

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

S. Morris,¹ S. Ridley,² V. Munro,³ and M. C. Christensen⁴ on behalf of the NovoSeven[®] Trauma Study Group

1 Reader, Health Economics Research Group, Brunel University, Uxbridge, Middlesex UB8 3PH, UK

2 Consultant in Anaesthesia and Intensive Care, Glan Clwyd Hospital, Rhyl, Denbighshire LL18 5UJ, UK

3 Head of Pricing and Health Economics, Europe North, Medical and Regulatory Affairs, Novo Nordisk Ltd, Broadfield Park, Brighton Road, Crawley, West Sussex RH11 9RT, UK

4 Senior Health Economist, Global Development, Novo Nordisk A/S, Krogshøjvej 55, DK-2880 Bagsværd, Denmark

Summary

The aim of this study was to assess the lifetime cost effectiveness of recombinant activated factor VII vs placebo as adjunctive therapy for control of bleeding in patients with severe blunt trauma in the UK. We developed a cost-effectiveness model based on patient level data from a 30-day international, randomised, placebo-controlled Phase II trial. The data were supplemented with secondary data from UK sources to estimate lifetime costs and benefits. The model produced a baseline estimate of the incremental cost per life year gained with recombinant activated factor VII relative to placebo of £12 613. The incremental cost per quality adjusted life year gained was £18 825. These estimates are sensitive to the choice of discount rate and health state utility values used. Preliminary results suggest that relative to placebo, recombinant activated factor VII may be a cost-effective therapy to the UK National Health Service.

Correspondence to: Dr Saxon Ridley

E-mail: saxon@domum.globalnet.co.uk

Accepted: 9 October 2006

Trauma is a major cause of death worldwide, accounting for an estimated 5 million deaths each year, or one in 10 of all deaths [1]. Uncontrolled bleeding is a major cause of mortality in trauma, and is responsible for 50% of trauma deaths that occur in hospital [2].

Recombinant activated factor VII (rFVIIa, NovoSeven[®], Novo Nordisk A/S, Bagsværd, Denmark) is currently approved in most regions of the world for the treatment of bleeding in haemophilia patients with inhibitors. In the USA and Europe, rFVIIa is also approved for the treatment of FVII deficiency. Additional approved indications in Europe include bleeding related to acquired haemophilia, and Glanzmann's thrombasthenia for patients refractory to platelet transfusions. Boffard et al. [3] recently reported the results from two international, randomised, placebo-controlled Phase II trials that investigated the use of rFVIIa as an adjunctive therapy for bleeding control in patients with severe trauma. Among patients with blunt trauma, a reduction in the transfusion of red blood cell (RBC) units was

observed with rFVIIa (estimated reduction of 2.0 RBC units per patient treated, $p = 0.07$). The need for transfusions of more than 20 units of RBC was significantly reduced (14% vs 33% of patients, $p = 0.03$). Boffard et al. [3] also identified a non-significant reduction in mortality and a trend toward fewer critical complications. Adverse events were evenly distributed between the treatment groups.

Although rFVIIa appears to be safe and effective in trauma patients, there is little evidence regarding its cost effectiveness. The aim of this study was therefore to provide a first assessment of the cost effectiveness of rFVIIa relative to placebo as adjunctive therapy for control of bleeding in patients with blunt trauma injuries in the UK.

Methods

We followed the approach recommended by the National Institute for Health and Clinical Excellence (NICE) when undertaking cost effectiveness analyses for technology

appraisals [4]. The primary outcome measure is the incremental cost per quality adjusted life year (QALY) gained with rFVIIa relative to placebo. We adopted the perspective of the National Health Service (NHS), and include all trauma-related health care costs accruing to rFVIIa and placebo. A lifetime time horizon was used, and future costs and benefits were discounted at a rate of 3.5%. All costs are presented in 2004 UK pounds sterling (£). To minimise potential bias towards rFVIIa, we attempted to make assumptions in our analysis that were either neutral or biased against rFVIIa.

The analysis was conducted at the patient level using data from Boffard et al. [3]. These data are limited to findings on morbidity, mortality and health care use up to 30 days post trauma. To assess lifetime cost effectiveness we supplemented the patient level data with secondary data sources: a cohort of 375 patients from the Trauma Audit and Research Network (TARN) [5] over the period 1996–2004; a cohort of 166 Scottish trauma patients admitted to the intensive care unit (ICU) of the Western Infirmary, Glasgow, between 1985 and 1992 [6]; and life tables for the general population in the UK [7].

Among patients alive at 48 h, Boffard et al. [3] detected a significant difference in blood transfusions between the rFVIIa and placebo groups (estimated reduction of 2.6 RBC units, $p = 0.02$), but they observed no significant difference in mortality rates at 30 days (25% vs 30%, $p = 0.58$). While recognising that rFVIIa did not have a statistically significant impact on survival, we considered our primary health outcome (QALYs) justified for the following reasons. First, blood transfusion is associated with a risk of post-transfusion complications and is an independent risk factor for developing infections and multiple organ failure which have a negative effect on both length and quality of life [8–10]. Second, the original trial was not powered to detect a statistically significant difference in mortality, and numerous case reports suggest that rFVIIa may impact upon mortality in severely injured trauma patients [11–22]. Third, the non-normal distribution of survival probability in trauma patients makes it difficult to detect a significant difference in mortality endpoints in clinical trials conducted in the acute trauma setting [23]. Nonetheless, our analysis is based on the assumption that the observed non-significant reduction in mortality reported in the Phase II study can be verified in a larger Phase III trial investigating rFVIIa in trauma.

Patients

The study sample is the intention-to-treat population of blunt trauma patients in Boffard et al. [3]. To be eligible for inclusion, patients had to have received six units of

RBC within 4 h of admission, and to be of known age ≥ 16 years (or legally of age according to local law) and < 65 years. Key exclusion criteria were: cardiac arrest prior to trial drug administration; gunshot wound to the head; Glasgow Coma Scale score < 8 unless in the presence of a normal head CT scan; base deficit $> 15 \text{ mEq.l}^{-1}$ or severe acidosis with $\text{pH} < 7.00$; transfusion of eight units or more of RBC prior to arrival at trauma centre; and injury sustained ≥ 12 h before randomisation.

Eligible patients were randomly allocated to receive either three intravenous injections of rFVIIa (200, 100 and $100 \mu\text{g.kg}^{-1}$) or three placebo injections. The first injection was administered immediately after transfusion of the 8th unit of RBC if the patient, in the opinion of the attending physician, would require additional transfusions. The second and third doses followed 1 and 3 h after the first dose. rFVIIa or placebo were administered in addition to standard trauma care at the participating hospitals, and no restrictions were imposed on procedures deemed necessary by the attending physician, including surgical interventions, resuscitation strategies and use of blood products.

Survival after 30 days

In the trial, data were collected on whether each patient died within the first 30 days post trauma and, if they died, their time to death in hours. We estimated survival after 30 days using a three stage approach.

In the first stage we used data from TARN [5] to model survival up to time of hospital discharge or death in hospital. Survivors in the trial at day 30 were assigned a survival probability based on the probability of survival for a matched cohort of patients in TARN. The matched cohort comprised 375 patients in the TARN database over the period 1996–2004 matching the inclusion and exclusion criteria in Boffard et al. [3] and who were alive at 30 days post trauma. The maximum time to hospital discharge among the TARN cohort was 90 days. We therefore used these data to predict the probability of survival from 30 to 90 days post trauma based on the number of patients in the cohort who died in the 30- to 90-day period.

In the second stage we used Scottish data from a cohort of 166 trauma patients admitted to the intensive care unit of the Western Infirmary, Glasgow, between 1985 and 1992 and alive at 90 days post trauma [6]. This cohort was followed until 1997, giving a minimum follow-up period of 5 years. We therefore used these data to model the probability of survival at 5 years given the patient was alive at 90 days post trauma. The predicted probability of survival at 5 years was modelled using logistic regression, in which survival at 5 years measured as a binary variable

was regressed against gender, age and whether or not the patient was still in the intensive care unit 30 days post trauma (see the Appendix for further details on the regression method used).

In the third stage, we used life table data for the general population in the UK for 2002–4 taken from the Government Actuary Department [7] to generate an age- and gender-specific residual life expectancy for each individual patient alive 5 years post trauma. We assumed the same life expectancy for patients at 5 years as for the general population. Niskanen et al. [24] followed 12 180 critically ill patients for 5 years and found the survival of trauma patients to be equal to that of the general population after 3 months. Wright et al. [6] found that Scottish ICU patients with trauma had no increased risk of death relative to the general population after 2 years.

Further details of the formula used to calculate total life years for each patient in the trial are given in the Appendix.

Health state utilities

Generating QALYs requires health state utilities for the key health states in a zero to one range, with death valued at zero and full health valued at one. A search of the literature was undertaken and one published study was identified with data on health state utilities for survivors of blunt trauma. Seguin et al. [25] reported a mean health state utility value for all survivors at hospital discharge of 0.67. We assumed conservatively that this value would persist for the remaining years of life of trauma survivors.

Costs

We calculated the health-care costs associated with rFVIIa and placebo in three stages. In the first stage we considered costs in the first 30 days post trauma, based on patient level health care resource-use data collected in Boffard et al. [3]. The costs included: rFVIIa drug acquisition costs; RBC units transfused in the first 48 h; fresh frozen plasma received in the first 48 h; platelets received in the first 48 h; cryoprecipitate received in the first 48 h; all surgical procedures received in the first 30 days; ICU costs in the first 30 days; and regular inpatient bed-days in the first 30 days. rFVIIa drug costs were calculated by multiplying the total dose in mg for each patient in the trial by the drug acquisition cost, which is £462.88 per mg (excluding VAT). The costs of blood products (RBC, fresh frozen plasma, platelets, cryoprecipitate) were calculated by multiplying the total volume received by their unit cost (£131.80 per unit, £0.13 per ml, £0.99 per ml and £0.91 per ml, respectively [26]). All surgical procedures undertaken after the administration of the study drug were included in the analysis. The duration of each surgical procedure in

minutes was calculated, based on the start and stop dates and times recorded in Boffard's trial [3]. The cost for each surgical procedure was then calculated using the formula $(D \times 6.4) + 788$, where D is the duration of each surgical procedure in minutes. The first term is the variable cost, and is based on a cost per minute of theatre time of £6.40 [27]. A fixed cost of £788 per surgical procedure was added, which included the cost of additional equipment and consumables [4]. The costs of ICU and regular inpatient ward days were estimated by multiplying the number of days recorded in the trial by the NHS reference costs per day, which are £1328 and £176, respectively [27].

In the second stage, which applies to all patients surviving the first 30-day period, we used data from the TARN cohort on length of hospital stay. We distinguished between patients still in the intensive care unit at day 30 and those on a regular inpatient ward. In the TARN database, of the 373 patients matching the inclusion and exclusion criteria in Boffard et al. [3], and alive at 90 days, 13 (3.5%) were in the intensive care unit 30 days post trauma. These patients had a mean residual length of stay in the intensive care unit of 10.7 days, followed by a mean stay on a regular inpatient ward of 20.2 days. In the 360 (96.5%) patients on a regular inpatient ward at 30 days and alive at 90 days, the mean residual length of stay on a regular inpatient ward was 18.5 days. These resource-use data were multiplied by the unit costs of intensive care unit and regular inpatient ward days given above.

In the third stage we estimated long-term health-care costs from 90 days post trauma until death. There are no data on long-term health-care costs for survivors of trauma in the UK. We therefore approximated these costs using the mean annual health expenditure per capita in the UK, which is £1654 [28]. This approach has been used in previous studies [29]. In addition to this, our baseline estimates also include a figure of £10 000 in the first year post trauma to cover rehabilitation costs. With this amount of money it would be possible to pay, for example, for a 9-week stay in a high dependency care home for disabled or 15 weeks in a residential care home for disabled people [30].

Cost effectiveness

Cost effectiveness is measured using incremental cost effectiveness ratios (ICERs). These summarise the incremental (or extra) costs incurred with rFVIIa relative to placebo and the incremental benefits. The incremental costs are the costs of rFVIIa minus the costs of placebo. The incremental benefits are the outcomes associated with rFVIIa (measured using life years and QALYs) minus the outcomes with placebo. The ICERs are the

incremental costs divided by the incremental benefits. These are interpreted as the incremental cost per life year gained and the incremental cost per QALY gained of rFVIIa relative to placebo. They summarise the extra costs incurred from the use of rFVIIa relative to placebo for each additional unit of outcome produced.

Results

Patients

In all, 158 blunt trauma patients were recruited to the Boffard et al. [3] trial. Of these, 10 were withdrawn before administration of rFVIIa or placebo, and consent was not confirmed for five patients. Hence the study sample comprised 143 patients. Sixty-nine patients were randomly allocated to receive rFVIIa and 74 to receive a placebo. Key baseline characteristics are shown in Table 1. The patients included in the trial were severely injured and relatively young. The cohort from TARN and Scotland, which only include patients who survived the first 30 or 90 days post trauma, were slightly older and less severely injured than the patients randomised in the trial.

Survival

Fifty-two (75%) patients randomly allocated to receive rFVIIa and 52 (70%) patients randomly allocated to placebo were alive 30 days post trauma. The difference was not statistically significant ($p = 0.58$). The mean time to death among those who died in the first 30 days

was 2.25 days (standard deviation (SD) = 3.43 days), or 0.006 years. In the TARN cohort, two of the 375 (0.53%) patients died in the period from 30 to 90 days. We therefore used a survival probability of 99.47% at 90 days for all survivors in the trial at 30 days. The mean time to death of the two patients who died in the TARN cohort was 43 days post trauma (SD = 3.5 days), or 0.118 years. In the Scottish data, 12 of the 166 (7%) patients died in the period from 90 days to 5 years. The mean time of death among these patients was 671 days post trauma (SD = 468 days), or 1.838 years. When the co-efficients from the regression model were applied to the patient level data in the trial, the mean predicted probability of survival at 5 years given that the patient was alive at 90 days post trauma was 0.937 (SD = 0.108). The mean discounted residual life expectancy among patients enrolled in the trial based on age- and gender-specific residual life expectancy for the general population was 22.0 years (SD = 3.4).

Costs

Trauma-related health care costs associated with rFVIIa and placebo are presented in Table 2. The mean total lifetime discounted costs are £70 882 (SD £31 121) with rFVIIa and £57 639 (SD £37 525) with placebo. The mean difference is £13 243 ($p = 0.02$; 95% Confidence interval (CI): £1973 to £24 516). The mean rFVIIa drug acquisition cost was £13 878 (SD £2798). Excluding the drug acquisition costs, rFVIIa was associ-

	Boffard et al. [3]		UK data	
	rFVIIa (n = 69)	Placebo (n = 74)	TARN cohort (n = 375)	Scottish cohort (n = 166)
Male	48 (70%)	52 (70%)	NA	130 (78%)
Age; years	33 (13)	35 (13)	36 (25)	38 (19)
Injury Severity Score (ISS)	33 (13)	32 (12)	22 (15)	NA
Number of ISS body regions injured				
1	6 (9%)	4 (5%)	NA	NA
2–3	29 (42%)	36 (49%)	NA	NA
>3	33 (48%)	32 (43%)	NA	NA
Glasgow Coma Scale				
≤ 8	11 (16%)	8 (11%)	NA	NA
9–12	11 (16%)	18 (24%)	NA	NA
13–15	47 (68%)	48 (65%)	NA	NA
Time from injury to hospitalisation				
0–1 h	20 (29%)	23 (31%)	NA	NA
1–2 h	23 (33%)	26 (35%)	NA	NA
2–4 h	12 (17%)	10 (14%)	NA	NA
>4 h	3 (4%)	6 (8%)	NA	NA
Unknown	11 (16%)	9 (12%)	NA	NA
In intensive care unit 30 days post trauma	5 (7%)	12 (16%)	13 (3%)	4 (2%)

Table 1 Selected baseline characteristics of intention-to-treat population in Boffard et al. [3], and patients from TARN [5] and from Scottish data [6] (both with limited data availability). Values are mean (standard deviation) or number (%).

Table 2 Costs analysis by component for rFVIIa vs placebo. Values are mean (SD) or mean difference (p value; 95% Confidence interval).

	Cost; £		
	rFVIIa (n = 69)	Placebo (n = 74)	Difference
rFVIIa drug acquisition cost	13 878 (2798)	0 (0)	13 878 (0.00; 13 218–14 539)
Red blood cells	1169 (1249)	1291 (1130)	-122 (0.54; -514–269)
Fresh frozen plasma	206 (326)	225 (251)	-19 (0.69; -115–77)
Platelets	359 (514)	389 (395)	-29 (0.70; -180–122)
Cryoprecipitate	35 (101)	52 (112)	-17 (0.35; -52–18)
Inpatient stay	1117 (1595)	813 (1303)	304 (0.22; -176–783)
Intensive care unit stay	14 858 (13 222)	16 905 (14 359)	-2047 (0.38; -6568–2474)
Surgery	2127 (2240)	1940 (2617)	187 (0.65; -610–984)
Sum of cost, days 1–30 (including all the above)	33 749 (14 027)	21 615 (16 130)	12 135 (0.00; 7189–17 081)
Sum of cost, days 1–30 (as above but excluding cost of rFVIIa)	19 871 (13 465)	21 615 (16 130)	-1744 (0.48; -6602–3114)
Sum of cost, days 31–90	3505 (4250)	4641 (5988)	-1136 (0.19; -2829–558)
Sum of discounted costs, after day 90	33 627 (20 582)	31 383 (21 237)	2244 (0.52; -4611–9100)
Total discounted cost	70 882 (31 121)	57 639 (37 525)	13 243 (0.02; 1973–24 516)
Total discounted cost not including cost of rFVIIa	57 003 (30 847)	57 639 (37 525)	-635 (0.92; -11 864–10 593)

ated with a lower total discounted cost, with a mean difference of -£635 (p = 0.92; 95% CI: -£11 864 to £10 583). This arises primarily through lower ICU costs (mean difference = -£2047, p = 0.38; 95% CI: -£6568 to £2474), which translates into spending approximately 1 day less in the ICU.

Cost effectiveness

The cost effectiveness results are shown in Table 3. Relative to placebo, rFVIIa yields on average an additional 1.05 life years (p = 0.54; 95% CI: -2.3–4.4) and an additional 0.70 QALYs (p = 0.54; 95% CI: -1.5–2.9). Combining these with the incremental cost of £13 243 means that for rFVIIa relative to placebo the incremental cost per life year gained and the incremental cost per QALY gained are £12 613 and £18 825, respectively.

Sensitivity analysis

The sensitivity of the cost effectiveness estimates to changes in the difference in mortality risk between rFVIIa vs placebo at 30 days, discount rate, cost per surgical procedure, long-term trauma costs, residual life expectancy and health-state utility values are shown in Table 4. Cost effectiveness is most sensitive to the difference in mortality risk between rFVIIa vs placebo at 30 days, to the discount rate and to the health-state utility values used. When the difference in mortality associated with rFVIIa vs placebo over the first 30 days is varied from 10% to 1% (the base case is 5%) the incremental costs per QALY gained range from £8990 to £89 897. Varying the discount rate for costs and benefits between 0% and 6% results in incremental costs per QALY gained ranging from £9347 to £26 772. Assuming health state utility values of 0.67 in first year post-trauma with UK age- and gender-specific population norms for

Table 3 Incremental costs per life year gained and incremental costs per QALY gained for rFVIIa vs placebo. Values are mean (SD) or difference (p value; 95% Confidence interval). The numbers in the table have been rounded off.

	rFVIIa (n = 69)	Placebo (n = 74)
Life years	15.80 (10.02)	14.75 (10.18)
QALYs (life years multiplied by health state utilities)	10.59 (6.72)	9.88 (6.82)
Total discounted costs; £	70 882 (31 121)	57 639 (37 525)
Life years gained (life years with rFVIIa minus those with placebo)	1.05 (0.54; -2.3–4.4)	
QALYs gained (QALYs with rFVIIa minus those with placebo)	0.70 (0.54; -1.5–2.9)	
Incremental costs (total discounted costs for rFVIIa minus those for placebo); £	13 243 (0.02; 1973–24 516)	
Incremental costs per life year gained (incremental costs divided by life years gained); £	12 613	
Incremental costs per QALY gained (incremental costs divided by QALYs gained); £	18 825	

Table 4 Sensitivity analysis of the incremental costs per life year gained and incremental costs per QALY gained for rFVIIa vs placebo. Values are £.

	Incremental costs per life year gained	Incremental costs per QALY gained
Baseline†	12 613	18 825
Difference in mortality risk at 30 days		
10%	6023	8990
9%	6692	9989
8%	7529	11 237
7%	8604	12 842
6%	10 039	14 983
4%	15 058	22 474
3%	20 077	29 966
2%	30 116	44 949
1%	60 231	89 897
Discount rate for costs, life years and QALYs		
0%	6262	9347
6%	17 937	26 772
Cost per surgical procedure		
Costs halved and calculated using the formula $(D * 3.2) + 394$	12 524	18 692
Costs doubled and calculated using the formula $(D * 12.8) + 1576$	12 791	19 091
Long-term trauma-related costs per patient		
£1654 in first year and £0 in all subsequent years	10 555	15 754
£20 000 + £1654 in first year and £1654 in all subsequent years	13 095	19 545
Adjustment to residual life expectancy data		
90% of age- and gender-specific residual life expectancy for the general population	13 811	20 614
Health state utility values		
0.67 in first year with UK age- and gender-specific population [31] norms for remaining years of life	12 613	15 406
Multivariate		
Utility values = 0.67 in first year with UK age- and gender-specific population norms for remaining years of life + Long-term trauma-related costs per patient = £1654 in first year and £0 in all subsequent years 90% of age- and gender-specific residual life expectancy for the general population + Long-term trauma-related costs per patient = £20 000 + £1654 in first year and £1654 in all subsequent years	14 346	21 412

†Baseline assumptions: difference in mortality risk at 30 days = 5%; discount rate for costs, life years and QALYs = 3.5%; cost per surgical procedure = $(D * 6.4) + 788$; long-term trauma-related costs per patient = £10 000 + £1654 in first year and £1654 in all subsequent years; adjustment to residual life expectancy data = 100% of age- and gender-specific residual life expectancy for the general population; health state utility values = 0.67 in first year and for each remaining year of life.

remaining years of life [31], the incremental cost per QALY gained falls to £15 406.

A cost-effectiveness acceptability curve is shown in Fig. 1. This provides a useful way to examine uncertainty in the value of the incremental cost-effectiveness ratios due to sampling variation, and uncertainty in the threshold level of cost effectiveness that the health-care programme needs to exceed to be considered cost effective. The curves are computed from the formulae given in Lothgren and Zethraeus [32] and are based on the incremental cost per QALY gained. If, for example, the NHS were willing to pay an extra £20 000 for an additional QALY, then rFVIIa would be cost-effective relative to placebo in 52% of situations in which rFVIIa is used in patients with blunt trauma. If the NHS were willing to pay an extra £30 000 for an additional QALY,

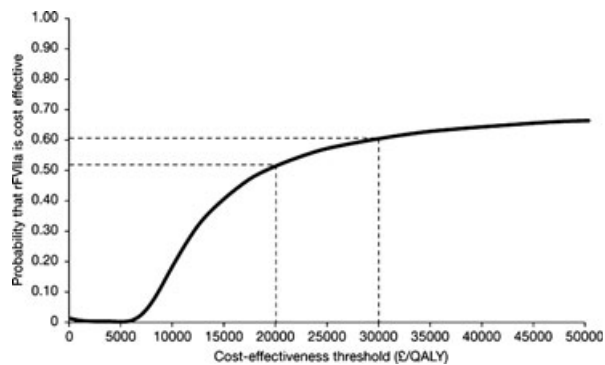


Figure 1 Cost-effectiveness acceptability curve for rFVIIa vs placebo based on the incremental cost per QALY gained. The dashed lines show the probability that rFVIIa is cost effective at a willingness to pay of £20 000 and £30 000.

rFVIIa would be cost-effective relative to placebo in 61% of situations.

Discussion

In this study we supplemented patient level data from an international, randomised, placebo-controlled Phase II trial with secondary data from UK sources to evaluate the lifetime cost effectiveness of rFVIIa relative to placebo as adjunctive therapy for control of bleeding in patients with blunt trauma injuries. In the baseline analysis the incremental costs per QALY gained for rFVIIa relative to placebo were £18 825. To judge whether this estimate indicates a cost-effective therapy requires information on the appropriate cost effectiveness threshold in the UK. Although no official thresholds have been published by the UK government, comments made by the Chairman of NICE suggest that a threshold of £20 000 to £30 000 per QALY gained has emerged from its deliberations [33] (according to NICE, additional equity reasons are required for interventions with an incremental cost-effectiveness ratio above £20 000 per QALY gained [4]). This implies that health care programmes that have a higher incremental cost per QALY gained are less likely to be funded. Looking at previous recommendations by NICE, Towse has also suggested that the threshold incremental cost per QALY gained is somewhere between £20 000 and £30 000 [34], though Devlin and Parkin used statistical evidence to support the view that the threshold is somewhat higher than the £30 000 level [33]. If we take the lower value of £20 000 as the threshold, the preliminary results suggest that, relative to placebo, rFVIIa may be a cost-effective therapy to the NHS.

In our analysis the mean rFVIIa drug acquisition cost was £13 878, and the incremental costs per patient treated with rFVIIa £13 243. Data from TARN suggest that 320–425 new cases meeting the inclusion and exclusion criteria in Boffard et al. [3] enter hospitals included in TARN each year [5]. As TARN contains approximately one half of all trauma-receiving hospitals in England and Wales, it is reasonable to double these numbers to get an annual incidence in England and Wales of 640–850 cases per annum. If this is the eligible treatment group for rFVIIa therapy, then total drug acquisition costs in England and Wales could be up to £8.9–11.8 million per annum and the total budgetary impact would be £8.5–11.3 million because of the associated other savings.

The study by Boffard et al. [3] was a clinical-proof-of-concept trial; not a trial designed to examine efficacy on clinical endpoints such as mortality. However, it is the only randomised controlled clinical trial to date which quantifies the effects of rFVIIa on mortality. While the true effect of rFVIIa on mortality in trauma is not known precisely we

used the best available evidence to generate our base case results. We examined the effect of uncertainty surrounding the mortality risk reduction in the sensitivity analysis. Unsurprisingly, as the mortality risk reduction achieved with rFVIIa relative to placebo is reduced, rFVIIa becomes less cost-effective, and vice versa. Subsequent Phase III studies could be used to verify the mortality risk reduction achieved with rFVIIa in trauma.

The long-term physical and psychological impact of critical illness is now becoming more apparent; for example, the survivors of severe adult respiratory distress syndrome suffer from muscle weakness for up to 1 year after discharge [35]. Critical care follow-up clinics and other enhancements in rehabilitation have recently been recommended by the Department of Health [36]. This cost-effectiveness analysis lends support to the further development of these services in that improvements in quality of life and functional outcome in survivors may improve the incremental cost per QALY gained of the more expensive interventions applied in an intensive care unit.

The study has several limitations. First, as acknowledged above, the analysis is based on preliminary data from a Phase II study using a surrogate marker for bleeding as primary endpoint. As the trial was not powered to detect a statistically significant difference in mortality, the observed difference in survival is uncertain and requires verification in future studies. This is important because the survival benefit represents an important driver of the cost effectiveness of rFVIIa relative to placebo and, as demonstrated in the sensitivity analysis, higher cost-effectiveness ratios are observed for absolute differences in survival of less than 5%. Second, the individual level trial data pertain only to the first 30 days post trauma. Ideally, we require long-term patient level data on the impact of rFVIIa on morbidity, mortality and health-care resource use. Third, lifetime health-state utility values for trauma patients do not exist. We therefore assumed, conservatively, that the utility value for trauma patients in the first year persisted throughout their remaining years of life. The sensitivity analysis indicates that cost effectiveness is sensitive to the health-state utility value used, and it is likely that our baseline assumption led to an underestimate of the QALYs gained. Fourth, due to the perspective chosen for the analysis, we did not include non-NHS costs associated with rFVIIa. It is unclear whether the inclusion of these costs would increase or decrease the incremental cost per QALY gained. Fifth, even though RBC transfusion was shown to be significantly reduced with rFVIIa in Boffard et al. [3], our study did not take into account the long-term consequences of blood transfusions. Consequently, there may have been some additional cost savings associated with rFVIIa that were not included.

Our analysis has highlighted a number of gaps in knowledge about the effectiveness and cost of rFVIIa for the control of bleeding in trauma patients. In particular, more research is required on the following: the long-term impact of rFVIIa on mortality and morbidity in trauma patients; the long-term health-care costs associated with rFVIIa treatment in trauma patients, the long-term health state utility values associated with rFVIIa treatment in trauma patients; the naturalistic cost-effectiveness analyses of rFVIIa therapy in trauma patients to investigate whether the cost effectiveness of rFVIIa in trauma patients can be replicated in real-life clinical practice; and the non-health care costs such as lost productivity associated with rFVIIa vs placebo in trauma patients.

In summary, we assessed the cost effectiveness of rFVIIa vs placebo as adjunctive therapy for the control of bleeding in patients with severe blunt trauma injuries in the UK on the basis of an international, multicentre, Phase II trial. Our preliminary results suggest that rFVIIa may be a cost-effective therapy in the NHS.

Acknowledgements

The authors acknowledge the NovoSeven[®] Trauma Study Group for their hard work examining the safety and efficacy of rFVIIa as adjunctive therapy in the treatment of severely injured trauma. In producing this manuscript, the authors also acknowledge the input of Anna D'Ausilio, Neill Calvert, David Grant and Nishma Patel of Fourth Hurdle Consulting Limited, and Fiona Lecky of the Trauma Audit and Research Network in supporting this work.

Conflict of interest

The original trial and cost-effectiveness analysis were funded by Novo Nordisk A/S, Bagsværd, Denmark. SM received consultancy fees and SR has received honoraria relating to lectures, the present study and other work from Novo Nordisk. VM and MC are employees of Novo Nordisk.

References

- Murray CL, Lopez AD. Mortality by cause for eight regions of the world. Global Burden of Disease Study. *Lancet* 1997; **349**: 1269–76.
- Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *Journal of Trauma* 1995; **38**: 185–93.
- Boffard KD, Riou B, Warren B, et al. Recombinant Factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *Journal of Trauma* 2005; **59**: 8–18.
- NICE. *Guidance to the Methods of Technology Appraisal*. London: NICE, 2004.
- TARN. <http://www.tarn.ac.uk> [accessed 6 February 2006].
- Wright JC, Plenderleith L, Ridley SA. Long term survival following intensive care: Subgroup analysis and comparison with the general population. *Anaesthesia* 2003; **58**: 637–42.
- Government Actuary's Department. Interim life tables. http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm [accessed 30 August 2006].
- Como JJ, Dutton RP, Scalea TM, et al. Blood transfusion rates in the care of acute trauma. *Transfusion* 2004; **44**: 809–13.
- Sauaia A, Moore FA, Moore EE, et al. Early predictors of postinjury multiple organ failure. *Archives of Surgery* 1994; **129**: 39–45.
- Moore FA, Moore EE, Sauaia A. Blood-transfusion: an independent risk factor for postinjury multiple organ failure. *Archives of Surgery* 1997; **132**: 620–5.
- Alcorn K, Aggarwal A. Single institution experience of recombinant activated factor VII (NovoSeven) in the management of intractable bleeding in surgical and trauma patients. *Blood* 2002; **100**: Abstract no. 3840.
- Aggarwal A, Catlett J, Alcorn K. Use of recombinant activated factor VII (rFVIIa) in the management of intractable bleeding in surgical and trauma patients. *Blood* 2001; **98**: Abstract no. 3883.
- Becton D, Saylor R, Morris J, et al. Treatment of bleeding with rFVIIa (NovoSeven[®]) in four diverse cases. *Blood* 2001; **98**: Abstract no. 1104.
- Clark AD, Gordon WC, Walker ID, et al. 'Last-ditch' use of recombinant factor VIIa in patients with massive haemorrhage is ineffective. *Vox Sanguinis* 2004; **86**: 120–4.
- Dutton RP, McCunn M, Hyder M, et al. Factor VIIa for correction of traumatic coagulopathy. *Journal of Trauma* 2004; **57**: 709–19.
- Kamphuisen PW, van den Akker JM, Kaasjager KAH, et al. Control of life-threatening pulmonary bleeding with activated recombinant factor VII. *American Journal of Medicine* 2002; **112**: 332–3.
- Kenet G, Walden R, Eldad A, et al. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; **354**: 1879.
- Kulkarni R, Daneshmand A, Guertin S, et al. Successful use of activated recombinant factor VII in traumatic liver injuries in children. *Journal of Trauma* 2004; **56**: 1348–52.
- Dincer AP, Abu-Hajir M, Christians KK, et al. Human recombinant activated factor seven, NovoSeven (rVIIa), in the management of massive bleeding despite adequate resuscitation in major trauma. *Blood* 2002; **100**: Abstract no. 3918.
- Morenski JD, Tobias JD, Jimenez DF. Recombinant activated factor VII for cerebral injury-induced coagulopathy in paediatric patients. *Journal of Neurosurgery* 2003; **98**: 611–6.
- O'Neill PA, Bluth M, Gloster ES, et al. Successful use of recombinant activated factor VII for trauma-associated

- hemorrhage in a patient without preexisting coagulopathy. *Journal of Trauma* 2002; **52**: 400–5.
- 22 Siegel LJ, Gerigk L, Tuettenberg J, et al. Cerebral sinus thrombosis in a trauma patient after recombinant activated factor VII infusion. *Anesthesiology* 2004; **100**: 441–3.
- 23 Riou B, Landais P, Vivien B, et al. Distribution of the probability of survival is a strategic issue for randomized trials in critically ill patients. *Anesthesiology* 2001; **95**: 56–63.
- 24 Niskanen M, Kari A, Halonen P. Five-year survival after intensive care: comparison of 12,180 patients with the general population. *Critical Care Medicine* 1996; **24**: 1962–7.
- 25 Seguin J, Garber B, Coyle D, et al. An economic evaluation of trauma care in a Canadian level trauma hospital. *Journal of Trauma* 1999; **47** (Suppl.): S99–S103.
- 26 National Blood Service. Impact of cost pressures, developments and cost reduction programmes. Appendix 2 Draft National prices 2006/2007. London: National Blood Service, 2005.
- 27 Department of Health. *NHS Reference Costs 2004*. London: Department of Health, 2005.
- 28 Yuen P. *OHE Compendium of Health Statistics*, 17th edn. London: OHE, 2006.
- 29 Southampton Health Technology Assessments Centre. *The Clinical and Cost-Effectiveness of Drotrecogin Alfa (Activated Xigris™) for the Treatment of Severe Sepsis in Adults: a Systematic Review and Economic Evaluation (Excluding Commercial in Confidence Data)*. Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. London: NICE, 2003.
- 30 Curtis L, Netten A. *Unit Costs of Health and Social Care*, 2005. Kent: PSSRU, 2005.
- 31 Szende A, Williams A, eds. *Measuring Self-Reported Population Health: an International Perspective Based on EQ-5d*. Rotterdam: EuroQol group, 2004.
- 32 Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Economics* 2000; **9**: 623–30.
- 33 Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Economics* 2004; **13**: 437–52.
- 34 Towse A. *What Is NICE's Threshold? An External View*. In: Devlin N, Towse A, eds. *Cost Effectiveness Thresholds: Economic and Ethical Issues*. London: King's Fund/Office for Health Economics, 2002.
- 35 Herridge MS, Cheung AM, Tansey CM, et al. for the Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *New England Journal of Medicine* 2003; **348**: 683–93.
- 36 Critical Care Stakeholder Forum. *Quality Critical Care*. London: Department of Health, 2005.
- 37 Tukey JW. One degree of freedom for non-additivity. *Biometrics* 1949; **5**: 232–42.
- 38 Pregibon D. Goodness of link tests for generalised linear models. *Applied Statistics* 1980; **29**: 15–24.

Appendix

Modelling the probability of survival at 5 years given being alive 90 days post trauma

The probability of survival at 5 years given the patient is alive 90 days post trauma was modelled on the Scottish cohort data ($n = 166$) using regression analysis. Survival at 5 years ($SURVIVAL = 1$ if yes, 0 otherwise) was regressed against gender ($FEMALE = 1$ if yes, 0 otherwise), age at time of trauma (AGE) and age squared ($AGESQ$) measured as continuous variables, and whether or not the patient was still in the ICU 30 days post trauma ($ICU30 = 1$ if yes, 0 otherwise) plus a constant term. These covariates were chosen because they were collected by Boffard et al. [3] and were also included in the Scottish data.

$SURVIVAL$ is a binary variable, and standard models for binary variables are the linear probability model (LPM), and the logit and probit models. We used the link test [37, 38] to choose between these specifications. The model of interest is estimated, and the linear prediction and its square are computed. The dependent variable is then regressed using the same specification (LPM, logit, probit) in a separate model against the linear prediction, the linear prediction squared and a constant term. If the model is correctly specified the squared linear prediction should have no explanatory power. The squared linear prediction term was insignificant for the logit model, so we used this specification.

The results from the model are:

$$\Pr(SURVIVAL) = \frac{e^Z}{1 + e^Z} \quad [1]$$

where

$$Z = 7.445 + (0.630 * FEMALE) + (-0.140 * AGE) + (0.001 * AGESQ) + (-2.264 * ICU30). \quad [2]$$

The explanatory power of the model can be approximated by the pseudo- R^2 , which was 0.212. The interpretation of the coefficients in eqn 2 is that all else being equal, females are more likely to survive to 5 years, and those in the ICU at 30 days are less likely to survive. Age has a non-linear effect, with the probability of survival declining with age, as shown in Fig. A1.

The co-efficients in Equation 2 (above) were applied to the patients in the Boffard et al. [3] trial to generate a patient specific predicted linear index Z . This is then transformed using eqn 1 to estimate the probability of survival to 5 years post trauma given that the patient is alive at 90 days.

Life expectancy

The life expectancy L for each patient is calculated as follows:

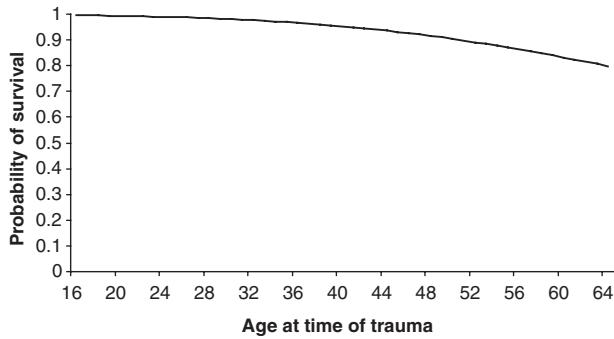


Figure A1 Probability of survival at 5 years given being alive at 90 days post trauma. The analysis is based on Scottish data ($n = 166$).

$$L = (d_1 * L_1) + (1 - d_1) [p_2 * L_2 + (1 - p_2) * \{p_3 * L_3 + (1 - p_3) * L_4\}] \quad [3]$$

where:

d_1 = a binary variable taking the value of one if the patient died in the 30-day trial period, and zero otherwise (obtained from Boffard et al. [3]);

L_1 = time to death in years if the patient died in the trial (obtained from Boffard et al. [3]);

p_2 = probability of death in days 30–90 assuming the patient is alive at day 30 (obtained from TARN [5]);

L_2 = time to death in years if the patient died in days 30–90 (obtained from TARN [5]);

p_3 = probability of death in the day 90–5-year period assuming the patient is alive at day 90 (obtained from the Scottish data [6]);

L_3 = time to death in years if the patient died in the day 90–5-year period (obtained from the Scottish data [6]);

L_4 = age- and gender-specific residual life expectancy for the general population in the UK (obtained from life tables [7]).