Cost-effectiveness of recombinant activated factor VII in the treatment of intracerebral haemorrhage

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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 the use of recombinant activated factor VII (rFVIIa; NovoSeven; NovoNordisk) in the treatment of intracerebral haemorrhage (ICH). Patients were assigned rFVIIa at a dose of 40, 80 or 160 microg/kg. This health technology was compared with standard care, which was defined as placebo.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients presenting to the emergency department with ICH. Other patient characteristics were: 18 years of age or older; entered hospital within 3 hours of ICH onset; not in a deep coma; no symptomatic thrombotic or vaso-occlusive disease within 30 days before ICH onset; and not taking anticoagulation agents at the time of ICH.

Setting
The study setting was inpatient care. The economic study was undertaken in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1998 and 2006. The resource use data were derived from studies and other sources published in 2005. The price year was 2005.

Source of effectiveness data
Patient baseline characteristics included in the economic evaluation were the patients' average age and weight. The efficacy data of rFVIIa and standard care included the percentage of patients achieving specific modified Rankin Scores (mRS) at day 90. The mortality data included in the model were age-specific all-cause mortality. This was adjusted by death hazard ratios to estimate mortality rates for ICH patients, stratified by mRS at 90 days.

Modelling
A decision tree with a lifetime horizon was developed. The model structure, including treatment pathways and outcomes, was well reported and a graphical depiction was provided.

Sources searched to identify primary studies
Patient characteristics were derived from those observed in clinical practice, based on published literature and analyses of the Healthcare Cost and Utilisation Project data and Medicare data. Clinical efficacy was derived from a randomised controlled trial (Mayer et al. 2005, see ‘Other Publications of Related Interest’ below for bibliographic details). All-cause mortality was derived from the US National Vital Statistics Report. Hazard ratios for ICH survivors were the same as those used in a study evaluating the long-term outcomes of stroke patients (Samsa et al. 1999, see 'Other Publications of Related Interest' below for bibliographic details).

Methods used to judge relevance and validity, and for extracting data
The process used to identify the data was not reported. No inclusion criteria were specified for any parameters. The method used to select estimates was neither reported nor discussed.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs), although the authors also reported life-years gained. Quality of life weights, stratified by mRS scores, were obtained from a published study. The benefits were discounted at a rate of 3% per annum.

Direct costs
The direct costs included in the analysis were those to the third-party payer (e.g. Medicare). The short-term costs (defined as the first 90 days after ICH) included in the analysis were hospital costs, medical management, outpatient physician visits, durable medical equipment, and skilled nursing facilities/rehabilitation/home health care after initial hospitalisation. The latter two categories were assumed to be incurred only by those patients with severe disability (mRS 5). Hospital daily costs were estimated from a 5% sample of the Medicare database and applied to the mean length of stay observed from unpublished data derived from the randomised controlled trial used to derive efficacy data. Long-term costs (i.e. those incurred beyond 90 days) comprised all direct medical costs (such as subsequent hospitalisations), outpatient visits, durable medical equipment and any other costs incurred by the payer. The costs incurred for each state of functional recovery were determined by applying long-term cost multipliers derived from Samsa et al. 1999, which assumed that once a patient reached a particular functional status, the costs were a function of disability.

Since the costs could be incurred over the patients' lifetime, all future costs were discounted at an annual rate of 3%. The costs were adjusted to 2003 prices using the medical component of the Consumer Price Index. The study reported the average costs. Resources and unit costs were not reported separately, although the authors did report initial length of stay stratified by mRS.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
No productivity losses were considered.

Currency
US dollars ($).

Sensitivity analysis
Parameter uncertainty was investigated through a series of one-way and probabilistic sensitivity analyses. The parameters analysed in the one-way sensitivity analyses were the cost multipliers, death hazard rates, hospital length of stay, distribution of patients across mRS groups, cost of medication, outpatient visits and durable equipment, quality of life weights and discount rates. The effects of varying these parameters were examined using plausible ranges from the literature, 95% confidence intervals, or by varying estimates by 20% in each direction. All model parameters were
assigned prior probability distributions in the probabilistic sensitivity analysis. No expected-value-of-information analysis was performed.

**Estimated benefits used in the economic analysis**
The discounted life-time years gained were 6.12 with standard care, 7.54 with rFVIIa 40 microg/kg, 7.80 with rFVIIa 80 microg/kg and 7.58 with rFVIIa 160 microg/kg.

The discounted life-time QALYs gained were 2.80 with standard care, 4.08 with rFVIIa 40 microg/kg, 4.52 with rFVIIa 80 microg/kg and 4.28 with rFVIIa 160 microg/kg.

**Cost results**
The life-time discounted average costs were $159,055 with standard care, $167,160 with rFVIIa 40 microg/kg, $153,264 with rFVIIa 80 microg/kg and $163,730 with rFVIIa 160 microg/kg.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained).

The results of the study showed that treatment with rFVIIa 80 microg/kg was dominant over all other options (i.e. it was both less costly and more effective). Compared with standard care, the incremental cost per QALY gained by treatment with rFVIIa was $6,308 for a dose of 40 microg/kg and $3,125 for 160 microg/kg.

Findings from the one-way sensitivity analysis showed that treatment with rFVIIa 80 microg/kg remained cost-effective, at a threshold of $50,000 per QALY gained, 99.7% of the time and was dominant 62.3% of the time when compared with standard care. These results were similar when compared against the 40 and 160 microg/kg doses.

**Authors' conclusions**
The study suggested that treatment of intracerebral haemorrhage (ICH) with recombinant activated factor VII (rFVIIa) 40 microg/kg and 160 microg/kg was cost-effective in comparison with standard care, whereas treatment with rFVIIa 80 microg/kg was both more effective and less costly than the other options compared.

**CRD COMMENTARY - Selection of comparators**
rFVIIa treatment was compared with standard care which, under the authors' definitions, involved treatment with placebo. It was unclear if acute treatment of ICH with a do-nothing approach, as the placebo comparator would suggest, was standard practice. You should decide if this intervention represents current practice in your own settings.

**Validity of estimate of measure of effectiveness**
The parameters were derived from published studies. The data do not appear to have been synthesised as each parameter in the model was derived from an individual source. The authors did not report any search methods used or inclusion criteria, nor did they provide any justification for their choice of estimates. The treatment efficacy data were derived from a Phase II clinical trial that was only powered to detect the effect of rFVIIa on haemorrhage growth. However, the authors reported that this was the only head-to-head study and the most robust available to perform an economic analysis.

**Validity of estimate of measure of benefit**
The estimation of health benefits (i.e. QALYs gained) was derived appropriately from a decision tree analytic model. As benefits could be incurred over the patients' lifetime, future QALYs were appropriately discounted. The quality of life weights were derived from a published study and no details of the valuation method were reported. The authors reported that quality of life weights from this study had also been used in numerous economic evaluations.
Validity of estimate of costs
The analysis of the costs was performed from the perspective of the third-party payer (e.g. Medicare). All the relevant categories of costs appear to have been included in the analysis, together with all the relevant major costs. Therefore, any omissions are unlikely to have affected the authors’ conclusions. The unit costs and resource use were derived from published sources. Medicare charges were used to proxy some prices, which was appropriate given the third-party payer perspective adopted in the analysis. All costs were appropriately converted to a specific price year using the medical component of the Consumer Price Index. Discounting was necessary, as the costs were incurred over a patients’ lifetime, and was appropriately performed. The authors evaluated uncertainty in the cost and effectiveness data by random sampling observations in probabilistic sensitivity analysis. They also conducted an exhaustive one-way sensitivity analysis.

The cost data were reported adequately. The authors reported the price year, which will aid any future inflation exercises, and the dates to which the costs and resource use related. However, they did not report the costs and the quantities separately, which will hamper the generalisability and transferability of the authors’ results to other settings.

Other issues
The authors reported that no other economic analysis had been performed specifically for ICH treatments. The issue of generalisability to other settings was partially addressed through the one-way sensitivity analysis, whereby epidemiological, efficacy and cost data were varied individually to assess their impact on the results. However, the authors did not acknowledge in their study any variations between different settings. The authors do not appear to have presented their results selectively, although they should have provided more details on the comparator used and a better definition of the current standard of care used for comparisons against rFVIIa. The authors’ conclusions reflected the scope of the analysis, and clearly emphasised that rFVIIa 80 microg/kg was dominant over all other treatment options.

The authors reported a number of further limitations to their study. First, they assumed that the long-term costs and outcomes were based on 90-day functional outcome, rather than other factors such as type of stroke. Second, the use of the 90-day outcome might overestimate costs over time, as patients have the potential to improve in the weeks after the 90-day cut-off point. Third, the efficacy data were derived from a single Phase II clinical trial, which was only powered to detect the effects of rFVIIa dose on haemorrhage growth. Finally, other non-direct costs, such as the costs of informal caregiving, were not included in the analysis.

Implications of the study
The authors recommend that additional studies with rFVIIa are necessary to further measure the impact of rFVIIa on functional outcome measures.

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Other publications of related interest
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**Indexing Status**
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**MeSH**
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