering pdFVIII, Guerois et al[9] reported on a study of the French haemophilia A population treated with a high purity pdFVIII concentrate, from 1988 to 1993. The study involved 56 previously untreated patients with a follow-up duration of 1 to 76 months (mean of 29 months). Five of the 56 PUPs developed inhibitors, of which only one was a high responder. Addiego et al[22] in a study of the treatment of haemophilia A using pdFVIII (Hemofil M®) found that only two of 23 'previously untreated patients with FVIII levels ≤ 3%' developed inhibitors. These 23 patients had received only monoclonally purified solvent/detergent treated FVIII concentrate while on study and on post study surveillance (p19).

Scharrer and Neutzling [21] conducted a review of 13 published inhibitor studies and following their evaluation concluded that there was 'no greater risk for children with severe haemophilia A receiving monoclonal or recombinant products in acquiring an inhibitor compared with patients receiving conventional products' (p757). However, they went on to say that ' .. it is likely that purification or virus inactivation methods may influence the antigenicity of factor VIII concentrates' (p757). Within the review undertaken, only five of the studies related exclusively to PUPs.

Although concerns exist as to the inhibitor forming properties of rFVIII, the current literature can offer no conclusive evidence to support the belief that rFVIII is more likely to result in the development of inhibitors. de Biasi[10] highlights that previous reports of inhibitor development, mainly based on prevalence figures, may have underestimated the 'true' risk of complication in patients treated with less pure FVIII concentrates (p544). de Biasi et al also placed emphasis on factors other than product type which may affect inhibitor development, for example, intensity of treatment, viral inactivation procedures, immunologic responses of the patient, and genetic predisposition of the patient.

2.3 Side Effects

Studies to date have shown that rFVIII is well tolerated and not associated with significant side effects. Lusher et al [17] reported that in 3,315 infusions administered to 95 patients, rFVIII concentrate was well tolerated, with three reports of minor adverse reactions (one report of urticaria, flushing, and erythema at the infusion site), p454. Bray et al,[16] following 33 months of clinical experience, reported that rFVIII was well tolerated and not associated with significant short-term adverse effects. Fukui et al [18] in a pilot clinical study of rFVIII reported no adverse reactions attributable to rFVIII found in 178 infusions.

2.4 Infectivity

2.4.1 'Known' Risk

With respect to the known infection risks, concern with pdFVIII has primarily focused on HIV, HCV, HBV, HAV and parvovirus B19.

Since the introduction of viral inactivation processes the risk of transmitting HIV, HCV and HBV is very small.[13,23] These viruses are lipid-enveloped and are very susceptible to treatment by solvent/detergent processes. There have been no cases of HIV transmission following treatment with clotting factor concentrate reported since 1986.[24] Following the introduction of solvent/detergent processes in the UK production of FVIII, there have been no reported cases of HIV, HBV or HCV.[25]

Inactivation methods, both heat treatment and solvent/detergent treatment, have been shown to be highly effective against HBV and HCV. Fricke et al[12] reported that 'thus far, no patient has been reported that has contracted hepatitis from use of a product treated in this way [i.e. heat treated and solvent/detergent treated]'.

Although the transmission of HBV has essentially been stopped,[24] it is also important to note that a vaccine is available for the prevention of HBV and all haemophilia A patients should be protected in this way. HBV can occur as a precore mutant infection, against which the vaccine may not prove to be effective, however, such instances are very rare.

The UK Haemophilia Centre Directors' Committee has previously referred to the substantial safety of pdFVIII products[26] commenting that pdFVIII products 'have a very small or negligible risk of transmission of HIV-1 or hepatitis viruses'. Plainly, the risk of viral transmission through FVIII concentrate posed by HIV, HBV and HCV is very small.

With HAV and parvovirus B19, the lack of a lipid envelope in the make-up of the virus makes it less susceptible to solvent/detergent methods and heat treatment methods have not proven as effective as in the case of lipid enveloped viruses i.e they appear relatively heat resistant.

Although some cases of HAV have appeared in haemophilia patients, HAV is only rarely transmitted by transfusion.[27] There have been no cases of HAV transmission reported where UK manufactured products have been used. However, a number of cases have been reported, within the last few years, in European countries (Germany, Ireland and Belgium), all associated with the use of the same FVIII concentrate (Octa V.I., OctaPharma).[24] The availability of a HAV vaccine should prevent any occurrence of HAV in treated patients.

Although the available HAV vaccine is not licensed for infants under one year of age, it is rare for a child to be given FVIII replacement therapy prior to walking age i.e. one to two years.[a] Furthermore, it is also important to note the risk of HAV infection from routes other than FVIII concentrate. HAV has a well documented cycle of infection in the general population with around 7,000 cases reported annually; school-aged children and young adults are most commonly affected.[28]

Heat treatment against parvovirus B19 has not been effective in preventing the transmission of the virus. Parvovirus B19 appears resistant to all current methods of viral inactivation, however, due to its high prevalence in the general population,[24,29,30] it is possible that haemophiliacs may be exposed to parvovirus regardless of the FVIII product used. Parvovirus B19 is spread, other than by blood borne infection, via the respiratory tract;[31] infection is common and occurs world-wide.[24] Cohen et al[30] found parvovirus B19 to be a common infection with around 60% of adult populations having specific IgG antibody. A study undertaken in Belgium by Peerlinck et al,[29] highlighted the high frequency of parvovirus B19 infection in patients with haemophilia and age matched controls. Peerlinck et al tested for antiparvovirus B19 IgG antibodies in haemophilia A patients and in controls finding overall that 93% of haemophilia patients and 75% of controls tested positive. They concluded that 'infection seems almost endemic in our [Belgium] population' (p555).

The clinical significance of human parvovirus B19 is a debated issue. Infection with human parvovirus B19 is usually asymptomatic or causes a minor feverish illness.[32] However, more severe illness can occur i.e. transient aplastic crisis in cases with underlying chronic haemolytic anaemia or chronic anaemia in immunocompromised hosts.[33] Such cases are thought to be rare, although the frequency of cases of severe illness is not reported in the present literature. A further concern is the effect of parvovirus B19 infection during pregnancy. It has been reported that during pregnancy parvovirus B19 infection may result in miscarriage or hydrops fetalis,[34] although current evidence is not conclusive. However, those carriers of haemophilia who may require treatment with FVIII concentrate during pregnancy will generally only receive FVIII concentrate in the period immediately prior to birth and in some cases the period immediately after birth.

The known risks associated with the use of pdFVIII concentrates are very small with respect to HIV, HBV and HCV. In terms of HAV the risk of infection is very low and the availability of an effective vaccine adds further protection. There is a risk of parvovirus B19 infection within

[a] Clinical opinion, personal communication with Sheffield Children's Hospital.

the general population as well as through the use of pdFVIII concentrate. Whilst parvovirus B19 may in some cases result in significant illness, most cases are clinically insignificant.

In the treatment of patients with rFVIII there should be no risk of transmitting known human blood borne viruses.[13] Although current products are stabilised in human albumin, this product has been shown to be virus safe (i.e. known viruses) through a simple heat treatment process.[35] Over the past 40 years, not a single case of viral transmission through the use of albumin has been reported,[35] although vigilance with respect to viral transmission has not been to the same degree with albumin as it has been with FVIII products.

Although those treated with FVIII products are protected through donor selection, blood donation screening, viral inactivation techniques and immunisation programmes, it is also necessary to prevent the spread of viral contamination within the manufacturing plant (both pdFVIII and rFVIII) and to avoid the recontamination of any process downstream of a point where viral infectivity has been reduced or eliminated i.e. good manufacturing practice (GMP).[36] Throughout the discussion of FVIII concentrate we have so far assumed that GMP prevails. Human error and the failure of GMP is a known risk factor associated with all FVIII production processes.

There have been a number of instances where the withdrawal of a product has been necessary for safety reasons. One example of this involves the manufacturer Centeon L.L.C. (USA). Due to failures in GMP Centeon L.L.C. has been subject to strict United States Food and Drug Administration (FDA) regulations, whilst appropriate GMP measures are introduced, including a restriction of trade and distribution. In September 1996 Centeon L.L.C. recalled one lot of human albumin (Albuminar-25) due to contamination with bacterial agents. Following this withdrawal, as a precautionary measure, Centeon withdrew a further nine additional lots of albumin and one lot of FVIII concentrate (Monoclate-P).
It is the case that in some instances product withdrawal has been instigated as part of the GMP itself and reflects the care taken in the manufacture and distribution of blood products. For example, in August 1996 Bio Products Laboratory (BPL) initiated a precautionary recall of product which had not been shown to be defective and which complied with UK and European regulatory requirements. However, as part of the industry driven GMP, BPL withdrew one batch of FVIII concentrate (Replenate) and 3 batches of albumin (Zenalb) as a purely precautionary measure. The withdrawal was due to concerns over one of the plasma pool start donations (BPL Recall of Product: Incident PR96/240). Although the concerns of

BPL were of a nature that manufacturing processes would eliminate, the recall decision was made to maintain public confidence in the manufacturing process.

Bordering between the known and unknown virus, there is presently some concern surrounding Creutzfeldt-Jakob disease (CJD). CJD is a disease of the central nervous system and little is known about the risk it poses in terms of blood borne transmission of disease. It is thought that the disease is caused by an infectious protein or prion which affects the normal plasma membrane protein.[24] Research is being undertaken to examine the possibility of CJD transmission by blood transfusion and some early research is taking place (USA and UK) to further examine the occurrence of CJD in the context of haemophilia.

2.4.2 'Unknown' Risk

Much of the literature focusing on viral transmission refers to risks associated with 'unknown' or future viruses. The issue of 'unknown risk' is a very subjective concept and can only be assessed based on known risk and experience. In the treatment of haemophilia using pdFVIII, the transmission of parvovirus B19 through the use of pdFVIII gives rise to concerns over the potential for a 'new' virus of similar structure, but with greater clinical significance. Should such a situation occur it would have dramatic consequences for the haemophilia population, yet, given the prevalence of parvovirus B19, the same situation would also prevail within the population at large. In the treatment of haemophilia through the use of rFVIII, the unknown risk can firstly be associated with the present albumin content of this product and the possibility of a 'future' (as yet unknown) human blood borne virus not being inactivated through the present viral inactivation process. Future rFVIII products, not involving human albumin, are in development and are expected to be marketed soon after the year 2000. Secondly, a further area of unknown risk associated with rFVIII lies in the possibility of cross-species infection, due to the use of mammalian cell expression systems in the production of rFVIII concentrate. The current literature has no direct data to support any concerns of cross-species viral transmission from FVIII or similar products. Although the risk of cross-species infection posed by rFVIII is very small, in a discussion of 'unknown' viruses it is an area with growing theoretical concern.

2.5 Immunosuppression

It has been suggested that the deterioration of the immune system of HIV infected haemophiliacs, as represented by CD4 lymphocyte counts, may stabilise or be less rapid in patients treated with high purity or recombinant FVIII concentrates.[37,38,39] Although there is no demonstrated benefit in terms of outcome or survival, the findings may be of interest in the medical management of HIV infected haemophiliacs.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Costs of Providing Recombinant Factor VIII

Within the current literature there is little discussion surrounding the aggregate cost consequences associated with a switch from pdFVIII to rFVIII. Outlined below are estimates of the expected FVIII expenditure per purchasing district, based on a population of 500,000, using a prevalence rate of 1 case per 10,000 population. Estimates are calculated based on an average FVIII consumption level per patient per year, reported by Haemophilia Centre Directors' (HCD) Annual Returns (1994). Presently, pdFVIII is exempted from VAT, whereas rFVIII is VAT chargeable (at a rate of 17.5%). NHS purchases of rFVIII will be subject to VAT charges which are non-reclaimable from HM Customs & Excise (VAT Leaflet 701/31/92, personal communication from HM Customs & Excise). With this VAT issue in mind, cost estimates below are discussed including VAT to give a 'typical purchaser' perspective. Estimates excluding VAT will also be presented to offer a 'public sector' perspective.

3.1.1 Factor VIII Product Costs

There is a wide range of FVIII products available (see United Kingdom Haemophilia Centre Directors Organisation (UKHCDO) 1997 guidelines for detail)[23] and, due to the competitive nature of the market for FVIII concentrates, list prices do not reflect the prices charged to purchasers. For the purpose of the cost analysis undertaken in this Guidance Note the prices shown below (Figure 1) will be used as a reflection of average prices charged per iu of FVIII. Prices for UK manufactured pdFVIII have been used (i.e. products manufactured by BPL). UK manufactured concentrate (BPL) represents over 50% of the FVIII concentrate used nationally (HCD Annual Returns 1994). The prices shown are supported by prices quoted in the literature[40] and both local clinical opinion and manufacturer opinion. However, prices are average prices and they may vary between purchasers.

Figure 1: Factor VIII Concentrate, Product Costs used in Cost Analysis

Factor VIII	Average Prices
Intermediate purity pdFVIII (BPL; 8Y)	£0.186 *per iu*
High Purity pdFVIII (BPL; Replenate)	£0.27 *per iu*
Recombinant FVIII (all)	£0.47 *per iu incl. VAT* - (£0.40 *per iu excl. VAT)*

3.1.2 Estimated Annual Costs - Average Annual Factor VIII Consumption Method

The figure reported in HCD 1994 Annual Returns shows a mean FVIII usage per patient treated of 63,766 iu[a] which would result in an annual FVIII consumption of 1.275 million iu, for a typical district population of 500,000, across an expected 20 cases of severe haemophilia A (assuming 40% of expected cases to be severe haemophilia). This level of FVIII consumption finds support in trial data covering FVIII replacement therapy.[15] Schwartz et al [15] on the basis of 5 months' home treatment in 56 previously treated patients, estimate a mean consumption of FVIII to be 78,234 iu per patient per year (range 500iu to 304,022iu per year).

Figure 2 details the estimated annual marginal costs associated with a switch from pdFVIII to rFVIII. Given an annual FVIII consumption of 1.275 million iu across severe cases of haemophilia, per typical purchaser population of 500,000, the estimated marginal costs associated with a switch from high purity pdFVIII to rFVIII are £255,064 per year per district including VAT.

[a] The HCD Annual Returns 1994 detail a total FVIII consumption (haemophilia A) of 151 million iu, a total number of treated haemophilia A patients of 2,368 and a mean FVIII consumption level per patient per annum of 63,766iu. (The Oxford Haemophilia Centre & Haemophilia Society).

Figure 2: Estimated Marginal Cost of a Switch from pdFVIII to rFVIII, Based on an Annual Consumption of 1.275 Million iu (Typical Purchaser Community of 500,000 Population).

On the basis of an annual FVIII consumption of 1.275 million iu, per district community, (average FVIII per patient per year of 63,766 iu- severe cases only) the following estimates of the marginal costs associated with a switch from high purity pdFVIII to rFVIII would apply:

	Incl. VAT	Excl. VAT
Marginal cost of rFVIII over high purity pdFVIII	**£255,064**	**£165,791**

3.1.3 Cost - General

The outline cost analysis above identifies the substantial aggregate financial impact of a switch from pdFVIII to rFVIII, with a marginal (extra) cost per district per year in excess of £250,000.

A further cost consideration for individual purchasers is the magnitude of the resource consequences for so called 'big bleed episodes' i.e. major bleeding episodes requiring considerable medical attention. These episodes are infrequent and clinical opinion suggests that, over a purchasing region covering 5 or 6 health authorities, only one major bleeding episode may occur per year. This supposition would be supported by the relatively infrequent occurrence of inhibitor compromised patients,[1] often a factor associated with 'big bleed episodes'. The quantity of medication required to treat these episodes is substantial, often running into £100,000 plus. A more expensive product, that is rFVIII, may have a significant impact on the cost of these individual cases, with the potential to produce a larger destabilising effect on the purchaser's budget. However, as detailed in Section 1.3, treatment of inhibitor compromised patients (or big bleed episodes) will usually involve treatment with products other than FVIII concentrate.

A further consideration is posed through the NHS Special Health Authority status of BPL (the UK plasma fractionation operation - England & Wales) which gives rise to the BPL operation being 'underwritten' by the Department of Health (DoH). As such, the DoH would be liable for any deficit (increased loss) which may result from a switch from pdFVIII to rFVIII. Should BPL products become more costly to produce as a result of reduced demand

for pdFVIII (due to issues of joint production) and should BPL be unable to recoup increased costs through product prices, due to the highly price sensitive nature of their products (as would be expected) it would fall to the DoH to offset any deficit (increased loss) which may occur. This may impact upon the general level of aggregate resource available within the DoH budget. Although it is difficult to establish an accurate assesment of any increased burden falling on the DoH, BPL estimate that the potential impact on their annual revenue, associated with a complete switch from pdFVIII to rFVIII, would be in the region of £15 million (total revenue in 1995/96 was £48.6 million), whilst plasma purchases would remain unchanged i.e. returns from their manufacturing process would be greatly reduced. This estimate assumes that no other market for their pdFVIII product is found.

3.2. Benefits / Consequences

It is not possible to quantify benefits in terms of direct outcomes e.g. cost per QALY, or life year saved, for a switch from pdFVIII to rFVIII. There is no literature to inform of any outcome benefit from rFVIII. Presently it has only been possible to identify the marginal cost consequences of differing treatment policies and allude to the 'intangible' benefits.

Although the area under consideration is an emotional subject, it is difficult to establish any tangible benefit from a product switch. The known risks are very small and the potential for viral transmission through pdFVIII of lipid-enveloped viruses may be countered with arguments showing little actual benefit.

In the case of HAV, a potential benefit could be expected in the form of a reduced risk of HAV transmission, although cases of transmission through FVIII are already very rare. However, it is possible to address HAV prevention through the use of a relatively inexpensive vaccination (Havrix® and Havrix Junior® SmithKline Beecham) which has a very good level of effectiveness. In the case of parvovirus B19, the clinical significance within haemophiliacs is regarded as very small,[12,13] and the likelihood of exposure within the general population is high[29,30] (see Section 2.4.1).

The potential for significant benefits lies within particular views surrounding 'intangible benefits' attributable to rFVIII. There is a belief among HCDs that rFVIII has advantages with respect to viral transmission. These, in view of the known risk of viral transmission, will in the main relate to non-lipid enveloped viruses which, as stated above, do not appear to represent benefits in terms of patient outcomes. However, there also seems to be a belief

among HCDs that rFVIII may be better placed to contend with the 'next' or 'unknown' virus. It is not possible to quantify future benefits relating to hypothetical future viruses which may affect haemophiliacs. It would seem reasonable to hypothesise about future unknown viruses, as history has shown that such challenges may appear. However, the source of such future unknown viruses is an arguable point. In both pdFVIII and rFVIII there seem to be avenues for discussion with respect to the unknown virus.

What may be obtained from rFVIII is an intangible benefit to patients and their families surrounding perceived risk. That is, although the risk of known virus transmission is low, it may be perceived to be greater by those exposed and, therefore, a perceived reduction through rFVIII may constitute a benefit of rFVIII treatment. On the other hand it could be argued that educating the haemophilic population to the extent of known risk may offer a similar benefit.

Although it is difficult to identify and quantify any tangible benefits, in terms of patient outcomes, it may be that such benefits, in this instance health gain, only constitute part of the decision-making process. Other ethical and distributional issues may play a significant role. Further discussion of this point is contained in Section 3.3.

3.3 Economic Assessment

Following the above discussions it may be helpful to place the potential costs and consequences of a switch from pdFVIII to rFVIII into a wider context, considering the full cost and what this cost buys.

An attempt to put the cost and benefit implications in perspective can be framed around the guidelines used by The Wessex Institute of Public Health.[41] The Wessex guidelines consider the scale of the benefits that a purchaser should expect a new therapy to demonstrate before it is considered for inclusion in the purchasing process. Part of their category rating system is set out in Table 3.

Table 3: Wessex Institute of Public Health: Category Rating System [41]

CATEGORY	STATUS

(A) <£3,000 per life year gained or Quality Adjusted Life Year Gained	Strongly Recommended
(B) £3,000 to £20,000 per life year gained or Quality Adjusted Life Year Gained	Recommended
(C) > £20,000 per life year gained or Quality Adjusted Life Year Gained	Recommended but High Cost

It has not been possible to put rFVIII in a 'cost per' framework as it is not possible to identify benefit in terms of patient outcomes. It is possible to consider a marginal treatment cost per patient per year (medication cost only). Based on the average annual FVIII consumption per patient of 63,766 iu (HCD Annual Returns 1994) and product prices stated in Figure 1, the marginal (extra) cost per patient per year[a] associated with rFVIII would be approximately £12,753 including VAT, when compared with high purity pdFVIII. Given the guidelines used by The Wessex Institute of Public Health, therapies with marginal costs in this range would need to offer substantial marginal benefit (i.e. one QALY per year) prior to being considered for inclusion in the purchasing process.

As indicated above it may be that for certain decisions 'health gain' is only one of the arguments within a particular decision. The Wessex Institute Guidelines assume a health gain maximising objective (the emphasis being upon a 'cost per' approach) which may not be applicable to all decisions faced by health care purchasers.

In a budget constrained climate, devotion of resources to interventions or therapies of unproven clinical benefit have the 'opportunity cost' of health gain forgone in other areas of health service delivery. In discussions surrounding a switch from pdFVIII to rFVIII it is important that this point is explicit and that the questions relating to the opportunity costs of devoting resources to rFVIII are addressed. Making resources of the magnitude discussed above (approx. £250,000 extra per year) available for other evidence-based options will most likely result in a net increase in the health gain of the community. Conversely, reducing presently provided services, to the extent of the resources required to purchase rFVIII as a replacement therapy for pdFVIII, will most likely result in a net loss in the present health gain status of the community.

[a] As the FVIII consumption figure is an average, this illustrative example is intended to be seen in the context of those patients with severe disease, although the HCD Annual Returns cover an average across all treated patients.

Having raised the issue of opportunity cost and the potential for numerous arguments to be competing within a decision making environment, it may be that society is 'prepared to forego efficient health gains in order to behave *fairly*' (emphasis by author).[42] Maynard[42] uses this equity concept to discuss an approach reflecting the idea of a 'fair innings', yet the treatment of the haemophilic population with rFVIII may be regarded as fair by decision makers in such a situation. However, should it be the case that decision makers fund rFVIII in order to 'behave fairly', it is important that they are encouraged to be explicit about the reasoning behind such a decision.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

4.1 United Kingdom Haemophilia Centre Directors Organisation: Recommendations

In a recent publication the UKHCDO offer 'guidelines on therapeutic products to treat haemophilia and other hereditary disorders'.[23] In their specific recommendations for haemophilia A they state rFVIII to be their treatment of choice for all patients.

The UKHCDO guidelines[23] also indicate their order of patient priority, based on 'ability to benefit', should the introduction of rFVIII not be across all patients. They offer the following as an order of priority for the introduction of rFVIII in such a case:

(1) HIV antibody negative patients:
- (a) previously untreated patients
- (b) HCV negative patients
- (c) HCV positive patients

(2) HIV antibody positive patients

To offer some insight into the cost consequences of the above priority ordering the proportion of patients likely to be in the above categories has been estimated.

As discussed in Section 1.2 it is difficult to be precise with respect to the true incidence of haemophilia A. In the absence of hard data it is estimated, based on HCD Annual Returns and clinical opinion, that on average no more than one new case of haemophilia A would present each year per typical purchaser district (500,000 population). It would seem reasonable for such a district to expect one new case of severe haemophilia A, previously untreated patient, every one to two years.

With respect to the number of HIV antibody positive haemophilia A patients, there is a scarcity of published material to call upon. A study carried out in 1985 by the UKHCD, [43] covering information on 2,609 patients from 81 haemophilia centres, reported that (a) of those patients with severe haemophilia A nearly 60% were HIV positive; (b) of those with moderate disease 23% were HIV positive; and (c) of those with mild disease 9% were HIV positive. Overall, 44% of those patients with haemophilia A were found to be HIV positive. Taking the data from that study it would be expected that, of the estimated 50 haemophilia A

patients within a typical district community, (20 severe cases and 30 moderate/mild cases; based on a prevalence of 1:10,000), approximately 22 cases would be expected to be HIV positive. Of those cases expected to be HIV positive, a large majority would be linked to severe cases of haemophilia i.e. 12 out of 20 cases of severe hamophilia A would be expected to be HIV antibody positive based on the study conducted in 1985.

In the above assessment of the number of HIV antibody positive haemophilia A patients, it would be reasonable to assume that the numbers of HIV positive haemophilia A patients indicated by the 1985 UKHCD study are not as applicable to the late 1990s as they were at the time of publication. It is expected that the figure given by the UKHCD[43] as an estimate of HIV positive haemophilia A sufferers (60% of severe cases and 44% overall), would be much lower today. A lower estimate would apply today due to (a) the fact that there has been no new case of HIV in the haemophilic population (as a result of FVIII products) since 1985, as detailed in Section 2.4.1.; and (b) the expectation that a proportion of HIV positive cases present in 1985 will have died, either as a result of the virus or due to other causes. The impact of HIV on the haemophilic population to date has been to such an extent that, of those suffering from severe haemophilia A, it is now expected that, due to a great number of HIV related deaths, only 10% to 20% would be expected to be HIV antibody positive.[a] That is, of the expected 20 cases of severe haemophilia A in a typical purchaser district (500,000 population) three of these cases would be expected to be HIV antibody positive.

It has also proved difficult to establish the extent of HCV within the haemophilic population, given current sources. When deducting those HIV positive haemophiliacs and PUPs from the available haemophilic population within a district (severe cases only) it would leave a potential HCV (HIV negative) population of 16 cases. It would seem reasonable for the purposes of this outline analysis to assume that 50% to 60% of these cases are HCV positive i.e. nine of the 20 cases of severe haemophilia A would be expected to be HCV positive.[b]

Given the patient category calculations above, the priority ordering of the UKHCDO can be 'roughly' costed out as shown in Table 4, which details the cost consequences based on earlier analysis of FVIII consumption across all known cases of haemophilia A at 63,766 iu per patient per year.

[a] Personal communication with Dr G Dolan, Haemophilia Centre Director, Queen's Medical Centre, Nottingham.
[b] Although this is an arbitrary assumption, personal communication with The Haemophilia Society offers some rationale/support for the figure.

Table 4: Expected Resource Consequences (£s) of Funding rFVIII (Compared with High Purity pdFVIII) in line with the UKHCDO Priority Order. Estimates are Based on Average FVIII Consumption per Patient per Year (63,766 iu, HCD Annual Returns 1994) Across Expected Cases of Severe Haemophilia A in a Typical Purchaser District of 500,000 Population.

UKHCDO PRIORITY ORDER GROUPING	NUMBER OF CASES 'SEVERE'	RESOURCE CONSEQUENCES (INCL. VAT) rFVIII VERSUS: HIGH PURITY pdFVIII	CUMULATIVE RESOURCE CONSEQUENCES rFVIII VERSUS: HIGH PURITY pdFVIII
1 (a)	1	£12,753	£12,753
1 (b)	7	£89,271	£102,024
1 (c)	9	£114,777	£216,801
2	3	£38,259	£255,060
Total	20		

Please Note: See Appendix A for analysis excluding VAT.

It is important to note that Table 4 is an example, given current information/assumptions and the current starting point perspective, to show one possible scenario. It would be expected that, in general, groupings 1(c) and 2 (HCV positive patients and HIV positive patients respectively) would decline in proportion to the haemophilic population at large and grouping 1(a), HIV negative PUPS, would grow each year.

Given the above considerations it is important, from a policy perspective, to recognise the future implications with respect to the UKHCDO order of patient priority. In applying the UKHCDO order of priority for introduction to rFVIII, the groupings 1(a) and 1(b), HIV negative PUPs and HIV/HCV negative patients respectively, would constitute a large majority of the future haemophilia A population.

A further important issue when considering Table 4 is that using average consumption per year data to calculate the marginal costs per patient, the analysis fails to reflect the relatively smaller FVIII consumption level which may actually apply to infants. As the level of FVIII consumed per patient relates to body weight, it is the case that young children will require a lower level of FVIII concentrate per treatment. On the other hand, using an average per patient per year level of FVIII consumption also fails to reflect the relatively higher levels of FVIII consumption which relate to prophylaxis in patients over 5 years of age. The cost analysis undertaken aims to give a broad district-wide estimate of the extra medication costs expected following a switch to rFVIII from pdFVIII. The methodology used is based on 'average' consumption data which best suits the 'actual' consumption figures available via

the HCD Annual Returns. However, to limit any potential misunderstanding which may arise from the approach taken in arriving at cost estimates, Table 5 offers guidance on the expected level of FVIII consumption per patient per year across differing patient characteristics.

When considering the 'expected' annual consumption levels per patient given in Table 5, it is important to note that the 'actual' FVIII consumption level, per district per year, will include an element of 'unexpected' FVIII consumption which is not accounted for in Table 5. For example, the extended FVIII doses needed in major bleeding episodes and the management of inhibitor compromised patients, neither of which may be taken into consideration in the consumption estimates given in Table 5.

A further insight, on the time effects of implementing the UKHCDO recommendations, is presented in Table 6. Table 6 incorporates cost estimates discussed in Section 3.1 with the estimates of actual FVIII usage across patient categories, discussed in Section 4.1 above (Table 5), and the expected mix of severe haemophilia A patients discussed in Section 4.1. Although the material presented in Table 6 rests on a number of assumptions, it is able to offer some guidance to purchasers concerning specific patient characteristics and the consequences of implementing the UKHCDO recommendations across specific patient categories.

TABLE 5: Patient Characteristics: Expected Level of FVIII Consumption per Patient per Year and Estimated Annual Marginal Cost per Patient Associated with a Switch from High Purity pdFVIII to rFVIII.

PATIENT CHARACTERISTICS (SEVERE HAEMOPHILIA A)	EXPECTED ANNUAL FVIII CONSUMPTION (approx.)	ESTIMATED ANNUAL MARGINAL COST (incl. VAT)
Child - Aged Under 1 Year[a] Regimen : On Prophylaxis	**39,000 iu**	**£7,800**
Child - Aged Under 1 Year[a] Regimen : 'On Demand'	**2-3,000 iu**	**£200- £600**
Child - Aged Over 1 Year & Under 5 Years Regimen : On Prophylaxis	**39,000 iu**	**£7,800**
Child - Aged Over 1 Year & Under 5 Years Regimen : 'On Demand'[b]	**8,200 iu**	**£1,640**
Child - Aged Over 5 Years & Under 12 Years Regimen : On Prophylaxis	**78,000 iu**	**£15,600**
Child - Aged Over 5 Years & Under 12 Years Regimen : 'On Demand'[b]	**9,800 iu**	**£1,960**
Child - Aged Over 12 Years & Under 16 Years Regimen : On Prophylaxis	**156,000 iu**	**£31,200**
Child - Aged Over 12 Years & Under 16 Years Regimen : 'On Demand'[b]	**51,200 iu**	**£10,240**
Adult - Over 16 Years Regimen : On Prophylaxis[c]	**156,000 iu**	**£31,200**
Adult - Over 16 Years Regimen : 'On Demand'[c]	**51,200 iu**	**£10,240**

(Source of consumption data: clinical data from Sheffield Children's Hospital)

[a] Note: It is rare for an infant under the age of one to need FVIII replacement therapy; should they need treatment they are only likely to be on a prophylaxis regimen if they have had a major bleeding episode.

[b] Note: Approx. 85% - 90% of infants with severe haemophilia A treated at Sheffield Children's Hospital are on a prophylactic regimen.

[c] Note: In the absence of clinical data to support the adult consumption of FVIII concentrate those figures available for children aged 12-16 yrs of age have been used.

TABLE 6 Guidance on Time Effects of UKHCDO Policy Options

A Predicted Pattern of FVIII Consumption and Cost Over Years 1 to 5, Based on the Expected Cases of Severe Haemophilia A and the UKHCDO Patient Priority Order. Costs are Based on the Marginal (extra) Costs Per Patient Per Year (incl. VAT) Associated with the use of Recombinant Factor VIII as Opposed to High Purity Plasma Derived Factor VIII.

YEARS ONE & TWO	FVIII POLICY (UKHCDO PATIENT CATEGORIES)[a]	EXPECTED PATIENTS[b]	CONSUMPTION OF FVIII (IU)[c]	MARGINAL COST[d] £	ACCUM. MARGINAL COST £
	1 (a)	1 PUP[e]	39,000	7,800	7,800
	1 (b)	7 Virus Free[f]	675,200	135,040	142,840
	1 (c)	9 HCV +ive[g]	565,600	113,120	248,160
	2	3 HIV +ive[h]	153,600	30,720	286,680
	TOTAL	20 Patients			286,680

YEARS THREE & FOUR	FVIII POLICY (UKHCDO PATIENT CATEGORIES)[a]	EXPECTED PATIENTS[b]	CONSUMPTION OF FVIII (IU)[c]	MARGINAL COST[d] £	ACCUM. MARGINAL COST £
	1 (a)	2 PUPs[e]	78,000	15,600	15,600
	1 (b)	7 Virus Free[f]	675,200	135,040	150,640
	1 (c)	9 HCV +ive[g]	565,600	113,120	263,760
	2	2 HIV +ive[h]	102,400	20,480	284,240
	TOTAL	20 Patients			284,240

YEAR FIVE	FVIII POLICY (UKHCDO PATIENT CATEGORIES)[a]	EXPECTED PATIENTS[b]	CONSUMPTION OF FVIII (IU)[c]	MARGINAL COST[d] £	ACCUM. MARGINAL COST £
	1 (a)	3 PUPs[e]	117,000	23,400	23,400
	1 (b)	7 Virus Free[f]	675,200	135,040	158,440
	1 (c)	9 HCV +ive[g]	565,600	113,120	271,560
	2	1 HIV +ive[h]	51,200	10,240	281,800
	TOTAL	20 Patients			281,800

[a] See discussion of UKHCDO recommendations in section 4.1.
[b] See discussion of expected patient mix in section 4.1.
[c] See discussion in section 4.1 concerning expected levels of FVIII consumption across patient type.
[d] See discussion of costs in section 3.1.
[e] Assumes 1 new case (PUP) of severe haemophilia every 2 years, per typical district population of 500,000. Assumes PUPs present as children aged 1-2 years who are treated on prophylactic regimen.
[f] Assumes 4 patients at 5-12 years old on prophylactic regimen, 2 patients at 12-16 years old on prophlylactic regimen and 1 adult patient on an 'on demand 'regimen.
[g] Assumes 1 patient at 12-16 years old on prophylactic regimen and 8 adult patients on an 'on demand' regimen
[h] Assumes all HIV antibody positive patients in category 2 are adults treated 'on demand'

Please note that these consumption and cost estimates are based on clinical estimates of FVIII consumption across broad categories of patient and do not include unexpected FVIII consumption, for example, that used in cases of inhibitor compromised patients or big bleed episodes.

4.2 Support Plasma Derived Factor VIII as the Treatment of Choice

The alternative to those policy options discussed in Section 4.1 would be to support the conventional treatment of haemophilia A with pdFVIII products as the treatment of choice. This policy option should also entail:

Vigilance with respect to new developments in the research literature concerning the further development of rFVIII products.

Assessment and monitoring of the vaccination of haemophiliacs against HAV and HBV.

Addressing the current level of anxiety in the haemophilic population by encouraging a programme of patient education to explain the very small known risk of viral transmission with pdFVIII products.

5. DISCUSSION AND CONCLUSION

The assessment of the available evidence relating to the use of rFVIII, as opposed to pdFVIII, in the management of haemophilia A, has shown that direct benefit in terms of health gain is unquantifiable. The relative merit proposed through the use of rFVIII, as advocated through clinical opinion (UKHCDO), would appear to lie in the belief that rFVIII is better placed than pdFVIII to contend with future, as yet unknown, viruses and agents. This belief, combined with the fact that the haemophilic population has suffered greatly from previous 'new' viruses (e.g. HIV), has prompted the UKHCDO to put forward recommendations for the use of rFVIII as the treatment of choice for all patients.

Cost estimates have been presented showing the expected marginal (extra) annual costs of a switch from high purity pdFVIII to rFVIII to be in excess of £250,000, when prescribed across all severe haemophilia A patients in a typical purchaser district. With respect to the partial funding of rFVIII across specific patient groups, in accordance with the priority order given by the UKHCDO, estimates have also been presented for purchaser guidance. Based on current information and current market prices for FVIII concentrate, the cost associated with the funding of rFVIII would appear to have a significant financial impact on any purchaser of health care services.

Discussions between the Trent Working Group on Acute Purchasing and clinicians have highlighted that conflicting viewpoints are present within the debate surrounding the use of rFVIII. The viewpoint evident from reported clinical opinion (i.e. UKHCDO), is one which places emphasis on protection against the threat from the unknown virus/agent. Whereas, purchasers of health care are faced with the need to maximise, as far as possible, the purchase of health gain subject to finite resources. Purchasers have many beneficial services competing for limited funds and are charged with making decisions surrounding which of these beneficial treatments to fund. In such circumstances costly new technologies need to demonstrate substantial marginal benefit prior to being considered for inclusion in the purchasing process.

Those seeking funding for the use of rFVIII, must accept that decision makers are placed in an unenviable position whereby they must either (i) decide not to fund the use of rFVIII and expose themselves to the consequences of the unquantifiable possibility of future infection causing viruses being transmitted through pdFVIII, (assuming rFVIII is better placed to contend with the unknown virus/agent); or (ii) decide to fund the use of rFVIII (across all

patients or across certain patient categories), thereby foregoing the opportunity of maximising the overall purchase of health gain for their population. Given the current financial climate, the decision to fund rFVIII would ultimately require the withdrawal of health care services currently purchased for other sectors of the community.

It is evident from the factors discussed so far that there are issues surrounding the use of rFVIII which go beyond the traditional cost and benefit approach of previous topics considered by the Trent Working Group on Acute Purchasing. However, it would seem reasonable to assume that, if price were not an issue, rFVIII would be adopted as the treatment of choice. Therefore, each purchaser must consider the opportunity costs associated with the use of rFVIII, within its own local community. These opportunity costs appear to be high based on today's information. The analysis presented here offers some insight into the complete or partial funding of rFVIII within a typical purchaser community.

In the absence of national guidelines and, in the absence of any additional funding to accommodate the currently significant costs associated with a switch from pdFVIII to rFVIII, purchasers must consider the purchase of rFVIII in the context of the wider health care demands of their respective communities.

Due to the controversy and uncertainty associated with the use of rFVIII, a number of Purchasing Groups have been assessing the potential use of rFVIII.[44,45,46] The initial findings of these Purchasing Groups appear to be in line with the presentation made in this report. For example, the assessment made by the Northern and Yorkshire Regional Drug and Therapeutics Centre[44] concludes that, on current evidence, changing all haemophiliacs to recombinant products would be premature, with the use of rFVIII across specific patient groups being of arguable value. However, such Purchaser Groups have taken differing approaches and in most cases work is still being undertaken to refine their views.

Where purchasers are unable to fund rFVIII it will be necessary to address those issues discussed in Section 4.2 of this paper.

As product price plays such a large part in the decision to fund the use of rFVIII, it may be appropriate to consider placing pressure on manufacturers, where possible, to reduce prices and also on Government Officers to address the anomalies which place VAT on the purchase of rFVIII.

APPENDIX A COST ANALYSIS OF POLICY OPTIONS (TABLE 4)

REPRODUCED TO SHOW ESTIMATES <u>EXCLUDING VAT</u>.

Table 4 (b): Expected Resource Consequences (£s) of Funding rFVIII (Compared with High Purity pdFVIII) in line with the UKHCDO Priority Order. Estimates Exclude VAT and are Based on Average FVIII Consumption per Patient per Year (63,766 iu, HCD Annual Returns 1994) Across Expected Cases of Severe Haemophilia A in a Typical Purchaser District of 500,000 Population.

UKHCDO PRIORITY ORDER GROUPING	NUMBER OF CASES 'SEVERE'	RESOURCE CONSEQUENCES **(EXCL. VAT)** rFVIII VERSUS: HIGH PURITY pdFVIII	CUMULATIVE RESOURCE CONSEQUENCES rFVIII VERSUS: HIGH PURITY pdFVIII
1 (a)	1	£8,290	£8,290
1 (b)	7	£58,030	£68,320
1 (c)	9	£74,610	£140,930
2	3	£24,870	£165,800
Total	20		

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