Cost effectiveness of recombinant activated factor VII for the control of bleeding in patients with severe blunt trauma injuries in the United Kingdom

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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 study examined recombinant activated factor VII (rFVIIa, Novo-seven; Novo Nordisk A/S) for the control of bleeding in patients with severe blunt trauma injuries. The procedure involved three intravenous injections of rFVIIa. The first injection was administered immediately after transfusion of the eighth unit of red blood cells (RBC) if the patient required additional transfusions. The second and third doses followed 1 and 3 hours after the first dose. rFVIIa was administered in addition to standard care.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised blunt trauma patients who had received six units of RBC within 4 hours of admission and were known to be aged 16 years or older and under 65. Exclusion criteria were:

- cardiac arrest prior to trial drug administration;
- gunshot wound to the head;
- Glasgow Coma Scale score of less than 8 unless in the presence of a normal head computed tomography scan;
- base deficit at least 15 milliequivalents per litre or severe acidosis with pH < 7.00;
- transfusion of eight units or more of RBC prior to arrival at the trauma centre; and
- injury sustained 12 hours or more before randomisation.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence and resource use data were primarily taken from a study published in 2005 (Boffard et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details). They were, however, supplemented by secondary data sources from 1985 to 2004. The price year was 2004.

Source of effectiveness data
NHS Economic Evaluation Database (NHS EED)
Produced by the Centre for Reviews and Dissemination
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The effectiveness data were derived from a review of published studies, supplemented with secondary data sources.

**Modelling**
A model was used to estimate the probability of survival 30 and 90 days post-trauma, which was not available from the primary effectiveness study. In the first instance, data from the Trauma Audit and Research Network (TARN) was used to model survival up to the time of hospital discharge or death in hospital. Survivors in the primary study at day 30 were assigned a survival probability based on the probability of survival for a matched cohort of patients in the TARN. The maximum time to hospital discharge among the TARN cohort was 90 days. Therefore, these data were used to predict the probability of survival from 30 to 90 days post-trauma.

In the second stage, Scottish data from a cohort of 166 trauma patients admitted to an intensive care unit between 1985 and 1992 (and followed until 1997) and alive at 90 days post-trauma were used. The authors used these data to model the probability of survival at 5 years given that the patient was alive at 90 days post-trauma.

In the final stage, life tables for the general population in the UK for 2002 to 2004 were used to generate age- and gender-specific life expectancies for each patient alive 5 years post-trauma, assuming the same life expectancy as the general population.

**Outcomes assessed in the review**
The outcome assessed in the review was the mortality rate.

**Study designs and other criteria for inclusion in the review**
The effectiveness data for survival up to 30 days were taken from a study that reported the results from two international, randomised placebo-controlled trials (Boffard et al. 2005). Two secondary data sources were used to model survival 30 and 90 days post-trauma. The first of these involved a cohort of 375 patients from TARN, and the second a cohort of 166 trauma patients.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Two primary studies appear to have been included in the review, supplemented with two secondary data sources.

**Methods of combining primary studies**
The studies were not combined.

**Investigation of differences between primary studies**
Not relevant.
Results of the review
There was no significant difference observed for mortality rates at 30 days post-trauma (25% in the rFVIIa group versus 30% in the placebo group; p=0.58);

0.53% of patients were observed to have died in the period from 30 to 90 days post-trauma;

the mean time to death was 43 days post-trauma (standard deviation, SD=3.5);

7% of patients died in the period from 90 days to 5 years;

the mean time to death was 671 days post-trauma (SD=468).

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The utilities of relevant health states were taken from a study found through a review of the literature. The methods used in the study were not reported. The benefits were discounted at a rate of 3.5% per year.

Direct costs
The costs were discounted at a rate of 3.5%. The unit costs were taken from a number of sources, mostly official publications, and were reported separately. Resource use and costs were calculated in three stages. In the first stage, costs in the first 30 days post-trauma, based on resource use in a published study (Boffard et al. 2005), were estimated. These costs were associated with the following:

rFVIIa drug acquisition costs;
RBC units transfused in the first 48 hours;
fresh frozen plasma received in the first 48 hours;
platelets received in the first 48 hours;
cryoprecipitate received in the first 48 hours;
all surgical procedures received in the first 30 days;
intensive care unit costs in the first 30 days; and
regular inpatient bed-days in the first 30 days.

In the second stage, the costs from day 30 to day 90 post-trauma were calculated on the basis of data from the TARN cohort. The costs included here were those relating to the cost of the intensive care unit and regular inpatient ward costs. In the final stage, long-term healthcare costs from 90 days post-trauma until death were calculated. These costs were approximated using the mean health expenditure per capita in the UK. In addition, baseline estimates included a figure of 10,000 in the first year post-trauma to cover rehabilitation costs. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically in the base-case analysis.

Indirect Costs
The indirect costs were not included in the analysis.
Currency
UK pounds sterling (¥).

Sensitivity analysis
A univariate sensitivity analysis was performed to assess the sensitivity of the cost-effectiveness estimate to changes in the following:

- the difference in mortality risk between rFVIIa and placebo at 30 days (from 10% to 1%);
- the discount rate (0% and 6%);
- the cost per surgical procedure (costs halved and doubled);
- the long-term trauma costs (1,654 in the first year and 0 in all subsequent years; 20,000 + 1,654 in first year and 1,654 in all subsequent years);
- residual life expectancy (90% of age and gender specific residual life expectancy for the general population); and
- health state utility values (0.67 in first year with UK age and gender specific population norms for the remaining years of life).

A multivariate sensitivity analysis involved varying a number of the variables simultaneously.

Estimated benefits used in the economic analysis
For a lifetime follow-up, 15.80 (SD=10.02) life-years and 10.59 (SD=6.72) QALYS were gained with the intervention and 14.75 (SD=10.18) life-years and 9.88 (SD=6.82) QALYS with the placebo.

Cost results
The mean total lifetime discounted costs were 70,882 (SD=31,121) for the intervention and 57,639 (SD=37,525) for the placebo.

The mean difference was 13,243 (95% confidence interval: 1,973 to 24,516; p=0.02).

Synthesis of costs and benefits
The estimated benefits and costs were combined by calculating the incremental cost per life-year and per QALY gained. For the intervention relative to placebo, the incremental cost per life-year gained was 12,613 and the incremental cost per QALY gained was 18,825.

The cost-effectiveness was most sensitive to the difference in mortality risk between the intervention and placebo at 30 days, the discount rate and the health state utility values used.

When the difference in mortality associated with the intervention and placebo over the first 30 days was varied from 10% to 1% (base-case 5%), the incremental cost per QALY gained ranged from 8,990 to 89,897.

Varying the discount rate for costs and benefits between 0% and 6% resulted in incremental costs per QALY gained ranging from 9,347 to 26,772.

Assuming health state utility values of 0.67 in the first year post-trauma with UK age- and gender-specific population norms for the remaining years of life, the incremental cost per QALY gained fell to 15,406.

Authors' conclusions
Relative to placebo, recombinant activated factor VII (rFVIIa) may be a cost-effective therapy for the UK National Health Service.

**CRD COMMENTARY - Selection of comparators**
Although no explicit justification was given for the comparator used, it was unclear what the current practice was in the UK. The authors did not discuss the existence of alternative treatments. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken. It was not stated how the studies were identified and selected for inclusion, therefore some relevant studies might have been omitted. Consequently, this might have biased the estimation of effectiveness parameters.

**Validity of estimate of measure of benefit**
While the primary study used in the effectiveness analysis did not demonstrate a significant difference in mortality rates between the rFVIIa and placebo groups, the authors provided an adequate justification for their use of QALYs as the primary outcome measure. The QALYs were calculated using health-related quality of life data. Discounting was performed in accordance with economic evaluation guidelines.

**Validity of estimate of costs**
All the categories of cost relevant to the perspective adopted appear to have been included in the analysis. The sources used to derive the costs and quantities were explicitly reported and appear to have been appropriate. While the costs were reported separately this was not always the case with the quantities, which might limit the possibility of replicating the analysis in other settings. The price year was reported, which will simplify reflation exercises in other time periods. Discounting was appropriate and was undertaken.

**Other issues**
The authors did not compare their findings with other studies, although this was probably due to an absence of studies that had focused on the issue. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The authors acknowledged some further limitations to their study. For example, the absence of long-term patient data on the impact of rFVIIa on morbidity, mortality and health care resource use, and lifetime health state utility values for trauma patients.

**Implications of the study**
The authors made a number of recommendations for additional research in this area. Research is needed on the long-term impact of rFVIIa on mortality and morbidity in trauma patients, the long-term healthcare costs associated with rFVIIa treatment in trauma patients, and the long-term health state utility values associated with rFVIIa treatment in trauma patients.

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**Bibliographic details**

**PubMedID**
Other publications of related interest
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Subject indexing assigned by NLM

MeSH
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