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 compared two treatment options for severe sepsis. Drotrecogin alfa (activated), i.e. the recombinant form of human activated protein C, plus conventional care was compared with conventional care alone. Conventional care was not described in detail.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a UK cohort of adult patients with severe sepsis and patients with severe sepsis and multiple organ failure. Details of the inclusion criteria were given in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study (Bernard et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details), although their exclusion criteria were not adopted in the current study.

Setting
The setting appears to have been secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 2001 and 2003, and from unpublished data from the Intensive Care National Audit and Research Centre (ICNARC) in 2003. The cost data were derived from sources from 2002 and 2003. Although the price year was not explicitly reported, it seems that all the costs were reported to reflect 2002 prices.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
The authors constructed a decision analytic model (Markov) in order to estimate and compare the cost-effectiveness of drotrecogin alfa (activated) plus conventional care versus conventional care alone. The authors reported that the development and the structure of the model were guided by the systematic review of the clinical and cost-effectiveness literature. Details of the systematic review were given in another study (Green et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details). Initially, patients in both treatment groups go through a 28-day survival period. Those who survive then progress through a 4-year period characterised by an increased risk of death in
comparison with the general population. If the patient survives this stage, they then progress into the final stage of the model which reflects a return to the normal patient life expectancy. The time horizon of the model was the patients’ lifetime.

Outcomes assessed in the review
The following main input parameters were identified from the literature and used in the model:

- 28-day mortality for patients with severe sepsis and for patients with severe sepsis and multiple organ dysfunction (MOD), and the equivalent relative risk (RR);
- the additional risk of a serious bleeding event during the 28-day survival period;
- the risk of death in years 1, 2, 3 and 4 following the 28-day survival period; and
- the health state value for survivors of severe sepsis.

Study designs and other criteria for inclusion in the review
The inclusion criteria for the review were not reported in this paper. However, the authors reported that the effectiveness data were mainly derived from a large randomised controlled trial (the PROWESS study). Data on the baseline population were derived from the ICNARC.

Sources searched to identify primary studies
The sources were not reported in this paper (see Green et al. 2005 for relevant details).

Criteria used to ensure the validity of primary studies
Not reported in this paper (see Green et al. 2005 for relevant details).

Methods used to judge relevance and validity, and for extracting data
Not reported in this paper (see Green et al. 2005 for relevant details).

Number of primary studies included
The authors mainly reported 5 studies as sources of effectiveness evidence. However, it was unclear how many studies were actually reviewed.

Methods of combining primary studies
The methods used were not reported in this paper (see Green et al. 2005 for relevant details).

Investigation of differences between primary studies
Not reported in this paper (see Green et al. 2005 for relevant details).

Results of the review
Twenty-eight-day mortality was 41.5% (40.8% to 42.3%) for patients with severe sepsis and 46.2% (45.3% to 47.1%) for patients with severe sepsis and MOD. The RR was 0.79 (0.68 to 0.92) for patients with severe sepsis and 0.78 (0.66 to 0.93) for patients with severe sepsis and MOD.

The additional risk of a serious bleeding event during the 28-day survival period was 1.5%.
The risk of death following the 28-day survival period was 19.4% in year 1, 5.68% in year 2, 4.75% in year 3 and 3.91% in year 4.

All other parameters used in the model (including health state values and resource use) were reported in full, but are too numerous to be reported here.

**Measure of benefits used in the economic analysis**

The measures of benefit used were the life-years gained (LYG) and health utility (quality-adjusted life-years, QALYs). The LYG were directly derived from the model using life expectancy and risk of death estimates from the literature. Given that health state values for survivors of severe sepsis were not available in the literature, the authors used quality of life data for a sample of patients with acute respiratory distress syndrome (at 12 months), which had been derived from a published study.

**Direct costs**

The following health service costs were included in the analysis:

- the cost of drotrecogin alfa (activated);
- the mean cost per patient (excluding Value Added Tax, VAT) for severe sepsis and severe sepsis with MOD;
- the mean cost of a serious bleed;
- the cost per day in the intensive care unit;
- the cost per day in another hospital ward;
- hospitalisation costs for severe sepsis survivors and non-survivors;
- hospitalisation costs for survivors and non-survivors with severe sepsis and MOD;
- the long-term mean annual NHS costs for patients aged 16 to 44 years, 45 to 64 years, and above 65 years; and
- a mean estimate of long-term NHS cost (excluding initial intervention and acute care).

The costs and the quantities of resources used were reported separately. The quantities of resources used were based on ICNARC unpublished data, while costs estimates were derived from published official sources. Since the costs were incurred over more than 2 years (patients’ lifetime), discounting was appropriately conducted. It appears that all costs were reported for the price year 2002.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

In line with the perspective adopted, the indirect costs were not included in the analysis.

**Currency**

UK pounds sterling (£).

**Sensitivity analysis**

The authors conducted various one-way sensitivity analyses to test the effect of variability in the data on the
robustness of the results. The following assumptions were tested:

- an adjustment factor of life expectancy for survivors of severe sepsis of 51%, as opposed to 70% used in the baseline analysis;
- long-term patient costs adjusted using a factor 0.51;
- long-term costs per patient per year higher than 10,000 in year 1;
- long-term costs per patient per year higher than 20,000 in year 1;
- no long-term costs;
- QALY weight/utility of 0.69;
- cost of drotrecogin alfa including VAT;
- RRs of 0.70, 0.75, 0.85, 0.90 and 0.95;
- probability of a serious bleeding event of 15%.

In addition, three multi-way sensitivity analyses were also conducted:

- QALY weight of 0.69 and exclusion of long-term costs;
- long-term costs per patient of 20,000 in year 1, with base-case values after that, and life expectancy adjusted to 0.51 of the population norm;
- long-term costs per patient of 20,000 in year 1, with base-case values after that, and life expectancy adjusted to 0.51, plus baseline all-cause mortality risk of 33.9% for patients with severe sepsis and MOD and 31.3% for patients with severe sepsis.

Assumptions used in the sensitivity analyses were mainly derived from published literature. In addition, a probabilistic Monte Carlo simulation was undertaken to address parameter uncertainty. Details of parameter distributions were not presented.

**Estimated benefits used in the economic analysis**

In the base-case analysis, an incremental analysis was conducted. When drotrecogin alfa (activated) plus conventional treatment was compared with conventional treatment alone it resulted in an incremental life-years gain (mean) of 1.144 (standard deviation, SD=0.343) and an incremental QALY gain (mean) of 0.686 (SD=0.208) for patients with severe sepsis. For patients with severe sepsis and MOD, the incremental life-year gain (mean) was 1.351 (SD=0.430) and the incremental QALY gain (mean) was 0.810 (SD=0.258).

**Cost results**

An incremental cost analysis was performed. When drotrecogin alfa (activated) plus conventional treatment was compared with conventional treatment alone, the incremental cost was 6,288 (SD=593) for patients with severe sepsis and 6,661 (SD=772) for patients with severe sepsis and MOD.

**Synthesis of costs and benefits**

An incremental cost-effectiveness analysis was performed. When drotrecogin alfa (activated) plus conventional treatment was compared with conventional treatment alone, the cost per additional LYG was 5,495 for patients with severe sepsis and 4,931 for patients with severe sepsis and MOD. The cost per QALY was 9,161 for patients with severe sepsis and 8,228 patients with severe sepsis and MOD.
The probabilistic Monte Carlo analysis demonstrated that at a willingness-to-pay of 20,000 per additional QALY, drotrecogin alfa (activated) plus conventional treatment is a cost-effective option in 98.7% of trials in patients with severe sepsis and MOD and 96.8% of trials in patients with severe sepsis alone.

Sensitivity analyses demonstrated that when an adjustment factor of 0.51 for life expectancy was used, the cost per QALY increased from 8,228 to 10,439 in patients with severe sepsis and MOD. The cost-effectiveness results were robust to variations in the longer term costs. The multi-way sensitivity analysis in which the long-term cost of 20,000 per patient in the first year was used, life expectancy was adjusted to 0.51 of the population norm and the 28-day mortality rate was 33.9 and 31.3 for the two patient groups, respectively, increased the cost per QALY to 14,645 for patients with severe sepsis and MOD and to 15,992 for patients with severe sepsis alone. Using the same assumptions as in the previous analysis, a probabilistic analysis demonstrated that at a willingness-to-pay of 20,000 per additional QALY, drotrecogin alfa (activated) plus conventional treatment is cost-effective in 83.1% of trials in patients with severe sepsis and MOD. If the threshold is increased to 30,000 per additional QALY, the intervention becomes cost-effective in 95.8% of trials.

The one-way sensitivity analyses demonstrated that the results were most sensitive to variations in the effectiveness of drotrecogin alfa. When an RR of 0.85 or 0.90 was used, the cost per QALY increased from 8,288 to 11,142 (RR=0.85) and to 15,637 (RR=0.90), respectively.

Authors' conclusions
The analysis demonstrated that "the use of drotrecogin alfa (activated) in accordance with the licence indication is a cost-effective treatment in UK clinical practice".

CRD COMMENTARY - Selection of comparators
The selection of the comparators was explicitly justified. The use of drotrecogin alfa (activated) has been recommended by the National Institute of Clinical Excellence in the UK as a treatment options for adult patients with severe sepsis and multiple organ failure. However, conventional treatment, although it represented standard practice in the authors' setting, was not described in any detail in this paper. You should decide if this represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
A systematic review was undertaken alongside the economic modelling. The authors stated that the review guided the development and structure of the model. However, it was unclear how much of the data used to populate the decision model were identified through the review. As the methodology and results of the review were not reported in this paper, it was difficult to ascertain whether the studies referred to and used to populate the model were those identified and included in the systematic review (see Green et al. 2005).

Validity of estimate of measure of benefit
The authors used LYG and health utility (QALYs) as measures of benefit in the economic analysis. However, because of the lack of published data, health values of a different study population (patients with acute respiratory distress syndrome) were adopted in the current study. The authors highlighted scarcity of data as an issue, and attempted to address some of the limitations through probabilistic sensitivity analysis.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the NHS paying for the intervention. It appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were reported separately thus enhancing the reproducibility of the results in other settings. The quantities of resources used were based on actual (unpublished) data, while cost estimates were derived from published sources. An extensive sensitivity analysis was conducted to assess the robustness of the estimates used. The discount rate was clearly reported and applied to all relevant future costs. Although the price year was not stated clearly, it can be inferred from the data
sources reported.

**Other issues**
The authors compared their findings with those from other studies and found them generally to be in agreement with studies conducted in European settings. Inconsistencies with studies conducted in North American settings were attributed to methodological differences. The issue of generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively. The study enrolled adult patients with severe sepsis and MOD and this was reflected in the authors’ conclusions. The authors reported that the main limitation to their study was the lack of published data on costs, life expectancy and health state values and the lack of long-term follow-up data on morbidity and mortality for patients with severe sepsis.

**Implications of the study**
The authors did not make explicit recommendations for changes in policy or practice, or the need for further research. However, the discussion highlighted areas where more information is required.

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**Other publications of related interest**


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