Cost-utility analysis of recombinant factor VIIa (NovoSeven) in six children with long-standing inhibitors to factor VIII or IX

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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 use of recombinant factor VIIa (rFVIIa) for the treatment of children with haemophilia and inhibitors to factor VIII or IX. The treatment consisted of an intravenous push injection of rFVIIa in a dose of 90 microg/kg, repeated in two hours. The treatment was mainly administered at home.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised children aged 0 to 18 years with haemophilia (A or B) and long-standing inhibitors to factor VIII or IX.

Setting
The setting was the community. The economic study was carried out at the Haemophilia Treatment Centre of the Royal Children's Hospital, Victoria, Australia.

Dates to which data relate
The period during which the effectiveness and resource use data were collected was not reported. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken both prospectively and retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations to determine the sample size were not performed. All patients treated at the study hospital were selected for the study during three phases. Phase 1 was the 6 months preceding the introduction of rFVIIa treatment. Phase 2 was the 6 months on rFVIIa treatment assessed retrospectively. Phase 3 was the 6 months on rFVIIa treatment assessed prospectively. A sample of 6 children was enrolled. The mean age of the children at baseline was 14 years (range:
11 - 16) and their mean weight was 49 kg (range: 30 - 68). The mean age of the children at completion was 15 years (range: 12 - 17) and their mean weight was 54 kg (range: 27 - 77). The baseline characteristics were presented.

**Study design**

This was a longitudinal before-and-after study, which was carried out in a single centre (the Royal Children's Hospital) and in three phases. The comparison was carried out between usual care (phase 1) and rFVIIa (phase 2 and phase 3). The patients were followed for 18 months. The losses to follow-up were not reported.

**Analysis of effectiveness**

The analysis was conducted on an intention to treat basis, with the mean changes from the remainder of the group substituted for missing data. The health outcomes assessed in the analysis were:

- the number of bleeds;
- the delay from assessment to treatment;
- the number of re-treatments within 24 hours of initial treatment;
- the number, duration and severity of painful episodes (scale of 0 - 5);
- days off school;
- the number of inpatient days;
- the number of emergency room visits; and
- days requiring wheelchair, sling or crutches.

All of the outcome measures were assessed using a questionnaire. This was in addition to patient and family interviews for the retrospective part of the study, and a diary documenting all events for the prospective part of the study. The primary health measure was the quality of life of the patients, as measured using the Australian Authorized Adaptation of the Child Health Questionnaire-Child Form (AUST CHQ-CF80). The AUST CHQ-CF80 comprises 80 items for the assessment of global health, physical activities, everyday activities, pain, social interaction, overall behaviour, general well-being, self-esteem, own health and family responses. The parents' form was the AUS CHQ-PF50, which assesses similar points from the perception of the parents or guardians.

The utility values were also determined using the EuroQol multiattribute utility valuation instrument. Three health-state scenarios, which were constructed from the outcomes reported in the questionnaire and diary for each of the study phases, were presented. The respondents were blinded to the study phase represented by the scenario. An average of the results of phases 2 and 3 was compared with phase 1; a statistical analysis was not conducted on account of the small sample size.

**Effectiveness results**

The number of bleeds was 28 with usual care and 18.3 with rFVIIa. This corresponded to a 34.5% reduction.

The number of major bleeds was 14.8 with usual care and 12.1 with rFVIIa. This corresponded to an 18.5% reduction.

The average delay from assessment to treatment was 37.4 hours with usual care and 6.0 hours with rFVIIa. This corresponded to an 84% reduction.

The number of re-treatments within 24 hours of initial treatment was 6 with usual care and 0.5 with rFVIIa. This corresponded to a 91.7% reduction.
The number of painful episodes was 12 with usual care and 10.6 with rFVIIa. The duration of these episodes was 130.8 hours with usual care and 19.1 hours with rFVIIa, while their severity was 4.3 (usual care) and 3.3 (rFVIIa), respectively. There was an 11.8% reduction in the number of painful episodes, an 85.4% reduction in their duration, and a 23.5% reduction in their severity.

The days off school were 37.5 with usual care and 25 with rFVIIa. This corresponded to a 33% reduction.

The number of inpatient days was 2 with usual care and 1.8 with rFVIIa. This corresponded to a 12.5% reduction.

The number of emergency room visits was 4.3 with usual care and 1.4 with rFVIIa. This corresponded to a 67.3% reduction.

The number of days requiring wheelchair, sling or crutches was 95.5 with usual care and 35 with rFVIIa. This corresponded to a 63.4% reduction.

Quality of life measurement resulted in improvements associated with rFVIIa in 9 of the 10 domains in the patient-reported questionnaire and all 8 domains of the parent-reported questionnaire. The only deterioration with rFVIIa was perceived in the domain of the overall behaviour.

The utility value was -0.11 for the scenario derived from phase 1, meaning that problems associated with haemophilia and inhibitors are perceived by some to be worse than death. The utility value was 0.47 for the scenario in phase 2 and 3.

The incremental utility improvement associated with the use of rFVIIa was 0.58.

Clinical conclusions
The effectiveness evidence showed that the use of rFVIIa represented a safe intervention and improved quality of life, as perceived by the patients and parents.

Measure of benefits used in the economic analysis
The benefit measure used in the economic analysis was the quality-adjusted life-year (QALY). This was derived from the effectiveness analysis using the EuroQol multiattribute utility valuation instrument.

Direct costs
Discounting was not carried out as the costs were incurred over 18 months. The unit costs were reported and the cost/resource boundary reflected the perspective adopted in the analysis. The cost items included in the analysis were drugs, personnel, visits and hospitalisation. The direct costs were estimated using actual data, derived from the study hospital and Medicare Benefit Schedule. The quantities were estimated from the patients' records. The period during which the quantities were collected was not reported. The costs were expressed in 1999 values.

Statistical analysis of costs
No statistical analysis of the costs was carried out.

Indirect Costs
The indirect costs were included in the analysis, the authors assuming that the indirect costs were captured through the utility values. Consequently, an explicit assessment of the indirect costs was not carried out.

Currency
Australian dollars (Aus$).
Sensitivity analysis
Sensitivity analyses were carried out to assess the robustness of the estimated cost-utility ratios to variations in both the utility values and cost estimates. The type of analysis performed was not stated.

Estimated benefits used in the economic analysis
As assessed in the effectiveness analysis, the incremental QALY gained with rFVIIa over usual care (for one year of treatment) was 0.58.

Cost results
The total annual costs per patient were $189,313 with usual care and $219,214 with rFVIIa. This resulted in an extra cost of $29,901 with rFVIIa.

Synthesis of costs and benefits
An incremental cost-utility analysis was carried out to combine the costs and benefits of the interventions. The extra cost per additional QALY gained with rFVIIa over usual care was $51,553. The sensitivity analyses found that the variables that most affected the results were the usage and cost of replacement products.

Authors’ conclusions
Treatment with recombinant factor VIIa (rFVIIa) proved to be cost-effective, with an incremental cost per quality-adjusted life-year (QALY) similar to that of other accepted health interventions.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. Several treatments, such as porcine FVII or human FVII, were considered as usual care since they were administered in phase 1 of the study. You should assess which treatment is currently used in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a longitudinal before-and-after design. This appears to have been appropriate since the same sample of patients underwent the treatments compared in the study, thus negating selection bias. The study sample appears to have been representative of the study population. However, as the authors acknowledged, the internal validity of the analysis was limited by the small sample size and the partially retrospective design of the analysis. In terms of the internal validity, it has to be noted that the patients represented 6 of the 26 paediatric patients in Australia suffering from haemophilia and inhibitors. Thus, it was difficult to aggregate even this small sample, and power calculations were not attempted. In terms of the study design, the authors acknowledged that the analysis "has the weakness of relying on memory and subjective assessment of a new treatment which may a priori be considered to be better than the old treatment".

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was represented by the QALYs, which were derived directly from the effectiveness analysis. The use of QALYs enables this treatment to be compared with other interventions implemented in the health care system.

Validity of estimate of costs
The authors stated that the study was conducted from a societal perspective. However, the indirect costs were not measured, but were assumed to have been implicitly assessed in the utility scores. Thus, it is debatable whether the perspective could, more appropriately, be described as that of the health care system. In this case, all the relevant categories of costs were included. The price year was reported, and the unit costs were given for all resources.
considered. However, the period during which the resource use data were collected was not reported. In addition, the costs were treated deterministically, although some sensitivity analyses on the costs were performed. It would have been useful, for transparency and generalisability, if the resource quantities had been reported.

**Other issues**
The authors made some comparisons of their findings with those from other studies. However, the issue of the generalisability of the study results to other settings was not addressed. In addition, few sensitivity analyses were carried out. The authors enrolled children with haemophilia and this was reflected in the study conclusions. The authors did not report the results of the sensitivity analyses clearly, although the effectiveness results were reported in full. The authors mentioned some limitations of the analysis. For example, the small sample size and the partially retrospective design of the study.

**Implications of the study**
The study results suggest the use of rFVIIa for the treatment of children with haemophilia since it was shown to be clinically effective and safe, and improved quality of life as perceived by the patients and parents, at a justifiable cost.

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