Cost-effectiveness analysis of alternative factor VIII products in treatment of haemophilia A

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The comparison of two groups of manufactured clotting factor concentrates for the treatment of patients with haemophilia A. Ultra-high purity and recombinant (UHP/R) factor VIII products were compared with intermediate and very-high purity (IP/VHP) factor VIII preparations.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population mainly comprised patients with haemophilia A, treated with manufactured factor VIII concentrates. The population was subdivided into three groups for modelling purposes. Each of these groups was further stratified according to five transmitted or potentially transmitted viruses. These were HIV, parvovirus B19, HAV, HBV and HCV. The patients were assumed to be:

- HIV seropositive (health risk 1);
- HIV seronegative but HCV seropositive (health risk 2); or
- seronegative for both HIV and HCV, but at risk for seroconversion to HAV or HBV.

Setting
The setting was both the community and secondary care. The study was conducted in the USA. The study involved the provision of blood products either in the home, or in an alternative setting that was not explicitly specified by the authors.

Dates to which data relate
The effectiveness data were gathered from a range of studies published from 1989 to 1996. The authors' assumptions, however, were based mainly on literature published between 1991 and 1997. The cost-effectiveness analysis was dated 1995. The price year was 1995.

Source of effectiveness data
The effectiveness data were derived mainly from a synthesis of published studies. The authors also made a number of assumptions about effectiveness, on the grounds of opinion at the outset of the study.

Modelling
Health-risk modelling scenarios were used to estimate the expected costs and health benefits of the factor VIII concentrates across a range of health problems.

**Outcomes assessed in the review**
The outcome assessed in the review was the patient's quality of life. The effect of treatment with the alternative factor VIII products was evaluated in three alternative scenarios.

For health risk model 1 (patient seropositive for HIV), the outcomes assessed were:

- the life span after seroconversion;
- the loss in quality-adjusted life-years (QALYs) for each 10% reduction in the CD4 cell count;
- the absolute CD4 count for IP/VHP versus UHP/R;
- the annual QALYs over the patient's life span for IP/VHP versus UHP/R;
- the probability of parvovirus B19 seroconversion;
- the probability of chronic anaemia from parvovirus B19 infection in the last 2 years of life;
- the loss in QALYs due to chronic anaemia;
- the probability of aplastic anaemia from parvovirus B19 infection in the last 2 years of life;
- the loss in QALYs due to aplastic anaemia; and
- the discounted total number of QALYs per patient over their life span.

For health risk model 2 (patient seronegative for HIV but seropositive for HCV), the outcomes assessed were:

- the time horizon after HCV seroconversion;
- the annual QALYs per patient;
- the probability of liver failure and a liver transplant (once only);
- the loss in annual QALYs after a liver transplant; and
- the discounted total number of QALYs per patient over a 30-year time horizon.

For health risk model 3 (patient seronegative for both HIV and HCV, but at risk for seroconversion to HAV and HBV), the outcomes assessed were:

- the probability of HAV seroconversion;
- the loss in QALYs per patient due to HAV infection;
- the average loss in QALYs per factor VIII product user due to HAV infection;
- the probability of HBV seroconversion;
- the discounted total lifetime loss in QALYs due to HBV infection; and
- the average loss in QALYs per factor VIII product user due to HAV (sic) infection.
Study designs and other criteria for inclusion in the review
The designs of the studies included in the review were not reported. Articles published between 1989 and 1997 were included, although the authors did not report any inclusion or exclusion criteria.

Sources searched to identify primary studies
The authors did not report the sources searched to identify the primary studies, although it was evident that they had used a range of both published and unpublished data.

Criteria used to ensure the validity of primary studies
The criteria used to ensure the validity of primary studies were not explicitly stated. The authors did, however, make reference to a study that was rejected on the basis of sample size.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 28 published studies and 2 sets of unpublished data were used in the health risk models. The types of primary studies used were unclear, as the authors did not clearly define the sources of the primary data.

Methods of combining primary studies
It was unclear if the authors combined the primary studies used to estimate the individual input parameters to the model.

Investigation of differences between primary studies
Not reported.

Results of the review
Health risk model 1 (patient seropositive for HIV).

The life span after seroconversion was 12 years: 10 years with a CD4 count greater than or equal to 200, and 2 years with a CD4 count less than 200. This was the same for all patients,

The loss in QALYs for each 10% reduction in the CD4 count was 0.22 per year. This was the same for all patients.

The absolute CD4 count (IP/VHP versus UHP/R) was 10% lower for IP/VHP users if the CD4 count was greater than or equal to 200. The absolute value was 20% lower for IP/VHP users if the CD4 count was lower than 200.

The annual QALYs over the life span (IP/VHP versus UHP/R) was 0.22 less for IP/VHP users if the CD4 count was greater than or equal to 200. The value was 0.44 less for IP/VHP users if the CD4 count was less than 200.

The probability of parvovirus B19 seroconversion was zero for UHP/R users and 0.45 for IP/VHP users.

The probability of chronic anaemia from parvovirus B19 infection in the last 2 years of life, if infected, was zero for UHP/R users and 0.33 for IP/VHP users.

The loss in QALYs due to chronic anaemia was 0.13 per year (over 2 years).

The probability of aplastic anaemia from parvovirus B19 infection in the last 2 years of life was zero for UHP/R users and 0.006 for IP/VHP users.
The loss in QALYs due to aplastic anaemia was 0.5 per year (over 2 years).

The discounted total number of QALYs per patient over their life span was 2.607 less for IP/VHP users than for UHP/R users.

Health risk model 2 (patient seronegative for HIV but seropositive for HCV).

The time horizon after HCV seroconversion was 30 years. This was the same for all patients.

The annual QALYs per patient was 14% lower for IP/VHP users if there was no liver failure.

The probability of liver failure and a liver transplant (once only) was 0.025 for IP/VHP users (once in the 1 to 25 years after seroconversion) and zero for UHP/R users.

The annual loss in QALYs after a liver transplant was 0.25 in the first year, 0.025 in each subsequent year (years 2 to 5) after transplant, and zero thereafter.

The discounted total number of QALYs per patient over a 30-year time horizon was 2.76 to 2.82 less for IP/VHP users. This varied with the occurrence of liver failure in the first 25 years after seroconversion.

Health risk model 3 (patient seronegative for both HIV and HCV, but at risk for seroconversion to HAV and HBV).

The probability of HAV seroconversion was 0.00533 for IP/VHP users and zero for UHP/R users.

The loss in QALYs per patient due to HAV infection was 0.17 (quality of life zero for 2 months).

The average loss in QALYs per factor VIII product user, due to HAV infection, was 0.0009 for IP/VHP users and zero for UHP/R users.

The probability of HBV seroconversion was 0.005 for IP/VHP users and zero for UHP/R users.

The discounted total lifetime loss in QALYs due to HBV infection was 0.25.

The average loss in QALYs per factor VIII product user, due to HAV (sic) infection, was 0.00125 for IP/VHP users and zero for UHP/R users.

**Methods used to derive estimates of effectiveness**
The authors made assumptions about effectiveness.

**Estimates of effectiveness and key assumptions**
The authors made three major assumptions at the outset of the study:

- the probability of seroconversion of HIV virus is zero for all factor VIII products;
- the rates of neutralising alloantibody inhibitor development in patients using both types of concentrates are closely similar, and hence there are no differences in the costs or quality of life effects between products due to inhibitors; and
- the efficacy and safety of UHP and R concentrates are the same.

**Measure of benefits used in the economic analysis**
The health benefits used were QALYs. The authors did not report the valuation methods used in the primary studies to derive the utility or quality adjustment weights for the estimation of the QALYs.
Direct costs
The analysis included the direct costs of total illness and treatment. These were expressed as the costs per case associated with either the UHP/R or IP/VHP products.

Health risk model 1 included the lifetime medical costs (assumed to be the same for all patients), the cost of chronic anaemia ($3,000), and the cost of aplastic anaemia ($95,000).

Health risk model 2 included the lifetime medical costs (assumed to be the same for all patients), and the cost of a liver transplant ($215,000).

Health risk model 3 included the cost of HAV infection ($1,265), the cost per user of HAV infection ($6.74 for IP/VHP users and $0 for UHP/R users), and the discounted total lifetime cost of HBV infection ($719).

The cost estimates were taken from published sources. The resource use and prices were not reported separately. It was unclear if the costs were based on unit prices or hospital charges. The discount rate was set at 3%. The price year was 1995.

Statistical analysis of costs
No statistical analysis of costs was reported.

Indirect Costs
No indirect costs were included in the analysis.

Currency
US dollars ($). No currency conversion rate was reported.

Sensitivity analysis
The authors stated that the complexity of the three health risk models made it difficult to provide a concise and meaningful sensitivity analysis. However, they did report the impact of varying QALY losses from 0.5 to 1.5 times their baseline values.

Estimated benefits used in the economic analysis
Health risk model 1: the discounted loss of QALYs for UHP/R, compared with IP/VHP, ranged from 0.906 QALYs per patient (assuming a 2-year life span) to 3.649 QALYs per patient (assuming a 20-year life span).

Health risk model 2: the discounted loss of QALYs for UHP/R, compared with IP/VHP, ranged from 2.764 QALYs per patient (assuming 1 year to liver failure or transplant) to 2.826 QALYs per patient (assuming no liver failure).

Health risk model 3: the discounted loss of QALYs for UHP/R, compared with IP/VHP, was not presented because the authors reported that the analysis showed negligible changes in QALYs.

The estimates of the health benefits included the knock-on effects of the factor VIII products, in terms of the risk of transmitting infections and the consequences of infection.

Cost results
Health risk model 1: the discounted lifetime additional medical costs (excluding the cost of the factor VIII product) per patient for UHP/R, compared with IP/VHP, ranged from $520 (assuming a 2-year life span) to $305 (assuming a 20-year life span).

Health risk model 2: the discounted lifetime additional medical costs (excluding the cost of the factor VIII product) per
patient for UHP/R, compared with IP/VHP, ranged from $5,375 (assuming 1 year to liver failure or transplant) to $0 (assuming no liver failure).

Health risk model 3: the discounted lifetime additional medical costs (excluding the cost of the factor VIII product) per patient for UHP/R, compared with IP/VHP, were not presented because the authors reported that the maximum price premium was $0.

The estimates of the costs included the knock-on costs of the factor VIII products, in terms of the risk of transmitting infections and the consequences of infection.

**Synthesis of costs and benefits**
The authors reported that there were no reliable ways of estimating the social costs (including research and development) of factor VIII products. In addition, the unit costs varied with the size and type of purchaser. For this reason, the authors decided to estimate the maximum price difference between UHP/R and IP/VHP at which the intervention was cost-effective. This was performed for two cost-effectiveness thresholds, $35,000 per QALY and $50,000 per QALY.

The maximum, discounted, lifetime additional purchase cost for UHP/R to be cost-effective at a threshold of $35,000 per QALY was between $32,230 (2 years) and $128,020 (20 years) for health risk model 1. The cost for health risk model 2 was between $102,125 (1 year to liver transplant or failure) and $98,923 (no liver failure). No estimate for health risk model 3 was reported.

The maximum, undiscounted, annual additional purchase cost for UHP/R to be cost-effective at a threshold of $35,000 per QALY was between $16,353 (2 years) and $8,354 (20 years) for health risk model 1. The cost for health risk model 2 was between $5,059 (1 year to liver transplant or failure) and $4,900 (no liver failure). No estimate for health risk model 3 was reported.

The maximum, undiscounted, additional purchase cost per unit for UHP/R to be cost-effective at a threshold of $35,000 per QALY was between $0.409 (2 years) and $0.209 (20 years) for health risk model. The cost per unit for health risk model 2 was between $0.126 (1 year to liver transplant or failure) and $0.123 (no liver failure). No estimate for health risk model 3 was reported.

The maximum, discounted, lifetime additional purchase cost for UHP/R to be cost-effective at a threshold of $50,000 per QALY was between $45,820 (2 years) and $182,755 (20 years) for health risk model 1. The cost for health risk model 2 was between $141,319 (1 year to liver transplant or failure) and $141,319. No estimate for health risk model 3 was reported.

The maximum, undiscounted, annual additional purchase cost for UHP/R to be cost-effective at a threshold of $50,000 per QALY was between $23,249 (2 years) and $11,926 (20 years) for health risk model 1. The cost for health risk model 2 was between $7,107 (no liver failure). No estimate for health risk model 3 was reported.

The maximum, undiscounted, additional purchase cost per unit for UHP/R to be cost-effective at a threshold of $50,000 per QALY was between $0.581 (2 years) and $0.298 (20 years) for health risk model 1. The cost per unit for health risk model 2 was between $0.178 (1 year to liver transplant or failure) and $0.175 (no liver failure). No estimate for health risk model 3 was reported.

The sensitivity analysis showed that each 10% increase in the relative loss of QALYs raised the cost-effective price premium by slightly more than 10%.

**Authors’ conclusions**
Ultra-high purity and recombinant (UHP/R) preparations were not uniformly more cost-effective than intermediate and very-high purity (IP/VHP) products across a range of health problems experienced by haemophilic patients. The relative cost-effectiveness of the two classes of prepared factor VIII products was sensitive to product prices.
**CRD COMMENTARY - Selection of comparators**

The authors reported that most patients in the USA received one of the factor VIII products included in the intervention or comparator categories (UHP/R and IP/VHP). Thus, the products would appear to represent current practice in the authors’ setting. You should decide if the two products included in the comparator represent current practice in your own setting. You should also consider whether it is relevant to your own setting to combine ultra-high purity and recombinant factor VIII products into one category, and intermediate and very-high purity products into another.

**Validity of estimate of measure of effectiveness**

The authors did not report whether a systematic search and review of the literature had been undertaken. Neither did they comment on the methods used to identify the relevant research and to minimise bias. It was also unclear as to whether the estimates from the primary studies were combined, or whether the authors considered the impact of differences between the primary studies when estimating the effectiveness.

The effectiveness data were modelled, but there were insufficient details of the model. For example, the structure, the sequence of events included in the model. In addition, it was not stated whether the model had been validated in terms of consistency or reliability, or whether it was representative of current practice. The authors noted that the analysis was not robust. Also, there was a dearth of epidemiological, quality of life or economic data on viral infections in people with haemophilia. The authors stated that they used conservative assumptions and that the model was too complex to provide a meaningful sensitivity analysis. However, they did report that the results were not sensitive to the rate of discount used, but were sensitive to the assumptions about the level of QALY losses.

**Validity of estimate of measure of benefit**

This study reported QALYs as the measure of benefit. The estimation of the benefits was modelled. The authors did not report any details of the methods used to generate the QALY values. In addition, the estimates of the health benefits were reliant on the structure of the model and the effectiveness estimates used. These factors meant that it was not possible to assess the robustness or validity of the estimated benefits.

**Validity of estimate of costs**

The authors reported that costs were estimated from a societal perspective but indirect costs were not included. The resource use and prices were not reported separately. Although not clearly stated, the unit costs appear to have been taken from the published sources used in the review. The authors stated that because the societal costs of factor VIII products were unknown, and the prices varied with market conditions, they conducted the analysis with treatment cost as a variable quantity. However, they illustrated the potential cost-effectiveness of UHP/R using the average wholesale prices of the products for 1995, for a person using 40,000 units per year. The authors reported the range of additional purchase costs at which UHP/R might be cost-effective, using the cost per QALY thresholds of $35,000 and $50,000. You should consider whether these additional costs and thresholds are likely to be relevant to your own setting.

A full sensitivity analysis was not reported. The authors reported that this was because of difficulties in providing a concise or meaningful sensitivity analysis, due to the complexity of the three health risk models.

**Other issues**

The authors did not compare their findings with those from other studies. They did, however, make reference to the guidelines established by the Medical and Scientific Advisory Council of the (US) National Haemophilia Foundation. The relative cost-effectiveness of the products depended on current medical practice, costs, and the price of the products. In addition, the cost-effectiveness of factor VIII products was not uniform across the spectrum of haemophilic patients. This suggested that it would be difficult to transfer the results of the analysis to alternative settings or populations.

The study considered three health risk scenarios and this was reflected in the authors' conclusions. The authors clearly reflected the limitations of the study in their conclusions. They stated that the "analysis does not and cannot establish
that UHP/R products are uniformly more (or less) cost-effective than IP/VHP products under all real world conditions”.

**Implications of the study**
The decision-maker must assess the patient's health problems and then review the actual prices or unit purchase costs of factor VIII concentrates, in order to determine which class of concentrates would be most suitable for a particular group of patients.

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