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Abstract

Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation

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Objectives: To assess the clinical and cost-effectiveness of drotrecogin alfa (activated) for the treatment of adults with severe sepsis in a UK context.
Data sources: Electronic databases. Data from the commercial use of the drug up to April 2002. Data from the manufacturer submission to the National Institute for Clinical Excellence (NICE).
Review methods: A systematic review of the literature and an economic evaluation were undertaken. Data were synthesised through a narrative review with full tabulation of results from included studies.
Results: The evidence on the effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis came primarily from one large pivotal randomised controlled trial, the PROWESS study. This study demonstrated a statistically significant absolute reduction in 28-day mortality of 6.5%. Longer term survival benefit was maintained to 90 days. By 9 months, the trend towards increased median survival was non-significant, although the survival curves did not cross. Results presented by the number of organ dysfunctions were not statistically significant, but when mortality rates for those with two or more organ failures were combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo. However, this report highlights a number of considerations relevant to the subgroup analyses reported for the PROWESS study. Published cost-effectiveness studies of treatment with drotrecogin alfa (activated) have applied a range of methods to the estimation of benefits, estimating an incremental gain per treated patient of between 0.38 and 0.68 life-years (for patients with severe sepsis). For patients with severe sepsis and multiple organ dysfunction, the manufacturer (Eli Lilly) estimated an incremental gain of 1.115 life-years per treated patient, compared to 1.351 life-years per treated patient estimated by the Southampton Health Technology Assessments Centre (SHTAC). These latter UK analyses are based on a patient group that is more severely affected by disease, where effectiveness is greater and the baseline risk of all-cause mortality is much higher (SHTAC analysis), these factors are associated with the noted difference in effect. The three published cost-effectiveness studies report cost for US and Canadian patient groups; for those patients with severe sepsis they report the additional cost per patient treated in a range around $10,000–16,000. The manufacturer's submission reports analysis for the UK, based on 28-day survival data in patients with severe sepsis and multiple organ dysfunction (the European licence indication), with the additional mean cost per treated patient estimated to be £5106. The analysis undertaken by SHTAC, for a UK group of patients with severe sepsis and multiple organ dysfunction, estimates an additional mean cost per patient treated of £6661. The manufacturer's submission to NICE presents cost-effectiveness estimates for drotrecogin alfa (activated) in the UK, in patients with severe sepsis and multiple organ dysfunction, at £6637 per quality-adjusted life-year (QALY) based on 28-day effectiveness data, and £10,937 per QALY based on longer term follow-up data. SHTAC developed an independent cost-effectiveness model and estimated a base-case cost per QALY of £8228 in patients with severe sepsis and multiple organ failure (based on 28-day survival data). Simulation results indicate that where the NHS is willing to pay £20,000 per QALY, drotrecogin alfa (activated) is a cost-effective use of resources in 98.7% of cases. Published economic evaluations report various

sensitivity analyses, with results sensitive to changes in the measure of treatment effect, but otherwise studies reported that results were robust to variations in most assumptions used in the cost-effectiveness analysis.
Conclusions: Drotrecogin alfa (activated) plus best supportive care appears clinically and cost-effective compared with best supportive care alone, in a UK cohort of severe sepsis patients, and in the subgroup of more severely affected patients with severe sepsis and multiple organ failure. The introduction of drotrecogin alfa (activated) will involve a substantial additional cost to the NHS. The treatment-eligible population in England and Wales may comprise up to 16,570 patients, with an estimated annual drug acquisition cost of over £80 million, excluding VAT. Further research is required on the longer term impact of drotrecogin alfa (activated) on both mortality and morbidity in UK patients with severe sepsis, on the clinical and cost-effectiveness of drotrecogin alfa (activated) in children (under 18 years) with severe sepsis, and on the effect of the timing of dosage and duration of treatment on outcomes in severe sepsis.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Bacteraemia The presence of viable bacteria in the blood.

Hypoperfusion Reduction in blood flow through a tissue.

Hypotension Systolic blood pressure of < 90 mmHg or a reduction of ≥ 40 mmHg from baseline.

Infection Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Intrahepatic cholestasis Intrahepatic impairment of bile flow. It is usually due to liver cell damage, but may be due to obstruction of intrahepatic bile ducts.

Lactic acidosis Acidosis caused by accumulation of lactic acid more rapidly than it can be metabolised.

Multiple organ dysfunction syndrome Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Nosocomial infection Infection not present or incubating before admittance to hospital, but generally occurring 48–72 hours after admittance.

Oliguria Excretion of a reduced amount of urine in relation to the fluid intake.

Purpura fulminans Rare fulminating, non-thrombocytopenic purpura that is often secondary to severe infections and is associated with a high mortality

Sepsis Systemic inflammatory response due to infection.

Septic shock Sepsis-induced shock with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Severe sepsis Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status.

Systemic inflammatory response syndrome Clinical manifestation of inflammation occurring in response to a clinical insult such as infection, trauma, burns or pancreatitis. The response is manifested by two or more of the following conditions: (1) temperature $>38^{\circ}$C or $<36^{\circ}$C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or arterial carbon dioxide tension <4.3 kPa (32 mmHg); and (4) white blood cell count $>12{,}000$ mm^{-3}, <4000 mm^{-3} or $>10\%$ immature (band) forms.

Tachycardia Excessive rapidity in the action of the heart; the term is usually applied to a heart rate >100 beat per minute.

Tachypnoea Abnormally rapid (usually shallow) respiratory rate. The normal resting adult respiratory rate is 12–20 breaths per minute.

Thrombocytopenia Decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting.

List of abbreviations

ACCP	American College of Chest Physicians
ADL	activities of daily living
APACHE II	Acute Physiology, Age and Chronic Health Evaluation Score II
aPC	activated protein C
APS	acute physiological score
ARDS	acute respiratory distress syndrome
ARR	absolute risk reduction
CCU	coronary care unit
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CMPD	Case Mix Programme Database
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
Da	drotrecogin alfa (activated)
DIC	disseminated intravascular coagulation
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D	EuroQol 5 Dimensions
EU	European Union
FCE	finished consultant episode
FDA	Food and Drug Administration
HCHS	hospital and community health services
HRG	Healthcare Resource Group
ICD	International Classification of Diseases
ICH	intracranial haemorrhage
ICNARC	Intensive Care National Audit and Research Centre
ICU	intensive care unit
IL	interleukin
INB	incremental net benefit
IP	infusion period
IQR	interquartile range
ITT	intention to treat
LOS	length of stay
LYG	life-year gained
MI	myocardial infarction
MOD	multiple organ dysfunction
MODS	multiple organ dysfunction syndrome
NICE	National Institute for Clinical Excellence
NR	not reported
ns	not significant
OD	organ dysfunction
OF	organ failure
ONS	Office for National Statistics
OR	odds ratio
PIP	postinfusion period
PROWESS	Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis study
QALY	quality-adjusted life-year
QWB	Quality of Well-Being
R&D	research and development
RCT	randomised controlled trial
rhAPC	recombinant human activated protein C
RR	relative risk
RRR	relative risk reduction
SAE	serious adverse event
SBE	serious bleeding event
SCCM	Society of Critical Care Medicine
SD	standard deviation
SE	standard error
SF-36	Short Form 36

continued

List of abbreviations *continued*

SHTAC	Southampton Health Technology Assessments Centre
SICS	Scottish Intensive Care Society
SIRS	systemic inflammatory response syndrome
SMR	standardised mortality rate
SOD	single organ dysfunction
SOFA	Sequential Organ System Failure (score)
TAFI	thrombin activatable fibrinolysis inhibitor
TISS	Therapeutic Intervention Scoring System
TNF	tumour necrosis factor
VAS	visual analogue scale
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Severe sepsis and septic shock are life-threatening systemic responses to infection and are the most common cause of death in intensive care units. The incidence of severe sepsis in the first 24 hours in intensive care in the UK is estimated to be 27.1%, equivalent to 21,191 cases in England and Wales per annum. Despite successful early resuscitation, overall 20–56% of patients with severe sepsis will die from their disease.

Current treatment of severe sepsis involves both treatment of the underlying infection, primarily with antibiotics and surgical débridement, and supportive treatments according to the signs and symptoms exhibited by the patient. Attempts to reduce mortality rates have focused on the use of anti-inflammatory therapies, with large randomised controlled trials (RCTs) targeting mediators such as tumour necrosis factor alpha (TNF-α), TNF-α receptor, interleukin-1 (IL-1), the IL-1 receptor and prostaglandins and bradykinins, as well as using large-dose corticosteroids. However, RCTs have generally failed to show any improvement in survival.

Drotrecogin alfa (activated) (Xigris®), a recombinant human activated protein C (rhAPC), is a new treatment for patients with severe sepsis. It has been licensed in the European Union for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The recommended standard treatment regimen for drotrecogin alfa (activated) is for 24 μg kg^{-1} body weight per minute for a period of 96 hours, and the mean acquisition cost per 70-kg patient, for a full 96-hour course, is estimated to be £4905 excluding VAT.

Objectives

To assess the clinical and cost-effectiveness of drotrecogin alfa (activated) for the treatment of adults with severe sepsis in a UK context.

Methods and results

A systematic review of the literature and an economic evaluation were undertaken. Data on the clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) were synthesised through a narrative review with full tabulation of results from included studies.

Number and quality of studies

Two RCTs assessing the effectiveness of drotrecogin alfa (activated) were identified; one Phase II RCT and one Phase III RCT (PROWESS study). The results of the Phase III RCT (PROWESS) have been published in five subsequent papers. A review on the safety of drotrecogin alfa (activated) was informed by the two identified RCTs, plus three otherwise unpublished prospective open-label studies. Data from the commercial use of the drug up to April 2002 also formed part of the review.

Quality assessment of the two RCTs was conducted according to the guidelines of the Cochrane Infectious Diseases Group, with addition of some topic-specific items relevant to the trials conducted in severe sepsis. Based on a quality assessment of the internal validity of the two RCTs, they may be regarded as being of good quality. It was not possible to assess the quality of the unpublished open-label studies.

Three published cost-effectiveness studies were identified, together with six published abstracts and two unpublished abstracts. The cost-effectiveness analysis submitted to the National Institute for Clinical Excellence (NICE) by the manufacturer of drotrecogin alfa (activated) has also been used to provide information on the cost-effectiveness of the technology.

Summary of benefits

The evidence on the effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis came primarily from one large pivotal RCT, the PROWESS study. This study demonstrated a statistically significant absolute reduction in 28-day mortality of 6.5% [95% confidence interval (CI) –10.7 to –2.2], equivalent to a relative risk of death of 0.79 (95% CI 0.68 to 0.92). Longer term follow-up of PROWESS patients showed that the survival benefit was maintained to 90 days (p = 0.048). By 9 months, the trend towards increased median survival was non-significant

(log-rank $p = 0.097$), although the survival curves did not cross.

A priori subgroup analyses showed a progressive reduction in the relative risk of death with increasing number of organ failures, from 0.92 (95% CI 0.63 to 1.35) in patients with one organ failure at baseline to 0.60 (95% CI 0.33 to 1.11) in those with five organ failures. Results presented by the number of organ dysfunctions were not statistically significant, but when mortality rates for those with two or more organ failures were combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo (0.78, 95% CI 0.66 to 0.93). However, this report highlights a number of considerations relevant to the subgroup analyses reported for the PROWESS study.

To estimate the cost-effectiveness of treatment with drotrecogin alfa (activated) it was necessary to extrapolate from effectiveness data from the PROWESS trial (i.e. short-term 28-day survival data) to longer term outcomes reflecting life-years and quality-adjusted life-years (QALYs) gained. To do this it was necessary to estimate the life expectancy of the additional survivors of severe sepsis, following treatment with drotrecogin alfa (activated). Published cost-effectiveness studies have applied a range of methods to the estimation of benefits, estimating an incremental gain per treated patient of between 0.38 and 0.68 life-years (for patients with severe sepsis). Analysis from the manufacturer (Eli Lilly) estimated an incremental gain of 1.115 life-years per treated patient, in patients with severe sepsis and multiple organ dysfunction. The Southampton Health Technology Assessments Centre (SHTAC) analysis estimated an incremental gain of 1.351 life-years per treated patient, in those patients with severe sepsis and multiple organ dysfunction. These latter UK analyses are based on a patient group that is more severely affected by disease, where effectiveness is greater and the baseline risk of all-cause mortality is much higher (SHTAC analysis); these factors are associated with the noted difference in effect.

Costs

The additional costs associated with drotrecogin alfa (activated) in patients with severe sepsis comprise the acquisition cost of the drug, an additional cost associated with an increased risk of severe bleeding episodes, hospitalisation costs associated with additional survivors of severe sepsis and, where deemed appropriate, the long-term healthcare costs associated with additional survivors of severe sepsis. There are variations in estimates of cost in the published literature. The three published cost-effectiveness studies report cost for US and Canadian patient groups; for those patients with severe sepsis they report the additional cost per patient treated in a range around $10,000–16,000.

The manufacturer's submission reports analysis for the UK, based on 28-day survival data in patients with severe sepsis and multiple organ dysfunction (the European licence indication), with the additional mean cost per treated patient estimated to be £5106. The analysis undertaken by SHTAC, for a UK group of patients with severe sepsis and multiple organ dysfunction, estimate an additional mean cost per patient treated of £6661.

Cost-effectiveness

Estimates of cost per life-year and cost per QALY in the published literature were from US and Canadian economic evaluations and ranged from $15,801 to $33,000 per life-year gained, and from $20,047 to $48,800 per QALY. These estimates were for patients eligible for inclusion in the PROWESS study (i.e. severe sepsis). For those US and Canadian patients regarded as having more severe disease, as indicated by an APACHE II score of 25 or more, the cost-effectiveness profile was more attractive (i.e. costs per life-year and per QALY are lower). For those patients with an APACHE II score of less than 25, published studies (USA and Canada) reported that drotrecogin alfa (activated) was generally regarded as cost-ineffective.

Patients with severe sepsis and multiple organ failure formed the relevant patient group for European analysis. The manufacturer's submission to NICE presented cost-effectiveness estimates for drotrecogin alfa (activated) in the UK, in patients with severe sepsis and multiple organ dysfunction, at £6637 per QALY based on 28-day effectiveness data, and £10,937 per QALY based on longer term follow-up data. SHTAC developed an independent cost-effectiveness model and estimated a base-case cost per QALY of £8228 in patients with severe sepsis and multiple organ failure (based on 28-day survival data). Simulation results indicated that where the NHS is willing to pay £20,000 per QALY, drotrecogin alfa (activated) is a cost-effective use of resources in 98.7% of cases.

Sensitivity analyses: cost-effectiveness analysis

Published economic evaluations reported various sensitivity analyses, with results sensitive to

changes in the measure of treatment effect (i.e. variations in the absolute or relative risk measure used), but otherwise studies reported that results were robust to variations in most assumptions used in the cost-effectiveness analysis. Where multiple changes were made to the base-case assumptions in the SHTAC cost-effectiveness model, the cost per QALY increased towards the estimates reported in the published US and Canadian economic analysis, but the intervention remained at a level that would be regarded as cost-effective to most decision-makers.

Conclusions

Limitations of the review and generalisability of the findings

The key limitation of the two RCTs was in the generalisability of the findings to the UK. The definition of severe sepsis used in the pivotal RCT (PROWESS) was stricter than applied in practice in the UK, and the trials included only patients developing severe sepsis within the first 24 hours of screening (intensive care). Drotrecogin alfa (activated) is licensed in Europe for treatment of patients with severe sepsis and two or more organ dysfunctions, with no further restrictions on its use. It may be that in practice it is used in a wider patient group than those included in the PROWESS study.

Cost-effectiveness analysis was generally limited by a lack of data on longer term survival and quality of life in patients surviving severe sepsis. The published literature on the cost-effectiveness of treatment with drotrecogin alfa (activated) was dominated by studies from USA and Canada, with limited generalisability to the UK. Furthermore, the cost-effectiveness analysis undertaken by SHTAC uses UK data on patients with severe sepsis as defined in the PROWESS study, as a baseline population, but it did not apply the exclusion criteria from the PROWESS study. This may be regarded as both a strength and a limitation of the model, as the in-practice use of these exclusion criteria, which do not form part of the European licence indication, is uncertain.

Other important issues regarding implications

The introduction of drotrecogin alfa (activated) would involve a substantial additional cost to the NHS. The treatment-eligible population in England and Wales may comprise up to 16,570 patients, with an estimated annual drug acquisition cost of over £80 million, excluding VAT.

Recommendations for research

Further research is required on the longer term impact of drotrecogin alfa (activated) on both mortality and morbidity in UK patients with severe sepsis, on the clinical and cost-effectiveness of drotrecogin alfa (activated) in children (under 18 years) with severe sepsis, and on the effect of the timing of dosage and duration of treatment on outcomes in severe sepsis.

Chapter 1

Aim of the review

Drotrecogin alfa (activated) (Xigris®), a recombinant human activated protein C (rhAPC), is a new treatment for patients with severe sepsis. It has recently been licensed in the USA and the European Union (EU) for the treatment of a subgroup of adult patients with severe sepsis who have a high risk of death. The aim of this report is to study the clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in adults in a UK context.

Chapter 2
Background

Description of underlying health problem

Definitions

Sepsis is a clinical response to infection in the body; patients present with both evidence of infection and clinical manifestations of systemic inflammation[1] [i.e. systemic inflammatory response syndrome (SIRS)]. SIRS has been defined by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM)[2] as two or more of the following conditions: (1) a temperature of >38ºC or <36ºC; (2) an elevated heart rate, (3) an elevated respiratory rate; and (4) an elevated or lowered white blood cell count. Severe sepsis is defined as sepsis associated with organ dysfunction, tissue hypoperfusion or hypotension. Septic shock is sepsis-induced shock with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities (see Glossary).

Aetiology and pathology

The clinical presentation of severe sepsis relates as much to host inflammatory response as to the type and location of the infection. Sepsis is most commonly caused by bacteria but can be caused by a variety of other microorganisms such as viruses and fungi. The predominant organisms causing community-acquired infections are Gram-positive bacteria, whereas for nosocomial-acquired infections Gram-negative organisms previously predominated.[1] However, the advent of multiresistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* is leading to a resurgence in Gram-positive infections in hospitals.[3,4] The most common sites for infections leading to severe sepsis include the lung, abdomen and urinary tract. Despite early microbiological culture being recommended before commencement of empirical antibiotic therapy, neither the site nor microbiological cause of the infection can be identified in a significant percentage of patients with severe sepsis.[1]

Pathologically, the presence in the body of microbiological products, such as bacterial endotoxin, leads to a host inflammatory response. These mediators cause a cellular response with the activation and migration of immunologically active cells to the site of infection, as well as a humoral response with release of immunologically active mediators such as cytokines and other inflammatory mediators. These processes make up the host inflammatory response, which attempts to eradicate the infection. If this host inflammatory response is inadequate or becomes uncontrolled it leads to damaging effects and a vicious cycle leading to cell death, organ failure and death.[1]

Epidemiology

Study of the epidemiology of severe sepsis and septic shock has been confounded by many factors in the past, including a lack of clear agreed definitions, marked disease heterogeneity and variations in case-mix. Recent work has allowed a greater understanding of the epidemiology of this condition, although understanding is still incomplete. A summary of the main epidemiological studies is provided in *Table 1*, with full details in Appendix 1.

In the USA, a large prospective observational cohort study of 847 hospitals found that three per 1000 population (or 2.26% of hospital discharges) had severe sepsis.[6] This is equivalent to 1500 cases per 500,000 population per annum with 51% receiving care in an ICU at some point during hospitalisation.[6] The projected increase in incidence of severe sepsis was 1.5% per annum. A recent US longitudinal study using hospital discharge data suggested an incidence of 1200 cases per 500,000 (in the year 2000) with a rise in the incidence of sepsis of 8.7% per annum.[4]

Large and mainly prospective studies of patients admitted to intensive care in both the USA[10,15] and Europe[5,7,16] (*Table 1*, Appendix 1) have found that between 5%[16] and 11%[15] of patients admitted to intensive care have severe sepsis on admission, with the incidence of severe sepsis or septic shock at some point during intensive care variously lying at 9%,[7] 11.6%,[16] 15.6%,[10] and 18.9%.[5]

Corresponding estimates for the UK are slightly higher. The Intensive Care National Audit and Research Centre's (ICNARC) prospective incidence study of their case-mix programme centres in England and Wales found that 27.1% of intensive care patients suffered from severe sepsis

TABLE 1 *Selected details of epidemiological studies*

Study/setting	Incidence	For severe sepsis patients only		
		No. of organ dysfunctions	**LOS (days)**	**Mortality**
Alberti *et al.*, 2002[5] International ICU admissions (>24 hour): *n* = 8353	38.7% sepsis 25.4% severe sepsis or septic shock			
Angus *et al.*, 2001[6] USA 847 hospitals: over 6 million admissions	192,980 (3 per 1000 population) severe sepsis	1: 73.6% 2: 20.7% 3: 4.7% ≥ 4: 1.0%	Mean LOS: Hospital: 19.6 LOS varied little with no. of ODs (range 18.5–22.8 days)	Hospital: 28.6%. By no. of acute ODs: 1: 21.2% 2: 44.3% 3: 64.5% ≥ 4: 76.2%
Brun-Buisson *et al.*, 1995[7] France ICU admissions: *n* = 11,828	9% (1052) severe sepsis	Documented infection only (*n* = 742) ≥ 2: 53%	Median LOS: ICU: 8.5 (range 1–87) Hospital: 11	Crude ICU: 56% Crude hospital: 59% 14 days: 46% 28 days: 56% (95% CI 52 to 60) 42 days: 60% (95% CI 57 to 64)
Moerer *et al.*, 2002[8] Germany ICU admissions: *n* = 385	All 385 patients had severe sepsis	1: 29% 2: 46% 3: 22%	Mean LOS: ICU: 16.6 ± 14.4 Hospital: 32.5 ± 25.0	ICU: 35.6% Hospital: 42.6%
Padkin, *et al.*, 2003[9] UK ICU admissions: *n* = 56,673	27.1% (95% CI 26.7 to 27.5%) severe sepsis in first 24 hours	1: 16.4% (15.8 to 17.0) 2: 34.4% (33.7 to 35.2) 3: 30.8% (30.0 to 31.5) 4: 14.7% (14.1 to 15.3) 5: 3.7% (3.4 to 4.0)	Median (IQR) LOS: ICU: 3.59 (1.50 to 9.33) Hospital: 18 (8 to 36)	Hospital: 47.3% By no. of ODs (95% CI) 1. 21.8% (20.2 to 23.5) 2: 36.0% (34.7 to 37.3) 3: 52.5% (51.1 to 53.9) 4: 75.1% (73.3 to 86.9) 5: 86.1% (83.0 to 88.8)
Rangel-Frausto, *et al.*, 1995[10] USA CCU and ward admissions: *n* = 3708	33% (1226) sepsis 15.6% (577) severe sepsis or septic shock			28-day mortality Severe sepsis/positive culture: 20% Severe sepsis/negative culture: 16% Shock: 46%
Salvo, *et al.*, 1997[16] Italy ICU admissions: *n* = 1101	16.3% (180) sepsis 5.5% (61) severe sepsis 6.1% (67) septic shock			Mortality by presence of sepsis on admission: Severe sepsis: 52.2% Septic shock: 81.8%

continued

TABLE 1 *Selected details of epidemiological studies (cont'd)*

Study/setting	Incidence	For severe sepsis patients only		
		No. of organ dysfunctions	**LOS (days)**	**Mortality**
Sands *et al.*, 1997[12] USA ICU and non-ICU patients: *n* = 12,001	8.9% (1063/12,001) severe sepsis		Mean (median) LOS: Hospital: 29 (20) ICU: 17.7 (8)	28-day mortality: 34% 5-month mortality: 45.3%
Scottish Intensive Care Society[13,14] UK ICU admissions: *n* = 3442	47% sepsis 20% severe sepsis 18% septic shock	Two-thirds of severe sepsis group had ≥ 1 OD		ICU mortality: Severe sepsis: 21.4% Septic shock: 52%
Teres *et al.*, 2002[15] USA ICU admissions: *n* = 21,480	11.3% (2434) severe sepsis at ICU admission		Mean (SD) LOS ICU: 8.48 (10.1) Hospital: 16.21 (16.7)	Overall: 36.3%

CCU, coronary care unit; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; OD, organ dysfunction.

during the first 24 hours of their intensive care stay.[9] The Scottish Intensive Care Society's (SICS) prospective audit of Scottish ICUs demonstrated a 38% incidence of severe sepsis and septic shock at some point during intensive care stay.[13]

It is clear from the marked variation in the quoted incidence of severe sepsis in these studies that significant problems still exist in defining the incidence and prevalence of severe sepsis. However, using data for England and Wales for 1997[9] there were 21,191 admissions with severe sepsis in the first 24 hours, or 255 per 500,000 population per year. If, as has been suggested by Angus and colleagues,[6] only 51% of severe sepsis is treated in an ICU in the USA, a more accurate annual incidence in the UK would lie at around 500 per 500,000. This is still only one-third of that seen in the USA.[4,6]

Age is the major factor to affect incidence. In one of the US studies[6] incidence rose 100-fold from children to patients aged 85 years and over. In the UK, incidence ranges from 70 per 500,000 in the 20–24-year age group to 790 per 500,000 per annum in the 75–79-year age group, with a higher rate in males than in females.[9]

Prognosis

Many factors affect the outcome from severe sepsis. Deaths arise either from acute organ dysfunction (related to acute circulatory failure) or from multiple organ failure associated with secondary hospital-acquired infections and other complications of underlying disease.[17]

Hospital mortality rates in patients with severe sepsis vary from 28.6% in the USA[6] to 47% in England and Wales, with rates from other studies generally lying in between (*Table 1*).[8,12,15] The number of acute sepsis-related organ system failures is a major predictor of mortality. For example, Angus and colleagues[6] found that of all hospitalisations with severe sepsis, almost three-quarters had only one acute organ dysfunction with an associated hospital mortality rate of 21.2%; mortality rates for those with two, three, or four or more organ failures were 44.3%, 64.5% and 76.2%, respectively. The UK study of patients with severe sepsis in the first 24 hours of intensive care[9] showed that although in this setting 84% of patients had two or more organ dysfunctions, the hospital mortality rates associated with one, two, three or four organ failures were 21.8%, 36.0%, 52.5% and 75.1%, respectively, very similar to

those of Angus and colleagues.[6] Other European studies of patients with severe sepsis in intensive care have shown that between 53%[7] and 71%[8] had two or more organ failures.

Mortality rates are also higher with increasing age, pre-existing disease or other medical conditions, and intensive care; for example, US hospital mortality increases with age from 10% in children to 38.4% in those aged 85 years and over.[6] In the UK overall mortality ranged from 17% in the 16–19-year age group to 64% in those over 85 years.[9]

It has been suggested that hospital mortality for severe sepsis is falling over time.[1] Recent evidence from the USA suggests that although percentage mortality may be falling the total number of deaths from sepsis is increasing owing to the increasing incidence.[4]

Scoring systems for patients with sepsis

Scoring systems have been developed as tools to allow the assessment of severity of disease and to estimate the probability of certain outcomes (such as death) for groups of patients. They utilise patient-based, disease-specific and acute physiological measurements to stratify groups of patients according to the risk of a stated outcome. As such, scoring systems present risk stratification for the occurrence of an outcome rather than prediction of an individual patient's outcome and can only be used for comparisons of outcomes between treatment groups, individual hospitals or healthcare systems.[18]

The APACHE (Acute Physiology, Age and Chronic Health Evaluation Score) scoring systems were the first to attempt to measure severity of illness in intensive care patients during the first 24 hours after intensive care admission.[19] APACHE II combines an acute physiological score (APS), derived from weighting 12 different physiological variables, with age and chronic health evaluation scores. It also uses a system for diagnostic coding and type of intensive care admission in calculating risk (see Appendix 2 for a further description of the APACHE II). The APACHE II system was developed and first validated in an American intensive care population and was later validated in a UK population.[20] Validation in the UK demonstrated major differences in case-mix and severity of illness between UK and American intensive care populations, thereby reducing the predictive accuracy of the score.[20] Other factors such as lead-time bias (treatment effect from interventions administered before the time of collection of variables, e.g. on intensive care admission) can also significantly affect the scoring system's predictive accuracy. As the APACHE II scoring system is only validated for risk prediction during the first 24 hours after intensive care admission and not to predict changes in that risk over time while in intensive care, its use for stratifying patients after intensive care admission is not appropriate and will inaccurately predict risk of death. It is widely recognised that it is inappropriate to use the APACHE II scoring systems to determine individual patient outcome, to limit or ration intensive care, or to determine the use of new treatments.[18] Furthermore, the high weighting that APACHE II gives to factors such as increased age and chronic ill health means that an older patient with severe co-morbidities can easily amass more APACHE II points and have an increased likelihood of receiving a treatment compared with a young and otherwise healthy patient.

In the USA the Food and Drug Administration (FDA) approval of drotrecogin alfa (activated) suggested APACHE II as a means of determining which patients have a high risk of death. However, the use of APACHE II at a patient level (i.e. prescribing decision) is not supported in the UK clinical community. The joint submission to the National Institute for Clinical Excellence (NICE) from the Intensive Care Society, SICS, the Royal College of Anaesthetists and the Royal College of Physicians[21] states their belief that the APACHE II severity scoring system is not an appropriate tool on which to base individual patient-level prescribing decisions.

Organ dysfunction scores allocate numerical values to the degree of organ system failure for individual patients and can look at trends in organ system failure with time. These scores have been developed not to predict outcome, but to allow comparisons between groups. The Sequential Organ System Failure (SOFA) score was developed in 1994 by a consensus technique.[22] It scores six different organ systems on a scale of 0 to 4 depending on the severity of dysfunction. The SOFA score has undergone extensive validation in various patient populations and can be used to quantify organ dysfunction on intensive care admission and the degree of organ dysfunction appearing with time on the ICU.

Many other scoring systems can be used to determine severity of disease, and predict risk of death or severity of organ failure in severe sepsis. Although they may have utility in a variety of

settings, their use is not relevant to the current assessment of the effectiveness of drotrecogin alfa (activated). The European licence indication is in severe sepsis patients with multiple organ failure, using multiple organ failure as a measure of disease severity.

Significance in terms of ill-health

Severe sepsis represents a major burden of ill-health for the community. This group of patients is known to have a poor health-related quality of life and to have a high relative risk of mortality in comparison to the general population in the years after intensive care, suggesting a significant ongoing burden of ill-health.[23–25] There is a scarcity of published information on quality of life in severe sepsis, with most studies characterising burden of disease in the context of hospitalisation (hospital resource use). In terms of intensive care, severe sepsis patients are responsible for a disproportionate level of resource utilisation, with severe sepsis representing 27.1% of ICU admissions, but accounting for 46.4% of all ICU bed-days and 33.3% of all hospital bed-days consumed by patients admitted to the ICU.[9,26]

Overall mean hospital length of stay for survivors of severe sepsis is reported to be between 16.2[15] and 19.6 days[6] in the USA, with median stays in Europe reported to be 11 days in France[7] and 18 days in the UK.[9] Mean hospital stay is longer in those patients admitted to the ICU (23.3 days) than in those not admitted to an ICU (15.6 days), but is also reported to vary little with number of organ dysfunctions (range 18.5–22.8 days).[6] Further US studies report that in those patients admitted to an ICU, mean length of intensive care stay is 8 days[15] and 18 days,[12] with a median value of 8 days in the latter study. Other reported median lengths of ICU stay are 3.6 days in the UK[9] and 8.5 days in France (range 1–87 days).[7] These differences in relative use of hospital and intensive care stay may reflect the differences in healthcare provision across countries.

Current service provision

It is believed that the majority of severe sepsis is managed in the intensive care environment in the UK, although as a condition it is by no means confined to intensive care.[6] There is marked variation in provision and supply of intensive care services between countries and within the UK. In the UK about 1% of acute hospital beds are designated as general intensive care beds, with a further 1% being designated as specialty intensive care beds.[27] There is a two-fold variation in intensive care bed provision between hospital trusts, and the level of dependency and case-mix can also vary markedly.[27] Although the number of general ICUs hardly changed between 1993 and 1998, the median number of beds within them rose from four to six.[27] The total number of beds and total expenditure on intensive care services in the UK are markedly less than in many other developed countries.[28]

Markers that may suggest inadequate intensive care provision in the UK include the fact that 8% of appropriate referrals to intensive care are refused admission owing to lack of resources, 5% of referrals are transferred to other centres and 5% of admissions are deemed as being discharged inappropriately early from intensive care owing to high bed demand.[27] The high postdischarge mortality seen in intensive care patients in general could be linked to inappropriate early discharge from intensive care owing to inadequate bed provision or may be due to lack of appropriate step-down facilities.[26,29] The apparent decline in mortality in some subgroups of patients with severe sepsis before the advent of drotrecogin alfa (activated) has led to suggestions that improvements in basic supportive measures are beneficial in the treatment of sepsis.[1,4]

Severe sepsis can be managed in other (non-ICU-specific) critical care hospital settings. Critical care is classified based on the level of care that an individual patient needs, regardless of location. The UK Department of Health[30] has proposed four definitions covering levels of care:

- level 0: patients whose needs can be met through normal ward care in an acute hospital
- level 1: patients at risk of their condition deteriorating, or those recently located from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team
- level 2: patients requiring more detailed observation or intervention including support for a single failing organ system or post-operative care, and those stepping down from higher levels of care
- level 3: patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multiorgan failure.

The availability of level 1 and level 2 hospital beds shows marked variation between hospitals.[27]

Although the availability of critical care beds has increased since 1999, a large number of hospitals still lack level 1 and 2 beds.[27,30] These variations in availability of critical care beds in the UK mean that significant numbers of patients with severe sepsis may receive care at the general ward level (level 0).

Description of standard care

Current treatment of severe sepsis involves both treatment of the underlying infection, primarily with antibiotics and surgical drainage, and supportive treatment according to the signs and symptoms exhibited by the patient. The correct choice of antibiotic has consistently been associated with improved outcomes;[1] however, 10% of patients do not receive prompt antibiotic therapy for the causative pathogen, resulting in a 10–15% increase in mortality compared with those who do receive appropriate therapy.[1]

Support of failing organs is also essential. Treatment usually involves haemodynamic management, primarily via administration of oxygen and fluid resuscitation. Respiratory failure is very common during sepsis, with up to 85% of patients requiring ventilatory support during their illness.[1] Up to half may develop acute respiratory distress syndrome (ARDS), which is associated with a high mortality rate.[1] Aggressive fluid resuscitation with or without vasopressor support will also be used to treat haemodynamic instability. Attempts to reduce mortality rates have focused on the use of anti-inflammatory therapies, with large randomised controlled trials (RCTs) targeting mediators such as tumour necrosis factor-α (TNF-α), TNF-α receptor, interleukin-1 (IL-1), the IL-1 receptor, prostaglandins and bradykinins, as well as using large-dose corticosteroids. These studies have failed to demonstrate an improved outcome in severe sepsis.[1] Since the publication of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial data, further RCTs have demonstrated evidence of benefit in severe sepsis and septic shock for treatments, including low-dose corticosteroids and early goal-directed fluid therapy.[31,32]

Variation in outcome

Variations in the outcome of intensive care treatment can be seen both between countries and within the UK. The standard measure used to compare the outcome from critical illness requiring intensive care is a standard mortality rate (SMR) based on the APACHE II system. In the UK, SMRs vary from approximately 0.90 to 2.05, suggesting marked variation in outcome both within the UK and compared with other countries.[27] However, comparison of crude mortality between units and between countries has many confounding factors. These include variations in case-mix such as underlying disease or diagnosis, variations in severity of illness, co-morbidity, age and emergency status, as well as factors such as 'lead-time bias' related to the timing of treatment. Organisational factors such as medical work patterns, nurse-to-patient ratios, intensive care bed numbers and intensive care demand may also cause variations.[18]

Current service cost

The cost of treating patients with sepsis is high, as a large proportion of patients require prolonged stays and aggressive treatment in intensive care. An intensive care patient is estimated to cost six times more per day than a ward patient and a high-dependency patient three times as much.[27] The average cost per patient day in UK ICUs was £1232 in 2002,[33] and the median total cost of care of patients with sepsis, estimated from a single ICU, was US$10,622 (IQR $3634 to $20,543).[34] One US study using charge data found the median cost to be $63,496 (IQR $26,366 to 137,046),[35] while another using administrative data estimated a mean hospital cost of $22,100 for each patient with severe sepsis.[6] Varying estimates may be due to differences in case-mix, sepsis definitions and treatments, but also to variation in healthcare provided between countries. Further, the ongoing burden of ill-health associated with patients who survive severe sepsis would suggest significant ongoing healthcare resource utilisation.[24,25]

Description of new intervention

Drotrecogin-alfa (activated) (Xigris®)

rhAPC is a new treatment for patients with severe sepsis. Activated protein C (aPC) is an endogenous protein that promotes fibrinolysis and inhibits thrombosis, as well as having anti-inflammatory actions. It probably exerts its action through modulation of the coagulation cascade and inflammatory responses associated with severe sepsis.[36] In patients with sepsis, protein C is depleted and the ability to produce endogenous activated protein C is impaired, shifting the balance towards greater systemic inflammation, intravascular coagulation and organ failure. The administration of activated as opposed to the non-activated form of protein C therefore has theoretical advantages.

Physiologically, activated protein C is known to have several major mechanisms that limit the microvascular injury seen in severe sepsis.[21] By inhibiting factors Va and VIIIa, activated protein C exerts an antithrombotic effect. It also inhibits plasminogen activator inhibitor-1 and limits the production of thrombin activatable fibrinolysis inhibitor (TAFI), thereby increasing thrombolysis. Finally, by blocking leucocyte adhesion to selectins, proinflammatory cytokine release is inhibited.[21]

Drotrecogin alfa (activated), produced by Eli Lilly, has recently been licensed in the EU for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care.[37] It was previously similarly approved by the FDA in November 2001 for "the reduction of mortality in adult patients with severe sepsis who have a high risk of death (e.g. as determined by APACHE II)".[38] The drug is contraindicated in patients at increased risk of bleeding, for example, those with active internal bleeding or intracranial pathology, or those receiving therapeutic-dose heparin.

A high proportion of severe sepsis patients will be cared for in an intensive care environment, although patients with severe sepsis can be identified in many areas within the hospital, including medical, surgical and paediatric units. The recommended standard treatment regimen for drotrecogin alfa (activated) is for 24 μg kg^{-1} body weight per minute for a period of 96 hours.[39] Delivery of the drug is by standard intravenous infusion methods using standard delivery equipment and it can be delivered by qualified nursing staff. It must be delivered through a dedicated lumen of a central venous catheter. These patients require no special follow-up beyond the normal ongoing care offered to intensive care patients.

The listed acquisition cost for drotrecogin alfa (activated) is £152.05 and £608.19, respectively, per 5-mg and 20-mg vial, excluding VAT.[11] The mean acquisition cost per 70-kg patient, for a full 96-hour course, is estimated to be £4905 excluding VAT. There is limited information on the current degree of diffusion (pattern of use) of the drug in the UK, but it has been estimated that between 10,000 and 21,000 patients per year in England and Wales may be eligible to receive it.[9,40]

Chapter 3
Effectiveness

Methods

The methods used for the current review of the clinical effectiveness of drotrecogin alfa (activated) follow those recommended by the Cochrane Infectious Diseases Group.[41]

Inclusion and exclusion criteria

Participants

Participants were hospitalised adult patients with severe sepsis or septic shock acquired either in the community or in the hospital. Severe sepsis is defined according to internationally accepted guidelines, as set out by the ACCP and SCCM in 1992.[2] Studies conducted in children (aged <18 years) were excluded.

Interventions

Drotrecogin alfa (activated) (i.e. recombinant human activated protein C) plus conventional care was compared with conventional care alone.

Study design

To establish the effectiveness of the intervention, only RCTs were included. To establish the safety of the drug all studies conducted in relevant participants were included. The generalisability of the available trial results to the UK context was estimated by comparing the participants and care used in the available RCT(s) to those in the UK.

Outcome measures

The primary outcome measure was all-cause mortality at the end of study follow-up. The side-effect profile of drotrecogin alfa (activated) was also covered. Additional secondary outcome measures that were considered include:

- death from septic shock
- length of hospital and/or ICU stay
- functional status (quality of life)
- APACHE II scores
- number of organ failures
- organ dysfunction
- duration of assisted ventilation
- nosocomial infection.

The expert panel for the review was consulted to determine the most appropriate outcome measures for the review.

Search strategy

Extensive electronic searches were conducted by an experienced information scientist, to identify both published and unpublished literature, including existing systematic reviews and primary studies evaluating the effectiveness of drotrecogin alfa (activated), relevant quality of life literature and economic evaluations.

The databases searched and search strategy used are documented in Appendix 3.

Further useful citations were retrieved through scanning the reference lists of all retrieved studies and contact with experts. Sponsor and other submissions were also checked for:

- any additional studies, or additional unpublished data relating to previously identified studies, meeting the inclusion criteria previously described
- relevant cost data
- data on current use of drotrecogin alfa (activated) for severe sepsis in England and Wales.

The titles and abstracts retrieved by the electronic searches were screened independently by two reviewers; the full papers for each study selected were obtained and assessed for inclusion, again by two reviewers. Any disagreements were resolved through discussion, with referral to a third reviewer where necessary. Reasons for exclusion of full papers were formally documented. Any 'commercial in confidence' data taken from the sponsor's submission has been clearly marked in the report submitted to the HTA programme and to NICE. A separate version with any such data removed has also been submitted.

Quality assessment and data extraction strategy

Quality assessment of RCTs was conducted according to the guidelines of the Cochrane Infectious Diseases Group,[41] with the addition of some topic-specific items relevant to trials conducted in people with sepsis[42] (Appendix 4).

Data extraction and quality assessment were conducted independently by two reviewers using

predesigned forms. Any disagreements were resolved through discussion, with referral to a third reviewer if necessary.

Methods of analysis/synthesis

For the primary end-point, trial data are presented as relative risks and 95% confidence intervals. Continuous data, such as length of hospital stay, are presented as mean and standard deviation. Data for the following subgroups are thought to be of particular relevance: severity of disease at baseline (e.g. APACHE II score), number of organ failures, and source and site of infection (e.g. hospital versus community acquired).

For the assessment of the incidence of side-effects, all available data on the clinical use of drotrecogin alfa (activated) in patients with severe sepsis were included.

Prospective observational data from ICNARC were obtained and used to examine the generalisability of the trial results to the UK setting.

Results

Quantity of research available

In total, 1016 titles and abstracts were retrieved from the literature searches and from screening the reference lists. From the 108 full papers obtained, seven full papers and three abstracts were selected for inclusion in the review. A flowchart of the results of the search and inclusion/exclusion decisions is provided in *Figure 1*, and a list of excluded studies is provided in Appendix 5.

Two RCTs assessing the effectiveness of drotrecogin alfa (activated) were identified (EVAA and PROWESS),[39,43] results for the latter (the PROWESS trial) having been published in five subsequent papers.[44–48] The US FDA has also published a clinical review of rhAPC to support its licensing decision.[38] This includes data not available in the other trial publications and also reports some exploratory analyses of the trial data. A cumulative safety review[49] provides data from the two RCTs plus three otherwise unpublished prospective open-label studies and data from the commercial use of the drug up to April 2002.

The sponsor's submission has provided unpublished data on the results of long-term follow-up of the PROWESS trial and further analyses related to the timing of the drug.[11] Further safety data relating to the ENHANCE study and the two other prospective open-label studies have also been provided, as well as unpublished data from the retrospective MERCURY study.

Study characteristics

Summary details relating to the included studies are provided in *Table 2*, with full details provided in Appendix 6.

Interventions

The first RCT[43] (study ID: EVAA) was a Phase II dose-ranging study, randomising 135 patients to one of seven drotrecogin alfa (activated) regimens or placebo (four regimens/doses for 48 hours, three for 96 hours). The second RCT was the pivotal PROWESS trial,[39] where 1728 patients were randomised to receive drotrecogin alfa (activated) on a continuous intravenous infusion for 96 hours at a dose of 24 μg kg^{-1} per hour or placebo. The investigators had planned to recruit 2280 patients; however, enrolment was suspended after the second interim analysis when a statistically significant reduction in 28-day mortality was found. The same drotrecogin alfa (activated) regimen was used in each of the open-label studies.[49] In both RCTs the placebo was a continuous intravenous saline solution for the same duration as the intervention arm. Neither study enforced a standardised approach to critical care (e.g. use of antibiotics, fluids, vasopressors or ventilatory support), although it appears that all studies were conducted exclusively on patients admitted to ICUs.

Participants

The eligibility criteria for the two RCTs were very similar. Both studies included patients aged 18 years or over, with known or suspected infection and with at least three signs of systemic inflammation and, for PROWESS,[39] sepsis-induced dysfunction of at least one organ or system lasting for no longer than 24 hours. For the EVAA study patients had to show evidence of cardiovascular, renal or respiratory organ failure.[43] These are a modification of the 'Bone criteria' for severe sepsis as laid out by the ACCP and SCCM Consensus Conference in 1992[2] (Appendix 8). The modification produces a more stringent definition of severe sepsis than the Bone criteria. In both studies, patients had to meet these criteria within 24 hours of screening and had to begin treatment within 24 hours (PROWESS)[39] or 36 hours (EVAA)[43] of meeting the inclusion criteria.

The main exclusion criteria for both studies were: presence of conditions that increased the risk of

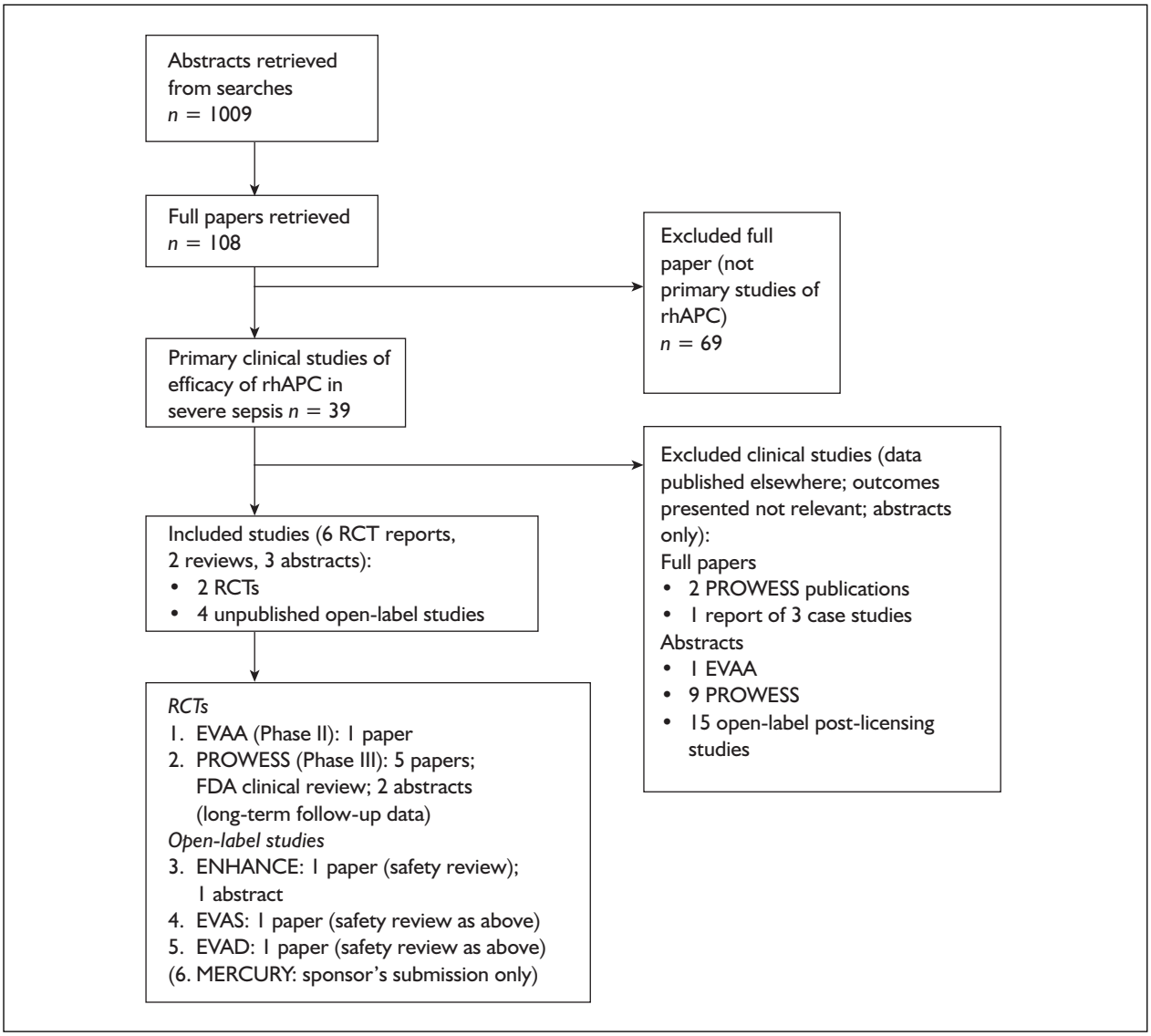

FIGURE 1 *Flowchart of search results*

bleeding; known hypercoagulable conditions or patient not expected to survive for 28 days owing to a co-morbid condition.

The open-label ENHANCE study[51] used similar inclusion and exclusion criteria to those of the PROWESS trial, but also included paediatric patients.[11] The two remaining prospective open-label studies were both compassionate use studies, one of which (EVBC) is reported to have also used criteria similar to those of the PROWESS study.[49] The other (EVAS) required only the clinical diagnosis of purpura fulminans and did not have the presence of thrombocytopenia as an exclusion criterion.[49]

The baseline characteristics of patients in the intervention and control arms of both RCTs are provided in *Table 3*. The mean age of participants was around 60 years and approximately half to two-thirds were male. Over half of the patients in PROWESS came from the USA or Canada, and none of the centres was based in the UK.[39] In comparison, 69% of patients in ENHANCE were from Europe and 20% of the total (n = 470) originated in the UK.[11]

Those patients included in the PROWESS study were more severely ill than those in the EVAA study, with 75% of patients having two or more organ failures in the former compared with 40% in the latter. The mean APACHE II score was considerably higher in PROWESS than in the EVAA study, although the version of APACHE II used in that study was stated to be modified such that the scores are not directly comparable. The characteristics of

TABLE 2 *Summary of included studies*

Study ID/design	Data meeting review inclusion criteria reported in published papers	Additional unpublished data included from sponsor's submission[11]
EVAA Phase II RCT	28-day mortality, safety data[43]	
PROWESS (EVAD) Phase III RCT	28-day mortality, safety data Pivotal trial publication[39] Prospective subgroup analyses[44,46] Retrospective subgroup analyses for multiple organ dysfunction subgroup[45] Impact on organ dysfunction[48] Long-term mortality and safety data (abstract only)[50] Additional safety data in cumulative safety review[49] Additional FDA analyses[38]	Long-term mortality Analyses relating to drug timing
ENHANCE (EVBE, EVBF, EVBG) Phase IV, open-label	28-day safety data for US subgroup (EVBE) published in abstract format[51] EVBF, EVBG unpublished Safety data for all three studies provided in cumulative safety review[49]	28-day safety data Data provided but not included:[1] 28-day mortality results
EVAS Open-label	Unpublished; safety data provided in cumulative safety review[49]	28-day safety data
EVBC Open-label	Unpublished; safety data provided in cumulative safety review[49]	28-day safety data
MERCURY Retrospective uncontrolled	Unpublished	Analyses relating to drug timing

TABLE 3 *Baseline characteristics of participants in included studies*

	EVAA[43]	**PROWESS (EVAD)[39]**
	rhAPC; placebo (*n* =90; *n* = 41)	**rhAPC; placebo (*n* = 850; *n* = 840)**
Age (mean±SD)	58 ± 14; 62 ± 16	60.5 ± 17.2; 60.6 ± 16.5
Age (years) (%): <60 <65 <75	NR	44.1; 43.6 51.4; 53.5 75.9; 78.5
Gender (% male)	63; 66	56.1; 58.0
Race (% Caucasian)	NR	81.8; 82.0
Region: North America Europe Intercontinental	NR	rhAPC (total%)[a] 54.4 (54.7) 30.1 (30) 15.5 (15.3)
APACHE II score	16.8 ± 5.2; 18.4 ± 6.9 (modified APACHE II)[b]	24.6 ± 7.6; 25.0 ± 7.8 SOD: 21.4 ± 7.1; 22.0 ± 7.2 MOD: 25.7 ± 7.5; 25.9 ± 7.8

continued

TABLE 3 *Baseline characteristics of participants in included studies (cont'd)*

	EVAA[43]	**PROWESS (EVAD)[39]**	
	rhAPC; placebo (*n* =90; *n* = 41)	**rhAPC; placebo (*n* = 850; *n* = 840)**	
Organ failures (%):			
1 system	61; 59	25.3; 24.2	
2 systems	32; 34	31.8; 32.5	
3 systems	7; 7	25.2; 26.0	
4 systems		14.0; 13.8	
5 systems		3.6; 3.6	
		≥ 2 systems 75% ≥ 3 systems 43% ≥ 4 systems 18%	
Mean (SD) no. of OFs at baseline[52]		2.39 (1.12); 2.40 (1.10)	
Organ-system failure (%):		rhAPC[11]	SOFA = 3 or 4[48]
Cardiovascular	62; 61	70.8	60.7; 64.4
Respiratory	57; 66	74.4	55.5; 60.4
Renal	27; 22	42.0	12.1; 11.6
Haematological	NR	16.2	5.3; 6.0
Hepatic	NR	–	2.7; 2.8
Mean SOFA score (SD):[48]			
Cardiovascular		2.6 ± 1.5; 2.7 ± 1.5	
Respiratory		2.7 ± 1.0; 2.7 ± 1.1	
Renal		1.1 ± 1.1; 1.1 ± 1.2	
Haematological		0.7 ± 0.9; 0.7 ± 1.0	
Hepatic		0.6 ± 0.8; 0.6 ± 0.9	
Time from first OF to start of drug infusion (hours)	NR	17.5 ± 12.8; 17.4 ± 9.1	
Septic shock:	70; 68	70.4; 71.7	
Use of (%):			
Vasopressors	NR	71.8; 75.5	
Dobutamine	NR	13.9; 13.5	
Mechanical ventilation (%):	74; 73	73.3; 77.6	
Pre-existing conditions (%):			
Hypertension		38.2; 35.0	
MI		12.1; 14.4	
Congestive cardiomyopathy		6.4; 9.0	
Diabetes		20.7; 22.4	
Pancreatitis	27; 12	3.4; 3.9	
Liver disease		2.1; 2.6	
COPD		22.2; 26.1	
Cancer		17.1; 18.8	
Recent trauma		3.3; 5.1	
Recent surgery (%):			
Elective	NR	5.8; 6.2	
Emergency		20.7; 21.2	
No history of surgery		73.5; 72.6	
Infections (%):			
Positive blood culture	NR	32.7; 32.5	
Gram staining of culture:			
Purely Gram negative		21.8; 23.3	
Purely Gram positive		25.8; 25.1	
Mixed		15.6; 13.9	
Unconfirmed		3.3; 5.4	
Negative culture or not obtained		33.5; 32.3	

continued

TABLE 3 *Baseline characteristics of participants in included studies (cont'd)*

	EVAA[43]	**PROWESS (EVAD)[39]**
	rhAPC; placebo (*n* = 90; *n* = 41)	**rhAPC; placebo (*n* = 850; *n* = 840)**
Site of infection (%):		
Lung	39; 49	53.6; 53.6
Abdomen	16; 17	20.0; 19.9
Urinary tract	14; 12	10.0; 10.2
Blood	18; 10	NR
Other	NR	16.4; 16.3

[a] Data not reported separately for placebo group.
[b] Modified APACHE II scores stated to be lower than APACHE II used in other sepsis trials.[43]
COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MOD, multiple organ dysfunction disease; NR, not reported; OF, organ failure; SOD, single organ dysfunction.
(Commercial in confidence information removed from *Table 3*.)

the US subgroup of the ENHANCE study were similar to those in the PROWESS study: the APACHE II score was slightly lower, and 73% of patients had two or more organ failures.

In PROWESS, the proportion of patients with hypertension at baseline was slightly lower in the placebo than in the control group, but the proportions of those with previous MI, congestive cardiomyopathy and diabetes were slightly higher.[39] A higher proportion of patients in the placebo group also had septic shock, as defined by the sponsor [but note that Lilly's definition of shock (arterial SBP systolic blood pressure ≤ 90 mmHg or mean arterial pressure ≤ 70 mmHg) is not consistent with more usual definitions], were being treated with vasopressors and were receiving mechanical ventilation. The FDA concluded that these differences could slightly favour the drotrecogin alfa (activated) group.[38]

(Commercial in confidence information removed.)

Very limited details of the patients included in the compassionate use studies are available from the sponsor submission.[11] **(Commercial in confidence information removed.)**

Patients in the retrospective MERCURY study were reported to differ from those in PROWESS: they were younger and more severely ill, and received drotrecogin alfa (activated) later.[11] No further data are available at this time.

Outcomes

The primary outcome in the PROWESS and ENHANCE studies was 28-day all-cause mortality,[39,51] although the PROWESS trial initially had two primary outcomes[39] (see PROWESS protocol changes, below). Mortality results for the ENHANCE study are not included in the assessment of the effectiveness of the drug as the study was not randomised; however, they are discussed below in terms of the generalisability of the PROWESS trial results. The sponsor submission provides follow-up data on the PROWESS patients up to 1 year.[11] Survival status was known for 94% of patients at 90 days and 93% at 1 year.[50] Twenty-eight-day mortality was also assessed in EVAA, but as a secondary outcome (the primary outcomes were anti-rhAPC antibody response, pharmacodynamic measures and safety-related outcomes). The latter were also assessed in PROWESS as secondary outcomes[39] and safety-related outcomes were assessed in all of the open-label studies.[49] The cumulative safety update provides combined safety data for all studies plus data on the commercial use of drotrecogin alfa (activated).[49]

Quality of included studies

The internal validity of the RCTs was assessed on four aspects, outlined in Appendix 4, the summary results of which are presented in *Table 4* and discussed below. The open-label studies have not yet been published in full and only very limited details were available from the sponsor's submission; therefore, it has not been possible to assess the internal validity of these studies. The generalisability of the studies to the UK context, particularly in terms of PROWESS, is discussed below at the end of the Results section.

Randomisation and allocation concealment

For the PROWESS study patient assignments were made through a central randomisation centre,

TABLE 4 *Internal validity of included RCTs*

Study	Random	Allocation concealment	Blinding	ITT analysis
EVAA[43]	Unclear	Unclear	'Double-blind'	Adequate
PROWESS[39]	Adequate	Adequate	Patient, investigator, sponsor	Adequate

stratified according to site.[39] The method and details of the randomisation procedure used for the EVAA study were not reported; therefore, both of these items were scored as 'unclear'.[43]

Blinding

Blinding appeared adequate in both RCTs. Patients and investigators were described as being blinded to treatment assignment in the PROWESS study, with foil-wrapped bags used to administer the interventions,[39] although EVAA was described only as double-blind.[43] Neither study mentioned blinding of outcome assessors.

Intention-to-treat analysis

Intention-to-treat (ITT) analysis was reported to have been used in both RCTs, although only patients who received the infusion for any length of time were included in most of the analyses. In the PROWESS study 38 patients never received any study drug [17 in the placebo group and 21 in the drotrecogin alfa (activated) group],[39] however, all randomised patients were followed for the entire 28-day study period, except for one patient in the drotrecogin alfa (activated) group who did not receive the study drug. For the ITT analysis where all patients were analysed in the group to which they were originally assigned, this patient was classified as having died on day 28. The overall trial result was presented both for the ITT population and for treated patients, and there were only small differences.

PROWESS methods of analysis

As discussed below, a very large number of subgroup analyses of the PROWESS mortality data has been conducted, some prospective and many retrospective in nature. Two points need to be emphasised regarding these analyses. First, it is now widely recognised in the methodological literature that such analyses should, as far as possible, be restricted to those chosen a priori and any retrospective analyses should be clearly identified.[53,54]

The original PROWESS publication states that "prospectively defined subgroup analyses were performed for a number of base-line characteristics, including the APACHE II score, the number of dysfunctional organs or systems, other indicators of the severity of disease, sex, age, the site of infection, the type of infection (Gram-positive, Gram-negative, or mixed), and the presence or absence of protein C deficiency".[39] It appears as though these are the analyses reported in the subsequent paper by Ely and colleagues.[46] That paper describes all of the subgroup analyses presented in it as 'prospectively defined' except for two, related to the presence of disseminated intravascular coagulation (DIC) and SOFA scores at baseline. The paper by Dhainaut and colleagues[45] presents subgroup analyses of those patients with multiple organ dysfunction, to support the European licence, and these are all presumably retrospective analyses. The FDA clinical review also reports additional subgroup analyses that the FDA team appears to have carried out on the trial data.[38] The prospective or retrospective nature of the subgroup analyses has been identified as far as possible in the sections below.

Second, subgroup analyses should always be based on formal tests of interaction, although even these should be interpreted with caution.[53,55,56] Reliance on subgroup *p*-values can give misleading indications of subgroup treatment effects.[53]

A Cochran–Mantel–Haenszel test was used for primary analysis in the PROWESS trial.[39] Groups were stratified on the basis of three baseline covariates (severity of disease, age and plasma protein C activity level) and the corresponding relative risk (RR) and 95% confidence intervals were calculated using a stratified log-rank test. The consistency of the effects of treatment on the risk of death in the subgroups was calculated by determining whether the relative risk and 95% confidence intervals for each subgroup included the observed relative risk for the entire population.

Potential treatment by subgroup interactions were stated to have been assessed in PROWESS in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines,[57] using the Breslow–Day test for homogeneity of odds ratios (ORs) across strata. This is a reasonable

approach, as the OR scale is the most generally accepted scale to perform interaction analyses across subgroups; however, limited details of the results of these analyses were presented.

Potential qualitative treatment by subgroup interactions (i.e. when a new treatment is beneficial in some subgroups but harmful in others) were assessed using the qualitative interaction range test.[39] It should be noted that qualitative interactions are thought to be unreliable estimates of direction of effect owing to inconsistent replication,[55] and the overall trial result is generally considered to be a better indication of direction of effect.

PROWESS protocol changes

Three main changes to the protocol of the PROWESS trial occurred. After 720 patients had been recruited (June 1999), a new placebo (0.1% albumin) was introduced and at around the same time (August 1999) a new master lot of cells was introduced to make drotrecogin alfa (activated). Extensive *in vitro* studies by the sponsor did not reveal differences between the old and new preparations of the drug. It is not clear why the new placebo was introduced, but it is likely that it would have improved the allocation concealment of the trial.

The eligibility criteria for the trial were amended (also in June 1999) to exclude those who were most likely to die from underlying disease within 28 days. The definitions of existing exclusion criteria were clarified and the following groups of patients were also excluded:

- patients who had undergone bone marrow, lung, liver, pancreas or small bowel transplantation
- patients who were moribund and death imminent
- those whose family had not committed to aggressive management of the patient
- patients with acute clinical pancreatitis without a proven source of infection.

The FDA compared the baseline demographics of patients included before and after the protocol amendment and concluded that "baseline demographics are strikingly similar".[38] The changes are likely to have increased the power of the trial to detect a true treatment effect, as those likely to die from causes other than sepsis would not have been able to benefit from drotrecogin alfa (activated) anyway. This could be reflected in the fact that the majority of the benefit from drotrecogin alfa (activated) occurred in the second half of the trial following the protocol amendments. However, from an analysis of the 81 patients recruited during the first half of the trial who would not have been eligible during the second half, the FDA conclude that "there was no systematic attempt to eliminate patients who would be less likely to respond to drotrecogin alfa (activated), that elimination of such patients did not increase the observed treatment effect and did not account for the larger observed treatment effect in the second half of the trial".[38]

In a further amendment, one of the originally specified primary outcomes [to demonstrate that drotrecogin alfa (activated) reduces 28-day mortality in protein C deficient patients with severe sepsis] was also dropped. According to the FDA's clinical review this was done to clarify that a single primary analysis would be conducted, as opposed to a possible interpretation that two or more primary analyses were being considered.[38] It is odd that more than one primary analysis was specified in the first place, but given that only 195 patients were not protein C deficient at baseline and that a larger effect from treatment was actually seen in these patients,[46] it is unlikely that this decision was made to increase the chance of demonstrating a significant benefit.

Assessment of effectiveness

Mortality: overall result

Overall 28-day mortality results are provided in *Table 5*. In the two RCTs, the mortality rate for patients receiving placebo was 34.1%[43] and 31.3%.[39] The corresponding absolute reduction in mortality from treatment with drotrecogin alfa (activated) was 5.2% (95% CI –23.0 to 0.11)[43] and 6.5% (95% CI –10.7 to –2.2)[39] for a relative risk of death of 0.85 (95% CI 0.50 to 1.44) and 0.79 (95% CI 0.68 to 0.92), respectively. The latter is the ITT result; when the analysis is restricted to treated patients only the relative risk is 0.80 (95% CI 0.69 to 0.94). For the dose-ranging study[43] all of the survival benefit was observed in the group receiving high-dose drotrecogin alfa (activated). Although two treatment durations of drotrecogin alfa (activated) infusion were also used in this study, results were not presented according to duration.

Long-term follow-up data from the PROWESS study indicate that survival was significantly better in the drotrecogin alfa (activated) group both in the hospital setting, absolute risk reduction (ARR) 5.2%, ($p = 0.023$), (95% CI –9.6 to –0.8),[11] $p = 0.023$) and at 90 days ($p = 0.048$, see

TABLE 5 *Overall 28-day mortality results*

Study	rhAPC; placebo	ARR % (95% CI)	Relative risk of death (95% CI)
EVAA[43]	28.9%; 34.1%	–5.2 (–23.0 to 0.11)	0.85 (0.50 to 1.44)
	Low-dose rhAPC: 35.3%	+1.2 (–1.9 to 20.3)	1.03 (0.59 to 1.82)
	High-dose rhAPC: 20.5%	–13.6 (–32.5 to 6.2)	0.60 (0.28 to 1.27)
PROWESS[39]			
ITT results	24.8%; 31.3%, $p = 0.003$	–6.5 (–10.7 to –2.2)*	0.79 (0.68 to 0.92)*
Treated patients	24.7%; 30.8%, $p = 0.005$	–6.1 (–10.4 to –1.9)*	0.80 (0.69 to 0.94)*
Combined result[49]	25.1%; 31.0%	–5.9 (–10.0 to –3.1)*	0.81 (0.70 to 0.94)*

* Statistically significant results.

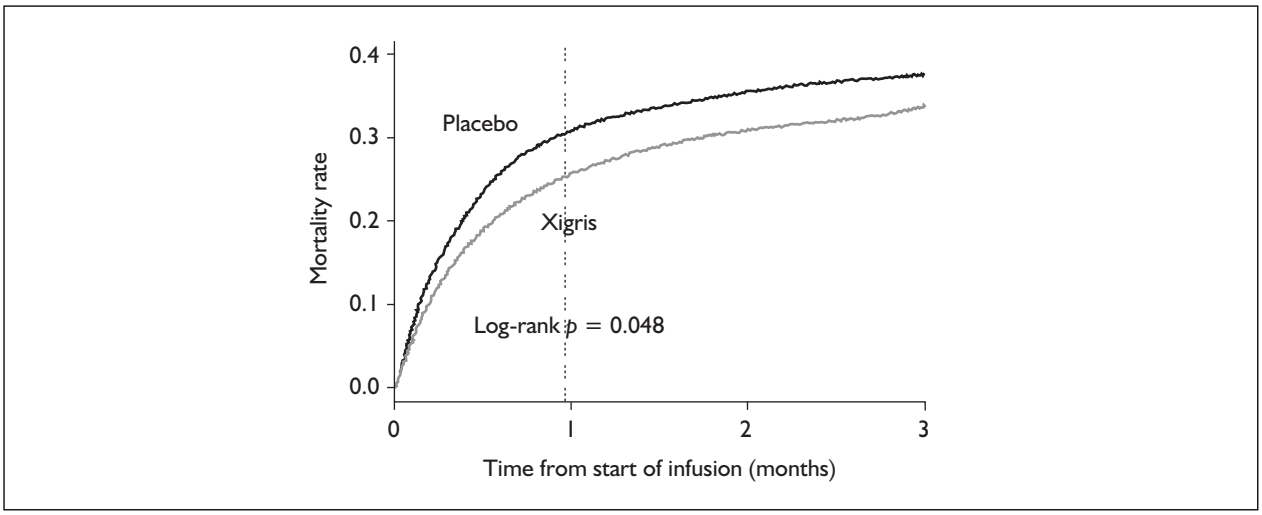

FIGURE 2 *PROWESS: long-term (90-day) mortality follow-up (all patients)[50] (accounting for other predictors of 90-day outcome)*

Figure 2).[50] It appears as though most of the benefit occurred before 90 days; however, mortality was consistently lower with drotrecogin alfa (activated) (*Figure 3*), with median survival of 846 days in the placebo group compared with 1113 days in the drotrecogin alfa (activated) group (log rank $p = 0.097$).[50] Survival status was known for 94% of patients at 90 days and 93% at 1 year.[50] Given that the sponsor's submission states that between 5800 and 10,000 patients would have been required for the PROWESS trial to have been adequately powered to detect a statistically significant improvement in long-term survival and that the survival curves do not in fact cross, it seems possible that the survival benefit from drotrecogin alfa (activated) is maintained in the longer term.

Mortality: subgroup analyses

A multitude of subgroup analyses of mortality for the PROWESS trial has been reported in several publications by the trial investigators[45–47] and the FDA.[38] The present authors designated a priori in the protocol that analyses according to severity of disease at baseline and source and site of infection would be of most relevance, and these are presented in *Tables 6* and *7* and discussed below. The results for the remaining subgroup analyses are provided in Appendix 9. It should be stressed that the RCTs were not powered to detect differences in subgroup mortality.

PROWESS trial: 28-day mortality according to disease severity

All of the subgroup analyses discussed in this section are described by the investigator as chosen a priori except where specifically described otherwise. A progressive reduction in the relative risk of death with increasing number of organ failures was observed, falling from 0.92 (95% CI 0.63 to 1.35) in patients with one organ failure at baseline to 0.60 (95% CI 0.33 to 1.11) in those with five organ failures. Results for the individual subgroups were not significant; however, when

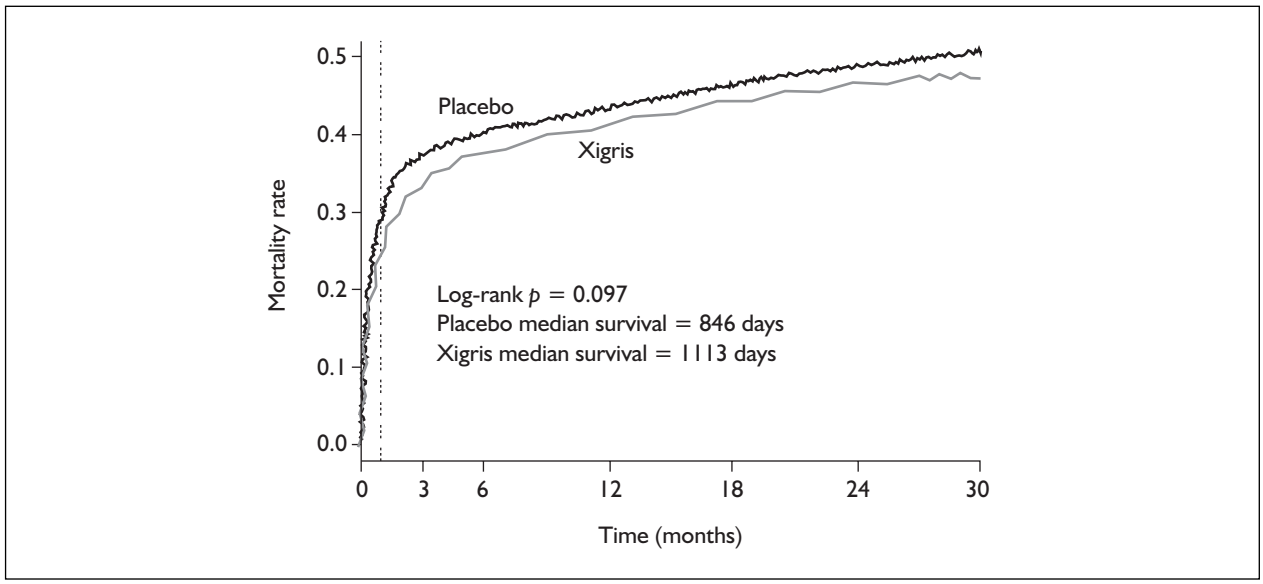

FIGURE 3 *PROWESS: long-term survival up to 30 months (all patients)*[50]

mortality for those with two or more organ failures was combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo (0.78, 95% CI 0.66 to 0.93).[45]

Results were also presented according to APACHE II and SOFA scores at baseline. As discussed in Chapter 2, these scoring systems are not designed to provide an indication of disease severity or outcome for individual patients and only reflect outcomes for populations of patients. In addition, the high weighting that the APACHE II score gives to increased age and severe co-morbidities means that if treatment is determined by such a score, younger and fitter patients would potentially be disadvantaged. The SOFA score is an organ dysfunction score that does not weight for age and co-morbidities, and is thus unlikely to demonstrate such effects.

Similar trends were observed when subgroups were analysed according to APACHE II score at baseline. Those patients with the lowest APACHE II scores at baseline experienced a non-significantly higher mortality rate with drotrecogin alfa (activated) treatment than with placebo (RR 1.25, 95% CI 0.78 to 2.02). Those in the highest two quartiles at baseline experienced significantly lower mortality when treated with drotrecogin alfa (activated) than with placebo (*Table 6*). When patients were divided according to SOFA quartile in a retrospective subgroup analysis, patients in all subgroups experienced survival benefit from drotrecogin alfa (activated), although the relative benefit was greatest in those in the first and fourth quartiles and was only statistically significant in the fourth quartile. (The raw data required to calculate the confidence intervals for the relative risks according to SOFA quartile were not available; however, the paper by Ely and colleagues[46] shows the relative risks and 95% confidence intervals in a forest plot.) The authors report that the formal statistical tests for a treatment by APACHE II score quartile interaction or treatment by SOFA quartile interaction were not significant ($p = 0.09$ and $p = 0.68$, respectively).[46] The formal statistical test for a qualitative interaction for the former result was also not significant ($p = 0.45$). In this case, trial data suggest that a true qualitative interaction of APACHE II score with treatment within the PROWESS population is unlikely.

In terms of individual patient-level disease severity, clinically relevant and meaningful indicators of disease severity include the presence or absence of shock or ARDS, the use of mechanical ventilation or vasopressor support at baseline. Data show that these clinically relevant indicators of disease severity do not allow reliable discrimination between patients who benefit from drotrecogin alfa (activated) and those who do not. On the one hand, patients who might be classified as the least severely affected using these indicators (e.g. those who did *not* have ARDS, were *not* on mechanical ventilation, or were *not* receiving vasopressor support) experienced a greater

TABLE 6 *PROWESS subgroup analyses: 28-day all-cause mortality according to clinical measures of baseline disease severity and infection site and type*[46]

		n	Mortality (%) rhAPC; placebo (*n* = 850; *n* = 840)	ARR (%, 95% CI)[a]	Relative risk of death (95% CI)[a]
Overall result		1690	31.3; 24.8	–6.5 (–10.9 to –2.3)*	0.79 (0.68 to 0.92)*
No. of OF at baseline	1	418	19.5; 21.2	–1.7 (–9.4 to 6.1)	0.92 (0.63 to 1.35)
	2	543	20.7; 26.0	–5.3 (–12.4 to 1.9)	0.80 (0.59 to 1.08)
	3	432	26.2; 34.4	–8.2 (–16.8 to 0.4)	0.76 (0.57 to 1.02)
	4	235	38.7; 46.6	–7.9 (–20.3 to 4.8)	0.83 (0.62 to 1.12)
	5	61	32.3; 53.3	–21.0 (–43.7 to 3.9)	0.60 (0.33 to 1.11)
	≥ 2[45]	1272	26.5; 33.9	–7.4 (–12.1 to –2.0)*	0.78 (0.66 to 0.93)*
APACHE II quartile	1st (3–19)	433	15.1; 12.1	+3.0 (–3.5 to 9.6)	1.25 (0.78 to 2.02)
	2nd (20–24)	440	22.5; 25.7	–3.2 (–11.2 to 4.8)	0.88 (0.63 to 1.22)
	3rd (25–29)	366	23.5; 35.8	–12.3 (–21.7 to –2.9)*	0.66 (0.48 to 0.91)*
	4th (30–53)	451	38.1; 49.0	–10.9 (–19.8 to –1.7)*	0.78 (0.63 to 0.96)*
SOFA quartile[b]	1st (0–7)	NR	15.3; 20.6	–5.3	0.74
	2nd (8–9)		25.7; 28.2	–2.5	0.91
	3rd (10–11)		29.7; 34.5	–4.8	0.86
	4th (>11)		33.5; 44.9	–11.4	0.75
ARDS (FDA analysis[38])[b]	No	1431	23.9; 30.6	–6.7 (–11.3 to –2.1)*	0.78 (0.66 to 0.92)*
	Yes	259	29.6; 32.1	–2.5 (–13.7 to 8.8)	0.92 (0.64 to 1.33)
Presence of shock (PROWESS definition)[c]	No	490	21.0; 22.3	–1.3 (–8.6 to 6.0)	0.94 (0.67 to 1.32)
	Yes	1200	26.3; 34.2	–7.9 (–13.1 to –2.8)*	0.77 (0.64 to 0.91)*
Presence of shock (FDA definition[38])[d]	No	633	21.0; 26.1	–5.1 (–11.8 to 1.5)	0.80 (0.61 to 1.07)
	Yes	1057	27.1; 33.5	–6.4 (–11.8 to –0.8)*	0.81 (0.68 to 0.98)*
Mechanical ventilation	No	415	17.6; 22.9	–5.3 (–12.4 to 1.9)	0.77 (0.52 to 1.13)
	Yes	1275	27.3; 33.1	–5.8 (–10.9 to –0.8)*	0.82 (0.70 to 0.97)*
Vasopressor support	No	633	17.9; 25.2	–7.3 (–15.1 to 0.3)	0.71 (0.50 to 1.02)
	Yes	1057	27.4; 32.7	–5.3 (–10.3 to –0.2)*	0.84 (0.71 to 0.99)*
Presence of pneumonia[11b]	Pneumonia	882	24.7; 32.0	–7.3 (–13.3 to –1.4)*	0.77 (0.62 to 0.95)*
	– community-acquired pneumonia	602	22.5; 31.3	–8.8 (–15.8 to –1.7)*	0.72 (0.55 to 0.94)*
	– nosocomial pneumonia[e]	280	30.0; 33.3	–3.3 (–14.3 to 7.3)	0.90 (0.64 to 1.27)
	Non-pulmonary infection	808	24.8; 29.6	–4.8 (–11.0 to 1.2)	0.84 (0.67 to 1.05)
Infection site	Lung	906	24.0; 33.6	–8.6 (–14.4 to –2.6)*	0.75 (0.61 to 0.91)*
	Intra-abdominal	337	27.6; 30.5	–2.9 (–12.6 to 6.8)	0.91 (0.65 to 1.26)
	Urinary tract	171	21.2; 20.9	+0.1 (–12.1 to 12.6)	1.01 (0.57 to 1.81)
	Other	276	22.3; 28.5	–6.2 (–16.4 to 4.1)	0.78 (0.52 to 1.18)
Infection type[44]	Bacterial	1016	22.6; 28.6	–6.0 (–11.3 to –0.6)*	0.79 (0.64 to 0.98)*
	– pure Gram +ve	426	22.5; 30.4	–7.9 (–16.1 to 0.8)	0.74 (0.54 to 1.02)
	– pure Gram –ve	402	23.7; 28.8	–6.1 (–14.5 to 2.4)	0.82 (0.59 to 1.15)
	– mixed Gram	96	20.7; 24.0	–3.3 (–15.1 to 8.6)	0.86 (0.50 to 1.47)
	Any fungus	62	50.0; 56.3	–6.2 (–29.2 to 17.6)	0.89 (0.56 to 1.42)
	Other organism	31	18.8; 20.0	–1.2 (–29.2 to 26.2)	0.94 (0.22 to 3.94)
	Unknown aetiology	268	25.9; 32.8	–6.9 (–14.3 to 0.4)	0.79 (0.61 to 1.02)

[a] ARR confidence intervals and RRs and CIs, or data to estimate them, provided in FDA report or estimated by SHTAC using data provided in the paper. Where CIs are not provided, insufficient data were available with which to estimate them.
[b] Retrospective subgroup analysis; all others are reported by the investigator as prospective in nature.
[c] PROWESS definition of shock: presence or absence of cardiovascular organ failure as defined in the inclusion criteria, with hypotension or vasopressor support within 6 hours prior to study drug administration.
[d] FDA definition of shock: patients with no cardiovascular organ failure by any assessment prior to the study drug administration, i.e. those with a cardiovascular SOFA of less than 3 (not requiring high-dose vasopressors), were included in the 'no shock' group.
[e] 241/280 had ventilator-associated pneumonia.
* Statistically significant results. NR, not reported.

TABLE 7 *PROWESS retrospective subgroup analyses: 28-day all-cause mortality in patients with multiple organ dysfunction according to clinical measures of baseline disease severity and infection site and type*[45]

		n	Mortality (%) rhAPC; placebo (*n* = 63; *n* = 637)	ARR[a] % (95% CI)	Relative risk of death[a] (95% CI)
Overall result		1271	26.5; 33.9	–7.4 (–12.4 to –2.4)*	0.78 (0.66 to 0.93)*
APACHE II quartile	1st (3–19)	266	14.5; 21.1	+6.6	1.46
	2nd (20–24)	320	26.1; 22.6	–3.5	0.87
	3rd (25–29)	294	41.4; 22.3	–19.1	0.54
	4th (30–53)	391	48.1; 37.6	–10.5	0.78
Overt DIC	No	945	24.6; 28.8	–4.2 (–9.8 to 1.5)	0.85 (0.69 to 1.06)
	Yes	326	31.6; 49.7	–18.1 (–28.5 to –7.4)*	0.64 (0.48 to 0.83)*
Mechanical ventilation	No	237	21.9; 25.7	–3.8 (–14.8 to –7.0)*	0.85 (0.54 to 1.34)
	Yes	1034	27.7; 35.6	–7.9 (–13.6 to –2.3)*	0.78 (0.64 to 0.93)*
Vasopressor support	No	347	23.2; 32.5	–9.3 (–18.7 to 0.1)	0.71 (0.51 to 1.0)
	Yes	924	27.8; 34.4	–6.6 (–12.5 to –0.6)*	0.81(0.67 to 0.98)*
Infection site	Lung	657	27.5; 36.4	–8.9	0.76
	Intra-abdominal	284	29.8; 32.9	–3.1	0.91
	Urinary tract	126	22.6; 25.0	–2.4	0.90
	Other	204	21.1; 33.0	–11.9	0.64
Infection type	Pure Gram +ve	320	23.8; 35.6	–11.8	0.67
	Pure Gram –ve	305	22.9; 32.1	–9.2	0.71
	Other/unknown	646	29.3; 34.0	–4.7	0.86

* Statistically significant results.
[a] ARR confidence intervals and RRs and CIs, or data to estimate them, provided in FDA report or estimated by SHTAC using data provided in the paper. Where CIs are not provided, insufficient data were available with which to estimate them.

relative reduction in all-cause mortality than those who would be classed as more severely affected using these indicators (*Table 6*). Results were significant only for those without ARDS, although this may be due to smaller numbers in the other two subgroups.

On the other hand, using the PROWESS definition of shock, which is less stringent than that of the ACCP/SCCM (the ACCP/SCCM definition requires both hypotension and evidence of perfusion abnormalities and the PROWESS study fails to make it entirely clear which modifications they have made to the ACCP/SCCM criteria for severe sepsis and septic shock), those in shock at baseline (i.e. more severely ill) experienced a larger and statistically significant reduction in mortality compared with those not in shock: relative risks 0.77 (95% CI 0.64 to 0.91) compared with 0.94 (95% CI 0.67 to 1.32). It is notable that when the FDA[38] attempted to analyse patients according to a more conventional definition of shock there appeared to be a similar treatment effect in those in shock and those not in shock at baseline (*Table 6*).

(Commercial in confidence information removed.)

PROWESS trial: 28-day mortality according to disease severity in patients with multiple organ dysfunction

Subsequent to the original trial publications the manufacturer has also published what appear to be retrospective subgroup analyses of those patients with multiple organ dysfunction (two or more organ dysfunctions).[45] Although insufficient data are currently available to estimate the confidence intervals for all of the relative risks, the absolute mortality rates were provided (*Table 7*) and the relative risks presented in forest plots.

Results were not presented according to SOFA score at baseline, but a similar pattern according to APACHE II score was seen as for all patients combined: excess mortality was observed in those in the lowest APACHE II quartile, and survival benefit was greatest (and statistically significant) in those in the highest quartiles. The trial investigators suggest this excess mortality in those with lower APACHE II scores could be due to an age imbalance in that group: there was a higher percentage of patients aged 65 years or over in the drotrecogin alfa (activated) than in the placebo group.[45]

The impact of three other indicators of disease severity was also assessed in subgroup analyses. As

in the case for the subgroup analyses of all patients, some of these indicators showed treatment effect to be greater in those with more severe disease and some showed treatment effect to be less. Those patients who had overt DIC at baseline had a greater benefit than those without overt DIC, with a larger reduction in all-cause mortality; relative risks 0.64 (95% CI 0.48 to 0.83) and 0.85 (95% CI: 0.69 to 1.06), respectively. The effect in the overt DIC group showed statistical significance, unlike the finding for those without overt DIC, despite a much larger proportion of patients (75%) being in the latter group. Those receiving mechanical ventilation also experienced a larger reduction in all-cause mortality than those not receiving mechanical ventilation (*Table 7*), but the difference was not as great and the number of patients in the latter group was small. Patients receiving vasopressor support, suggesting the presence of septic shock, experienced a mortality benefit that was smaller than those not being treated with vasopressors at baseline (this is the opposite finding to the analysis for all patients combined). Both results were of borderline statistical significance (*Table 7*).

PROWESS trial: long-term mortality according to disease severity
(Commercial in confidence information removed.)

PROWESS trial: 28-day mortality according to infection site and type
When all patients are considered, those where the primary site of infection was the lung experienced the highest absolute and relative risk reduction in mortality[49] (*Table 6*). This was the only group with a statistically significant result; however, it also included by far the largest number of patients (906/1690).

Opal and colleagues[44] presented results according to type of infection, that is, causative microorganism group (*Table 6*). Patients with bacterial infections made up the majority of patients in PROWESS, and overall the absolute risk reduction and relative risk of death in these patients were very similar to the overall trial result, as were results in the second largest group, those with infections of unknown microbial aetiology. Results in those with fungal or other infections were not as favourable; however, the number of patients in these groups was far too small for a reliable evaluation. Focusing on those with bacterial infections, patients with Gram-positive infection experienced a slightly higher relative risk reduction than those with Gram-negative infection, although neither result was statistically significant. (Data for these subgroups were also reported by Ely and colleagues,[46] but the differences between the subgroups were greater. The present authors can find no reason for this discrepancy.)

Reported retrospective analyses for patients with multiple organ dysfunction according to these categories show similar or smaller differences between groups[48] (*Table 7*). In particular, patients with Gram-positive and Gram-negative infections had relative risks of death of 0.67 and 0.71, respectively. Confidence intervals for these estimates could not be calculated because of a lack of data; however, the paper by Dhainaut and colleagues[45] shows the confidence intervals for both to be very similar, although results are only statistically for the Gram-positive group.

Mortality: result of logistic regression analysis
A multivariable logistic regression model of predicted risk of mortality in the PROWESS study[39] found that the same or lower mortality rates were observed with drotrecogin alfa (activated) compared with placebo in all predicted risk of mortality classes, and all predicted risk of mortality subgroup results were consistent with the overall PROWESS results.

Visual inspection of the multivariable regression data showed that the absolute benefit with drotrecogin alfa (activated) increased in patients at higher risk of death.[39]

Additional outcomes (excluding safety)
Death from septic shock
The published cumulative safety review[49] provides data on the causes of death for the 509 deaths in the two RCTs. Sepsis-induced multiple organ dysfunction was the most common cause of death, causing 47.9% of the 236 deaths in the drotrecogin alfa (activated) group and 39.2% of the 273 deaths in the placebo group (*Table 8*), followed by refractory septic shock, causing 20.8% and 23.8% of deaths, respectively. When these numbers are considered in terms of the overall reduction in the relative risk of death, drotrecogin alfa (activated) did not reduce the risk of death from sepsis-induced multiple organ dysfunction (relative risk 0.99, 95% CI: 0.77 to 1.27), but did reduce the risk of death from refractory septic shock by an amount bordering on statistical significance (relative risk 0.71, 95% CI: 0.49 to 1.01).

Impact on organ dysfunction
The initial RCT (EVAA) suggested that treatment

with drotrecogin alfa (activated) did not confer any benefits in terms of number of days free from organ failure; although there were non-significant trends in favour of high-dose drotrecogin alfa (activated) in the number of days free from SIRS, and from respiratory, CNS and circulatory failure.[43]

The PROWESS study assessed the impact of drotrecogin alfa (activated) on organ dysfunction by examining mean SOFA scores throughout the study and the resolution or development of organ dysfunction during days 1–7[48] (*Table 8*). Overall, there were reported to be no significant differences in mean total SOFA scores between groups over either days 1–7 ($p = 0.463$) or days 1–28 ($p = 0.329$), although the actual mean scores per group were not presented. When the mean SOFA scores were examined according to individual organ systems, the mean cardiovascular dysfunction scores were significantly lower and mean hepatic scores significantly higher in the drotrecogin alfa (activated) group compared with placebo when SOFA scores were averaged over both 1–7 days and 1–28 days.

When patients in the PROWESS study were examined according to type of organ dysfunction present at baseline, these organ dysfunctions resolved during days 1–7 in a higher proportion of patients in the drotrecogin alfa (activated) group compared with placebo for all organ systems except for hepatic organ dysfunction.[48] Results were significant only for those with cardiovascular or respiratory dysfunction at baseline (assessed by the need for vasopressors and mechanical ventilation, respectively), possibly because these groups had the largest patient numbers. When patients were analysed according to who developed new organ system dysfunction after starting treatment with drotrecogin alfa (activated), a significantly lower proportion of patients in the drotrecogin alfa (activated) group developed new haematological organ dysfunction (assessed by platelet count) during days 1–7 compared with placebo; hazard ratio 0.82 (95% CI 0.67 to 0.99). The likelihood of developing other new organ system dysfunctions did not differ significantly between treatment groups, although the development of cardiovascular or renal dysfunction was non-significantly higher in the drotrecogin alfa (activated) group (*Table 8*).

Impact on functional status

In terms of functional status, for the PROWESS trial[52] the mean ADL score in the drotrecogin alfa (activated) group at day 28 was slightly higher than that in the placebo group (2.50 versus 2.44) and a slightly higher proportion of patients in the drotrecogin alfa (activated) group was fully independent (ADL score of 0), although there were no statistically significant differences. The Therapeutic Intervention Scoring System (TISS-28) is a scale used to measure the time required to perform 28 therapeutic tasks in the ICU and is said to provide an objective indicator of the resources needed to care for a patient; no significant differences in mean TISS-28 scores between drotrecogin alfa (activated) and placebo at 28 days were found.[11]

For the PROWESS trial, 46.8% of drotrecogin alfa (activated) survivors were discharged to home compared with 42.8% of placebo survivors; 73% of additional survivors from drotrecogin alfa (activated) were discharged directly to home or to their previous location (i.e. a skilled nursing home or another hospital).[11] Data from the US subgroup of the ENHANCE study indicated that at day 28, 42% of survivors were at home and not on paid support.[51]

Length of stay

The Phase II RCT (EVAA)[43] reported that treatment with drotrecogin alfa (activated) was associated with a non-significant reduction in the mean number of hospital-, ICU- and ventilator-free days; with reductions of 1.5 ($p = 0.376$), 1.2 ($p = 0.539$) and 0.5 ($p = 0.84$) days, respectively. More reliable data from the PROWESS trial[39] indicate that drotrecogin alfa (activated) did not appear to have any impact on overall length of hospital or ICU stay. Hospital stay in both groups was almost 21 days for survivors and just over 8 days for non-survivors, and ICU stay almost 13 days and just under 8 days, respectively (*Table 8*).

Timing of drug administration

The general consensus regarding the treatment of severe sepsis is that prompt initiation of appropriate therapies leads to improved outcomes.[1]

Vincent and colleagues (2003), as reported in the sponsor's submission,[11] used a database of outcomes in placebo-treated patients to suggest that the outcome for patients with severe sepsis may be determined within the first day of therapy. Very limited information is available on the methods used, but by using change in vasopressor use as a proxy for improved, stable or worsening dysfunction, they appear to demonstrate that improvement in cardiovascular and/or renal function on the initial study day was highly predictive of 28-day survival. *Figure 4*

TABLE 8 *PROWESS results: impact of drotrecogin alfa (activated) on other outcomes*

Outcome	Patient group	*n*	rhAPC; placebo	
Death from septic shock (%) (for both RCTs combined[49])	MOD	509 (1821)	47.9; 39.2 (12.0; 12.1)[a]	ARR: –0.1 (–3.1 to 2.9)[a] RR: 0.99 (0.77 to 1.27)
	Refractory septic shock		20.8; 23.8 (5.2; 7.4)[a]	ARR: –2.2 (–4.5 to 0.00)[a] RR: 0.71 (0.49 to 1.01)[a]
Impact on organ dysfunction[48]				
Mean SOFA score, overall and for individual organ systems			Days 1–7:	Days 1–28:
	Overall	1690	NR; NR, $p = 0.463$	NR; NR, $p = 0.329$
	Cardio	NR	1.63; 1.78, $p = 0.029$	1.20; 1.35, $p = 0.022$
	Hepatic	NR	0.62; 0.52, $p = 0.035$	0.55; 0.47, $p = 0.057$
	Respir	NR	NR, p = ns	NR; NR, p = ns
	Haem	NR	NR, p = ns	NR; NR, p = ns
	Renal	NR	NR, p = ns	NR; NR, p = ns
Resolution of organ dysfunction from baseline (during days 1–7)[b]	OD present:		% Resolving:	Hazard ratio (95% CI):
	Cardio	1482	63.3; 56.9, $p = 0.009$	1.19 (1.04 to 1.36)*
	Hepatic	1598	17.5; 12.7, $p = 0.009$	1.41 (1.09 to 1.82)*
	Respir	1040	56.8; 51.4, $p = 0.365$	1.08 (0.92 to 1.27)
	Haem	681	56.4; 55.1, $p = 0.905$	1.01 (0.83 to 1.24)
	Renal	590	44.7; 50.5, $p = 0.209$	0.86 (0.68 to 1.09)
Development of organ dysfunction in those without the relevant OD at baseline (days 1–7)			% New dysfunction:	Hazard ratio (95% CI):
	Cardio	208	64.4; 57.7, $p = 0.320$	1.19 (0.84 to 1.69)
	Hepatic	67	92.6; 94.7, $p = 0.771$	0.93 (0.55 to 1.56)
	Respir	646	20.4; 17.0, $p = 0.253$	1.23 (0.86 to 1.76)
	Haem	1004	37.2; 43.9, $p = 0.041$	0.82 (0.67 to 0.99)*
	Renal	950	23.3; 22.8, $p = 0.934$	1.01 (0.78 to 1.32)
Impact on other outcomes[52]				
Length of hospital stay (mean days[c])	Survivors	1221	20.7; 20.9	
	Non-survivors	469	8.3; 8.5	
Length of ICU stay (mean days[c])	Survivors	1221	12.9; 12.7	
	Non-survivors	469	7.6; 7.7	
Functional status at day 28	ADL score[d]	1221		
	0		47%; 44%	
	1		5%; 6%	
	2		3%; 4%	
	3		6%; 5%	
	4		5%; 8%	
	5		10%; 8%	
	6		24%; 25%	
	Mean score at day 28		2.50; 2.44	
Effect of drug timing[11]	rhAPC administration (hours):		ARR (95% CI)	RR (95% CI)
	1st quartile (<11.07)	422	–6.5 (–15.1 to 2.2)	0.80 (1.59 to 1.08)
	2nd quartile (11.08–17.75)	425	–5.5 (–14.0 to 3.2)	0.83 (0.61 to 1.12)
	3rd quartile (17.8–22.5)	424	–3.5 (–11.9 to 4.9)	0.88 (0.64 to 1.20)
	4th quartile (>22.52)	417	–9.0 (–17.2 to –0.6)	0.70 (0.51 to 0.98)

[a] Data in parenthesis, ARRs and RRs relate to number of deaths from each cause out of total number of patients in the trials.
[b] Percentage of patients whose organ dysfunction resolved during days 1–7 was lower for those with APACHE II = 25 than for those with lower APACHE II scores. No significant interactions between treatment and disease severity were found for any organ system (all $p = 0.206$).
[c] Standard deviations not provided.
[d] ADL scale assesses functional dependence in six domains (bathing, dressing, toileting, transferring, feeding and continence); a score of 6 indicates full dependence, while 0 indicates fully independent.
* Statistically significant results.
ADL, activities of daily living; Cardio, cardiovascular; Haem, haematological; MODS, multiple organ dysfunction (sepsis-induced) syndrome; ns, not significant; Respir, respiratory; RRR, relative risk reduction.

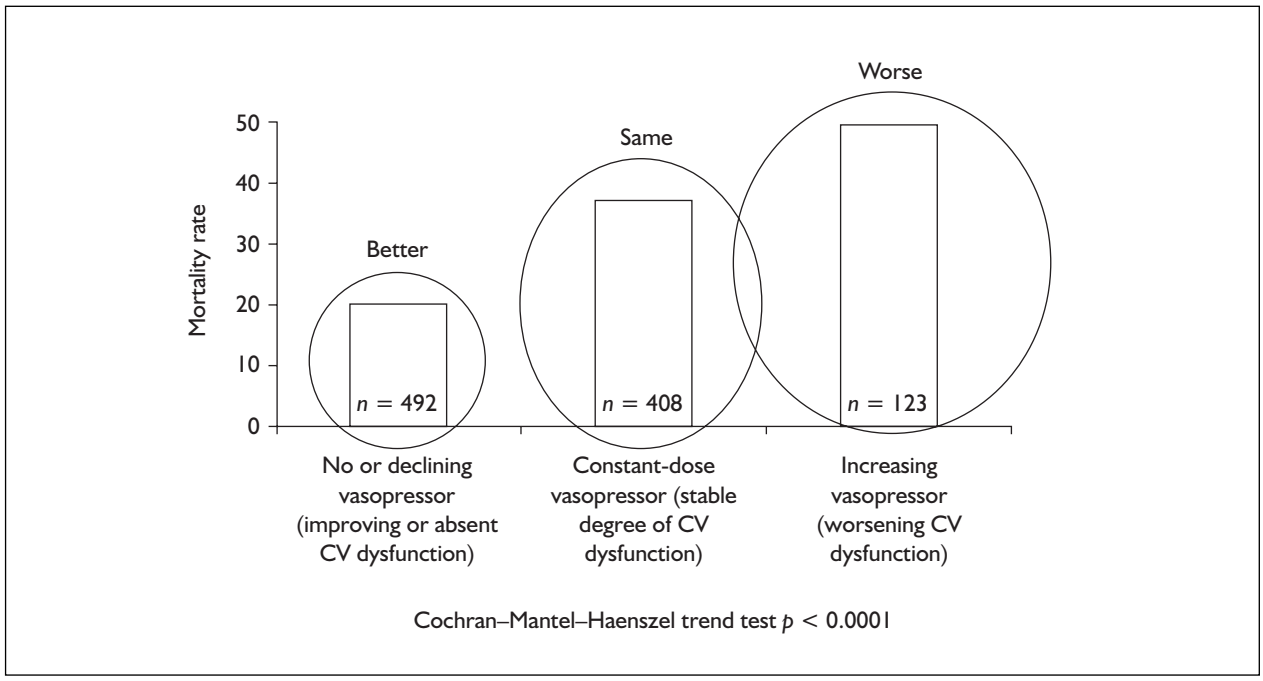

FIGURE 4 *Mortality by trend in vasopressors[11] (data from combined placebo data set). CV, cardiovascular.*

demonstrates results for cardiovascular dysfunction. Continued improvement in cardiovascular function on the next day was also reported to improve odds of survival. Improvement in other organ systems or beyond the first study day was not associated with improved survival.[11]

An analysis of mortality by time from first organ failure to study drug administration in PROWESS demonstrated a survival benefit regardless of the time at which drotrecogin alfa (activated) was administered (*Figure 5*).[11] Data in *Table 8* show that when drotrecogin alfa (activated) was administered in the first to third quartiles the relative risks of death lay between 0.80 and 0.88 and are not statistically significant. The relative risk when drotrecogin alfa (activated) was administered in the fourth quartile was larger and significant at 0.70 (95% CI 0.51 to 0.98). The importance of this result is difficult to interpret given the retrospective nature of the subgroup analyses.

Limited results from the retrospective MERCURY study were also provided in the sponsor's submission (Wheeler and colleagues, 2004, Schmidt and colleagues, 2003, as reported in the sponsor's submission[11]). In this study, patients were stratified by time from severe sepsis documentation to start of drotrecogin alfa (activated) as follows: same calendar day (25.4%), next calendar day (41.6%) or later (33.9%).

Hospital survival was higher for patients with prompt initiation of rhAPC (same day 67.2%, next day 59.6%, later 48.4%, $p = 0.016$). This result may have been affected by the patient profile in the study, as although patients were younger they were also reported to have more severe disease than those in PROWESS; however, the relationship was reported to remain after stratifying by the number of organ dysfunctions ($p = 0.001$) or by vasopressor use ($p < 0.001$) at the time of severe sepsis documentation. After controlling for age, vasopressors, mechanical ventilation and other organ dysfunctions at severe sepsis documentation, prompt initiation of drotrecogin alfa (activated) was associated with a lower risk of death, OR 0.52 (95% CI: 0.45, 0.60).

Adverse effects

There were no significant differences in the incidence of serious adverse events (SAEs) between drotrecogin alfa (activated) and placebo in either RCT (*Table 9*).[39,43] Although the incidence of bleeding events was significantly higher in the drotrecogin alfa (activated) arm of the PROWESS study the difference in serious bleeding events (SBEs) was not ($p = 0.06$ for all SBEs).[39]
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Data on adverse events in all of the studies have been published in the cumulative safety review,[49] although it appears that data for all of the patients in the open-label studies were not available at the

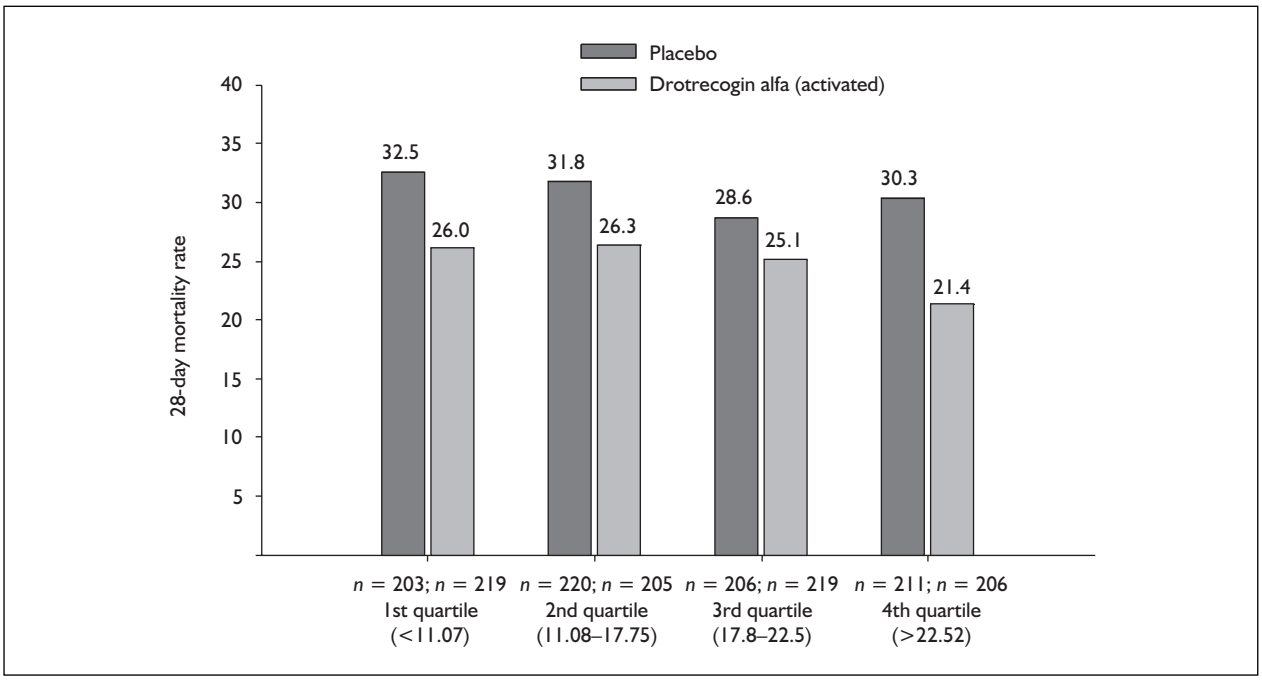

FIGURE 5 *Mortality rates by time (hours) from first organ failure to study drug administration*[11]

time of that review (*Table 10*). There are also slight discrepancies in number of SBEs reported in the individual trials compared with those in the cumulative safety review. The safety review reports that 20 (2.3%) patients in the placebo groups of the controlled trials experienced a serious bleeding event compared with 148 (5.3%) of those who had received drotrecogin alfa (activated) in any clinical study at that time. Slightly more than half of the events in the drotrecogin alfa (activated) arm occurred during infusion of the drug (79 compared with 69 postinfusion). The investigator considered 58 of these events to be related to drotrecogin alfa (activated); the incidence of non drug-related events (21/2786; 0.8%) was therefore similar to the SBE event rate during infusion in the placebo arms of the RCTs (6/881; 0.7%).[49]

When data for intracranial haemorrhage (ICH) were pooled, no patients receiving placebo experienced an ICH compared with 16 (0.6%) of drotrecogin alfa (activated)-treated patients; approximately half of these (nine) were fatal (*Table 10*) and most were drug related (12/16).[49]

Generalisability of results to the UK setting

The generalisability of a study's results is primarily dictated by the similarity of the clinical setting in which the intervention is to be applied to that of the trial, in terms of both the patients and the intervention and care available.

Eli Lilly obtained UK data from ICNARC which matched patients as closely as possible to both the PROWESS definition for severe sepsis and the PROWESS inclusion and exclusion criteria to admissions in their Case Mix Programme Database (CMPD).[11] This provides as close a picture as possible of those UK patients who would have been eligible for the trial. Data on patients matching the PROWESS definition for severe sepsis and the trial inclusion criteria only have been presented in a published paper from ICNARC,[9] and the present authors obtained further information related to these data directly from ICNARC.

The ICNARC data plus corresponding data from the PROWESS and ENHANCE studies are presented in *Table 11*. These indicate that patients in the UK had a higher disease severity in terms of number of organ failures compared with those included in the PROWESS study. Nevertheless, when the PROWESS inclusion and exclusion criteria were applied, the 28-day mortality was similar to the placebo group of PROWESS, although hospital mortality was higher. When only the PROWESS inclusion criteria were applied (population UK2 in *Table 11*), the incidence of organ failures was similar to that reported in patients in the ENHANCE study; however, the 28-day mortality for these patients (41.5%) was much higher than that in ENHANCE (25.3%). This probably reflects both the fact that patients at the

TABLE 9 *Number (%) of adverse events (to 28-day follow-up)*

	≥ 1 SAE[a]			≥ 1 bleeding event			SBE[b] Any (during infusion)			ICH during infusion Any (fatal)		
	rhAPC	**Placebo**	***p***	**rhAPC**	**Placebo**	***p***	**rhAPC**	**Placebo**	***p***	**rhAPC**	**Placebo**	***p***
EVAA[43] rhAPC: 90 Placebo: 41	35 39%	19 46%	0.42	NR	NR		4 (2) 4% (2%)	2 (0) 5% (0%)		NR	NR	
PROWESS[11,39] rhAPC: 850 Placebo: 840	106 12.5%	102 12.1%	0.84	212 (160) 24.9% (18.8%)	149 (92) 17.7% (10.8%)	Both <0.001	30 (20) 3.5% (2.4%)	17 (8) 2.0% (1.0%)	0.06 (NR)	2 (2) 0.2% (0.2%)	0 (0) 0%	NR

[a] Serious adverse events:[43] events leading to death, hospitalisation, cancer, congenital abnormality or drug overdose, or those that were life-threatening, resulted in severe or permanent disability, or were deemed serious by the physician.

[b] Serious bleeding events:[39,43] those serious adverse events that involved bleeding, including (1) any ICH, (2) a need for transfusion of 2 or more[43] or 3 or more[39] units of packed red blood cells on 2 consecutive days, (3) life-threatening bleeding (an event in which the patient was at risk of death at the time of the event).

(Commercial in confidence information removed.)

TABLE 10 *Adverse events: combined results from cumulative safety review*[49]

		SBE[a]	During infusion		Postinfusion		ICH during infusion All (fatal)	
	Total *n*	*n* (%)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	%
Placebo	881	20 (2.3%)	6	0.7 (0.3 to 1.5)	14	1.6 (0.8 to 2.7)	0	0.0%
rhAPC: all clinical studies	2786	148 (5.3%)	79	2.8 (2.3 to 3.5)	69	2.5 (1.9 to 3.1)	16 (9)	0.6% (0.3%)
RCTs[b] (EVAA, PROWESS)	940	35 (3.7%)	20	2.0 (1.3 to 3.3)	15	1.6 (0.9 to 2.6)		
Open-label studies (ENHANCE)	1578	94 (6.0%)	49	3.1 (2.3 to 4.1)	45	2.9 (2.1 to 3.8)		
Compassionate use studies (EVAS, EVBC)	268	19 (7.1%)	10	3.7 (1.8 to 6.8)	9	3.4 (1.6 to 6.3)		
rhAPC: commercial use	3991	34 (0.9%)					8	0.2%

[a] Defined as any ICH, and life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of 3 units of packed red cells on 2 consecutive days.
[b] Note: numbers do not add up to those reported in original trial publications.[39,43]

TABLE 11 *Generalisability of PROWESS results*

	UK 1[a] (*n* = 17,025)[c]	UK 2[b] (*n* = 15,362)[d]	PROWESS (EVAD)[39] rhAPC; placebo	ENHANCE[11]
Age (mean±SD)	61.9	60.8 (16.9)	60.5 ± 17.2; 60.6 ± 16.5	59.1
Mean APACHE II score	18.9		24.6; 25.0	22.0
Incidence of OF				
1 system	19.8	16.4	25.3; 24.2	15.6
2 systems	41.0	34.4	31.8; 32.5	29.7
3 systems	28.8	30.8	25.2; 26.0	29.6
4 systems	9.0	14.7	14.0; 13.8	18.3
5 systems	1.3	3.7	3.6; 3.6	6.7
≥ 2 systems		83.6%	75%	84.4% (72.9%)
≥ 3 systems		49.2%	43%	54.7% (39.9%)
≥ 4 systems		18.4%	18%	
28-day mortality (%) (95% CI)	32.7	41.5 (40.8 to 42.3)	24.8; 31.3	25.3 (23.5 to 27.0)
28-day mortality by no. of ODs				
1 system		17.8 (16.3 to 19.4)	19.5; 21.2	
2 systems		30.2 (29.0 to 31.5)	20.7; 26.0	
3 systems		47.3 (45.9 to 48.8)	26.2; 34.4	
4 systems		71.8 (69.9 to 73.6)	38.7; 46.6	
5 systems		83.3 (79.9 to 86.3)	32.3; 53.3	
≥ 2 systems		46.2 (45.3 to 47.1)	26.5; 33.9	
Hospital mortality (%) (95% CI)	39.2	47.3 (46.5 to 48.1)	29.4; 34.6	
Hospital mortality by no. of ODs				
1 system	18.0	21.8 (20.2 to 23.5)		
2 systems	32.7	36.0 (34.7 to 37.3)		
3 systems	46.2	52.5 (51.1 to 53.9)		
4 systems	71.5	75.1 (73.3 to 76.9)		
5 systems	77.6	86.1 (83.0 to 88.8)		
≥ 2 systems	44.0	51 (50.1 to 51.9)	32.0; 36.6	

[a] UK admissions with PROWESS inclusion and exclusion criteria applied.
[b] UK admissions with only PROWESS inclusion criteria applied.
[c] ICNARC analyses done for Lilly based on 61,458 admissions between 1996 and 2000; analyses for ICNARC CCM 2003 paper based on 56,673 admissions between December 1995 and February 2000.
[d] 6983/15,362 (45.5%) would have met PROWESS exclusion criteria.

highest risk of death were excluded from the clinical studies and that patients in the UK tend to be admitted to the ICU at a later stage in their disease.

The implications of these data are covered further in the discussion (Chapter 7).

Summary of effectiveness results

In summary, the main evidence for the effectiveness of drotrecogin alfa (activated) comes from one large pivotal RCT, the PROWESS study. Overall, the study has high internal validity. Although several protocol changes during the course of the study could be cause for concern, there is no evidence that these changes have biased the study's results in any way. In patients with severe sepsis, drotrecogin alfa (activated) leads to an absolute reduction in mortality of 6.5% (95% CI –10.7 to –2.2) for a relative risk of death of 0.79 (95% CI 0.68 to 0.92) (ITT results). For patients with multiple organ dysfunction, for whom the drug has been licensed in Europe, the corresponding absolute risk reduction and relative risk reductions are 7.4 (95% CI –12.4 to –2.4) and 0.78 (95% CI 0.66 to 0.93).

A large number of further subgroup analyses has been conducted and the authors have highlighted their concerns regarding the interpretation of these. Analyses stratified by APACHE II scores suggest that those with lower APACHE II scores have worse or even negative outcomes compared with those with higher scores. As discussed in Chapter 2, the APACHE II system should not be used for individual patient treatment decisions and it potentially biases treatment towards the elderly. Furthermore, when the results according to APACHE II are considered alongside other, perhaps more clinically relevant, indicators of disease severity (e.g. use of mechanical ventilation, vasopressor support or presence of shock at baseline), some indicators show a greater effect in the more severely ill, whereas others show less effect.

Chapter 4
Economic analysis

Introduction

The aim of this chapter is to assess the cost-effectiveness of drotrecogin alfa (activated) plus conventional care (best supportive care) versus conventional care alone in adults with severe sepsis in England and Wales. The economic analysis comprises a systematic review of the literature on the cost-effectiveness of drotrecogin alfa (activated), a review of the manufacturer (Eli Lilly) submission (cost-effectiveness section) to NICE, and the presentation of an economic model and cost-effectiveness results from the Southampton Health Technology Assessments Centre (SHTAC).

Systematic review of the literature

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations comparing drotrecogin alfa (activated) plus conventional care with conventional care alone, in the treatment of adult severe sepsis. The details of databases searched and search strategy are documented in Appendix 3. Manufacturers' and sponsors' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by an information scientist and thereafter further screening was undertaken by a health economist. The full text of relevant papers was obtained and inclusion criteria were applied.

Economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of drotrecogin alfa (activated) plus conventional care versus conventional care alone in adults with severe sepsis.

Results of the systematic review: cost-effectiveness

The literature search identified three published cost-effectiveness studies[52,58,59] and six published abstracts.[60–65] Two further unpublished abstracts were identified by the review team.[66,67] The Eli Lilly submission to the NICE Technology Appraisal Programme also reported cost-effectiveness findings.[11]

The quality of economic evaluations has been assessed in outline for internal validity (i.e. the methods used) using a standard checklist[68] (see Appendix 10), and for external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions (see Appendix 11).

This review of the cost-effectiveness literature places emphasis on the published economic evaluations and the Eli Lilly submission to NICE. Outline detail is given for those studies published as abstracts only. *Table 12* reports summary results for the cost-effectiveness studies identified (further detail can be found in Appendix 12). Appendix 13 presents a detailed review on those papers published in full.

All economic evaluations reported on the cost-effectiveness of conventional care plus drotrecogin alfa (activated) versus conventional care alone. Most cost-effectiveness studies report estimates of cost per life-year gained (LYG) saved, and a cost per quality-adjusted life-year (QALY). The cost-effectiveness analysis from the PROWESS investigators, and from Fowler and colleagues,[59] also shows an estimate of the cost per life saved. The methods used in the studies to estimate costs and benefits are discussed below, followed by consideration of the cost-effectiveness findings.

Economic evaluations: estimation of benefits

Summary of methods

To estimate survival benefits from drotrecogin alfa (activated), effectiveness data are needed on the relative mortality between comparator groups, information is required on the patient characteristics (age, gender, severity of disease) for those groups, the life expectancy of survivors of severe sepsis is required, and for the estimation of QALYs, the quality of life (health state values) associated with years of life following the episode of severe sepsis is needed.

All reported economic evaluations have used the PROWESS trial data to estimate the benefits associated with drotrecogin alfa (activated). Studies have used data from PROWESS on those patients

treated, rather than the data on randomised patients (i.e. they do not use data from the PROWESS ITT analysis). There is some variation across studies in the specification of intervention and comparator groups used to calculate cost-effectiveness results, and the subsequent use of absolute or relative risk data on all-cause mortality. Where studies have used the comparison of patient groups described in the PROWESS study, they have applied data on the ARR associated with drotrecogin alfa (activated). Where cost-effectiveness has been determined through the comparison of a country-specific baseline cohort of patients with severe sepsis, studies have used RR data from the PROWESS analysis (and from the post hoc analysis of PROWESS reported by the FDA). Effectiveness data reported from PROWESS, and from the post hoc analysis of PROWESS reported by the FDA, are available across a range of subgroups; however, cost-effectiveness results have generally been reported using the effectiveness findings (ARR and RR data) for the overall PROWESS trial group, and for those patients more severely affected by disease, that is, those patients with two or more organ dysfunctions or those patients with higher APACHE II scores, or both.

Published economic evaluations

The cost-effectiveness analysis from the PROWESS investigators[52] used the primary clinical end-point from the trial, where observed mortality was 30.8% for placebo and 24.7% for drotrecogin alfa (activated) ($p = 0.005$). Angus and colleagues[52] calculate an age–gender-specific life expectancy for each 28-day survivor, using US life-table data, and adjust the life expectancy by a factor of 0.51 (i.e. survivors of severe sepsis were attributed 51% of the life expectancy of the relevant age–gender population norm, to allow for a reduction in life expectancy following an episode of severe sepsis). This adjustment factor is reported by Quartin and colleagues[23] and is discussed further below. QALYs are generated by assigning each 28-day survivor the average quality-adjusted survival of the general population norm of someone with the same life-expectancy (i.e. they are given a QALY profile for an older person). Estimates of quality of life were from the Beaver Dam Health Outcomes Study, a US cohort study using a sample of the general population. The average 28-day survivor in the analysis was 58.1 years old and projected to live for an additional 12.3 years at an average utility of 0.68, resulting in 8.5 QALYs. The incremental life-years gained were 0.48 ± 0.29 and the incremental QALYs gained were 0.33 ± 0.21 per treated patient.

The cost-effectiveness analysis from Manns and colleagues[58] applied relative risk data from PROWESS to a baseline cohort of Canadian severe sepsis patients. A cohort study was undertaken as part of the economic evaluation to provide data on patient characteristics, baseline mortality and resource use. Baseline 28-day mortality in the Canadian cohort ($n = 787$) was 30.7%. The cohort study reported baseline 28-day mortality by age group and by APACHE II score (in those with a score of ≤ 24 and those ≥ 25). These subgroup analyses were undertaken in the economic evaluation, using effectiveness data from PROWESS by age and effectiveness data from the FDA by APACHE II score. The study estimated life expectancy using data from the cohort study on subsequent risk of death among survivors of severe sepsis, and mortality rates for the Canadian population. Again, the data on subsequent risk of death were available by age group and APACHE II score. The authors report only cost per life-year gained in their baseline analysis, but adjusted life expectancy for quality of life to estimate cost per QALY in further analyses. They used a health-state value of 0.60 for patients surviving severe sepsis, with this estimate being from a published study,[69] reporting health-related quality of life 1 year after discharge in a group of patients admitted to intensive care with ARDS (see discussion below). This condition (ARDS) was reported by the authors as similar to sepsis in terms of mortality and severity of illness. For 'all patients' the incremental gain in life-years per patients was 0.38 years, and the incremental gain by age groups varied between 0.30 years and 0.40 years. By APACHE II score the incremental gain in life-years was 0.01 years for those with a score of less than or equal to 24, and 0.76 years for those with a score greater than or equal to 25.

The analysis from Fowler and colleagues[59] considers a cohort of patients with severe sepsis defined according to the characteristics of the PROWESS study patient group. They used a decision-analytic model, with a Markov modelling process, to estimate additional survival benefits associated with drotrecogin alfa (activated), and the longer term consequences of additional survival benefits in terms of life-years gained and QALYs. The analysis used data on ARR from PROWESS, and from FDA analysis of PROWESS data by disease severity (using APACHE II scores). Analysis was undertaken for patients matching the PROWESS criteria (i.e. all patients), and according to disease severity, as measured by an APACHE II score of at least 25 and less than 25.

Life expectancy was estimated using US life tables, and an adjustment to life expectancy over an 8-year period to allow for the effects of severe sepsis on rates of mortality. The authors also cite the study by Quartin and colleagues[23] as a source for data on the adjustment of life expectancy, but they do not report the exact methods used. Utilities and values for the health states in the Markov process were stated to be from published estimates of health-related quality of life that were similar to the states describing the transitions for patients with severe sepsis. The study assumed that utility associated with severe sepsis requiring critical care might be similar to a life-threatening bacterial infection in the setting of neutropenia or leukaemia (values of 0.44 and 0.50 were used, respectively, for acute severe sepsis with and without treatment complications). A health-state value of 0.64 was used for subacute septic illness beyond the treatment period, and a value of 0.80 was used to represent postsepsis survival. These values, for survival after the acute septic illness, were assumed to be similar to those for long-term survival following similar acute illnesses. No supporting data or arguments for this were presented.

Fowler and colleagues[59] estimated that in the 'all patients' group, drotrecogin alfa (activated) resulted in an incremental gain in life-years of 0.68, with an incremental QALY gain of 0.54. By disease severity, incremental life-year gains were 1.4 (1.12 QALYs) for those patients with an APACHE II score of at least 25, and 0.02 life-years (0.017 QALYs) for those with a score less than 25.

Abstracts

The published cost-effectiveness abstracts do not offer very much detail on methods used. The abstracts from Launois and colleagues[65] and Riou-Franca and colleagues[67] applied PROWESS data to a baseline population of French patients, with mortality data and patient characteristics informed from the French Cub-Rea database. Launois and colleagues report an incremental gain in life-years of 0.42 years for the 'all-patients' analysis. Riou-Franca and colleagues estimated an incremental gain of 0.64 life-years (0.38 QALYs) in patients with severe sepsis and multiple organ failure.

The abstracts from Neilson and colleagues[62] and Lucioni and colleagues[63] used ARR data from PROWESS for a comparison of patients fitting the overall PROWESS criteria, and for those PROWESS patients with two or more organ dysfunctions. Sacristan and colleagues[64] and Neilson and colleagues[61] used ARR data from PROWESS for a comparison of patients with two or more organ dysfunctions. These studies used country-specific data from life tables (for country-specific life expectancy) with mortality data from PROWESS. The authors report that life expectancy was adjusted for severe sepsis, but do not offer detail on this in the abstracts. In their analysis for Germany, Neilson and colleagues[61] report an adjusted life expectancy of 9.9 years per survivor, or a gain of 0.59 years per patient treated. Sacristan and colleagues[64] report that hospital survivors were estimated to live 12.2 years.

Davies and colleagues[60] used data from PROWESS on ARR for a comparison of all patients in PROWESS and those patients with two or more organ dysfunctions. The authors used country-specific data from life tables to estimate country-specific life expectancy, applying two methods to adjust life expectancy to reflect increased mortality associated with survivors of severe sepsis. First, as above, they used an adjustment factor of 0.51, from a published study (Quartin[23]), across all patients. Second, patient-specific 5-year survival was estimated using data from a published cohort study reporting on adult patients admitted to intensive care.[25] Using this second method, following a period of 5 years, where patients surviving severe sepsis were attributed a greater mortality risk, the patient returned to the population norm for mortality risk. The study applied a health-state utility of 0.69, from a published abstract reporting on a cohort of sepsis patients.[70] This utility was applied across all patients to estimate incremental QALY gains. When applying the first method for life expectancy estimates, the authors report an adjusted mean life expectancy across the all-patients group of 9.93 years, and 16.46 years when applying the second method. Applying the second method for life expectancy in the patient group with two or more organ dysfunctions resulted in an adjusted life expectancy of 20.14 years per patient, an incremental gain in life-years of 1.05 years per patient (an incremental QALY gain of 0.73).

Coyle and colleagues[66] in an unpublished abstract, report on the cost-effectiveness of drotrecogin alfa (activated) in Canada for the treatment of severe sepsis patients at an increased risk of death (defined as an APACHE II score of ≥ 25). Effectiveness data used were from PROWESS, long-term survival data and associated utilities were obtained from a systematic review of the literature, and the estimated incremental QALY gain was 0.66. The abstract does not offer further information on the estimation of benefits.

Eli Lilly submission to NICE

The cost-effectiveness analysis from Eli Lilly was based on patient-level data from the PROWESS placebo and treatment group, for patients meeting PROWESS criteria and having multiple organ failure. The analysis applied data on 28-day all-cause mortality for PROWESS for patients with multiple organ failure (ARR of 7.4%), with an adjustment made to guard against double-counting hospital mortality (mortality in hospital, but after day 28) and mortality in year 1 following survival at day 28; an adjusted ARR of 7.26% is used in the cost-effectiveness model. Further survival analysis was undertaken using ARR data from longer follow-up of PROWESS patients. **(Commercial in confidence information removed.)** The analysis used age–gender patient profiles from the PROWESS placebo and treatment arms, and attributed an expected life expectancy using data from UK life tables, to estimate future survival benefits. Future life expectancy was adjusted over years 1–4, following survival of severe sepsis, using data from an observational study by Wright and colleagues[25] (discussed below). The data were used in a Cox proportional hazards model to estimate relative risks for death per year following survival of severe sepsis, with relative risks of 1.058 and 1.049 estimated per year for male and female patients, respectively. Based on estimates of survival after intensive care,[23,25,59] this estimate per year would seem to be low for the first year following survival of severe sepsis, with the Eli Lilly analysis making only a small adjustment to the ARR of death at 28 days to account for this (i.e. adjustment to ARR from 7.4% to 7.26%). The mean discounted life expectancy per extra survivor was 15.37 years, using data on 28-day survivors. The estimated life-year gains per patient treated were 1.115 years (based on 28-day survivors). Where data were used from longer term follow-up studies the life expectancy per extra survivor was 15.25 years and the incremental gain was 0.706 years.

The cost-effectiveness analysis from Eli Lilly used a single point estimate of 0.69 as a health-state utility to weight future life-year gains, that is, to calculate QALYs. This point estimate was from an abstract published by Drabinski and colleagues[70] (discussed below).

Economic evaluations: estimation of costs

Summary of methods

Methods used to estimate cost vary across studies. Angus and colleagues[52] use PROWESS data to estimate directly the differential costs between treatment groups, based on cost data from a US cohort of patients. Manns and colleagues[58] used data from a specific cohort study on the baseline conventional care cohort. Fowler and colleagues[59] used data on cost and resource use from a US cohort study. Eli Lilly applied PROWESS effectiveness data to estimates of cost based on UK data for length of hospital stay for severe sepsis patients. All studies used data from PROWESS to estimate the cost for drotrecogin alfa (activated). The published economic evaluations used estimates of future healthcare costs in their analysis, whereas Eli Lilly argue strongly against doing so.

Published economic evaluations

Angus and colleagues[52] measured costs for their base-case analysis (i.e. cost per life saved) as the differences in healthcare costs (hospital, physician, study–drug and postdischarge costs) between treatment and placebo during the first 28 days of the study. Hospital costs were estimated using a cost cohort of US patients with detailed billing records and costs were adjusted to reflect year 2000 US dollars. Study drug costs were estimated using per patient dosage in PROWESS. Postdischarge costs (up to 28 days) were estimated by assigning each day a cost depending on patient location and summing over total days (using $1170 per day for acute care, $270 per day for nursing home and $200 for formal or informal supportive care at home). For the reference-case analysis (i.e. lifetime analysis), the costs were as the base case plus lifetime costs post-day 28, which were calculated using age-specific annual healthcare costs for the USA (US database costs, from the National Centre for Health Statistics). Each patient's cost profile was estimated using costs related to their remaining years of life, rather than their actual age, to adjust for the fact that higher costs are attributable to sepsis survivors. Owing to the use of a cost cohort in the calculation of overall patient costs, the authors corrected for potential imbalances between the cost cohort and the overall trial population by deriving an average adjusted cost, incorporating the make-up of the two groups across survivors and non-survivors, and by ICU admission status (surgical or non-surgical). Under the short-term base-case analysis, treatment with drotrecogin alfa (activated) increased costs by $9800 ± 2900 per patient treated. For the lifetime reference-case analysis the costs increased by $16,000 ± 4200 per patient treated.

Manns and colleagues[58] estimated the costs for conventional care for severe sepsis in the ICU and on the hospital ward, and the costs associated with

longer term care for survivors of severe sepsis. Costs for conventional care comprised the mean hospital cost and physician charge per day, summed over the hospital stay. Longer term healthcare costs were based on estimates derived from the cohort study, which provided costs for years 1–3, with costs assumed to remain constant over time, after year 3 (mean cost following discharge in year 1 was $14,181, year 2 was $4698, with year 3 and thereafter at $4579). In their base-case analysis the perspective for costs was that of a third party payer, but subsequent analysis explored the broader societal perspective by incorporating indirect costs, which were based on an estimate of lost production caused by early death. Indirect costs were estimated using a published estimate of patients who were discharged from a general ICU and were subsequently employed (16.9% of patients under 61 years), together with the average gross salary for a full-time Canadian worker. Intervention costs comprised the purchase cost of drotrecogin alfa (activated) (assumed to be $6800 per patient) and a small cost allowance per patient to cover the additional cost associated with an increased risk of serious bleeding in patients treated with drotrecogin alfa (activated), with an increased risk of 1.5% being reported in the PROWESS study. Manns and colleagues used a published estimate of cost related to treatment of serious bleeds ($8306 per episode) and estimated the additional cost per patient for treatment of serious bleeds to be $122. Manns and colleagues do not report the incremental costs per patient, but they can be estimated from their cost-effectiveness results to be around $10,615.

Fowler and colleagues[59] estimated intervention costs, hospitalisation costs and longer term healthcare costs associated with survivors of severe sepsis. They used a modelling approach and present findings for patients defined using PROWESS characteristics (all patients) and for patients defined using the APACHE II score (the group with a score ≥ 25 and the group with a score <25). The authors used a lifetime horizon and a discount rate of 3% for future costs. Cost estimates are presented in 2001 US dollars. The cost used for drotrecogin alfa (activated) was $6800. The analysis included costs associated with serious bleeding (cost estimate of $1237 per event used) and a cost associated with all-cause death ($5310). The estimated cost for hospitalisation was calculated using data from a US observational cohort study of hospital discharge records (for 1995) from seven large US states. Future healthcare costs for survivors were estimated using age adjusted US medical expenditure data. Fowler and colleagues estimated total costs associated with treating all severe sepsis patients with drotrecogin alfa to be $61,751, and the cost for usual care to be $51,006, a net cost difference of $10,745. The net cost difference for patients with an APACHE II score of at least 25 was $15,166, and $6851 for those with an APACHE II score of less than 25.

Abstracts

Abstracts from Neilson and colleagues,[61,62] Lucioni and colleagues[63] and Sacristan and colleagues[64] applied PROWESS data on resource use with country-specific unit costs, generally covering drug costs, costs to day 28 and costs to final hospital discharge. Riou-Franca and colleagues[67] estimated costs using PROWESS trial data, the French CubRea database and a literature review, and estimated an incremental cost per patient treated of $7545. The authors included treatment and initial hospitalisation in their cost estimate, and surprisingly their incremental cost per patient was lower than their cost for drotrecogin alfa (activated); this is attributed to the fact that in the CubRea database hospital costs for non-survivors are greater than for survivors of severe sepsis. Launois and colleagues[65] do not report methods for cost calculations, but report the incremental cost per patient (all patient group) treated with drotrecogin alfa (activated) to be €7623.

Davies and colleagues[60] calculated cost per hospital stay, using UK-specific data on resource use, and cost for drotrecogin alfa (£4496) from the PROWESS study data. They report the mean additional cost of caring for an extra survivor, excluding drotrecogin alfa (activated), at £2433, with total incremental cost per patient at £4642 (this estimate is based on drug cost plus a 6% chance of incurring additional health care costs for extra survivors).

Coyle and colleagues[66] used resource use data from PROWESS and applied Canadian unit costs. Cost data were from analysis of data for a sample of Canadian patients. The abstract does not offer detail on cost methods, but reports an incremental cost of $15,600 (presumably Canadian dollars, but not stated), associated with drotrecogin alfa (activated).

Eli Lilly submission to NICE

The Eli Lilly analysis used an estimate of the intervention cost based on findings from PROWESS, where the mean cost for drotrecogin alfa (activated) was £4717 for all PROWESS patients with multiple organ dysfunctions at baseline. Hospitalisation cost by survival status is

estimated based on UK data from ICNARC on length of stay adjusted according to a PROWESS placebo distribution of organ dysfunction. Unit costs of £1337 and £200 per day were applied, respectively, to ICU and other wards for each day per hospital stay. Based on survival data at day 28, Eli Lilly estimated that the total additional cost per patient treated was £5106. Using data from the longer term follow-up study the additional cost per patient treated was £5331. No allowance was made for additional risks associated with SBEs. Eli Lilly did not include healthcare costs for the longer term care of additional survivors in the drotrecogin alfa (activated) treatment group. They argue that such costs should not be included (see discussion below, SHTAC cost-effectiveness analysis).

Economic evaluations: estimates of cost-effectiveness

Summary

Table 12 presents the summary findings on cost-effectiveness from the reported economic evaluations. A more detailed table, with summary detail on methods, subgroup analyses and sensitivity analyses, is presented in Appendix 12. The published papers report similar findings on cost-effectiveness for the 'all patients' group, with the PROWESS study and Manns and colleagues[58] reporting $33,000 and $27,936, respectively, per LYG, with estimates of $48,800 and $46,560, respectively, per QALY. Estimates from Fowler and colleagues[59] are slightly lower, with cost per LYG at $15,801 and cost per QALY at $20,047 for analysis of their 'all patients' group. These studies also report cost-effectiveness by severity of disease (as defined by the APACHE II score), where patients with an APACHE score of 25 or more have a lower cost per life-year (and QALY) than the 'all patients' analysis, and patients with an APACHE score of 24 or less are associated with a very unfavourable cost-effectiveness profile [in the PROWESS analysis, the conventional care strategy dominates drotrecogin alfa (activated), in Manns and colleagues the cost per life-year for this group is $575,054, and Fowler and colleagues report a cost per life-year of over $400,000].

Cost-effectiveness estimates in the reported abstracts are variable, but all are lower than those in the published studies discussed above. The European studies have in many cases focused on the European licence indication for drotrecogin alfa (activated), which refers to severe sepsis and multiple organ dysfunction. The effectiveness of treatment in this patient group is greater than the general 'all patients' group reported in PROWESS (e.g. studies have used an ARR of 7.3–7.4% versus an ARR of 6.1%), hence the cost-effectiveness profile is more attractive.

Davies and colleagues,[60] in a UK study, report a cost per-life year for the PROWESS patient group between £7037 and £9519, depending on the method used to estimate life expectancy (with the cost per QALY estimate for this group being between £10,199 and £13,796). Cost per life-year and cost per QALY for the patient group with multiple organ dysfunction are £4716 and £6385, based on the more attractive of the methods for estimating life expectancy for survivors of severe sepsis. This analysis does not include longer term costs for survivors of severe sepsis.

The analysis from Eli Lilly[11] reports a cost per QALY of £6637 (£4580 per LYG) in those patients with multiple organ dysfunction, based on PROWESS 28-day all cause mortality data. A further cost per QALY of £10,937 (£7547) was estimated based on all-cause mortality data observed at a longer term follow-up (based on hospital mortality at final patient discharge on day 297).[11]

Generalisability

The cost-effectiveness findings from the published economic evaluations are based on non-UK populations, with Angus[52] and Fowler[59] using US resource use and cost data, and Manns[58] reporting analysis for a Canadian population; therefore, the generalisability of findings to England and Wales is limited. This also applies to the abstract from Coyle and colleagues.[66] Furthermore, the licence indication in North America is different to that in Europe, where the indicated patient group comprises those patients with severe sepsis and multiple organ dysfunction.

European abstracts present specific analyses for their respective countries, although many use the two comparator groups from PROWESS rather than country-specific baseline cohorts of severe sepsis patients. Again, the generalisability of these analyses is limited in the context of the relevant patient group in England and Wales. Davies and colleagues[60] present analyses for the UK, with UK-specific data on resource use and life expectancy; therefore, the findings are relevant to the UK population, but they used the comparison of PROWESS patient groups (drotrecogin alfa versus placebo) and not a specific UK cohort for the baseline mortality for severe sepsis.

The submission from Eli Lilly uses data from the PROWESS trial on patient characteristics and

TABLE 12 *Summary findings for published cost-effectiveness studies and abstracts*

Study	Cost-effectiveness estimates: summary findings
Angus *et al.*, 2003[52] (for the PROWESS Investigators)	Reference case: $33,000 per LYG Reference case: $48,800 per QALY gained Reference case: by severity: APACHE score: < 24: cost-ineffective; 25–29: $28,400; 30–53: $31,100 Base-case analysis: $160,000 per life saved Base-case, cost per life saved, by severity, APACHE II quartiles: 3–19: conventional care dominates; 20–24: $495,800; 25–29: $76,100; 30–53: $98,700
Manns *et al.*, 2002[58]	All patients (with relative risk of death reported in PROWESS study): Cost per LYG $27,936 Cost per QALY $46,560 By severity (with relative risk of death reported in FDA reanalysis): APACHE II ≥ 25: $19,723 per LYG ($32,872 per QALY) APACHE II <25: $575,054 per LYG ($958,423 per QALY)
Fowler *et al.*, 2003[59]	For 'all patient' analysis: Cost per LYG $15,801 Cost per QALY £20,047 For patients with APACHE II ≥ 25: cost per life-year $10,833, cost per QALY $13,493 For patients with APACHE II <25: cost per life year $342,550, cost per QALY $403,000
Davies *et al.*, 2002[60] [abstract]	For severe sepsis patients defined according to PROWESS: Cost per life-year saved is £7037–9519, and cost per QALY is £10,199–13,796, depending on the method used to estimate life expectancy For severe sepsis patients (as above) with ≥ 2 organ dysfunctions, cost per life-year saved is £4716 and cost per QALY is £6385
Launois *et al.*, 2002[65] [abstract]	Cost per additional life-year saved reported at €18,446. Other results reported for subgroups ranged from €10,005 to €31,833.
Neilson *et al.*, 2002[61] [abstract]	Incremental cost per LYG reported at €14,400.
Neilson *et al.*, 2002[62] [abstract]	Germany: €14,400 per LYG Austria: €15,400 per LYG For high-risk patients, with ≥ 2 or more organ dysfunctions, cost per life-year reported at €10,400 for Germany and €11,300 for Austria
Lucioni *et al.*, 2002[63] [abstract]	Cost per LYG: €13,436 for the severe sepsis patient group €9660 for severe sepsis patients with multiple organ failure
Sacristan *et al.*, 2002[64] [abstract]	Base case: cost per LYG reported at €9799, for patients with multiple organ failure (€13,594 for patients with severe sepsis)
Coyle *et al.*, 2002[66] [abstract]	Incremental cost per QALY reported at $15,500
Riou-Franca *et al.*, 2003[67]	Incremental cost per QALY reported at $19,685 for patients with severe sepsis and multiple organ failure
Eli Lilly submission, 2003[11]	PROWESS patients with multiple organ dysfunction: 28-day survival data: cost per LYG £4580, cost per QALY £6637 Longer term follow-up data: cost per LYG £7547, cost per QALY £10,937

baseline risk, and combines this with UK data on life expectancy and length of stay. The submission states that it has used the optimum surrogate control for PROWESS, that is, data on a UK severe sepsis population matched to the PROWESS definition for severe sepsis and the PROWESS inclusion/exclusion criteria. Data on baseline risk for PROWESS were 30.8% and the controls used in the Eli Lilly analysis (ICNARC-matched data) had a baseline risk of 32.7%. It may be that this patient group is the optimum surrogate for the PROWESS control group (i.e. conventional care), but it does not necessarily reflect the in-practice patient population in the UK. The licence indication in Europe is for severe sepsis patients with multiple organ failure, it does not use or specify the licence indication using PROWESS criteria (inclusion and/or exclusion) and therefore some consideration is required on the use of such strict criteria for the specification of the baseline patient group for the UK cost-effectiveness analysis. In practice, the inclusion and exclusion criteria for PROWESS may not be adhered to.

Life expectancy for survivors of severe sepsis

As discussed above, effectiveness data show an improvement in 28-day all-cause mortality for patients treated with drotrecogin alfa (activated) compared with the conventional care cohort; however, the benefits from treatment in terms of life-years and QALYs are dependent on the number of years that survivors are expected to live after they survive the episode of severe sepsis. The studies used in the published cost-effectiveness analyses (and the industry submission) to inform on the adjustment of life expectancy in survivors of severe sepsis are discussed below.

Quartin and colleagues

Quartin and colleagues[23] report findings from a US cohort study examining the magnitude and duration of the effects of sepsis on survival. The study compared survival of 1505 patients screened for a controlled trial (conducted in the 1980s) of corticosteroids in the treatment of sepsis (the VASSCS trial[71]), with 91,830 non-septic hospitalised patients. Patients enrolled in the sepsis cohort met the criteria for SIRS and they were considered by investigators to be unlikely to die of a disorder other than sepsis within 14 days. Data on underlying disease were extracted from International Classification of Disease (ICD-9) codes in patient treatment notes. Patients with sepsis and controls were of a similar age, with both populations almost entirely male. Data on a range of co-morbidities were reported, with significant differences between the two groups (sepsis patients had more chronic disorders and had spent more time in hospital the year before screening). The sepsis group included non-severe sepsis; 224 (15%) met criteria for septic shock and 674 (45%) met criteria for severe sepsis. The study reports on survival analysis, using Cox proportional hazards techniques, to assess the risk of dying associated with each level of sepsis severity relative to the control population. During the 8-year follow-up period patients with sepsis (all categories) were at higher risk of dying than were controls. However, those patients with severe sepsis only remained at increased risk of death (compared with controls) through 5 years after the septic episode. Survivors of uncomplicated sepsis appeared at increased risk of dying compared with controls beyond 5 years, in analysis of all-cause mortality data. However, where analysis is adjusted for death from non-septic causes all categories of sepsis patients returned to a level of risk comparable with that of patients with similar conditions who had not had sepsis.

Quartin and colleagues[23] report that after 8 years, 1229 of the 1505 patients with sepsis had died, with sepsis costing the average patient 2.36 years of life and the average 30-day survivor 1.32 years of life during the follow-up period. Extrapolating beyond 8 years, the authors report that sepsis reduced the mean remaining lifespan from 8.03 years to 4.08 years in 30-day survivors.

Quartin and colleagues[23] have been frequently cited in the cost-effectiveness studies discussed above, whereby studies have used an adjustment parameter of 0.51 for the adjustment of life-expectancy in survivors of severe sepsis. They do not directly report an adjustment factor of 0.51, but report estimates of the relative risk of dying for patients with sepsis relative to controls by sepsis severity and time interval (both adjusted and non-adjusted analysis). *Table 13* presents the relative risks reported by Quartin and colleagues in their analysis of unadjusted mortality. It would appear that their reporting of the reduction of lifespan from 8.03 years to 4.08 years in 30-day survivors is the source for the parameter of 0.51 which is used in the cost-effectiveness studies. However, where cost-effectiveness studies adjust life-expectancy data this generally means an adjustment to estimates of life expectancy from general population statistics, rather than from a hospital discharge cohort as used by Quartin and colleagues.

The finding by Quartin and colleagues of an increased risk of death for survivors of sepsis (by

TABLE 13 *Estimates of relative risk of dying for patients with sepsis relative to controls by sepsis severity and time interval*[a]

Time interval	Uncomplicated sepsis RR (95% CI)	Severe sepsis RR (95% CI)	Septic shock RR (95% CI)
0–30 days	5.0 (4.2 to 5.9)	12.1 (10.8 to 13.6)	16.8 (14.0 to 20.0)
31–90 days	4.9 (3.9 to 6.2)	8.3 (6.8 to 10.3)	8.5 (5.7 to 12.8)
91–180 days	3.5 (2.6 to 4.8)	4.3 (3.1 to 6.0)	8.7 (5.4 to 14.2)
181–365 days	1.6 (1.1 to 2.4)	3.4 (2.4 to 4.8)	5.2 (2.9 to 9.6)
1–2 years	2.3 (1.7 to 3.0)	3.1(2.3 to 4.2)	
2–5 years	1.7 (1.4 to 2.1)	2.2 (1.7 to 2.8)	
5–8 years	1.6 (1.2 to 2.1)	1.2 (0.8 to 1.7)	

Source: Quartin *et al.*,[23] Table 4.
[a] Relative risks were calculated by means of univariate Cox proportional hazards regression.

TABLE 14 *Survival of critically ill patients compared with an age- and gender-matched general population*

Year	Critically ill patients at start (*n*)	Deaths recorded within year (*n*)	Expected deaths (*n*)	Actual mortality (%)	95% CI of observed to expected deaths[a]
1	2104	766	540.2	36.4	14.4 to 16.1
2	1338	76	29.8	5.7	2.0 to 3.1
3	1262	60	29.2	4.8	1.6 to 2.6
4	1202	47	27.9	3.9	0.2 to 3.2
5	1155	43	28.5	3.7	1.1 to 2.0
6	1112	31	25.5	2.8	
7	939	16	20.7	1.7	
8	758	11	17.7	1.5	
9	614	14	13.3	2.3	

Source: Wright *et al.*,[25] Table 2.
[a] Year 6 onwards do not include 95% CIs as the patients entering this period represent an incomplete cohort.

category) compared with controls (certainly over the first year after hospitalisation and probably for as long as 5 years thereafter) indicates that mortality in severe sepsis patients is a serious concern beyond the typical clinical trial end-point of 28 days. The study demonstrates that much of the mortality attributable to sepsis occurs after this time-frame. The study has limitations in that it is based on treatment practice in the mid-1980s, and both populations are almost entirely male. The study is an observational design, so it is not possible to adjust fully for differences between patients with sepsis and controls. The authors warn over the use of ICD-9 data and over potential biases in the reporting of co-morbidities between groups. Furthermore, they warn that there is a possibility that some of the sepsis patients may have suffered from SIRS but may have not been septic.

Wright and colleagues

Wright and colleagues[25] report a retrospective cohort study on 2104 adult patients admitted to the ICU at a teaching hospital in Glasgow over the period 1985–1992, with follow-up until 1997. The study compared the long-term survival of critically ill patients, who were followed up for a minimum of 5 years and a maximum of 12 years, with that of an age- and gender-matched general population (for Scotland). The mean age of intensive care patients was 53.6 years (SD 18.3), mean APACHE II score was 14.7 (SD 7.8) and mean ICU stay was 4.5 days (SD 7.2). 202 patients were in the diagnostic category 'septic shock'. For all critically ill patients ICU mortality was 20.6% and 5-year mortality was 47.1%; for those diagnosed with septic shock ICU mortality was 41.6% and 5-year mortality was 62.9%. For those patients surviving intensive care the 5-year mortality was 33.4%. Age and APACHE II score were significant predictors of five-year mortality ($p < 0.0001$). Wright and colleagues report survival data as shown in *Table 14*; they do not report survival data by diagnostic category (e.g. for septic shock patients only), although they do report hazard ratios, which offer a comparison across diagnostic categories.

Limitations highlighted by the authors are the possibility of missing some deaths owing to data matching with registration of death, and loss to follow-up. The sample was from an ICU that did not cover neurosurgical or paediatric care, and it was from a specific Scottish population. However, the study has shown that long-term survival of critically ill patients is not fully understood, and it indicates that for survivors of intensive care a greater rate of mortality prevailed for 4 years, after which mortality matched that of the general population.

Manns and colleagues

In their cost-effectiveness study Manns and colleagues[58] report findings from a cohort study that was undertaken to obtain estimates of mortality and direct healthcare costs for survivors of severe sepsis. The cohort comprised 787 patients, with all but one said to match the PROWESS inclusion criteria. The baseline mortality was 30.7% at 28 days and 36% before hospital discharge. The study reports subsequent risk of death for hospital survivors (n = 504): 12.2% in year 1, 5.2% in year 2 and 4.2% in year 3. Risk of subsequent death is also reported by age group and by APACHE II score.

Health-related quality of life after survival of severe sepsis

The present authors undertook a literature search to identify studies to inform on the health-state values/utilities associated with severe sepsis (see Appendix 3 for details of databases searched and the search strategy). The literature search did not identify any published studies reporting on health-state values/utilities for patients with severe sepsis, and only one published abstract was identified relating to severe sepsis.[70] There is little information in general on quality of life outcomes after intensive care, never mind following severe sepsis.[69] Heyland and colleagues[72] report that less than 2% of all intensive care studies evaluate health-related quality of life. Statements in the cost-effectiveness literature support this finding (i.e. a lack of published data), with authors commenting that there is an absence of empirical data on health-state values/utilities for severe sepsis.[52,58]

Health state values/utilities

The abstract from Drabinski and colleagues[70] offers some findings on the health-state utility associated with sepsis, reporting an interim analysis on 93 patients from an ongoing prospective multicentre cohort study involving 701 patients with severe sepsis. The abstract does not offer detail on the criteria for severe sepsis. In the study the health status of patients was assessed over time (days 30, 60, 90 and 180) using the EuroQol 5 Dimensions (EQ-5D) health-status instrument, including the use of a visual analogue scale (VAS). Patients completed initial assessments while in hospital and follow-up assessments via telephone interviews. The mean age of patients was 60 years (SD 17 years), with 52% of patients being male. The abstract reports a utility score, presumably from the tariff values available by EQ-5D health-state description (although this is not stated), and a VAS score for each assessment. *Table 15* reports the data presented in the abstract, indicating an improvement in utility scores over time.

TABLE 15 *Health status assessment among sepsis survivors*

Time of assessment	EQ-5D value	VAS score
30 days	0.53	0.61
60 days	0.62	0.68
90 days	0.68	0.71
180 days	0.69	0.72

Source: interim analysis from Drabinski *et al.*[70]

Drabinski and colleagues report that improvement in health utilities was influenced primarily by improvements in mobility, self-care and usual activities. Several cost-effectiveness studies have reported the use of data from Drabinski,[70] but the level of detail offered in the abstract does not allow the quality of the study to be considered.

Supporting information on quality of life associated with severe sepsis

A study by Angus and colleagues,[69] which reports on quality-adjusted survival in the first year after ARDS, was used in the economic evaluation from Manns and colleagues[58] to inform on the health-state value of patients after severe sepsis. Angus and colleagues collected data on quality-adjusted survival, measured as QALYs using the Quality of Well-Being (QWB) scale, as part of a multicentre ARDS trial of inhaled nitric oxide therapy. There were no differences between comparisons in the trial and they report data on the entire trial cohort. The QWB scale assesses quality of life across two dimensions: function (using descriptive scales for mobility, physical activity and social activity) and a range of symptoms. Responses to the questionnaire provide a profile that is used in conjunction with tariff values for the QWB scale. The QWB scale uses decrements in well-being (from a position of 1.0 reflecting asymptomatic/

optimum function) based on weights derived from a US sample of the general population, for health states described using the three QWB descriptive scales, and additional decrements based on reported symptoms.[73] Angus and colleagues collected QWB data at 6 and 12 months after study enrolment, via a structured telephone interview. The overall study cohort (n = 200) had a mean age of 48.6 years (SD 17), with 66.2% being male. There was loss to follow-up over both 6 months (n = 32) and 12 months (n = 45).[69]

The study reports a mean QWB value of 0.59 (SD 0.015) at 6 months and 0.60 (SD 0.015) at 12 months, the mean scores both being significantly lower than a control population of patients with cystic fibrosis (0.76 ± 0.035). The authors report that QWB scores varied by age, although they do not report data in detail (in a figure only). As well as offering some data on the quality of life of patients with ARDS, the study further supports the belief that mortality in critically ill patients is excessive beyond the typical trial end-point of 28 days. The authors highlight that one limitation in the study was the inability to measure premorbid quality of life; they also highlight that the population was relatively young and was selected for a clinical trial, and may be unrepresentative of the overall ARDS population.

Ridley and colleagues[24] report on changes in quality of life after intensive care, comparing quality of life in survivors of intensive care with population norms. The study uses quality of life as measured by the Short Form 36 (SF-36) health-status questionnaire. Patients discharged from the adult ICU supporting the Norfolk and Norwich Hospital (UK) were enrolled, with 166 patients completing the SF-36 (at discharge). Response data were compared with data available on population norms for those of working age in the UK (75 of the 166 respondents were aged under 65 years). Normal quality of life data for patients over 65 years were not available for comparison, but the study found no significant differences in patients aged above and those aged below 65 years. The authors report that patients requiring critical care (ICU) have lower scores than a normal population before admission (premorbid quality of life) for all dimensions of the SF-36. Patients admitted to the ICU owing to an acute life-threatening pathology, who were previously fit and healthy (n = 21, aged under 65 years), reported overall scores on the eight dimensions of the SF-36 that were significantly higher than patients who had pre-existing ill-health before ICU admission, and their scores were not significantly different from the population norm values.

SHTAC cost-effectiveness analysis

SHTAC cost-effectiveness model

Statement of the decision problem and perspective for the cost-effectiveness analysis

SHTAC has developed a simple decision-analytic model to estimate the cost-effectiveness of drotrecogin alfa (activated) plus conventional care versus conventional care alone in a UK cohort of adult patients with severe sepsis. The model estimates cost-effectiveness in adult patients with severe sepsis as defined using the inclusion criteria for the PROWESS study, and for those patients with severe sepsis and multiple organ failure. The perspective of the cost-effectiveness analysis is that of a third party payer, the NHS in England and Wales. Costs associated with patient care from the NHS and personal social services are included in the analysis, together with all known patient benefits.

Strategies/comparators

The use of drotrecogin alfa (activated) was described in detail in Chapter 2, along with the relevance of using conventional care alone as the comparator strategy.

Model type and rationale for the model structure

At present, trial data are limited to findings on short-term all-cause mortality. The model, a probabilistic decision-analytic model, was therefore developed to estimate the long-term survival benefits from conventional care plus drotrecogin alfa (activated) versus conventional care alone, on the basis of effectiveness data from the PROWESS study on 28-day all-cause mortality available for comparator groups.

The model structure is described in *Figure 6*. It was informed by a systematic search of the literature on severe sepsis to identify relevant literature on the epidemiology of severe sepsis, the treatment of severe sepsis, and issues related to mortality and morbidity associated with disease. Discussions with physicians involved in the treatment of patients with severe sepsis in intensive care also informed the structure of the model.

Given the similar hospital treatment and experiences of the comparator groups, as shown by the PROWESS data, and as supported by intensive care physicians, it was deemed reasonable to consider the longer term

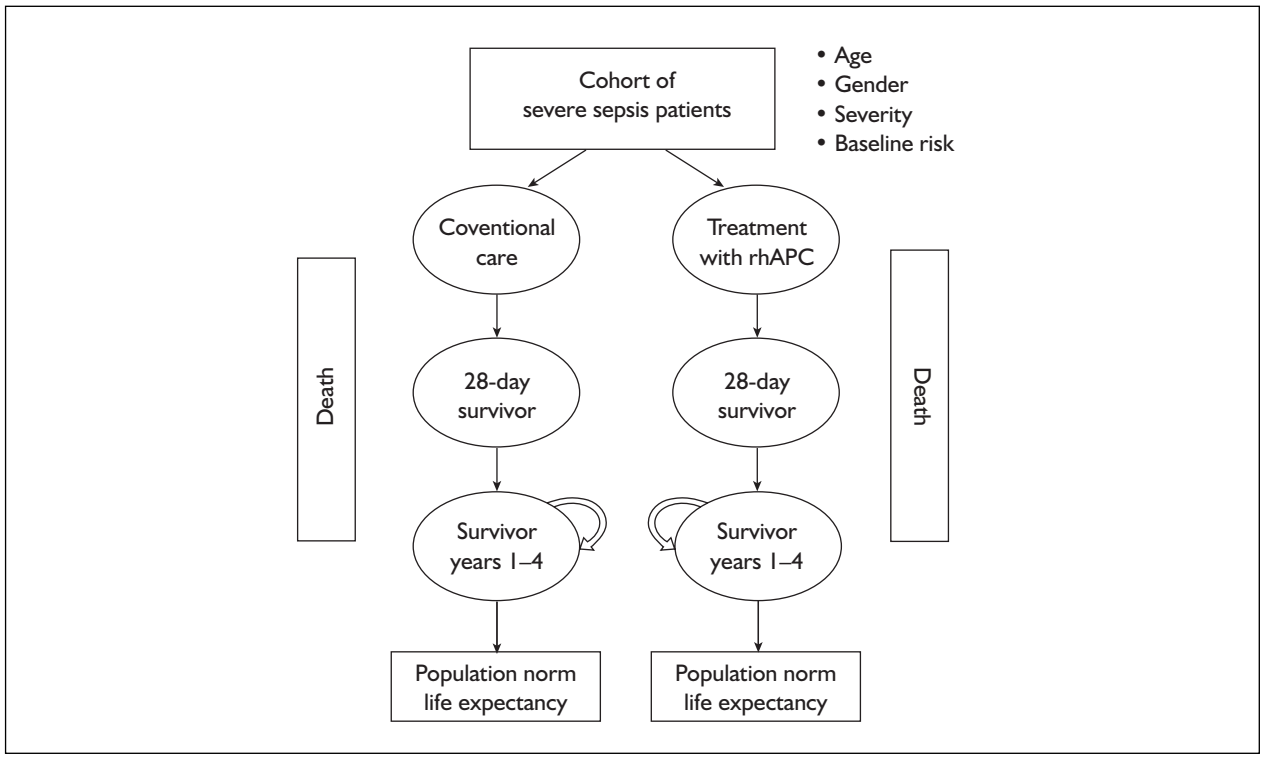

FIGURE 6 *Flow diagram showing the basic structure of the SHTAC model*

implications of treatment for those patients surviving to day 28. The decision model simulates the experiences of a cohort of 1000 patients for both conventional care and conventional care plus drotrecogin alfa (activated), in order to consider the differences between the two treatment options. Each simulation for a 1000 patient cohort constitutes a trial, and the mean incremental effects per patient are recorded per trial, for a total of 1000 trials.

Baseline cohort of adult patients with severe sepsis

The model uses data on a baseline cohort of UK patients with severe sepsis, defined according to the criteria used in the PROWESS study, applying the same inclusion criteria as PROWESS (but not the same exclusion criteria). Data on this baseline population are from ICNARC[74] (*Table 16*). This patient group was used as it is deemed to represent the in-practice patient group for severe sepsis, and contains the subgroup of patients relevant to the European licence indication for drotrecogin alfa (activated), that is, those with severe sepsis (using the same criteria as PROWESS) and multiple organ failure. Applying the exclusion criteria as used in PROWESS would further refine this patient group, but it is not clear in practice how criteria will be applied; therefore, the group meeting the licence indication was used as a baseline in the model.

Data sources

Data used in the model are presented in *Table 16*.

Effectiveness data

The findings from a systematic review on the clinical effectiveness of drotrecogin alfa (activated) were reported in Chapter 3. For the cost-effectiveness analysis, data from the PROWESS study on 28-day all-cause mortality were applied. Data were applied on the relative reduction in all-cause mortality at day 28, for all randomised patients (RR 0.79, 95% CI 0.68 to 0.92) and for those patients with two or more organ dysfunctions (RR 0.78, 95% CI 0.66 to 0.93). When using relative risk data there is very little difference between the effectiveness of treatment in these two patient groups, unlike in the effectiveness data reported using ARR. A log-normal distribution is used in the cost-effectiveness model for the relative risk.

PROWESS findings showed a difference in SBEs between groups, with 3.5% of those patients treated with drotrecogin alfa (activated) and 2% of those in the conventional care cohort experiencing an SBE. This difference (1.5%) was not statistically

TABLE 16 *Model inputs/assumptions for SHTAC cost-effectiveness analysis*

Variable/parameter	Description	Data [Distribution]	Source
Baseline cohort characteristics	Age, mean (SD)	60.8 (16.9) [normal distribution], bounded by limits of 16 and 100 years	ICNARC[74]
	Gender (% male)	54.27% [normal distribution]	ICNARC[9]
Baseline risk	28-day mortality for patients with severe sepsis	41.5% (40.8–42.3%) [normal distribution]	ICNARC[9]
	28-day mortality for patients with severe sepsis and MOD	46.2% (45.3–47.1%) [normal distribution]	ICNARC[74]
Effectiveness data	Patients meeting PROWESS criteria	RR 0.79 (0.68 to 0.92) [log-normal distribution]	PROWESS[39]
	Patients meeting PROWESS criteria with ≥ 2 ODs	RR 0.78 (0.66 to 0.93) [log-normal distribution]	PROWESS[39]
	Additional risk of SBE	1.5%	PROWESS[39]
Life-expectancy data	Data for life expectancy by age for the general population of England and Wales	Age-specific life expectancy	ONS (Government Actuary's Department, interim tables, 1999–2001)[75]
	Mean life expectancy (years) estimated for the above age-gender patient group, mean (SD)	22.56 (12.98), no discounting	SHTAC model
Adjustment of life expectancy	Following 28-day survival: Risk of death year 1 Risk of death year 2 Risk of death year 3 Risk of death year 4	 19.40% 5.68% 4.75% 3.91%	Using data from Wright *et al.*, 2003[25]
Health-state value	Health-state value used in the analysis for survivors of severe sepsis	0.60 (±0.015) [beta distribution]	Angus *et al.*, (2001)[69]
Cost for drotrecogin alfa (activated)	Mean cost per patient (excluding VAT)	£4775 £4716 (≥ 2 ODs)	Davies *et al.*, 2002[60]
Cost for serious bleed	Cost for major bleed; very major procedures for gastrointestinal bleeds (HRG F61)	£3182	NHS Reference Costs 2002[33]
Hospital resource use, mean (SD)	LOS in ICU (days): survivors of severe sepsis; severe sepsis plus MOD	7.8 (10.5); 8.8[a]	ICNARC[74]
	LOS in ICU (days): non-survivors of severe sepsis; severe sepsis plus MOD	6.4 (10.1); 6.1[a]	ICNARC[74]

continued

TABLE 16 *Model inputs/assumptions for SHTAC cost-effectiveness analysis*

Variable/parameter	Description	Data [Distribution]	Source
	Length of overall hospital stay (days): survivors of severe sepsis; severe sepsis plus MOD	36.6 (36.7); 38.6[a]	ICNARC[74]
	Length of overall hospital stay (days): non-survivors of severe sepsis; severe sepsis plus MOD	18.9 (26); 18.3[a]	ICNARC[74]
Hospital costs	Cost per day in ICU	£1232 (range: 50% of NHS Trusts £1077–1439)	NHS Reference Costs 2002[33]
	Cost per day on other ward	£200	Davies *et al.*, 2002[60]
Estimated hospitalisation cost	Severe sepsis: Survivors Non-survivors Severe sepsis and MOD: Survivors Non-survivors	 £15,370 £10,384 £16,802 £10,156 Model uses above mean estimates with a gamma distribution, based on an estimated SD of 20% of the mean	As above under resource use and hospital costs
Long-term NHS costs	Annual cost per patient (general population): Aged 16–44 years Aged 45–64 years Aged 65+ years	 £708.47 £985.19 £1807.84 (assuming a standard of 20% of the mean)	SHTAC estimate based on Department of Health Annual Expenditure Data for HCHS, Hospital Episode Statistics (Department of Health) and population data for England and Wales (ONS)
	Weighted annual cost (weighted using proportions by age group)	£1290	
	Mean (SD) estimate of long-term NHS cost (excluding initial intervention/acute care): Base case Discounting at 3.5% No discounting	 £17,062 (£3294) £22,112 (£9155) £35,459 (£17,737)	SHTAC model
Discount rate	Future costs	6%	By convention/NICE guidance
Discount rate	Future benefits (life-years)	1.5%	By convention/NICE guidance

[a] SD data not known.
NCHS, hospital and community health services; ONS, Office for National Statistics.

significant ($p = 0.06$); however, it is regarded as clinically significant. Furthermore, as stated earlier in this report, combined results from a cumulative safety review show that 2.3% of patients in placebo groups have SBEs, compared with 5.3% of patients treated with drotrecogin alfa (activated). In the SHTAC model comparative data from PROWESS are applied; however, given that there may be a greater expectation of SBEs when using a UK baseline cohort defined using the PROWESS inclusion criteria, and not the exclusion criteria, this issue is examined in sensitivity analysis.

Life expectancy

As discussed above, life expectancy for survivors of severe sepsis is not the same as that for the general population. The SHTAC model uses an estimate of the mean life expectancy for the severe sepsis patient group, calculated using ICNARC data on the age–gender mix for severe sepsis patients, and life-expectancy data (by age–gender) for the general population of England and Wales.[75] A patient-level probabilistic model is used to estimate the mean life expectancy for the patient group (discounted where appropriate). This model is run before the cost-effectiveness model to inform on data inputs for mean life-expectancy for 28-day survivors of severe sepsis, and the mean long-term NHS cost associated with life expectancy following severe sepsis (i.e. costs other than initial intervention and hospitalisation costs). The modelling of these data draws a sample of 1000 consecutive patients, using data on age and gender from ICNARC, assigns each patient an age–gender-specific life expectancy, and thereafter calculates a patient-level cost for long-term NHS resource use (data used in this estimate are discussed below). A mean value for these input parameters is determined by running a patient-level model through 1000 iterations. Mean normal life expectancy for the patient group is estimated to be 22.56 years (SD 12.98); this mean value is used in the cost-effectiveness model, but probabilistic sampling using the measure of dispersion in the cohort model is not done, as this seems intuitively incorrect (i.e. some of the 1000 patient cohorts would be attributed a very low, or negative, life expectancy based on the calculated patient-level distribution). However, distributions for age and gender, and a measure of uncertainty surrounding the estimates of long-term NHS costs (annual cost by age) have been considered when modelling the point estimates used in the cost-effectiveness model.

To allow for the fact that the life expectancy for survivors of severe sepsis is not the same as that of the general population, the SHTAC model transits 28-day survivors (in the cohort) through a period of 4 years, where they are at increased risk of death (compared with the general population), based on data from Wright and colleagues[25] (see *Figure 6*). Wright and colleagues show a greater risk of death in critically ill intensive care patients through years 1–4 following ICU discharge (*Table 17*). In sensitivity analyses the present group also takes a different methodological approach to the estimation and adjustment of life expectancy for survivors of severe sepsis, applying an adjustment factor of 0.51 to all 28-day survivors, to show life expectancy of survivors of severe sepsis at 51% of that of the general population norm (age- and gender matched). As discussed above, this method has been used in a number of the cost-effectiveness studies/abstracts reported (with studies citing Quartin and colleagues).[52,60,62,63]

Health-state values/utilities

A systematic search of the literature was undertaken (discussed above) and no published studies were identified with data on health-state utilities for survivors of severe sepsis; one abstract was identified.[70] The estimates used to date in published cost-effectiveness studies are discussed above. This remains an area of uncertainty. Given the limitations in the empirical literature, the SHTAC model applies the data (0.60 ± 0.015) reported by Angus and colleagues for the quality of life of a sample of patients with ARDS (at 12 months), to quality adjust life-year gains.[69] Data from Drabinski and colleagues,[70] showing an EQ-5D value of 0.69 (at 180 days), are applied in the sensitivity analyses.

Discounting of future benefits

A discount rate of 1.5% was applied to future benefits. This is the current convention in UK cost-effectiveness analysis, and is in line with guidance from NICE. Other discount rates have been applied in sensitivity analyses (0% and 3.5%).

Cost data

Intervention cost (28-day cost)

The 28-day intervention cost used in the model comprises the acquisition cost for drotrecogin alfa (activated) and an allowance per patient for the cost for the additional risk of SBEs. The list price for drotrecogin alfa (activated), excluding VAT, is £152.05 per 5-mg vial and £608.19 per 20-mg vial.[11] Davies and colleagues[60] estimate the mean drug cost to be £4775 based on the PROWESS trial group, and £4716 for those patients in the PROWESS trial with two or more organ dysfunctions (these data make some allowance for

TABLE 17 *Estimate of mortality/life expectancy, years 1–5, after discharge from intensive care*

Period/year	Critically ill patients at start (*n*)	Deaths recorded within period (*n*)	Mortality (%)
ICU	2104	434	20.63
Year 1, after ICU[a]	1711	332	19.40
Year 2	1338	76	5.68
Year 3	1262	60	4.75
Year 4	1202	47	3.91
Year 5	1155	43	3.72

Data on deaths recorded from Wright *et al*.[25]
[a] Following ICU discharge [mean ICU stay was 4.5 days (SD 7.2 days)].

the fact that not all patients will receive the full dose). There is a reasonable level of certainty over the mean acquisition cost; therefore, this point estimate has been used in the model. This acquisition cost excludes VAT, which is payable by the NHS with no direct opportunity to reclaim the VAT; therefore, sensitivity analysis has been undertaken where the cost for drotrecogin alfa (activated) includes VAT (£5610 and £5541, respectively).

Cost data for serious bleeding episodes were taken from the NHS reference costs, produced by the Department of Health in the UK.[33] The mean cost associated with very major procedures for gastrointestinal bleeds [Healthcare Resource Group (HRG) code F61] is £3182 for non-elective inpatient procedures. The cost range across all NHS trusts is reported at £410–9833, with the range across 50% of trusts at £1731–3804. For simplicity, the mean cost per patient treated was calculated by combining the mean cost for a bleeding episode with the additional risk per patient of experiencing a serious bleed (1.5%), resulting in a cost per patient of £47.73. The probability of serious bleeds could have been built into the decision model, but on the grounds of parsimony it was included in the simplistic way described.

Hospital cost

The cost for hospitalisation (excluding drotrecogin alfa) comprises costs associated with days spent in the ICU and days spent in hospital in a non-ICU setting. Costs were estimated using data on resource use (LOS) from ICNARC,[74] multiplied by ICU unit costs (cost per day) from the NHS reference cost database, and an estimate of non-ICU unit cost (cost per day) from published sources.[60] Length of stay data from ICNARC, by survival status, are from patients with severe sepsis defined according to PROWESS criteria (*Table 16*). The mean hospital cost for severe sepsis survivors was estimated to be £15,640 and the mean cost for non-survivors £10,384. For survivors and non-survivors of severe sepsis and multiple organ failure mean hospital costs of £16,802 and £10,156, respectively, were estimated (although there are no data on standard deviations for length of stay in this group, the variation is expected to be similar to that in the broader severe sepsis patient group).

There is considerable uncertainty around both the cost per day and the number of days per hospital stay (*Table 16*); therefore, uncertainty surrounding hospital cost was introduced by applying a standard deviation of 20% to the point estimate and allowing it to vary in the probabilistic approach to the modelling of cost-effectiveness.

Longer term costs

The estimates for the hospital stay associated with the episode of severe sepsis were discussed above; however, where patients survive severe sepsis they will continue to use NHS resources over their lifetime, regardless of the reason for the resource use. This may be related to the consequences of severe sepsis or to other reasons. The sparse literature on longer term survival after sepsis and on the quality of life associated with critically ill patients suggests that patients surviving severe sepsis are generally in worse health than the general population, although this depends on the reasons for admission (i.e. acute condition compared with chronic). There is no reason to believe that survivors of severe sepsis treated with drotrecogin alfa (activated) are any different from survivors receiving conventional care. All published cost-effectiveness studies included lifetime healthcare costs for survivors of severe sepsis,[52,58,59] whereas the studies reported in abstract format did not include such costs. SHTAC believes that there is evidence indicating that survivors of intensive care will incur additional NHS costs compared with age- and gender-matched members of the general population,[76]

but also feels that it is not possible to disentangle the causes leading to such NHS resource use (i.e. in this patient group long-term costs may be non-sepsis related); therefore, it is not possible to say with any certainty whether additional longer term healthcare costs should be classed as an impact of severe sepsis, and whether they should be taken into account in the overall cost for treatment. For example, where longer term survival is included in the benefits associated with treatment including drotrecogin alfa (activated), it may be that this longer term survival benefit is a result of subsequent NHS care after the initial hospitalisation, and in such cases it would seem reasonable to include future NHS costs (together with future benefits) in the cost-effectiveness analysis. However, it may also be argued that treating a survivor of severe sepsis for injuries related to a road traffic accident should not be held in balance against the effectiveness of drotrecogin alfa (activated).

Coughlin and Angus,[77] in their review of methods for the economic evaluation of new therapies for critical illness, argue in favour of including longer term healthcare costs (unrelated to the therapy being evaluated) for additional survivors. However, there is no agreement among health economists on the inclusion, in economic evaluations, of unrelated healthcare costs in later years of life.[78] Drummond and colleagues[79] argue that the inclusion of future unrelated costs should be guided by considerations over (1) the extent to which future healthcare is a necessary consequence of the programme being evaluated, and (2) the availability of data. They use as an example in their discussion the evaluation of a new drug for treatment of septic shock in intensive care, concluding that it would seem reasonable to assume that costs for treatment of a patient's underlying morbid condition should be included in the evaluation. Regardless of the rationale for including longer term healthcare costs, in the UK there are no good quality cost data on the long-term costs associated with NHS treatment (unlike in the USA, where billing databases are available to provide information on such issues). In this regard, Drummond and colleagues[79] suggest that it is often difficult to be more precise than an average annual per capita health expenditure estimate.

The base-case cost-effectiveness analysis makes some allowance for lifetime healthcare costs associated with survivors of severe sepsis. These estimates are crude, and do not make any distinction between the costs associated with patients surviving sepsis or other members of the general population. The methods used are described in Appendix 14. In brief, data were taken from the Department of Health for NHS expenditure on hospital community and family health services, and hospital episode statistics by patients' age (grouped into 15–44, 45–64 and 65+ years), and the cost per patient per year was estimated using population data for England and Wales. The estimates are shown in *Table 16*. Where the long-term follow-up costs for those patients who survive beyond year 4 were estimated, age-specific costs were used for each year of survival in the estimates. Where allowances were made for follow-up cost for those patients who do not survive beyond year 4, the proportions of patients with severe sepsis in the respective age bands (from the simulated patient-level data) were used combined with the estimated annual cost per year for the age categories.

The use of longer term costs is controversial, and opinion differs on their inclusion or exclusion. Therefore, cost-effectiveness findings are reported based on both the inclusion and exclusion of longer term healthcare costs.

Discounting of future costs

A discount rate of 6% has been applied to future costs. This is the rate used by convention in economic evaluations in the UK, and is in line with current guidance from NICE. Other discount rates have been applied in sensitivity analyses (0% and 3.5%).

Presentation of results

Findings are reported on the mean incremental gain in life-years (QALYs), and mean incremental cost, per treated patient, based on a cohort analysis of 1000 patients (trial) and a simulation of 1000 trials. The incremental cost per life-year gained and incremental cost per QALY were estimated. Using the mean incremental benefits and cost per trial, the net benefit associated with treatment was estimated, and a cost-effectiveness acceptability curve (CEAC) plotted, showing the probability of a positive net benefit based on a range of threshold values for the willingness to pay (WTP) per QALY.

The mean cost per life saved is also reported, for base-case assumptions (i.e. the difference in the mean total cost per 1000 patients treated with conventional care alone, and those treated with conventional care plus drotrecogin alfa, divided by the mean difference in 28-day survival per 1000 patient cohort).

TABLE 18 *Cost per life-year and cost per QALY for drotrecogin alfa (activated) plus conventional care versus conventional care alone, using base-case assumptions*

Population	Patients with severe sepsis and ≥ 2 ODs Mean (SD)	Patients with severe sepsis Mean (SD)
Incremental life-years	1.351 (0.43)	1.144 (0.343)
Incremental QALYS	0.810 (0.258)	0.686 (0.208)
Incremental cost	£6661 (772)	£6288 (593)
Cost per life-year	£4931	£5495
Cost per QALY	£8228	£9161

TABLE 19 *Non-discounted cost per life-year and cost per QALY for drotrecogin alfa (activated) versus conventional care, using other base-case assumptions*

Population	Patients with severe sepsis and ≥ 2 ODs Mean (SD)	Patients with severe sepsis Mean (SD)
Incremental life-years	1.569 (0.513)	1.352 (0.398)
Incremental QALYS	0.941 (0.308)	0.811 (0.240)
Incremental cost	£7958 (£1783)	£7398 (1368)
Cost per life-year	£5071	£5473
Cost per QALY	£8462	£9120

Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Sensitivity analysis was undertaken to address uncertainty in the cost-effectiveness analysis. Methodological and structural uncertainty were considered by addressing the methods for inclusion of long-term healthcare costs and by considering different methods for the estimation of life-expectancy and life-year gains. Heterogeneity in the patient groups was also addressed, with analysis presented for all UK severe sepsis patients, and those patients with severe sepsis and two or more organ dysfunctions. Parameter uncertainty has been considered, where possible, as part of the probabilistic modelling process, with distributions around point estimates allowing variation within the main analysis (e.g. age, gender, baseline risk, relative risk data); however, this was not possible in all instances. Therefore, where parameter values have not been varied in a probabilistic manner, sensitivity analysis was undertaken on these parameters by rerunning probabilistic analysis with different point estimates.

SHTAC cost-effectiveness results

Cost-effectiveness findings are presented for two patient groups: (1) UK patients with severe sepsis matching the PROWESS inclusion criteria, and (2) UK patients with severe sepsis matching the PROWESS inclusion criteria, who also have multiple organ dysfunction. Findings are presented for the incremental cost per life-year gained and for the incremental cost per QALY. Cost-effectiveness results, applying base-case assumptions, are presented in *Table 18*. For drotrecogin alfa (activated) plus conventional care versus conventional care alone, the cost per life-year and cost per QALY for patients with severe sepsis are £5495 and £9161, respectively. For patients with severe sepsis and multiple organ dysfunction the cost per life-year and cost per QALY are £4931 and £8228. Cost-effectiveness findings based on zero discounting of future costs and benefits are presented in *Table 19*.

As cost-effectiveness ratios are not suited to the estimation of confidence intervals, the net monetary benefit approach was used to characterise the uncertainty surrounding the results of the cost-effectiveness analysis. Net monetary benefit is an alternative decision rule for cost-effectiveness analysis. It is calculated using a figure stating the WTP for an outcome (e.g. QALY), with the net benefit formula based on the value that one is willing to pay per outcome multiplied by the outcomes obtained, less the cost incurred (i.e. WTP per QALY × QALYs – Costs). Where the net monetary benefit statistic is greater than zero the intervention would be regarded as a cost-effective use of resources (i.e. you are getting value for money by paying less than you would be willing to pay).

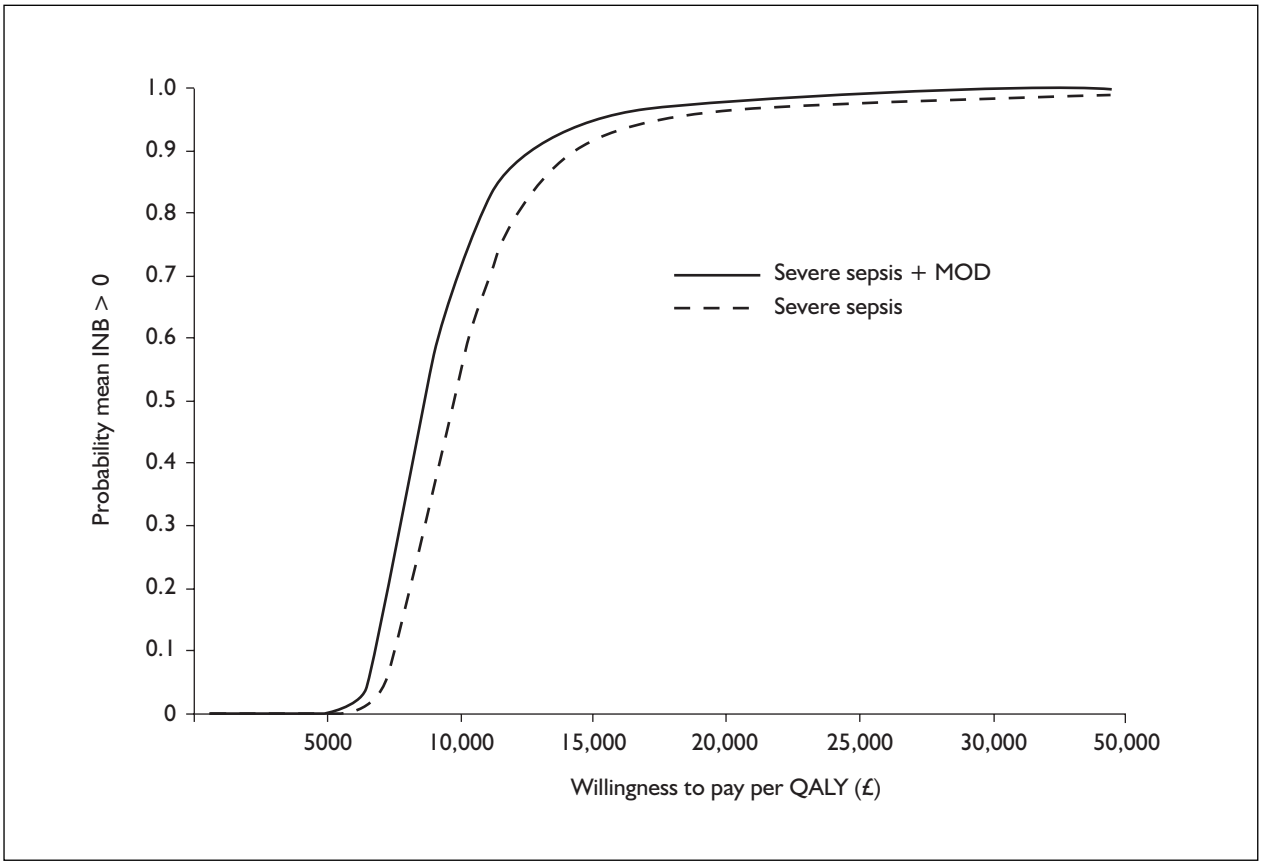

FIGURE 7 *CEAC for drotrecogin alfa (activated). INB, incremental net benefit.*

Using the net monetary benefit approach in the assessment of the cost-effectiveness of drotrecogin alfa (activated), if it was assumed that the NHS would be prepared to pay £20,000 per additional QALY, the intervention is shown to be cost-effective in 98.7% of trials in patients with severe sepsis and multiple organ dysfunction, and 96.8% of trials in patients with severe sepsis.

Figure 7 presents the CEACs, which plot the findings for net monetary benefit, for a range of values on the WTP per QALY.

Cost per life saved

The cost per life saved, at base-case assumptions, is estimated at £73,744 (i.e. the difference in the mean total cost per 1000 patients treated, divided by the mean difference in 28-day survival per 1000 patient cohort). The cost per life saved based on including only initial (acute) intervention and hospital costs is estimated at £61,468.

Subgroups: cost-effectiveness

As discussed above, there has been a number of subgroup analyses on the PROWESS effectiveness data. The authors have warned against conflicting findings across patient groups (i.e. all PROWESS patients, versus those with multiple organ dysfunction) and, more importantly, they have warned over methodological concerns over the subgroup analyses undertaken. General findings indicate that drotrecogin alfa (activated) is cost-effective in the licence indication patient group; therefore, the acceptability of further subgroup analyses in the overall assessment of the intervention is open to debate. However, given that there will be interest in the cost-effectiveness of drotrecogin alfa (activated) in specific subgroups, the sensitivity analyses include a range of results by differing effectiveness (relative risk reduction), and the reader should consider these in the context of the specific subgroup of interest (there are no separate data on other model inputs by subgroup).

Sensitivity analyses

Sensitivity analysis was undertaken to consider the effect of uncertainty on the estimated cost-effectiveness of drotrecogin alfa (activated) across the two patient groups (i.e. severe sepsis, severe sepsis plus multiple organ failure). Findings are presented in *Table 20*. To address the issue of heterogeneity (in patient groups), separate analyses were run for (1) UK patients with severe

TABLE 20 *Sensitivity analysis of the cost per life-year gained and cost per QALY, for treatment with drotrecogin alfa (activated)*

Variable used in analyses	Severe sepsis and MOD		Severe sepsis	
	Cost per QALY	Cost per LYG	Cost per QALY	Cost per LYG
Baseline analysis	£8,228	£4,931	£9,161	£5,495
Discount rate for costs and benefits at 3.5%[a]	£10,797	£6,475	£11,646	£6,985
Long-term costs:				
(a) Where costs per patient per year are higher in year 1 (£10,000)	£8,962	£5,373	£9,964	£5,972
(b) Where costs per patient per year are higher in year 1 (£20,000)	£9,691	£5,823	£10,735	£6,441
Life-expectancy method: Where life expectancy is adjusted by factor of 0.51 (long-term costs × 0.51)	£10,439	£6,266	£11,655	£6,996
Excluding long-term costs	£6,691	£4,020	£7,525	£4,515
QALY weight/utility value; using estimate of 0.69 from Drabinski *et al.*[70]	£7,145	£4,930	£7,867	£5,429
QALY weight at 0.69 and excluding long-term costs (similar to Eli Lilly analysis)	£5,826	£4,020	£6,544	£4,515
Probability of SBEs at 15%	£8,812	£5,287	£9,765	£5,850
Cost of drotrecogin alfa, including VAT	£9,303	£5,583	£10,406	£6,251
Effectiveness data, using RR of				
0.70	£6,778	£4,065	£6,992	£4,195
0.75	£7,486	£4,494	£8,137	£4,882
0.85	£11,142	£6,687	£11,957	£7,179
0.90	£15,637	£9,375	£16,774	£10,080
0.95	£28,868	£17,267	£31,404	£18,804
(assume the same SE as base case)				
Assuming longer term costs are £20,000 in year 1, base-case values thereafter; and life expectancy is estimated using the parameter value of 0.51 from Quartin *et al.*[23]	£11,648	£6,986	£12,796	£7,670
Assuming longer term costs are £20,000 in year 1, base-case values thereafter, and life expectancy is estimated using the parameter value of 0.51 from Quartin *et al.*;[23] plus baseline all-cause mortality (risk) at 33.9% (MODS) and 31.3% (severe sepsis)[a]	£14,645	£8,801	£15,992	£9,607

[a] See Appendix 15 for CEACs for analysis at a discount rate of 3.5% for costs and benefits, and multiway sensitivity analysis.

sepsis meeting the PROWESS inclusion criteria, and (2) UK patients with severe sepsis meeting the PROWESS inclusion criteria and having two or more organ dysfunctions.

Methodological and structural uncertainty

Sensitivity analysis is reported for the use of a different method for the adjustment of life expectancy for survivors of severe sepsis (*Table 20*). The base-case method was the use of data from Wright and colleagues,[25] with an increased all-cause mortality for survivors of severe sepsis over years 1–4. In separate analysis, life expectancy was adjusted using the parameter of 0.51 commonly cited from the study by Quartin and colleagues[23] (as discussed above). When using a parameter of 0.51 (i.e. patients are attributed 51% of the life expectancy of age–gender-matched population norms) to adjust life expectancy, the incremental life-year gains were smaller (subsequently, the long-term NHS costs are lower) and the cost per life-year and cost per QALY increased over the base-case findings (i.e. cost per QALY increases from £8228 to £10,439 in the patient group with severe sepsis and multiple organ failure). (In this sensitivity analysis an adjustment was also made to

the longer term patient costs calculated and used in the base-case analysis, using a factor of 0.51. Although this underestimated the true long-term costs for the period of life expectancy in question, it was felt to be sufficiently accurate to help to guide the present analysis.)

Sensitivity analysis is also reported to consider different methods for the estimation of longer term NHS costs, for additional survivors of severe sepsis (*Table 20*). Where long-term NHS costs were excluded, the cost per life-year and cost per QALY estimates were lower than base-case values; in patients with severe sepsis and multiple organ dysfunction the cost per QALY fell from £8288 to £6691. Where it was assumed that NHS costs are substantial in the first year following survival of severe sepsis (post-hospital survival), at either £10,000 per patient or £20,000 per patient, with subsequent annual costs assumed to be equal to the estimates for the general population, the cost-effectiveness estimates increased, with cost per QALY for patients with severe sepsis and multiple organ dysfunction rising from £8228 to £8962 and £9691, respectively.

A number of changes to the methods and assumptions in the model were introduced simultaneously, with base-case assumptions altered to reflect (1) a follow-up NHS cost of £20,000 per survivor in the first year after the severe sepsis episode, (2) life expectancy adjusted to 0.51 of the population norm (as in Quartin[23]), and (3) baseline risk of death altered to reflect the 28-day mortality rate in the PROWESS placebo group (i.e. 31.3% and 33.9%, for the two patient groups) (*Table 20*). This analysis reports a cost per QALY of £14,645 in patients with severe sepsis and multiple organ dysfunction (and £15,992 for patients with severe sepsis alone). In this multiway sensitivity analysis the net monetary benefit statistic indicates that where the NHS is prepared to pay £20,000 per QALY the intervention is cost-effective in 83.1% of trials (patient with severe sepsis and multiple organ dysfunction); where the threshold is £30,000 per QALY the intervention is cost-effective in 95.8% of trials (see Appendix 15).

Parameter uncertainty

Probabilistic analysis was used to consider uncertainty on parameter values simultaneously. This was possible for patient age, gender, baseline risk and risk adjustment data (effectiveness data), together with hospital cost per patient and the quality weighing of life-years gained. Where parameter values were not varied in a probabilistic manner, or where alternate point estimates may be expected, sensitivity analysis on these parameters was undertaken by rerunning probabilistic analysis with different point estimates (*Table 20*).

Applying a QALY weight of 0.69 per life-year gained (base case is 0.60) resulted in a slightly lower cost per QALY. An increase in the expected rate of SBEs, using a probability of 15% (base case is 1.5%) increased the cost-effectiveness ratios slightly. An increase in the acquisition cost of drotrecogin alfa (activated) to reflect a price including VAT resulted in an increase in the cost-effectiveness estimates (e.g. to £9303 per QALY for patients with severe sepsis and multiple organ dysfunction).

Where a less favourable effectiveness profile for drotrecogin alfa (activated) was assumed, using a relative risk of 0.85 or 0.90, the cost per life-year/QALY increases substantially, for example from a base case of £8288 to £11,142 and £15,637, respectively, per QALY in patients with severe sepsis and multiple organ failure.

Chapter 5

Implications for other parties

Drotrecogin alfa (activated) has demonstrated a significant survival benefit in reported RCTs. However, there are no data on the longer term quality of life in these patients. An increase in absolute survival benefit of around 6% would lead to a significant number of additional patients returning to the community with ongoing healthcare and other related care needs. As stated previously, this patient group is known to have a poor health-related quality of life and high relative risk of mortality in comparison to the general population in the years after intensive care, which would suggest a significant ongoing burden of ill-health.[25,50,80] A significant proportion of this burden would be on families and carers.

The increased burden of ill-health and associated increased healthcare resource utilisation seen in severe sepsis survivors would lead to a financial burden for families and carers of the patient. This burden of ill-health is likely to lead to increased healthcare resource utilisation, especially in primary care.

Chapter 6

Factors relevant to the NHS

In the SHTAC cost-effectiveness analysis it was estimated that where drotrecogin alfa (activated) is introduced for the treatment of severe sepsis patients with multiple organ dysfunction, the additional mean cost per patient treated is £6661. The majority of this cost is the acquisition cost for drotrecogin alfa (activated), which is estimated at £4905 (excluding VAT) for a full course of treatment in a 70-kg patient.

Data from ICNARC report an estimated prevalence of severe sepsis (in the first 24 hours) at 27.1% of ICU admissions, with 83.6% of these patients having multiple organ dysfunction.[9] Based on data for 1997, ICNARC estimate that 21,191 patients had severe sepsis in the first 24 hours of intensive care admission in England and Wales (95% CI 18,800 to 23,740).[9] Assuming that 83.6% of these patients have multiple organ dysfunction leads to an estimate of a treatment eligible population of 16,570 patients in England and Wales, with an estimated annual drug acquisition cost of £86.9 million, excluding VAT (£97.1 million including VAT), and an estimated overall additional cost to the NHS of £118 million (excluding VAT). Not all treatment eligible patients will be prescribed drotrecogin alfa (activated) (e.g. because of contraindication where there is a risk of serious bleeding), but given that many patients will have severe sepsis outside an ICU setting and after intensive care, this estimate offers an indication of the impact of the intervention on the NHS pharmaceutical budget, and NHS costs more broadly.

Considering a regional population of 500,000 people, similar to a former health authority region, one would expect to see an average of 255 patients with severe sepsis (in first 24 hours of admission), with 213 of these patients expected to have multiple organ dysfunction. This patient group would incur an estimated drug acquisition cost of £1.05 million (excluding VAT) and an overall additional cost of £1.42 million.

Chapter 7
Discussion

Main effectiveness results

The evidence for the effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis comes primarily from one large pivotal RCT, the PROWESS study.[39] A much smaller Phase II RCT[43] and some unpublished open-label studies have also been conducted using very similar protocols to that of PROWESS. The PROWESS study demonstrated a statistically significant absolute reduction in mortality in the order of 6.5% (95% CI 2.2 to 10.7), equivalent to a relative risk of death of 0.79 (95% CI 0.68 to 0.92).[39] Long-term follow-up of these patients showed that the survival benefit was maintained to 90 days ($p = 0.048$), but by 9 months the trend towards increased median survival was non-significant (log-rank $p = 0.097$), although the survival curves did not cross.[50] Given that the trial was not powered to detect a statistically significant improvement in long-term survival, it seems possible that the survival benefit from drotrecogin alfa (activated) is maintained in the longer term.

A large number of subgroup analyses of the PROWESS data has been performed. As discussed in Chapter 3, all of the inherent problems with subgroup analyses should be borne in mind when considering these results. As the European licence for drotrecogin alfa (activated) is for patients with two or more organ dysfunctions, this study has focused on those related to disease severity. A priori analyses showed a progressive reduction in the relative risk of death with increasing number of organ failures, from 0.92 (95% CI 0.63 to 1.35) in patients with one organ failure at baseline to 0.60 (95% CI 0.33 to 1.11) in those with five organ failures. All of the confidence intervals for these subgroups overlapped the overall estimate and none was statistically significant; however, the formal test for an interaction between number of organ dysfunctions and treatment effect was not reported. When mortality rates for those with two or more organ failures were combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo (0.78, 95% CI 0.66 to 0.93).[45]

Other subgroup analyses of those with multiple organ dysfunction found that the survival benefit was greatest (and statistically significant) in patients in the highest two APACHE II quartiles, in those with overt DIC, receiving mechanical ventilation or receiving vasopressor support at baseline; thus, the benefits could appear to be greatest in those with more severe disease.[45] However, it should be strongly emphasised that these were retrospective subgroup analyses and with small numbers of patients per group. Furthermore, other subgroup analyses not related to disease severity also showed differences in treatment effect; for example, male patients experienced a larger and statistically significant effect compared with female patients. Subgroup analyses of the entire cohort, which have slightly more patients, yet are still underpowered, indicate that subgroup effects could be occurring owing to any number of factors, including age, race, the presence of co-morbidities, and infection site and type.[46]

Several other outcomes were considered in the PROWESS study. Those organ dysfunctions present at baseline resolved during days 1–7 in a higher proportion of patients in the rhAPC group compared with placebo for all organ systems except for hepatic organ dysfunction.[48] The likelihood of developing new organ system dysfunctions was significantly reduced by drotrecogin alfa (activated) only for haematological organ dysfunction. In terms of functional status at day 28, there was little difference between groups, although a higher proportion of rhAPC survivors was discharged to home compared with placebo survivors, suggesting that the additional survivors produced by drotrecogin alfa (activated) did not have a higher morbidity than those treated with conventional care.

For adverse events, the incidence of SBEs was much higher with drotrecogin alfa (activated) than with placebo, although for PROWESS the difference was not statistically significant.[39] As might be expected, the incidence was higher in the large open-label study than in the treatment arm of PROWESS.

Limitations in the evidence

Despite several protocol changes during the PROWESS study, as discussed above, the trial is

quite strong in terms of internal validity. The randomisation and allocation concealment procedures followed were adequate and the study was double-blinded. For the ITT analysis, all patients were followed up, except for one assigned to drotrecogin alfa (activated) who was attributed with a negative outcome in the analysis. The benefit from drotrecogin alfa (activated) occurred after the protocol changes, but it is likely that this was due to the exclusion of patients likely to die from causes other than sepsis within the 28-day follow-up period. There is also some problem with the multiplicity of subgroup analyses that were performed. Although the authors stated that they had used appropriate statistical tests to identify treatment by subgroup interactions, in general the results of these were poorly reported in the text.

The key limitation of the PROWESS evidence for drotrecogin alfa (activated) lies with the generalisability of the PROWESS study to the UK population. First, the definition of severe sepsis that was used in the PROWESS trial is stricter than that usually applied in practice. PROWESS required evidence of infection, at least three SIRS criteria plus at least one organ dysfunction.[39] The usual definition requires evidence of infection, at least two SIRS criteria plus at least one organ dysfunction, hypoperfusion or hypotension.[2] Second, only patients developing severe sepsis within the first 24 hours of screening (presumably intensive care admission in many cases) were included.[39] As discussed in the section on the epidemiology of sepsis (Chapter 2), the incidence of severe sepsis at any stage during intensive care stay may be up to double that on admission, and the same incidence of severe sepsis cases may be found outside the ICU.

The pragmatic nature of the study (i.e. that it was non-prescriptive regarding supportive care) increases the generalisability of the trial's results; however, both of the points discussed above provide more serious limitations to the generalisability of the PROWESS study. The patients included were a highly selected population and the results have been demonstrated only in an intensive care setting. It is not clear whether the same results could be achieved in practice. Although clinicians may follow the PROWESS inclusion and exclusion criteria when making decisions on the use of drotrecogin alfa (activated), at least initially, the European licence is for patients with severe sepsis and two or more organ dysfunctions; further restrictions on its use have not been made. It seems reasonable to envisage that in practice drotrecogin alfa (activated) may eventually be used in a wider population than that included in PROWESS, and in a less specialist setting.

Although the results from the ENHANCE study indicate that similar mortality rates can be achieved in an open-label study, this study was performed using a very similar protocol to that of the PROWESS study and may not be a true reflection of clinical practice.

Limitations of the review

The systematic nature of the review means that the reviewers are likely to have identified the majority of the published studies. The literature search was comprehensive, using a wide range of electronic databases and relatively broad search terms, such that all of the indexed literature should have been picked up. Two reviewers were involved at every stage in the review procedure, such that mistakes due to human error should be limited. A recognised quality assessment checklist was adapted and applied to each of the included studies. The available evidence was categorised according to quality and reliability.

Empirical evidence suggests that studies with significant or favourable results are more likely to be published than those with non-significant or unfavourable results; however, in this case, where the drug has only recently been licensed, and has essentially been licensed on the basis of a single trial, other non-company-funded RCTs are unlikely to have been performed and, if they have, are unlikely yet to be in the public domain.

Cost-effectiveness: statement of principal findings

Three published economic evaluations and eight abstracts were identified to provide information on the cost-effectiveness of drotrecogin alfa (activated) plus conventional care versus conventional care alone. The manufacturer's submission to NICE also provided analysis on the cost-effectiveness of treatment. Methods for assessing costs and benefits varied across studies, as did findings. However, all economic evaluations report cost-effectiveness of drotrecogin alfa (activated) compared with conventional care alone in patients with severe sepsis, at a level that may be regarded as acceptable for a new life-saving technology of this nature.

The three published economic evaluations report findings from a US or Canadian perspective, in

US dollars, with cost per life-year for patients defined as having severe sepsis ranging from $15,801 to $33,000. Cost per QALY estimates ranged from $20,047 to $48,800. The studies by Angus and colleagues[52] and Manns and colleagues[58] are regarded by SHTAC as better quality studies than the economic evaluation reported by Fowler and colleagues,[59] owing to a greater transparency in the methods used, and it is the latter of these published evaluations that reports the lower of the cost-effectiveness estimates in the range discussed.

All three published economic evaluations report findings for patients with severe sepsis grouped by severity of disease, as measured by the APACHE II instrument. All three evaluations report that cost-effectiveness estimates for patients with an APACHE score greater than or equal to 25 are more attractive than the 'all patients' analysis, and that cost-effectiveness estimates for those patients with a score of less than 25 are unattractive. Angus and colleagues[52] report that drotrecogin alfa (activated) was cost-ineffective for those patients with an APACHE II score of less than 25 (there were no incremental QALY benefits). Manns and Fowler report cost per QALY estimates in excess of $400,000 for patients with severe sepsis with an APACHE II score of less than 25.[58,59]

Cost-effectiveness findings for Europe, reported in abstract form, and in the analysis reported by Eli Lilly,[11] are generally more attractive (i.e. cost per QALY estimates are lower) than those reported in the published US and Canadian studies. This would appear to be due to a combination of factors, mainly relating to (1) the European licence indication being specific to a more severely affected patient group (i.e. severe sepsis with multiple organ dysfunction), with marked differences in the ARR for this group compared with the 'severe sepsis' patient group (i.e. ARR of 7.4% versus 6.1%), (2) the cost estimates for both hospitalisation and longer term healthcare costs being much lower in the European analyses, and (3) methods for the assessment of quality-adjusted life expectancy varying between studies.

The estimates of cost per QALY presented by Davies and colleagues[60] and by Eli Lilly,[11] for the UK (severe sepsis with multiple organ dysfunction), are under £11,000. The SHTAC analysis estimates the cost per QALY for UK patients with severe sepsis and patients with severe sepsis and multiple organ dysfunction at £9161 and £8288, respectively. The analyses for the UK, and for Europe more broadly, report findings for the patient group regarded as being more severely affected by disease, that is, those with severe sepsis and multiple organ failure.

Sensitivity analysis indicates that the cost-effectiveness estimates are sensitive to changes in the effectiveness data, to changes in intervention cost, and to changes in methods applied to estimate costs and benefits. However, all findings from the sensitivity analysis undertaken are still in a cost per QALY range that would be regarded as acceptable to most decision-makers. It is only when various alterations are made to the SHTAC base-case assumptions simultaneously (i.e. including higher NHS follow-up costs in the first year after survival, adjusting life-expectancy for survivors by a factor of 0.51 and assuming a baseline 28-day mortality rate of 30%) that the cost per QALY begins to resemble the results presented in the published US and Canadian economic evaluations.

Limitations: cost-effectiveness

The published literature on the cost-effectiveness of drotrecogin alfa (activated) is based on analysis for US and Canadian patients, and its generalisability to Europe and the UK is limited. The literature on the cost-effectiveness of treatment in Europe has been published in abstract form only. This literature is limited in the detail it offers and has not been subject to peer review; therefore, it is not possible to comment on the quality of the studies.

There is uncertainty surrounding the in-practice patient group that may receive drotrecogin alfa (activated). The PROWESS study had specific inclusion and exclusion criteria, and these criteria are not reflected generally in the licensed indications for treatment. The cost-effectiveness analysis presented by the manufacturer applies effectiveness data on ARR from the PROWESS study, together with detail on age and gender for patient groups, to UK data on resource use and life expectancy. The baseline 28-day all-cause mortality in the placebo group is 30.8%, and this may not reflect the in-practice patient group or baseline mortality. The model developed by SHTAC uses data from ICNARC on a UK cohort of patients with severe sepsis, and applies effectiveness data on the RRR in patients treated with drotrecogin alfa (activated). The baseline cohort of UK patients with severe sepsis used in the SHTAC cost-effectiveness model is defined using the PROWESS inclusion criteria, but not the exclusion criteria used in the PROWESS trial. The baseline risk in this patient population is much

greater than the risk of death associated with the placebo group in PROWESS (e.g. 41.5% versus 30.8% in patients with severe sepsis). The exclusion criteria for PROWESS may be applied by clinicians where treatment decisions are made, but the licensed indication for treatment in Europe does not specify the inclusion and exclusion criteria applied in PROWESS; therefore, treatment decisions may be made regardless of the PROWESS criteria. It would seem reasonable to assume that the PROWESS exclusion criteria relating to increased risk of bleeding may be adhered to in a UK setting, given the increased risk of bleeding indicated in the trial; however, exclusion criteria related to the presence of underlying disease and the short-term risk of death may not be applied as rigorously in practice as they were in a trial setting.

There is uncertainty over parameter estimates used in published cost-effectiveness studies, and in the analysis undertaken by Eli Lilly and SHTAC. Mortality following 28-day (or hospital) survival of severe sepsis, and the health-related quality of life (i.e. health utility/value) associated with survivors, are key areas of uncertainty. There is an absence of longer term data on mortality following severe sepsis, and the data from Wright and colleagues[25] were used to estimate mortality after 28-day survival (to adjust life-expectancy for survivors of severe sepsis compared with controls) in the UK severe sepsis patient group (by both SHTAC and Eli Lilly, although in different formats). In the SHTAC analysis, mortality data reported by Wright and colleagues[25] are used to estimate risk of death over years 1–4, following survival at day 28; however, these data are not from a patient group with severe sepsis. Furthermore, data are only available as mean point estimates (per year) and there is no measure of distribution (e.g. standard deviation) around these mean values. Data from Manns and colleagues[58] offer some support (i.e. their data are not dissimilar) to the parameters used in the SHTAC model. Results from the SHTAC simulation modelling show that the data used in the model (from Wright[25]), with base-case assumptions, adjust normal life expectancy by a factor of 0.70 (i.e. the survivors of severe sepsis in the cost-effectiveness model experience, on average, 70% of the life expectancy of the population norm for England and Wales), in patients with severe sepsis and multiple organ failure.

Utility data used in the SHTAC analysis are not from health states describing severe sepsis. The SHTAC analysis uses published data on ARDS to provide information on the health-state values for survivors of severe sepsis, following the methods applied by Manns and colleagues.[58]

Further research

Further research is required on:

- the longer term impact of drotrecogin alfa (activated) on both mortality and morbidity in UK patients with severe sepsis
- the longer term resource consequences of treatment with drotrecogin alfa (activated), to inform the debate over the inclusion of long-term costs in the cost-effectiveness analysis
- the clinical and cost-effectiveness of drotrecogin alfa (activated) in children (under 18 years) with severe sepsis
- the effect of the timing of dosage and duration of treatment with drotrecogin alfa (activated) on outcomes in severe sepsis
- Phase IV implementation studies, to test whether the demonstrated outcome benefit from drotrecogin alfa (activated) in severe sepsis can be replicated in clinical practice to establish the long-term and real-life effectiveness of the treatment. Such studies would provide accurate clinical drug usage data as well as relevant cost-effectiveness data. They may also be useful in recognising rare and long-term side-effects of treatment. These studies would take the form of case-controlled studies, observational research and rigorous clinical audit using high-quality clinical databases
- comparisons between outcome benefits from drotrecogin alfa (activated) and other known or new treatments for severe sepsis [e.g. the effect of combining low-dose systemic corticosteroid therapy with drotrecogin alfa (activated) in the treatment in adults with severe sepsis].

Chapter 8
Conclusions

Drotrecogin alfa (activated) plus best supportive care appears clinically and cost-effective compared with best supportive care alone, in a UK cohort of severe sepsis patients, and in the subgroup of more severely affected patients with severe sepsis and multiple organ failure.

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Appendix 1

Details of epidemiological studies

Study/setting/design	Patient characteristics	Disease severity	Length of stay (days)	Mortality
Alberti *et al.*, 2002[5] International 28 ICUs in eight countries (two in UK) Prospective multicentre cohort study of 14,364 (≥ 18 years) unselected consecutive patients admitted to ICU over 1 year. Used ACCP/SCCM criteria Short stay: (<24 hours in ICU): 6011 Long stay: (>24 hour in ICU): 8353 Only long-stay results reported here	3946/8353 (47%) of long-stay patients (>24 hours in ICU) had sepsis or sepsis-related conditions: Infection without SIRS: 707 (17.9%) Sepsis: (1115) (28.3%) Severe sepsis: (944) (23.9%) Septic shock: (1180) (29.9%) As % of all long-stay ICU patients: Sepsis: 38.7% Severe sepsis or septic shock: 25.4% Source of sepsis infection (severe sepsis/septic shock): Community-acquired: 33% Hospital-acquired: 30% ICU-acquired: 37%		For long-stay patients Median ICU LOS: 6 (3–34). Median hospital LOS: 16 (3–69)	Crude ICU mortality: All patients: 20.4% (95% CI 19.5 to 21.2) Crude hospital mortality: All patients: 26.6% (95% CI: 25.6 to 27.6)
Angus *et al.*, 2001[6] USA 847 hospitals Prospective cohort study of 192,980 cases of severe sepsis over 1 year. Severe sepsis defined as acute care hospitalisations with ICD-9-CM codes for both a bacterial or fungal infectious process and a diagnosis of acute organ dysfunction	192,980 (3%) of all hospitalisations had severe sepsis. Of these: Underlying co-morbidity: 55% ICU care: 51.1% Ventilated in an intermediate care unit but never received ICU care: 6.2% Surgical conditions: 28.6% Medical: 41.4%	Number of acute ODs: 1: 73.6% 2: 20.7% 3: 4.7% ≥ 4: 1.0%	Mean hospital LOS: Overall: 19.6 Non-survivors: 19.9 Survivors: 19.4 ICU: 23.3 No ICU: 15.6 LOS varied little with no. of ODs (range 18.5–22.8 days)	Hospital mortality: Overall: 28.6%. Patients with ICU admission: 34.1% By no. of acute ODs: 1: 21.2% 2: 44.3% 3: 64.5% ≥ 4: 76.2%

continued

Study/setting/design	Patient characteristics	Disease severity	Length of stay (days)	Mortality
Brun-Buisson *et al.*, 1995[7] France 170 adult ICUs (specialised coronary care units excluded) Prospective survey of 11,828 consecutive admissions to ICU over 2 months. ACCP/SCCM definitions	Frequency of severe sepsis in ICU patients: 9% (n = 1052) (1) Documented infection (n = 742, 6.3%, 95% CI 5.8 to 6.7): Mean age 61.4 ± 17 years, 63% male Medical admission: 64% Emergency surgery/trauma: 25% Scheduled surgery: 11% Infection: Community-acquired: 48% Hospital-acquired: 52% [185 (48%) of which were ICU-acquired] (2) Highly probable clinical infection (n = 310); similar characteristics reported for those with probable sepsis	(1) Documented infection: Mean APACHE II: 26.2±8.5 ≥ 1 chronic organ system dysfunction: 55% ≥ 2 acute organ system failures: 53% Shock: 71% (2) No significant differences in those with only clinically documented infection, except that they more often had hypotension (83% vs 77%, p = 0.03)	Median ICU LOS: All ICU patients: 2 All sepsis patients: 8.5 (range 1–87) Median hospital LOS: All sepsis patients: 11 Survivors: 34 Non-survivors: 4	Crude ICU mortality: All ICU patients: 17% Documented sepsis: 56% Crude hospital mortality (documented sepsis only): Overall: 59% 14–day: 46% 28–day: 56% (95% CI 52 to 60%) 42-day: 60% (95% CI 57 to 64%) Rates for culture-negative sepsis reported to be similar: 28-day mortality: 60% (95% CI 55 to 66%)
Moerer *et al.*, 2002[8] Germany Two surgical/medical adult ICUs Retrospective cohort study of 385 patients with severe sepsis (1997–2000). Used ACCP/SCCM definitions	162/385 (42%) infected on admission 238/385 (62%) acquired infection following admission (overlap between groups) 58% male	Organ failure therapy: Respiratory failure therapy only: 29% Respiratory failure and blood disorder therapy: 42% Respiratory failure and renal function therapy: 4% Respiratory failure, blood disorder and renal function therapy: 22%	Mean ICU LOS: Overall: 16.6 ± 14.4 Infected on admission: 16.7 ICU-acquired infection: 18.2 Survivors vs non-survivors: 18.4 vs 14.4 Mean hospital LOS: 32.5 ± 25.0	ICU mortality: Overall: 35.6% Infected on admission: 41.4% Acquired infection: 31.1% Hospital mortality: Overall: 42.6% Infected on admission: 47.5% Acquired infection: 37.4% 83.5% of deaths occurred in ICU

continued

Study/setting/design	Patient characteristics	Disease severity	Length of stay (days)	Mortality
Padkin *et al.*, 2003[9] UK 91 adult general ICUs Comparative audit of 56,673 adult ICU admissions from December 1995 to February 2000. Selected patients with severe sepsis in first 24 hours of ICU as defined by inclusion criteria for PROWESS study[39]	15,362 (27.1%) of adult ICU admissions had severe sepsis during first 24 hours (95% CI 26.7 to 27.5%) Median age 65 years (IQR 51–73) 54.3% male Non-surgical: 35.3% Emergency surgical admissions: 34.5% Elective surgical admissions: 7.4% 6983 (45.5%) would not have been eligible for PROWESS owing to trial exclusion criteria	Number of ODs at baseline (95% CI): 1: 16.4% (15.8 to 17.0%) 2: 34.4% (33.7 to 35.2%) 3: 30.8% (30.0 to 31.5%) 4: 14.7% (14.1 to 15.3%) 5: 3.7% (3.4 to 4.0%) APACHE II score >22: 47.3%	Median (IQR) ICU LOS: Overall: 3.59 (1.50–9.33) Survivors: 3.93 (1.74–10.27) Non-survivors: 3.49 (1.25–9.23) Median (IQR) hospital LOS: Overall: 18 (8, 36) Survivors: 25 (14–46) Non-survivors: 11 (4–23)	Hospital mortality: Overall: 47.3% By no. of ODs (95% CI) 1: 21.8% (20.2 to 23.5%) 2: 36.0% (34.7 to 37.3%) 3: 52.5% (51.1 to 53.9) 4: 75.1% (73.3 to 86.9) 5: 86.1% (83.0 to 88.8)
Rangel-Frausto *et al.*, 1995[10] USA Three critical care units and three wards of a 900-bed teaching hospital Prospective, concurrent incidence surveys of adult patients with >12 hours in ICU and ≥ 2 criteria for SIRS over a 9-month period. ACCP/SCCM definitions used Patients followed up for 28 days or until hospital discharge	Over 28-day follow-up 68% (2527/3708) of all patients admitted had ≥ 2 criteria for SIRS 60% male Mean age: 54.7±17.2 years (men), 55.7±18.1 years (women) Surgical procedures: 47% Surgical ICU: 857 Medical ICU: 804 Cardiovascular ICU: 542 Non-ICU: 1486	Mean APACHE II score on admission to CCU: 18.5 ± 9 (range 2–71) Sepsis: 649 (26%) (56% diagnosed on admission) Severe sepsis: 467 (18%) (42% diagnosed on admission) Septic shock: 110 (4%) (29% diagnosed on admission) Thought to be clinically septic: a further 892 (35%) Of all patients admitted to ICU: Diagnosed with sepsis: 1226 (33%) Severe sepsis or septic shock: 577 (15.6%)		Crude 28-day mortality rate of patients with SIRS: 224/2527 (9%) 28-day mortality per group (numbers not reported): Culture-positive sepsis: 16% SIRS and suspected, but undocumented infection: 10% Severe sepsis and positive culture: 20% Severe sepsis and negative culture: 16% Shock (with or without positive culture): 46% Additional 111 died in 3-month follow-up: SIRS group: 41% Sepsis: 10% Severe sepsis: 44% Septic shock: 5% Additional 115 died between 3- and 6-month follow-up: SIRS group: 27% Sepsis: 25% Severe sepsis: 44% Septic shock: 5%

continued

Study/setting/design	Patient characteristics	Disease severity	Length of stay (days)	Mortality
Salvo *et al.*, 1995[16] Italy 99 ICUs Prospective, multicentre cohort study. Preliminary analysis of 1101 patients presented. First three consecutive patients admitted at beginning of each month were enrolled. Patients classified using ACCP/SCCM definitions Patients followed up until hospital discharge	On admission: No sepsis: 421 (38.2%) SIRS: 573 (52.0%) Sepsis: 50 (4.5%) Severe sepsis: 23 (2.1%) Septic shock: 33 (3.0%) At any time during the study: SIRS: 637 (58.0%) Sepsis: 180 (16.3%) Severe sepsis: 61 (5.5%) Septic shock: 67 (6.1%)			Mortality (according to characteristics on admission): No sepsis: 24.0% SIRS: 26.5% Sepsis: 36.0% Severe sepsis: 52.2% Septic shock: 81.8%
Sands *et al.*, 1997[12] USA Eight academic tertiary care centres Prospective observational study of weighted random sample of all ICU patients and of non-ICU patients from whom a blood culture was obtained (12,001 patients). Severe sepsis defined using ACCP/SCCM criteria 5-month follow-up	1063/12,001(8.9%) had severe sepsis: 56% male Mean age: 59 years Emergency admissions: 46% As % of 1342 sepsis episodes in 1063 patients: Septic shock at onset: 25% Location at onset: ICU: 55% Emergency department: 12% Non-ICU patient care unit: 33%		Mean (median) LOS: Severe sepsis: 29 (20) All patients: 17.3 (10) Mean (median) ICU stay: Severe sepsis: 17.7 (8) All patients: 4.4 (1)	As % of 1342 severe sepsis episodes in 1063 patients: 28-day mortality: 34% 5-month mortality: 45.3%
SICS, 2002[13,14] UK 25 ICUs Prospective audit of 3442 patients with sepsis at any point during ICU stay 5-month follow-up	1618/3442 (47%) of ICU admissions had or developed sepsis during ICU admission Severe sepsis: 20% Septic shock: 18%	Two-thirds of severe sepsis group had ≥ 1 organ failure Mean SOFA score: Sepsis: 1.8 Severe sepsis: 5.2 Septic shock: 10.7 Mean APACHE II score: Sepsis: 17.8 Severe sepsis: 19.8 Septic shock: 24.3	All sepsis patients: ICU: mean 9.02, median 5.1	ICU mortality: Sepsis: 9.25% Severe sepsis: 21.4% Septic shock: 52%

continued

Study/setting/design	Patient characteristics	Disease severity	Length of stay (days)	Mortality
Teres *et al.*, 2002[15] USA 50 ICUs: project IMPACT Observational study of ICU admissions: 2434 patients with severe sepsis at ICU admission and 19,046 patients without sepsis at ICU admission. Used ACCP/SCCM definitions	2434 (11.3%) ICU patients had severe sepsis at ICU admission Elective surgery: 7.6% Emergency surgery: 14.3% Non-operative: 62.6% Mean age: 63.6 ± 17.1 years		Mean (SD) ICU LOS No sepsis: 4.8 (6.5) Sepsis: 8.48 (10.1) Survivors: 8.15 Non-survivors 9.06 Mean (SD) hospital LOS: No sepsis: 10.57 (11.7) Sepsis: 16.21 (16.7) Survivors: 18.48 Non-survivors: 12.22	Mortality (not clear whether in-hospital): Sepsis: 36.3% No sepsis: 15.8%

Appendix 2
Description of APACHE II scoring system

Brief description of APACHE II

APACHE II is a severity of disease classification system designed by Knaus and colleagues[19] to evaluate acutely ill patients. It was developed from a prototype APACHE system[81] and is based on the use of basic physiological principles to stratify patients prognostically by risk of death. The original APACHE system provided weightings for 34 potential physiological measures, the sum of which represented an acute physiological score (APS).

The APACHE II system uses 12 physiological measurements, and is based on the hypothesis that the severity of acute disease can be measured by quantifying the degree of abnormality of these multiple physiological variables. The APACHE II system is intended to be as independent of therapy as possible and to be valid for a wide range of diagnoses. The system is intended to be easy to use and based on data available in most hospitals.

The 12 physiological measurements used in APACHE II were chosen for maximal explanatory power in a multivariate analysis.

The physiological variables included are:

- temperature (rectal, ºC)
- mean arterial pressure (mmHg)
- heart rate (ventricular response)
- respiratory rate (non-ventilated or ventilated)
- oxygenation [alveolar arterial oxygen gradient (A–aDO_2)] or arterial oxygen tension (PaO_2) (mmHg)
  - inspirational oxygen fraction (FIO_2) = 0.5, record A–aDO_2
  - FIO_2 < 0.5, record only PaO_2
- arterial pH
- serum sodium (mmol l^{-1})
- serum potassium (mmol l^{-1})
- serum creatinine (mg 100 ml^{-1}) (double point score for acute renal failure)
- haematocrit (%)
- white bloodcell count (total/mm^3 in 1000s)
- Glasgow Coma Score (GCS) (Score = 15 minus actual GCS).

The recorded value for each measurement is based on the most deranged value during each patient's initial 24 hours in an ICU. Also included in the scoring system are an age criterion and a chronic health criterion. (See detail in Figure 1 reported in Knaus and colleagues,[19] p. 820.)

Validation of APACHE II

Knaus and colleagues[19] report work undertaken to validate the APACHE II system. They evaluate validity, by assessing the association of APACHE II with hospital mortality in unselected but carefully described ICU admissions from 13 US hospitals.

They report that for each five-point increase in APACHE II, there was a significant increase in death rate. Death rates ranged from 1.9% for patients with 0–4 points to 84% for patients with 35 or more points. They report that the overall risk of hospital death varied according to the disease of the patients. For instance, "patients with congestive heart failure admitted with APACHE II scores of 10 to 19 had a lowered observed hospital death rate than septic shock patients with similar scores (13% vs 26%, respectively)" (p. 823). Therefore, they conclude that to compute risk of death, it is crucial to combine the APACHE II score with a precise description of the disease.

In their assessment, using a decision criterion of a risk greater than 0.50 in predicting death, the overall correct classification rate in patients was 86%. For this risk, the sensitivity was 47.0%, the specificity was 94.9%, the predictive value positive was 69.6% and the predictive value negative was 87.9%. Classifications were also presented for different predicted risks (0.70–0.90).

The authors report that first day APACHE II scores do not perfectly predict death rates for

individual patients, and there were indications that the worst APACHE II scores tended to be at ICU admission.

The authors suggested that expected death rates based on APACHE II scores can be compared with actual death rates as a test of therapeutic efficacy for patients in particular diagnostic groups. However, within particular diagnostic groups, APACHE II scores can only provide a minimal description of severity of disease. Additional indicators relevant to particular diseases may be important.

It was suggested that for particular research questions, the 12 physiological variables may be sufficient without adding points for age and chronic disease. These additional factors may not be needed for risk stratification in studies in which the end-point is not hospital mortality.

In an appendix to their paper the authors report a method to compute predicted death rates based on the APACHE II score. Important factors include whether the patient was postemergency surgery and their diagnostic category. Weights for each diagnostic category are provided by the authors. "To compute predicted death rates for groups of acutely ill patients, for each individual compute the risk (R) of hospital death with the following equation; then sum the individual risks and divide by the total number of patients.

$$\ln (R/1 - R) = -3.517 + (\text{APACHE II score} \times 0.146) + (0.603, \text{ only if postemergency surgery}) + (\text{Diagnostic category weight} = 0.113 \text{ for Cardiovascular failure or insufficiency from sepsis})$$

" (see detail on p. 828).

Notes

1. Rowan and colleagues[20] report that validation of APACHE II in the UK demonstrated major differences in case-mix and severity of illness between UK and American intensive care populations, thereby reducing the predictive accuracy of the score.
2. It is recognised that it is inappropriate to use the APACHE II scoring systems to determine individual patient outcome, to limit or ration intensive care, or to determine the use of new treatments' scores.[18]

Appendix 3

Documentation of search strategy used

Published literature was identified from the following databases using the strategy below:

- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- HTA Database
- MEDLINE and PubMed
- EMBASE
- BIOSIS
- TOXLINE
- Cochrane Controlled Trials Register (CCTR)
- Science Citation Index
- Biomed Central
- NHS Economic Evaluations Database (NHS EED)
- EconLit

Unpublished research or research in progress:

- National Research Register
- Early Warning System (EWS)
- Index to Scientific and Technical Proceedings (ISTP)
- CSA Conference Papers Index
- Current Controlled Trials
- Clinical Trials.gov
- Zetoc (general and conferences)
- SIGLE (grey literature)
- FDA http://www.fda.gov
- EMEA http://www.emea.eu.int

Search strategy (for database Pre-MEDLINE, MEDLINE)

- sepsis.ti,ab. (30430)
- Sepsis Syndrome/ (1432)
- Shock, Septic/ (11940)
- septic shock.ti,ab. (6452)
- SEPSIS/ (5356)
- Septicemia/ (19691)
- septicemia.ti,ab. (7204)
- septicaemia.ti,ab. (3755)
- exp septicemia/ (45752)
- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (65131)
- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (76675)
- drotrecogin.ti,ab. (66)
- drotrecogin.rw. (75)
- xigris.mp. [mp=ti, ab, rw, sh] (12)
- zovant.mp. [mp=ti, ab, rw, sh] (0)
- activated protein c.ti,ab. (2154)
- recombinant protein c.ti,ab. (29)
- 12 or 13 or 14 or 16 or 17 (2225)
- 11 and 18 (199)

Appendix 4

Quality assessment tool used

The Cochrane Infectious Diseases group recommends that study quality should be based on four methodological aspects, as set out by Jüni and colleagues.[82]

Allocation concealment

- Adequate: patients and investigators enrolling patients cannot foresee assignment
- inadequate: allocation concealment not reported or reported and approach not considered to be adequate
- unclear: if allocation concealment reported but method not described.

Adequate methods include a priori numbered or coded drug containers of identical appearance, central randomisation, sequentially numbered, opaque, sealed envelopes; and other description that contained convincing elements of concealment.

Generation of allocation sequence

- Adequate: if sequences are suitable to prevent selection bias and the method used is described
- inadequate: if sequences could be related to prognosis
- unclear: if randomisation reported but method not described.

Adequate methods include random numbers generated by computer, table of random numbers, drawing lots of envelopes, tossing a coin, shuffling cards, throwing dice and other methods of allocation that appear to be unbiased.

Inadequate methods include case record number, date of birth, and day, month or year of admission.

Blinding

Report which of the following are aware of the treatment the patient is receiving:

- patient
- healthcare provider
- outcome assessor

Intention-to-treat analysis

- Adequate: if more than 90% of patients randomised in the trial were included in the analyses
- inadequate: if it is not clear how many patients were originally randomised into the trial, or less than 90% of those randomised were included in the analysis.

The following issues relate to the generalisability of studies of patients with sepsis to the UK context and are adapted from the quality assessment criteria set out by Graf and colleagues.[42]

Definition of sepsis and severe sepsis

Sepsis is a multifaceted disease and the criteria for definition of severe sepsis and septic shock can vary. It is important to examine the definitions used in the included studies and to assess the ease of applying the often strict inclusion and exclusion criteria of a trial situation to usual clinical practice.

The Cochrane Infectious Diseases Group[41] recommends that studies should use the criteria set out by the ACCP and SCCM[2] in 1992 (the Bone criteria) or some modification of them combined with a requirement for:

- confirmed infection (e.g. positive blood culture, Gram stain in bronchoalveolar

lavage or sputum, bacteriuria or positive local microbiological culture results), or
- objective clinical evidence for infection (e.g. consolidation or pulmonary cavitation on chest radiograph, catheter infection with erythema, induration, pus or tenderness at the site, localised inflammation with swelling, induration or erythema).

Definitions of sepsis, severe sepsis and septic shock, from the Bone criteria, are provided in the Glossary.

Admission diagnoses and patient characteristics

Distribution of underlying disease and co-morbid states, and how these compare with those in the UK.

Standard care

Were standard care and co-morbidity treatment comparable to those routinely given to patients with similar characteristics in the UK? There is known heterogeneity in the treatment of sepsis between centres.

Appendix 5

List of excluded studies

Excluded clinical studies on rhAPC

Angus DC, Vincent JL, Artigas A, Clermont G, Linde-Zwirble WT, Shanies HM, *et al*. The effect of recombinant human activated protein C (rhAPC) on organ dysfunction and functional recovery in severe sepsis. *Crit Care Med* 2000;**28**:69. Reason: PROWESS – abstract only. Data published in full in Vincent *et al.*, 2003.[48]

Barie PS. Drotrecogin alfa (activated) has a favorable benefit/risk profile in surgical patients with severe sepsis. *Crit Care Med* 2002;**30**:427. Reason: open-label study – abstract only.

Bernard GR, Hartman DL, Helterbrand JD, Fisher CJ. Recombinant human activated protein C (rhAPC) produces a trend toward improvement in morbidity and 28 day survival in patients with severe sepsis. *Crit Care Med* 1999;**27**:4. Reason: EVAD – abstract only. Data published in full in Bernard *et al.*, 2001.[43]

Bernard GR, Larosa SP, Laterre PF, Ely EW, Dhainaut JF, Fisher CJ, *et al.*, The efficacy and safety of recombinant human activated protein C for the treatment of patients with severe sepsis. *Crit Care Med* 2000;**28**:67. Reason: PROWESS – abstract only. Data published in full in Bernard *et al.*, 2001.[39]

Bernard GR, Larosa SP, Laterre PF, Ely EW, Dhainaut JF, Fisher CJ, *et al.*, The efficacy and safety of recombinant human activated protein C for the treatment of patients with severe sepsis. *Crit Care Med* 2001;**29**:469. Reason: PROWESS – abstract only. Data published in full in Bernard *et al.*, 2001.[39]

Bernard GR, Macias WL, Vincent JL. Drotrecogin (alfa) activated cumulative safety update. *Chest* 2002;**122**:50S. Reason: safety data – abstract only. Data published in full in Bernard *et al.*, 2003.[49]

Chapital A, Yu MH, Conde A, Wang J. Effect of activated protein C on peripheral circulation in septic shock patients. *Crit Care Med* 2002;**30**:432. Reason: open-label study – abstract only.

Clarke H, Barlows TG, Machado C, Dalin G, Prager R. Drotrecogin alfa (activated): implementing institutional guidelines for use and assessing treatment outcomes in patients with severe sepsis. *Pharmacotherapy* 2002; **22**:1374–5. Reason: open-label study – abstract only.

Dhainaut J, Laterre P, Basson B, Vincent J. Drotrecogin alfa (activated) in severe sepsis patients with 2 or more organ dysfunctions. *Intensive Care Med* 2002;**28**:307. Reason: PROWESS – abstract only. Data reported in full in Dhainaut *et al.*, 2003[45].

Ely EW, Angus DC, Williams MD, Bates B, Qualy R, Bernard GR. Drotrecogin alfa (activated) treatment of older patients with severe sepsis. *Clin Infect Dis* 2003;**37**:187–95. Reason: PROWESS – full paper, but only reports outcomes in patients aged 75+. This is not one of the prespecified subgroups of interest for this report.

Evans HL, Milburn ML, Calloway T, Volles TF, Lowson SM, Sawyer RG. Treating medical and surgical patients with activated protein C: a preliminary comparison. *Crit Care* 2003;**7**:P022. Reason: open-label study – abstract only.

Higgins T, Steingrub J, Tereso G, Tidswell M, Higgins A. Recombinant activated protein C in sepsis: a single center's experience. *Crit Care Med* 2002;**30**:431. Reason: open-label study – abstract only.

Kinasewitz GT, Margolis B, Freebairn RC, Russell JA, Utterback BC, Basson B, *et al.* Changes in markers of coagulation and inflammation in patients with severe sepsis treated with recombinant human activated protein C. *Crit Care Med* 2000;**28**:68. Reason: open-label study – abstract only.

Kulkarni S, Naureckas E, Cronin DC. Solid-organ transplant recipients treated with drotrecogin alfa (activated) for severe sepsis. *Transplantation* 2003;**75**:899–901. Reason: report of three case studies of patients following solid-organ transplant.

Kupfer Y, Yoon T, Chawla K, Tessler S. Drotrecogin alfa has limited usefulness in the treatment of severe sepsis. *Crit Care Med* 2002;**30**:428. Reason: open-label study – abstract only.

LaRosa S, Vincent JL, Bellomo R, Russell JA, Laterre P-F, Artigas A, *et al.*, Baseline characteristics of patients enrolled in the phase III trial of rhAPC in severe sepsis. *Crit Care Med* 2000;**28**:A48. Reason: abstract only. Data published in full in Bernard *et al.*, 2001.[39]

Macias WL, Dhainaut JF, Yan SC, Helterbrand JD, Seger M, Johnson G, III, *et al.* Pharmacokinetic–pharmacodynamic analysis of drotrecogin alfa (activated) in patients with severe sepsis. *Clin Pharmacol Ther* 2002;**72**:391–402. Reason: PROWESS – full paper; pharmacodynamic outcomes only.

Macias WL, Helterbrand J, Derchak PA. Influence of patient heterogeneity on treatment effect of drotrecogin alfa (activated) in PROWESS. *Crit Care Med* 2002;**30**:439. Reason: PROWESS – abstract only.

Maskin BC. Low levels of protein C in severe sepsis. *Crit Care Med* 2002;**30**:429. Reason: open-label study – abstract only.

Morris P, Garber G, Laterre PF, Levy H. Drotrecogin alfa (activated) reduced the number of deaths attributed to cardiovascular and pulmonary organ failure in patients with severe sepsis. *Crit Care Med* 2001;**29**:32. Reason: open-label study – abstract only.

Quap CW, Tran JI, Jackson A, Ham CW, Gupta V. The use of recombinant human activated protein C (rhAPC, drotrecogin alfa (activated)) in the management of patients with sepsis in the community hospital setting. *Crit Care Med* 2002;**30**:433. Reason: open-label study – abstract only.

Riker RR, Fraser GL, Schlichting DE, Wilkins SL. Cutting edge science from the clinical trial to the bedside: first 8 months use of drotrecogin alpha activated (APC) for severe sepsis. *Crit Care Med* 2002;**30**:434. Reason: open-label study – abstract only.

Ruiz-Santana S, Caceres JJ, Marcos JA, Negrin H. Drotrecogin alfa (activated) treatment prolongs filter survival time in patients with severe sepsis on continuous venovenous hemofiltration. *Crit Care Med* 2002;**30**:436. Reason: open-label study – abstract only.

Savani D, Boylen T. Clinical outcomes and adverse effects of patients treated with drotrecogin alfa. *Crit Care Med* 2002;**30**:435. Reason: open-label study – abstract only.

Swerlein A, Conty W, McCluskey C. Initial experience with drotrecogin alfa activated in two large tertiary care facilities. *Crit Care Med* 2002;**30**:437. Reason: open-label study – abstract only.

Tidswell M, Steingrub J, Higgins TL, Kozikowski LA. Activated protein C therapy in patients with ARDS/ALI and severe sepsis. *Crit Care Med* 2002;**30**:430. Reason: open-label study – abstract only.

Um J, Coyle SM, Calvano SE, Lowry SF. Drotrecogin alfa (activated) in a human endotoxin model. *Crit Care Med* 2002;**30**:440. Reason: open-label study – abstract only.

Wittbrodt E, Rose C. Experience with drotrecogin alfa activated (DAA) in a tertiary care hospital. *Crit Care Med* 2002;**30**:438. Reason: open-label study – abstract only.

Additional excluded studies (not primary studies on rhAPC)

Drotrecogin alfa: new preparation. For some cases of severe sepsis? *Prescrire International* 2003;**12**:55–7.

Alberio L, Lammle B, Esmon CT. Protein C replacement in severe meningococcemia: rationale and clinical experience [published erratum appears in *Clin Infect Dis* 2001; 15;**32**:1803]. *Clin Infect Dis* 2001; **32**:1338–46.

Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, *et al*. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002; **28**:108–21.

Anel RL, Kumar A. Experimental and emerging therapies for sepsis and septic shock. *Expert Opin Investig Drugs* 2001;**10**:1471–85.

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**:1303–10.

Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, *et al*. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003;**31**:1–11.

Astiz ME, Rackow EC. Septic shock. *Lancet* 1998; **351**:1501–5.

Banks SM, Gerstenberger E, Eichacker PQ, Natanson C. Long-term cost effectiveness of drotrecogin alfa (activated): an unanswered question. *Crit Care Med* 2003;**31**:308–9.

Bearden DT, Garvin CG. Recombinant human activated protein C for use in severe sepsis. *Ann Pharmacother* 2002;**36**:1424–9.

Bernard G, Artigas A, Dellinger P, Esmon C, Faist E, Faust SN, *et al*. Clinical expert round table discussion (session 3) at the Margaux Conference on Critical Illness: the role of activated protein C in severe sepsis. *Crit Care Med* 2001;**29** (Suppl): 7.

Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. *Crit Care Med* 2003;**31**:S85–93.

Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, *et al*. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. *JAMA* 1995;**274**:968.

Cohen H, Welage LS. Strategies to optimize drotrecogin alfa (activated) use: guidelines and therapeutic controversies. *Pharmacotherapy* 2002;**22**:223–35S.

Crowther MA, Marshall JC. Continuing challenges of sepsis research. *JAMA* 2001;**286**:1894–6.

Dasta JF, Cooper LM. Impact of drotrecogin alfa (activated) on resource use and implications for reimbursement. *Pharmacotherapy* 2002;**22**:216–22S.

De Jonge E, van der Poll T, Kesecioglu J, Levi M. Anticoagulant factor concentrates in disseminated intravascular coagulation: rationale for use and clinical experience. *Semin Thromb Hemost* 2001;**27**:667–74.

Dhainaut JF. Introduction: rationale for using drotrecogin alfa (activated) in patients with severe sepsis. *Am J Surg* 2002;**184**:5–10S.

Dhainaut JF, Yan SB, Cariou A, Mira JP. Soluble thrombomodulin, plasma-derived unactivated protein

C, and recombinant human activated protein C in sepsis. *Crit Care Med* 2002;**30**:s318–24.

Edbrooke DL, Hibbert CL, Kingsley JM, Smith S, Bright NM, Quinn JM. The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care unit. *Crit Care Med* 1999;**27**:1760–7.

Eichacker PQ, Natanson C. Recombinant human activated protein C in sepsis: inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials. *Crit Care Med* 2003;**31**:S94–6.

Eichacker PQ, Parent C, Kalil A, Esposito C, Cui X, Banks SM, *et al*. Risk and efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med* 2002;**166**:1197–205.

Ely EW, Bernard GR, Vincent JL. Activated protein C for severe sepsis. *N Engl J Med* 2002;**347**:1035.

Esmon CT. Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. *Crit Care Med* 2001;**29**(Suppl):51.

Esmon CT. The normal role of activated protein C in maintaining homeostasis and its relevance to critical illness. *Crit Care* 2001;**5** Suppl 2:S7–12.

European Agency for the Evaluation of Medicinal Products. *European public assessment report (EPAR) – Xigris*. London: Committee for Proprietary Medicinal Products, EMEA; 2002.

Food and Drug Administration. *Product approval information – licensing action: drotrecogin alfa (activated) Xigris*. Rockville, MD: FDA; 2001.

Freeman BD, Buchman TG. Coagulation inhibitors in the treatment of sepsis. *Expert Opin Investig Drug*s 2002; **11**:69–74.

Garces K. Activated protein C for severe sepsis. *Issues in Emerging Health Technologies. Canadian Coordinating Centre for Health Technology Assessment* 2002;**30**:1–4.

Goldfrad C, Padkin A. J, Young JD, Rowan K. Admissions with severe sepsis: ICU and hospital resource use in England, Wales and Northern Ireland. *Intensive Care Med* 2001;**2:**,S252. Epidemiology paper.

Graf J, Doig GS, Cook DJ, Vincent JL, Sibbald WJ. Randomized, controlled clinical trials in sepsis: has methodological quality improved over time? *Crit Care Med* 2002;**30**:461–72.

Greisman SE, Johnston CA, Gosnell MS. Recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**345**:219–21.

Griffin JH, Zlokovic B, Fernandez JA. Activated protein C: potential therapy for severe sepsis, thrombosis, and stroke. *Semin Hematol* 2002;**39**:197–205.

Grinnell BW, Joyce D. Recombinant human activated protein C: a system modulator of vascular function for treatment of severe sepsis. C*rit Care Med* 2001; **29**:s53–60.

Hassan E, Mann HJ. Current issues regarding the use of drotrecogin alfa (activated). *Pharmacotherapy* 2002; **22**:215S.

Ioannidis JP, Chew P, Lau J. Standardized retrieval of side effects data for meta-analysis of safety outcomes. A feasibility study in acute sinusitis. *J Clin Epidemiol* 2002;**55**:619–26.

Kapur S, Kupfer Y, Tessler S. Recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**345**:219–20.

Knaus W, Draper E, Wagner D, Zimmerman J. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;**13**:818–29.

Labbos J, Bradsher J, Kirkpatrick P. Drotrecogin alpha (activated). *Nat Rev Drug Discov* 2003;**2**:13–14.

Langham J, Thompson E, Rowan K. Randomised controlled trials from the critical care literature: identification and assessment of quality. *Clinical Intensive Care* 2002;**13**:73–83.

Larosa SP. Sepsis: menu of new approaches replaces one therapy for all. *Cleve Clin J Med* 2002;**69**:65–73.

Laterre PF, Heiselman D. Management of patients with severe sepsis, treated by drotrecogin alfa (activated). *Am J Surg* 2002;**184**(6: Supp 1):39s–46s.

Laterre PF, Wittebole X. Clinical review: Drotrecogin alfa (activated) as adjunctive therapy for severe sepsis: practical aspects at the bedside and patient identification. *Crit Care* 2003.

Launois R, Riou Franca L, Guidet B, Aegerter P, Huet X, Meshaka P, *et al*. Cost effectiveness analysis of drotrecogin alfa (activated) as a treatment for severe sepsis in hospitalised patients. *Crit Care* 2002;**6**:P116.

Levi M. Benefit of recombinant human activated protein C beyond 28-day mortality: there is more to life than death. *Crit Care Med* 2003;**31**:984–5.

Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al.*, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250–6.

Livingston BM, MacKirdy FN, Howie JC, Jones R, Norrie JD. Assessment of the performance of five intensive care scoring models within a large Scottish database. *Crit Care Med* 2000;**28**:1820–7.

Lyseng-Williamson KA, Perry CM. Drotrecogin alfa (activated). *Drugs* 2002;**62**:617–30.

Mann HJ. Recombinant human activated protein C in severe sepsis. *Am J Health Syst Pharm* 2002;**59**:S19–23.

Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002; **347**:993–1000.

Mathiak G, Neville LF, Grass G. Targeting the coagulation cascade in sepsis: did we find the "magic bullet"? *Crit Care Med* 2003;**31**:310–11.

Morris PE, Light RB, Garber GE. Identifying patients with severe sepsis who should not be treated with drotrecogin alfa (activated). *Am J Surg* 2002;**184** (Suppl):24.

O'Connor PE. Recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**345**:220–1.

Ott A, Verbrugh HA. Recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **345**:220–1.

Padkin A, Rowan K, Black N. Using high quality clinical databases to complement the results of randomised controlled trials: the case of recombinant human activated protein C. *BMJ* 2001;**323**:923–6.

Padkin AJ, Goldfrad C, Young JD, Rowan K. The prevalence of severe sepsis in the first 24 hours in the ICU in England, Wales and Northern Ireland. *Intensive Care Med* 2001;**27**:S252.

Palazzo M, Soni N. Critical-care studies: redefining the rules. *Lancet* 1998;**352**:1306–7.

Pastores SM. Drotrecogin alfa (activated): a novel therapeutic strategy for severe sepsis. *Postgrad Med J* 2003;**79**:5.

Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995;**273**:117.

Rittenhouse BE. The relevance of searching for effects under a clinical-trial lamppost: a key issue. *Med Decis Making* 1995;**15**:348–57.

Rollins G. Case made for aggressive, early treatment of severe sepsis and septic shock. *Report on Medical Guidelines and Outcomes Research* 2001;**12**:1–2.

Schein RM, Kinasewitz GT. Risk–benefit analysis for drotrecogin alfa (activated). *Am J Surg* 2002;**184** (Suppl):38.

Shah ND, Vermeulen LC, Santell JP, Hunkler RJ, Hontz K. Projecting future drug expenditures – 2002. *Am J Health Syst Pharm* 2002;**59**:131–42.

Siegel JP. Assessing the use of activated protein C in the treatment of severe sepsis. *N Engl J Med* 2002; **347**:1030–4.

Sollet JP, Garber GE. Selecting patients with severe sepsis for drotrecogin alfa (activated) therapy. *Am J Surg* 2002;**184**:S11–18.

Vanscoy GJ. Management challenge with drotrecogin alfa (activated) [review]. *Am J Health Syst Pharm* 2002; **59**:S23–9.

Vincent JL. Drotrecogin alfa: a new approach in the treatment of severe sepsis. *Expert Opin Biol Ther* 2002;**2**:659–64.

Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;**347**:1027–30.

Wiedemann HP. Activated protein C was cost-effective for prolonging survival in a subgroup of patients with severe sepsis. *ACP J Club* 2003;**138**:81.

Wyncoll D. Treating severe sepsis with drotrecogin alfa (activated). *Hosp Med (London)* 2003;**64**:168–72.

Appendix 6

Characteristics of included studies

Study ID/sponsor	Relevant publications	No. of participants	Intervention group	Control group	Outcomes	Comment
EVAA Eli Lilly Phase II (randomised)	Bernard *et al.*, 2001[43]	135 randomised, 131 treated	rhAPC 48-hour continuous i.v. infusion: 12 $\mu g/kg^{-1}$ per hour, $n = 11$ 18 $\mu g/kg^{-1}$ per hour, $n = 11$ 24 $\mu g/kg^{-1}$ per hour, $n = 12$ 30 $\mu g/kg^{-1}$ per hour, $n = 12$ rhAPC 96-hour continuous i.v. infusion: 12 $\mu g/kg^{-1}$ per hour, $n = 14$ 18 $\mu g/kg^{-1}$ per hour, $n = 15$ 24 $\mu g/kg^{-1}$ per hour, $n = 15$	Saline continuous i.v. infusion: 48 hours, $n = 26$ 96 hours, $n = 15$	Primary clinical outcomes: Frequency of SAEs and SBEs, and assessment of anti-aPC antibody response[c] Primary pharmacodynamic measures: changes in D-dimer, fibrinogen, platelet and IL-6 levels Secondary outcomes: 28-day all-cause mortality, use of intensive care and hospital resources, OD	Additional interventions except for high-dose heparin were given at the discretion of the treating physician and not prespecified in the study protocol
PROWESS (EVAD) Eli Lilly Phase III	Bernard *et al.*, 2001[39] Vincent *et al.*, 2003[48] Ely *et al.*, 2003[46a] Dhainaut *et al.*, 2003[45b] Angus *et al.*, 2002[50] [abstract only] FDA clinical review, 2002[38]	1728 randomised, 1690 treated	rhAPC 96-hour continuous i.v. infusion: 24 $\mu g/kg^{-1}$ per hour, $n = 850$	Saline (0.9% with or without 0.1% human serum albumin) continuous i.v. infusion	Primary outcomes: 28-day all-cause mortality[46a,45b] Long-term follow-up (15–45 months) provided in Angus *et al.*[50] Secondary outcomes: OD (SOFA scores, evolution/resolution of OD)[48] Pharmacodynamic outcomes (D-dimer levels, IL-6 levels, plasma protein C activity level, microbiological cultures)[48] Safety[c] (SAEs: serious bleeding or thrombotic event)[45]	Additional interventions as above Composition of placebo changed after 720 patients recruited (June 1999) Inclusion/exclusion criteria changed in August 1999 Primary outcome analyses performed on treated patients and ITT. ITT only reported here FDA clinical review,[38] provides further trial data and reanalyses

continued

Study ID/sponsor	Relevant publications	No. of participants	Intervention group	Control group	Outcomes	Comment
ENHANCE (EVBE, EVBF, EVBG) Phase IV (published abstract provides partial data)	EVBE Bernard *et al.*, 2002[51] [abstract only] EVBF, EVBG: unpublished	1578 treated,[49] 273 reported[51]	rhAPC 96-hour continuous i.v. infusion: 24 $\mu g/kg^{-1}$ per hour	No control group	Outcomes: 28-day mortality, safety[c] (SBEs, ICH)	Inclusion and exclusion criteria were identical to those of PROWESS
EVAS	Unpublished	28 treated (compassionate use, purpura fulminans)	rhAPC for minimum of 96-hour continuous i.v. infusion: 24 $\mu g/kg^{-1}$ per hour	No control group	Outcomes: Safety[c]	
EVBC	Unpublished	240 treated (compassionate use)	rhAPC 96-hour continuous i.v. infusion: 24 $\mu g/kg^{-1}$ per hour	No control group	Outcomes: Safety[c]	
Cumulative safety update Includes data for all listed trials plus commercial use data	Bernard *et al.*, 2003[49]	3667 patients in clinical trials 3991 patients in commercial use	rhAPC 96-hour continuous i.v. infusion: 24 $\mu g/kg^{-1}$ per hour	2 RCTs (EVAA and EVAD), plus five open-label studies, see above for details	Outcomes: 28-day mortality, safety (SBE rates)	

[a] A priori subgroup analyses.
[b] Post hoc subgroup analyses according to single/multiple organ dysfunction.
[c] Safety data for all patients also provided in cumulative safety update.[49]

Appendix 7

Completed data extraction forms

Reference and design	Interventions	Subjects	Outcome measures
Bernard *et al.*[43] **Recruitment date:** not stated **Location:** USA, Canada **Setting:** 40 community or academic medical institutions **Publication status:** published 2001 **Design:** double-blind, randomised, placebo-controlled, multicentre, dose-ranging, Phase II clinical trial **Trial sponsor:** funded by Eli Lilly & Co.	**Recombinant human activated protein C (rhAPC):** *Stage I:* Dose: 12, 18, 24 or 30 μg kg^{-1} per hour Duration: 48 hours continuous i.v. infusion *Stage II:* Dose: 12, 18, or 24 μg kg^{-1} per hour Duration: 96 hours continuous i.v. infusion **Details of placebo:** saline (no further details) continuous i.v. infusion **Other aspects of care provided:** decisions regarding the use of antimicrobial agents, i.v. fluids, cardiovascular and respiratory support, and surgical intervention were left to the treating physician and not prespecified in the protocol	**Total number of patients:** 135 patients randomised, of whom 131 received rhAPC (n = 90) or placebo (n = 41) **Numbers of patients in each group:** *Stage I:* rhAPC 12 μg kg^{-1} hour = 11 rhAPC 18 μg kg^{-1} hour = 11 rhAPC 24 μg kg^{-1} hour = 12 rhAPC 30 μg kg^{-1} hour = 12 placebo = 26 *Stage II:* rhAPC 12 μg kg^{-1} hour = 14 rhAPC 18 μg kg^{-1} hour = 15 rhAPC 24 μg kg^{-1} hour = 15 placebo = 15 **Baseline characteristics:** Age (years): rhAPC 58 ± 14, placebo 62 ± 16 Weight (kg): rhAPC 86 ± 29, placebo 76 ± 17 Gender: rhAPC 63% male, placebo 66% male Modified APACHE II score: rhAPC 16.8 ± 5.2, placebo 18.4 ± 6.9 Septic shock: rhAPC 70%, placebo 68% Mechanical ventilation on day before infusion: rhAPC 74%, placebo 73% Infection site (%): Lung: rhAPC 28, placebo 24 Intra-abdominal: rhAPC 16, placebo 17 Blood: rhAPC 18, placebo 10 Urinary tract: rhAPC 14, placebo 12 Organ failures (%): 1 system: rhAPC 61, placebo 59 2 systems: rhAPC 32, placebo 34 3 systems: rhAPC 7, placebo 7 Organ system failure (%): Cardiovascular: rhAPC 62, placebo 61 Respiratory: rhAPC 57, placebo 66 Renal: rhAPC 27, placebo 22 **Inclusion criteria:** patients ≥ 18 years with severe sepsis and known/suspected site of infection. (Criteria for severe sepsis were a modification of SIRS as defined by the ACCP/SCCM Consensus Conference, with details given in Appendix 1.[43]) In brief, ≥ 3 signs of SIRS, and cardiovascular, renal or respiratory organ failure; these criteria had to be met within 24 hours. Patients had to begin treatment within 36 hours of meeting inclusion criteria **Exclusion criteria:** (details given in Appendix 2[43]). Patients with active or increased risk of bleeding, known hypercoagulable condition, not expected to live >6 hours or survive for 28 days owing to co-morbid condition, known or suspected sustained irreversible cessation of brain function, or patients with ESRD on renal dialysis.	**Primary outcomes:** frequency of SAEs, SBEs and assessment of anti-aPC antibody response **Primary pharmacodynamic measures:** changes in D-dimer, fibrinogen, platelet and IL-6 levels **Secondary outcomes:** assessments for 28-day all-cause mortality, morbidity markers (utilisation of intensive care and hospital resources) and OD **Length of follow-up:** 28 days

continued

Reference and design	Interventions	Subjects	Outcome measures
NB. Symbols refer to specific studies: *Vincent *et al.*,[48] †Ely *et al.*[46] and ‡Dhainaut *et al.*,[45] where no symbol is shown the study is Bernard *et al.*[39]			
Bernard *et al.*[39] (efficacy) Vincent *et al.*[48] (organ dysfunction)* Ely *et al.*[46] (subgroup analyses)† Dhainaut *et al.*[45] (MOD)‡ **Recruitment date:** July 1998 to June 2000 **Location:** 164 centres in 11 countries **Setting:** clinical **Publication status:** published 2001, 2003*, 2003†, 2003‡ **Design:** RCT, double-blind, placebo-controlled, multicentre **Trial sponsor:** supported by Eli Lilly	**Drotrecogin alfa (activated) (Da):** Dose: 24 μg kg^{-1} hour i.v. at a constant rate Duration: 96 hours **Details of placebo:** 0.9% saline with or without 0.1% human serum albumin i.v. at a constant rate **Other aspects of care provided:** the study protocol did not call for a standardised approach to critical care (e.g. use of antibiotics, fluids, vasopressors or ventilatory support). Da and placebo patients also received standard supportive care	**Total number of patients:** 1728 patients randomised, of whom 1690 received Da or placebo **Numbers of patients in each group:** Da group = 850, placebo group = 840 Patient numbers not reported separately for centres ‡ MOD *n* = 1271, Da 634, placebo 637; SOD *n* = 419, Da 216, placebo 203 **Baseline characteristics:** Age (years): Da 60.5 ± 17.2, placebo 60.6 ± 16.5 Gender: Da 56.1% male, placebo 58.0% male APACHE II score: Da 24.6 ± 7.6, placebo 25.0 ± 7.8 Septic shock: Da 70.4%, placebo 71.7% ‡ Age: SOD all 57.6 ± 17.7, Da 58.4 ± 18.3, placebo 56.8 ± 17.0 MOD all 61.5 ± 16.4, Da 61.2 ± 16.8, placebo 61.8 ± 16.1, $p = 0.0001$ Gender (% Male): SOD all 245 (58.5%), Da 124 (57.4%), placebo 121 (59.6%) MOD all 719 (56.6%), Da 353, (55.7%), placebo 366 (57.5%), $p = 0.531$ Ethnicity (% white): SOD all 331 (79.0%), Da 173 (80.1%), placebo 158 (77.8%) MOD all 1053 (82.8%), Da 522 (82.3%), placebo 531 (83.4%), $p = 0.079$ * Sepsis-related OD involving ≥ 2 organ systems present in 75% of cohort, ≥ 3 organ systems in 43%, ≥ 4 organ systems in 18% Number with organ failure (SOFA = 3 or 4): Cardiovascular: Da 516/850 (60.7%), placebo 541/840 (64.4%) Respiratory: Da 465/838 (55.5%), placebo 498/825 (60.4%) Renal: Da 103/849 (12.1%), placebo 97/837 (11.6%) Haematological: Da 45/845 (5.3%), placebo 50/840 (6.0%) Hepatic: Da 21/777 (2.7%), placebo 21/763 (2.8%) *Infections:* Hospital acquired Bacteriologically documented (positive blood culture): Da 32.7%, placebo 32.5% Gram negative bacteria: Da 21.8%, placebo 23.3% Gram positive bacteria: Da 25.8%, placebo 25.1% Documented pseudomonad: Da 6.6%, placebo 5.1%	**Primary outcomes:** death from any cause **Secondary outcomes:** D-dimer levels, IL-6 levels, plasma protein C activity level, microbiological cultures, SAEs (serious bleeding or thrombotic event) [91]variate analysis of prospectively defined subgroups: demographics, recent surgery within 30 days of study entry, site of infection (lung, intra-abdominal, urinary tract or other), type of infecting organism as determined by investigator, protein C deficiency, baseline coagulation parameters of prothrombin time class, activated partial thromboplastin time class, platelet class, IL-6 levels, ventilator or vasopressor use, types and numbers of ODs, and APACHE II quartile † In addition, for two non-prospective subgroups: baseline overt DIC status and baseline total SOFA score quartile † Multivariable logistic regression analysis: used stepwise logistic regression using data from placebo group to generate a predicted risk of mortality model (inclusion criteria and model calculations given in appendix).

continued

Reference and design	Interventions	Subjects	Outcome measures
		Urinary tract: Da 10.0%, placebo 10.2% Pneumonia (*Streptococcus pneumoniae*): Da 12.5%, placebo 11.3% Abdominal: Da 20.0%, placebo 19.9% ‡ Prior or pre-existing conditions listed for many conditions, including: % COPD: SOD all 78 (18.6%), Da 40 (18.5%), placebo 38 (18.7%) MOD all 330 (26.0%), Da 149 (23.5%), placebo 181 (28.4%) $p = 0.002$ % Recent trauma: SOD all 20 (4.8%), Da 7 (3.2%), placebo 13 (6.4%) MOD all 51 (4.0%), Da 21 (3.3%), placebo 30 (4.7%) $p = 0.485$ % Recent surgery: SOD all 96 (22.9%), Da 49 (22.7%), placebo 47 (23.2%) MOD all 406 (31.9%), Da 196 (30.9%), placebo 210 (33.0%), $p = 0.0005$ APACHE II: SOD all 21.7 ± 7.2, Da 21.4±7.1, placebo 22.0 ± 7.2 MOD all 25.8 ± 7.6, Da 25.7 ± 7.5, placebo 25.9 ± 7.8, $p = 0.0001$ Mechanical ventilation: SOD all 241 (57.5%), Da 117 (54.2%), placebo 124 (61.1%) MOD all 1034 (81.4%), Da 506 (79.8%), placebo 528 (82.9%), $p < 0.0001$ Shock: SOD all 153 (36.5%), Da 83 (34.4%), placebo 70 (34.5%) MOD all 1047 (82.4%), Da 515 (81.2%), placebo 532 (83.5%), $p < 0.0001$ Use of any vasopressor: SOD all 133 (31.7%), Da 63 (29.2%), placebo 70 (34.5%) MOD all 924 (72.7%), Da 453 (71.5%), placebo 471 (73.9%), $p < 0.0001$ Overt DIC: SOD all 52 (12.4%), Da 23 (10.7%), placebo 29 (14.3%) MOD all 326 (25.6%), Da 171 (27.0%), placebo 155 (24.3%), $p < 0.0001$ Non-overt DIC: SOD all 367 (87.6%), Da 193 (89.4%), placebo 174 (85.7%) MOD all 945 (74.4%), Da 463 (73.0%), placebo 482 (75.7%) ‡ Markers of coagulation and inflammation: median level (IQR): Plasma D-dimer ($\mu g\ ml^{-1}$): SOD all $n = 375$, 3.48 (2.02–6.71), Da $n = 193$, 3.42 (1.88–6.62), placebo $n = 182$, 3.59 (2.11–6.77) MOD all $n = 1175$, 4.51 (2.36–9.07), Da $n = 599$, 4.51 (2.48–8.93), placebo $n = 576$, 4.51 (2.24–9.13), $p = 0.0001$ Serum IL-6 ($pg\ ml^{-1}$): SOD all $n = 401$, 245.3 (78.3–770), Da $n = 209$, 233.6 (89.6–591.2), placebo $n = 192$, 251.6 (71.4–1038.5) MOD all $n = 1234$, 657.2 (172.2–3907), Da $n = 618$, 734.1 (190.1–3960.0), placebo $n = 616$, 599.7 (162.5–3792.0), $p = 0.0001$	‡ SOFA scores collected at baseline and daily throughout the 28-day study; presence of DIC was assessed post hoc; APACHE II scores were recorded as the most extreme values in the 24 hours before drug administration. **Length of follow-up:** 28 days after start of infusion or until death

continued

Reference and design	Interventions	Subjects	Outcome measures
		Plasma protein C activity (%): SOD all $n = 377$, 56 (39–75), Da $n = 194$, 54 (38–74), placebo $n = 183$, 58 (40–76) MOD all $n = 1197$, 45 (29–63), Da $n = 605$, 44 (28–61), placebo $n = 592$, 46 (30–64), $p = 0.0001$ Protein C deficiency (<81%): SOD all: deficient 305 (72.8%), not deficient 72 (17.2%), unknown 42 (10.0%), Da: deficient 156 (72.2%), not deficient 38 (17.6%), unknown 42 (10.2%), placebo: deficient 149 (73.4%), not deficient 34 (16.8%), unknown 20 (9.9%) MOD all: deficient 1074 (84.5%), not deficient 123 (9.7%), unknown 74 (5.8%), Da: deficient 553 (87.2%), not deficient 52 (8.2%), unknown 29 (4.6%), placebo: deficient 521 (81.8%), not deficient 71 (11.2%), unknown 45(7.1%), $p < 0.0001$ **Inclusion criteria:** (criteria for severe sepsis were a modification of the Bone criteria, with details given in Appendix 1[43]). In brief, known or suspected infection present on basis of clinical data at time of screening, and met following criteria within 24 hours: (1) ≥ 3 signs of systemic inflammation; (2) sepsis-induced dysfunction of ≥ 1 organ or system lasting for no longer than 24 hours. Patients had to begin treatment within 24 hours after meeting inclusion criteria. **Exclusion criteria:** (details given in Appendix 2[43]). Age <18 years or weight >135 kg, conditions that increased the risk of bleeding, known hypercoagulable condition; or not expected to survive for 28 days owing to co-morbid condition	

continued

Reference and design	Interventions	Subjects	Outcome measures
Bernard *et al.*[49] **Recruitment date:** up to 12th April 2002 **Location:** USA + others (not specified) **Setting:** clinical **Publication status:** published 2003 **Design:** an analysis of safety of Da in seven completed and ongoing studies (two RCTs, three open-label trials, two compassionate use studies) and data from commercial use. Data obtained from databases **Trials:** F1K-MC-EVAA F1K-MC-EVAD[a] F1K-MC-EVAS F1K-MC-EVBE[b] F1K-MC-EVBF[ab] F1K-MC-EVBG[b] F1K-MC-EVBC [a]PROWESS [b]ENHANCE **Trial sponsor:** financial support from Eli Lilly & Co.	**Drotrecogin alfa (activated) (Da):** Dose: 24 $\mu g\ kg^{-1}$ per hour Duration: 96 ± 1 hour Above regimen used for five studies. One study gave above dosage for a minimum of 96 hours. One study gave 12, 18, 24, 30 $\mu g\ kg^{-1}$ per hour for 48 hours or 12, 18, 24 $\mu g\ kg^{-1}$ per hour for 96 hours. Commercial use studies were expected to give 24 $\mu g\ kg^{-1}$ per hour for 96 hours total duration (specific details not available) **Details of placebo:** saline or 0.1% albumin in saline for RCTs	**Total number of patients:** 7658 (6777 Da, 881 placebo) **Numbers of patients in each study type:** RCTs: 1821 (940 Da, 881 placebo) Open-label: 1578 Compassionate use: 268 Commercial use: 3991 **Baseline characteristics:** not reported **Inclusion criteria:** all studies except for one compassionate-use study (which required only the clinical diagnosis of purpura fulminans and did not exclude those with thrombocytopenia) used inclusion and exclusion criteria similar to the PROWESS study. Severe sepsis was defined as presence of known/suspected infection, systemic response to infection and ≥ 1 associated acute OD. Patients in commercial use studies were expected to have severe sepsis and be at high risk for death (as assessed by APACHE II) **Exclusion criteria:** high risk of bleeding, severe thrombocytopenia, those taking antiplatelet agents or receiving systemic heparin anticoagulation	**Primary outcomes:** (1) 28-day all-cause mortality (28 days after infusion start) was assessed for all but one ongoing study (compassionate use), where 7-day mortality was assessed for a subset of non-US patients and 28-day mortality was estimated (method given). Mortality rate for commercial use patients not available (2) Serious bleeding complications, including ICH, life-threatening bleeding event, requirement for ≥ 3 units of blood transfusion per day for 2 consecutive days, or meeting other criteria defining SAEs. Events were recorded for up to 28 days from start of Da infusion for all but one ongoing study (compassionate-use). All bleeding events were assessed as 'procedure-related' or 'non-procedure-related' **Secondary outcomes:** none **Length of follow-up:** 28 days for all studies except for one, where 7-day events were recorded and 28-day events were estimated
Results [number, rate (95% CI)] **Deaths at follow-up:** Controlled trials, Da: 236/940, 25.1% (22.4 to 28.0%) Open-label studies, Da: 398/1578, 25.2% (23.1 to 27.4%) Compassionate-use studies, Da: 70/268, 26.1% (21.0 to 31.8%) Combined mortality rate (all clinical trials), Da: 704/2786, 25.3% (23.7 to 26.9%) Commercial use studies: data not available Combined placebo rate: 273/881, 31.0% (28.0 to 34.2%) The leading causes of death in the two controlled clinical trials were sepsis-induced multiple organ failure, refractory septic shock and respiratory failure. There were numerically fewer deaths from the latter two causes in Da patients than in placebo patients, while for multiorgan failure, the reverse was true			

continued

Serious bleeding events
Controlled trials, Da: IP 20/940, 2% (1.3 to 3.3%); PIP 15/940, 1.6% (0.9 to 2.6%); total 35/940, 3.7%*
Open-label studies, Da: IP 49/1578, 3.1% (2.3 to 4.1%); PIP 45/1578, 2.9% (2.1 to 3.8%); total 94/1578, 6.0%*
Compassionate use studies, Da: IP 10/268, 3.7% (1.8 to 6.8%); PIP 9/268, 3.4% (1.6 to 6.3%); total 19/268, 7.1%*
Combined SBE rate (all clinical trials), Da: IP 79/2786, 2.8% (2.3 to 3.5%); PIP 69/2786, 2.5% (1.9 to 3.1%); total 148/2786, 5.3%
Commercial use studies, Da: 34/3991, 0.9% spontaneously reported to the pharmacovigilance database
Combined placebo rate: IP 6/881, 0.7% (0.3 to 1.5%); PIP 14/881, 1.6% (0.8 to 2.7%); total 20/881, 2.3%*
In all clinical trials, the occurrence of SBEs which were considered by the investigator to be related to Da was 58/79 during IP (i.e. 58/2786, 2.1%) and 8/69 for PIP (i.e. 8/2786, 0.3%)
In all patients receiving Da in all clinical trials, SBEs associated with invasive procedures accounted for 58/148 (39.2%) of the total number of events. In the PROWESS trial, 16/30 (53.3%) and 4/17 (23.5%) of SBEs in Da and placebo patients, respectively were associated with invasive procedures; whereas non-procedure-related (spontaneous) SBE were similar between Da and placebo patients
The incidence of SBE was highest during the first day of therapy for all Da patients

Serious bleeding events: ICH
Controlled trials: 2/940, 0.2% Da; 1/881, 0.1% placebo (all fatal outcome). Both events in the Da group occurred during the IP and were associated with severe thrombocytopenia
Open-label studies, Da: IP 11/1578, 0.7%; PIP 10/1578, 0.6%
Compassionate use studies, Da: IP 3/268, 1.1%; PIP 6/268, 2.2%
Combined ICH rate (all clinical trials): IP 16/2786, 0.6%; PIP 16/2786, 0.6%; overall 28-day ICH event rate 32/2786, 1.1%
Commercial use studies: 8/3991, 0.2%

Serious bleeding events (non-ICH) associated with fatal outcome
Controlled trials: 4/940, 0.4% Da; 1/881, 0.1% placebo
Combined (all clinical trials): 3/2786, 0.1%. All occurred during the IP, and all were considered related to Da; one involved thrombocytopenia with severe coagulopathy

NB. It is not clear why four events are reported for controlled trials and only three are reported for all clinical trials.

For open-label and compassionate use studies, the causal relationship of Da to SBE was assessed using investigator assignment of causality (related or not related) and by comparing events that occurred IP with those PIP. IP = actual duration of infusion plus 1 calendar day (study days 1–5); PIP = study days 6–28.

*Reviewer calculated the total by summing bleeding events for the infusion period and postinfusion.

Methodological comments
- Allocation to treatment groups: method and details of randomisation for controlled clinical trials not stated.
- Blinding: for controlled trials, the cause of death was adjudicated by blinded physicians for all patients using death summaries provided by the investigators. No details given regarding blinding during studies.
- Comparability of treatment groups: baseline characteristics not stated. Comparisons between clinical trial types were avoided owing to lack of final, validated baseline data for ongoing clinical trials.
- Method of data analysis: results reported as absolute number of events and event rate estimates (percentage and 95% CI).
- Sample size/power calculation: not reported.
- Attrition/dropout: not reported.

General comments
- Generalisability: an analysis of all available data on the safety of drotrecogin alfa treatment in adult patients with severe sepsis. All studies except for one used inclusion/exclusion criteria similar to PROWESS. Patient characteristics not reported, therefore unsure whether representative population.
- Outcome measures: appropriate. Mortality rates for completed clinical trials were obtained from validated clinical trial databases. Estimates of 28-day all-cause mortality rates for ongoing clinical studies were obtained from trial-specific databases created using trial-specific tracking tools. 28-day rate = 28 days after start of infusion.
- Intercentre variability: not reported.
- Conflict of interests: financial support from Eli Lilly and Company. One author is a consultant, and a second author an occasional consultant to Eli Lilly; four other authors are employees of Eli Lilly and company.

Da, drotrecogin alfa; IP, infusion period; PIP, post-infusion period.

Appendix 8

ACCP/SCCM definitions of severe sepsis

American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference

Definitions for Sepsis and Organ Failure and Guidelines for the use of innovative therapies in sepsis (1992)[2]

The consensus meeting was held with the goal of developing a broad definition of sepsis to improve detection and allow early therapeutic intervention. Another goal was to improve standardisation of research protocols.

Definitions (Table 1, p. 1646)

- Infection: microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
- Bacteremia: the presence of viable bacteria in the blood.
- Systemic inflammatory response syndrome (SIRS): the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: (1) temperature >38ºC or <36ºC; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg; and (4) white blood cell count >12,000 mm^{-3}, <4000 mm^{-3}, or >10% immature (band) forms.
- Sepsis: the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38ºC or <36ºC; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg; and (4) white blood cell count >12,000 mm^{-3}, <4000 mm^{-3} or >10% immature (band) forms.
- Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status.
- Septic shock: sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
- Sepsis-induced hypotension: = a systolic blood pressure <90 mmHg or a reduction of ≥ 40 mmHg from baseline in the absence of other causes for hypotension.
- Multiple organ dysfunction syndrome (MODS): presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

SIRS (systemic inflammatory response syndrome) is an inflammatory process independent of its cause: "the systemic inflammatory response to a variety of severe clinical insults" (p. 1646). These changes should be an acute change from baseline without other known causes, such as chemotherapy-induced neutropenia and leukopenia. SIRS can occur in the context of a variety of conditions, both related to infection and not.

Organ system dysfunction is a frequent complication of SIRS, including multiple organ dysfunction syndrome (MODS).

"When SIRS is the result of a confirmed infectious process, it is termed sepsis" (p. 1646). Therefore, sepsis refers to the systematic inflammatory response to the presence of infection. In association with infection the manifestations are the same as for SIRS. It should be determined whether these changes are a part of the direct systemic response to an infectious process and whether these changes are acute alterations from baseline without other known causes.

"Bacteraemia is the presence of viable bacteria in the blood. The presence of viruses, fungi, parasites, and other pathogens in the blood should be described in a similar manner (i.e., viremia, fungemia, parasitemia, etc.)" (p. 1646).

There appears to be a continuum of severity encompassing both infectious and inflammatory components. There seem to be definable phases

on the continuum that characterise populations at increased risk of morbidity and mortality. One such phase should be termed severe sepsis or sepsis with organ system dysfunction. The stages were proposed to have independent prognostic implications, but that hypothesis had not been prospectively tested at the time of writing the consensus statement.

Organ dysfunction is thought of in terms of a dynamic process in which there is a continuum of change over time. The term dysfunction is used to identify a process in which organ function is not capable of maintaining homeostasis. "The detection of altered organ function in the acutely ill patient constitutes a syndrome that should be termed multiple organ dysfunction syndrome"(MODS) (p. 1648). This way of thinking about organ dysfunction was proposed to facilitate an understanding of the dynamic nature of the process, to facilitate early recognition of organ abnormalities to initiate earlier treatment, to facilitate the use of organ function over time in prognosis.

MODS may be either primary or secondary. Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself. Secondary MODS is not a direct response to the insult itself, but develops as a consequence of a host response. "MODS may be understood to represent the more severe end of the spectrum of severity of illness that characterises SIRS/sepsis. Thus secondary MODS usually evolves after a latent period following the inciting injury or event, and is most commonly seen to complicate severe infection" (p. 1648). At the time that these definitions were proposed, specific criteria for quantifying individual organ dysfunctions had not been determined.

The use of the definitions proposed along with risk stratification or probability-risk estimation techniques measure the position of individual patients along the continuum of severity. The use of these techniques was proposed to aid in the precision of the evaluation of new therapies. How the initial risk or probability risk was to be determined was not discussed in this publication. It was recommended that when patients are identified as having SIRS or MODS, sequential (daily or more frequent) risk stratification or probability estimation techniques should be applied to describe the course of the syndromes. These recommendations were proposed to develop a comprehensive model of disease progression that did not exist at the time of the consensus meeting. Various ideal criteria for the variables in such a model were discussed. At the time of the publication, it had not been determined which physiological, clinical or metabolic variables caused and which were caused by the inflammatory response.

Innovative therapy in severe sepsis generally involves an attempt to alter the systemic inflammatory response, which differs from supportive therapy or therapy directed at the causative organism.

The publication includes a discussion of the requirements for conducting useful, high-quality trials in therapies for severe sepsis. The recommendations include: the use of the terminology outlined in this publication, selective choice of patients, designs with well-defined end-points, reporting cost of therapy and quality of life, and the analysis of adverse outcomes. To address potential predictors of clinical outcomes, the comparability of non-investigational treatments and patient characteristics should be demonstrated between groups. Potential predictors such as underlying disease and the referral source of the patients should be addressed. Severity-of-illness scoring systems should be used to stratify patients' risk, to the extent that the scoring system has been independently demonstrated to predict outcome in septic patients. The time between fulfilment of entry criteria and the administration of the intervention should be noted and analysed, as well as other possible indicators of lead-time bias.

There is a final discussion of the criteria to be considered for putting individual patients on an innovative therapy outside the context of a clinical trial.

Appendix 9

Additional PROWESS subgroup analyses: 28-day all-cause mortality according to demographic and other characteristics

		Results for all patients[46] (prospective analyses)				Results for patients with ≥ 2 organ dysfunctions[45] (retrospective analyses)			
		n per group	Mortality (%) rhAPC; placebo (*n* = 850; *n* = 840)	ARR[a] % (95% CI)	RR of death (95% CI)[a]	*n* per group	Mortality (%) rhAPC; placebo (*n* = 634; *n*= 637)	ARR (%, 95% CI)[a]	RR of death (95% CI)[a]
Age (years)	<65	886	15.6; 20.9	–5.3 (–10.5 to –0.3)*	0.74 (0.56 to 0.99)*	314[b]	14.9; 18.3	–3.4	0.81
	≥ 65	804	34.4; 42.2	–7.8 (–14.5 to –1.1)*	0.81 (0.68 to 0.97)*	324	20.0; 28.7	–8.7	0.71
						326	36.1; 39.2	–3.1	0.92
						307	35.4; 49.7	–14.3	0.71
Gender	Male	964	24.3; 31.0	–6.7 (–12.3 to –1.0)*	0.78 (0.64 to 0.96)*	719	25.5; 35.0	–9.5 (–16.1 to –2.8)*	0.73 (0.58 to 0.91)*
	Female	726	25.2; 30.6	–5.4 (–11.9 to 1.1)	0.82 (0.65 to, 1.04)	552	27.8; 32.5	–4.7 (–12.4 to 2.9)	0.85 (0.66 to 1.10)
Racial origin	Caucasian	1384	24.5; 31.1	–6.6 (–11.3 to –1.9)*	0.79 (0.66 to 0.94)*				
	Non-Caucasian	306	25.8; 29.8	–4.0 (–14.0 to 6.1)	0.87 (0.60 to 1.24)				
Region	USA/Canada		24.9; 32.3	–7.4	0.77				
	Europe	NR	25.8; 30.3	–4.5	0.85				
	Other		22.0; 26.8	–4.8	82.1				
Recent surgery	No/unknown	1188	23.5; 30.9	–7.3 (–12.4 to –2.3)*	0.76 (0.63 to 0.92)*	865	25.1; 34.0	–8.9 (–14.9 to –2.8)*	0.74 (0.60 to 0.91)*
	Yes	502	27.8; 30.7	–2.9 (–10.9 to 5.0)	0.90 (0.69 to 1.19)	406	29.6; 33.8	–4.2 (–13.2 to 4.9)	0.88 (0.66 to 1.16)
Congestive heart failure	No/unknown	NR	29.2; 23.7	+5.5	1.23				
	Yes		38.9; 47.4	–8.5	0.82				
Cancer	No/unknown	1387	25.0; 28.5	–3.5 (–8.1 to 1.2)	0.88 (0.74 to 1.04)	1030	26.3; 31.4	–5.1 (–10.7 to 0.4)	0.84 (0.69 to 1.01)
	Yes	303	28.3; 41.1	–12.8 (–23.3 to –2.1)*	0.69 (0.50 to 0.94)*	241	27.4; 43.8	–16.4 (–27.9 to –4.2)*	0.62 (0.44 to 0.89)*
COPD	No/unknown	1282	24.2; 27.1	–2.9 (–7.6 to 1.9)	0.89 (0.74 to 1.08)	941	25.8; 29.8	–4.0 (–9.8 to 1.7)	0.86 (0.70 to 1.06)
	Yes	408	26.5; 41.6	–15.1 (–24.0 to –5.9)*	0.64 (0.48 to 0.84)*	330	28.9; 44.2	–15.3 (–25.4 to –4.9)*	0.65 (0.48 to 0.88)
Cardio-myopathy	No	NR	NR			1175	25.7; 32.1	–6.4 (–11.6 to –1.2)*	0.80 (0.67 to 0.96)*
	Yes					96	40.0; 50.8	–10.8 (–30.3 to 10.0)	0.79 (0.48 to 1.23)
Immuno-compromised	No	1534	24.1; 30.5	–6.4 (–10.8 to –1.9)*	0.79 (0.67 to 0.93)*	NR	NR		
	Yes	156	29.9; 34.8	–4.9 (–19.7 to 9.7)	0.86 (0.55 to 1.36)				

* Statistically significant results.

[a] ARR confidence intervals and RRs and confidence intervals, or data to estimate them, were provided in the FDA report or estimated by SHTAC using data provided in the paper. Where CIs are not provided, insufficient data were available with which to estimate them.

[b] Age subgroups: 50, 51–65, 66–75, >75 years.

Appendix 10

Internal validity of economic evaluations

Item	Angus et *al.*, 2003[52]	Manns et *al.*, 2002[58]	Fowler et *al.*, 2003[59]	Eli Lilly Submission, 2003[11]
1. Well-defined question	✓	✓	✓	✓
2. Clear description alternatives	✓	✓	✓	✓
3. Reasonable study type	✓	✓	✓	✓
4. Effectiveness established	✓	✓	✓	✓
5. Estimates related to population risks	? Trial population assumed to reflect population	✓	? Trial population assumed to reflect population	? Trial population assumed to reflect population
6. Relevant costs and consequences identified	✓ ? Long-term healthcare costs included	✓ ? Long-term healthcare costs included	✓ ? Long-term healthcare costs included	✓ ? Long-term healthcare costs not included
7. Costs and consequences measured accurately	✓ Trial data used to measure costs and consequences	✓ Specific Canadian cohort study used for baseline risk and resource use	✓ ? PROWESS effectiveness data and patient groups. Hospital cost data were from an observational cohort study	✓ ? Apply UK life expectancy and cost data to PROWESS effectiveness profiles
8. Costs and consequences valued credibly	✓ ? Health-state utilities from US tariff values. Cost data based on US cost cohort. Long-term costs from US database information	✓ ? Utility data from a study on ARDS, not severe sepsis	? Utility values used were not for severe sepsis, but deemed to be similar by authors	✓ UK cost data used ? Utility data from an unpublished study, cited as an abstract
9. Differential timing considered	✓	✓	✓	✓
10. Incremental analysis performed	✓	✓	✓	✓
11. Sensitivity analysis performed	✓	✓	? Findings not reported in detail	✓ ? Main reported sensitivity analyses limited to one-way analysis
12. Modelling conducted reasonably	✓ ? Model based on PROWESS patient group	✓	? Description of modelling unclear	✓ ? Do not use UK baseline population

?, unclear or unknown; ✓, item included or judged as acceptable to be internally valid.

Appendix 11

External validity of economic evaluations

Item	Angus *et al.*, 2003[52]	Manns *et al.*, 2002[58]	Fowler *et al.*, 2003[59]	Eli Lilly Submission, 2003[11]
1. Patient group: are the patients in the study similar to those of interest in England and Wales?	×	×	×	?
2. Healthcare system/setting: comparability of available alternatives? Similar levels of resources? No untoward supply constraints? Institutional arrangements comparable?	×	×	×	?
3. Treatment: comparability with clinical management?	?	?	?	?
4. Resource costs: comparability between study and setting/population of interest?	Intervention cost only	Intervention cost only	Intervention cost only	✓ ?
5. Marginal versus average costs: what difference does this make?	N/A	N/A	N/A	N/A

?, unclear or unknown; ✓, item judged as suitable to generalise to England and Wales with or without some readjustment; ×, factor judged as not suitable, as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable.

Appendix 12

Summary methods and findings from published economic evaluations and abstracts reporting cost-effectiveness studies

Study	Methods	Cost-effectiveness	Subgroup analyses	Sensitivity analyses
Angus *et al.*, 2003[52] (for the PROWESS Investigators)	Base-case analysis (CE_{base}) presents cost per life saved; based on (1) incremental costs as the difference in healthcare costs (hospital, physician, study–drug and postdischarge costs up to day 28) between treatment and placebo during the first 28 days, and (2) incremental effects as difference in 28-day all-cause mortality Reference case analysis ($CE_{reference}$) presents cost per LYG and cost per QALY gained; based on (1) incremental costs as the difference in lifetime healthcare costs between treatment and placebo; day 1–28 costs (as CE_{base}) plus post-day-28 lifetime costs, and (2) incremental effect as the number of life-years and QALYs gained Costs and effects discounted at 3%	CE_{base}: $160,000 per life saved (with 84.7% and 97.9% probabilities that the ratio was <$250,00 and < $500,000 per life saved) $CE_{reference}$: $33,000 per life-year gained (with a 89.1% probability that the ratio was <$100,000 per LYG) $CE_{reference}$: $48,800 per QALY gained (with a 82% probability that the ratio was <$100,000 per QALY gained) $CE_{reference}$: incremental LYG = 0.48 ± 0.29, and incremental QALYs gained = 0.33 ± 0.21 per treated patient. Incremental costs $16,000 ± $4,200 per patient treated	CE_{base}: by severity, APACHE II quartiles: 3–19: conventional care dominates (no survival benefit from intervention) 20–24: $495,800 25–29: $76,100 30–53: $98,700 $CE_{reference}$: by severity, APACHE II quartiles: 3–19: dominated (QALY benefit) 20–24: dominated (QALY benefit) 25–29: $28,400 30–53: $31,100 (plus shock status, age <60 or >60 years, prior location, infection site, etc.)	Authors state that CE_{base} was generally robust to assumptions and estimates of costs and effects (but they do not present any results of sensitivity analyses on the estimate of effect) Authors state that variations in cost components cause "negligent-to-moderate" changes in cost-effectiveness findings Authors state that only a 75% variation in survival or quality of life lifts the cost-effectiveness of the intervention above $100,000 per QALY
Manns *et al.*, 2002[58]	Baseline analysis presents cost per LYG for a Canadian cohort of patients. Results presented in US dollars ($), based on 2001 Can$, converted to US$ (US$1 = Can$1.47) Baseline 28-day mortality rate for all patients in the conventional care cohort was 30.7% For those patients with APACHE II score of ≤ 24 = 18.5%, for a score of ≥ 25 54.5% Costs and outcomes discounted at an annual rate of 5%	All patients (with relative risk of death reported in PROWESS study): Cost per LYG $27,936 Cost per QALY $46,560 For 'all patients' the incremental gain in life-years per patient was 0.38 years Incremental costs around $10,615 (Estimates also presented by age groupings, but not far away from the above estimates)	By severity (with relative risk of death reported in FDA reanalysis): APACHE II score of ≥ 25 = $19,723 per LYG ($32,872 per QALY) APACHE II score of ≤ 24 = $575,054 per LYG ($958,423 per QALY)	Authors state that analysis was not sensitive to plausible variations in estimates of the cost of hospital stay, the subsequent cost of healthcare or the discount rate used for future costs and effects. It was also not sensitive to indirect costs Analysis was sensitive to the estimate of relative risk of death; as the relative risk approached the upper 95% confidence limit (0.94), the cost per LYG increased to $74,612 Where APACHE II subgroups were reanalysed using the relative risk data from the PROWESS study (i.e. assuming no difference in risk/effectiveness by severity), the cost per LYG for those patients with an APACHE II score of ≤ 24 was $35,652 ($24,484 for those with a score of ≥ 25)

continued

Study	Methods	Cost-effectiveness	Subgroup analyses	Sensitivity analyses
Fowler *et al.*, 2003[59]	Cost-effectiveness of rhAPC [drotrecogin alfa (activated)] in severe sepsis patients (USA analysis), compared with usual care Cost-effectiveness model (Markov). Patient group defined according to PROWESS data Effectiveness data from PROWESS. Cost data from Medicare/Medicaid rates and from the published literature Used lifetime horizon for analysis, discounted all future costs and benefits at 3% p.a. Costs in US$ (2001)	For 'all patient' analysis: Cost per LYG $15,801 Cost per QALY $20,047 Patients with APACHE II score ≥ 25: Cost per LYG $10,833 Cost per QALY $13,493 Patients with APACHE II score <25: Cost per LYG $342,550 Cost per QALY $403,000		Abstract states that over a broad range of parameter changes the cost per QALY remained under $30,000. A probabilistic sensitivity analysis is reported showing a <1% chance of simulations having a cost per QALY >$50,000
Davies *et al.*, 2002[60] [abstract]	Cost-effectiveness analysis based on clinical-effectiveness shown in PROWESS, using ARR for mortality difference Analysis presented for two patient groups: (1) for the overall PROWESS patient population and (2) for the 75% of patients in PROWESS who had ≥ 2 ODs. Life-years discounted at 1.5%, QALY value of 0.69 used	Method (1): PROWESS overall: Cost per life-year saved £9519 Cost per QALY £13,796 Method (2): PROWESS ≥ 2 ODs: Cost per life-year saved £7037 Cost per QALY £10,199	For patients with ≥ 2 ODs, cost per life-year saved is £4716 and cost per QALY is £6385	Cost per QALY stated to be robust to substantial reductions ARR. At ARR of 4.8% the cost per QALY is reported at £10,253 Alternative estimates of utility are reported to have had very little effect other than at much reduced levels of effectiveness
Launois *et al.*, 2002[65] [abstract]	Cost-effectiveness analysis, using a baseline population from the CubRea database (Paris, France), which shows similar characteristics to the PROWESS control group, and effectiveness data from PROWESS No data provided on methods to estimate life expectancy. No data presented on source for cost data	Cost per additional life-year saved reported at €18,446	Other results reported for subgroups ranged from €10,005 to €31,833	Monte Carlo bootstrap methods showed that 96.3% of results were cost-effective against a threshold WTP of €53,357

continued

Study	Methods	Cost-effectiveness	Subgroup analyses	Sensitivity analyses
Neilson *et al.*, 2002[61] [abstract]	Cost-effectiveness study, comparing drotrecogin alfa (activated) with conventional therapy for patients with severe sepsis in Germany Combines data from PROWESS on resource use and outcomes with Germany-specific unit costs	Incremental cost per LYG reported at €14,400 Additional analyses reported against modifications to the costing structure, for European and German data, with cost per life-year gained at €14,800 and €13,000	No further results reported	Sensitivity reported to have been undertaken on several parameters, producing cost-effectiveness estimates within the published ranges for other life-saving interventions in Germany
Neilson *et al.*, 2002[62] [abstract]	Cost-effectiveness of drotrecogin alfa (activated) in Germany, Austria and Switzerland Decision-analytic model, with results from perspective of health service payer PROWESS data on ARR used	Results presented for Germany and Austria, as €14,400 and €15,400 per LYG respectively (where LYG were discounted at 3%, results were €22,400 and €24,700)	For high-risk patients, with ≥ 2 ODs, results were €10,400 for Germany and €11,300 for Austria (discounting benefits at 3% results were €13,500 and €15,100, respectively)	No sensitivity analyses presented, but abstract states that applying other local life tables, unit costs and patterns of care did not alter the conclusion that drotrecogin alfa (activated) is a cost-effective treatment for severe sepsis
Lucioni *et al.*, 2002[63] [abstract]	Cost-effectiveness analyses for drotrecogin alfa (activated) for severe sepsis in Italy Decision modelling approach used, based on PROWESS outcome data and resource use, applying Italy-specific unit costs	Incremental cost per LYG reported at €13,436 for the severe sepsis patient group. For severe sepsis patients with multiple organ failure the cost per LYG is reported at €9660	For severe sepsis patients with multiple organ failure the cost per LYG is reported at €9660	None reported
Sacristan *et al.*, 2002[64] [abstract]	Cost-effectiveness of drotrecogin alfa (activated) in severe sepsis patients with multiple organ failure, in Spain Decision-analytic model approach, with an NHS perspective Effectiveness data and resource use data from the PROWESS trial, with Spanish unit costs Base-case analysis did not apply any discounting	Base case: cost per LYG reported at €9799 for patients with multiple organ failure (€13,594 for patients with severe sepsis)	Base-case analysis was on those with multiple organ failure	Sensitivity analyses not reported in detail. Abstract states that sensitivity analysis indicated that the largest influence on costs were the assumptions of the discount and reduction in life expectancy of patients

continued

Study	Methods	Cost-effectiveness	Subgroup analyses	Sensitivity analyses
Coyle *et al.*, 2002[66] [abstract]	Cost-effectiveness analysis of drotrecogin alfa (activated) in the treatment of severe sepsis in Canada Patients with severe sepsis at an increased risk of death (defined as an APACHE II score ≥ 25). Decision-analytic model, using Monte Carlo simulation Effectiveness data and resource use data were from the PROWESS trial	Incremental cost per QALY reported at $15,500 Using a threshold WTP of $50,000 per QALY, the net benefit of drotrecogin alfa is estimated to be $8800 (95% CI –$9000 to $38,000) ($ values assumed to be Canadian dollars, not stated in abstract)	No subgroup analysis. Main analysis refers to those patients with APACHE II score of ≥ 25	No details of sensitivity analyses reported. Abstract states that variables contributing most to the uncertainty were length of initial hospitalisation, mortality during hospitalisation and the utility of survivors
Riou-Franca *et al.*, 2003[67] [abstract]	Cost-effectiveness analysis comparing drotrecogin alfa (activated) plus standard care versus standard care alone in French severe sepsis patients with multiple organ failure Decision-analytic model/decision tree Data from a French population of severe sepsis patients (CubRea database, Paris). Life expectancy estimated using database, including data on co-morbidities Life expectancy of survivors adjusted by half Utility weight of 0.60 used	Cost per LYG US $11,812 Cost per QALY US$19,685 (presume this is non-discounted future costs and benefits)	No subgroup analyses reported other than sensitivity analyses	Probabilistic sensitivity analysis reported. Cost-effectiveness stated to be sensitive to the parameter for the relative risk of death. Also sensitive to discounting of costs and benefits

continued

Study	Methods	Cost-effectiveness	Subgroup analyses	Sensitivity analyses
Eli Lilly submission, 2003[11]	Cost-effectiveness modelled based on PROWESS patient groups with ARR Effectiveness data from PROWESS used (28-day survival), and secondary analyses reported using longer term follow-up data on PROWESS patients (all-cause mortality data at final patient discharge, on day 297). Patient group defined according to PROWESS criteria, with multiple organ failure No long-term costs Future benefits discounted at 1.5% Health-state utility weight of 0.69 used Life expectancy modelled using data on increased risk of death in years 1–5 after episode of severe sepsis	PROWESS patients with multiple organ dysfunction: Based on 28-day survival data: Cost per LYG £4,580 Cost per QALY £6,637 Estimated LYG per patient treated = 1.115 years (based on 28-day survivors). Additional cost per patient treated estimated at £5106. Using data from longer term follow-up: Cost per LYG £7547 Cost per QALY £10,937	No subgroup analyses reported outside the sensitivity analyses	Sensitivity analyses reported based on varying assumptions on costs, discount rate and utility values Results are presented for one-way sensitivity analyses. Sensitivity analysis reports that a 20% increase in the cost of drotrecogin alfa produces a 18% increase in the cost per QALY. Of the sensitivity analyses presented, the utility parameter shows the greatest effect; with utility values of 0.45 the cost per QALY of the two cost-effectiveness analyses increases by 53% to £10,178 and £16,770, respectively

Appendix 13

Data extraction (CRD format) of published economic evaluations

Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis

Angus DC, Lind-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, Laterre PF, Vincent JL, Bernard G, van Hout B, for the PROWESS Investigators

This record was compiled by SHTAC following the format used by the NHS CRD Economic Evaluation Database.

Health technology

Drotrecogin alfa (activated), a recombinant form of human activated protein C (Xigris®, Eli Lilly).

Disease

Severe sepsis.

Type of intervention

Treatment.

Hypothesis/study question

Primary objective stated to be the assessment of the incremental cost-effectiveness of drotrecogin alfa (activated) over the 28-day study period (PROWESS study). Also estimated longer term cost-effectiveness of drotrecogin alfa (activated) compared with placebo for patients with severe sepsis, referring to this as a reference-case analysis. The comparator in the clinical trial used for the clinical effectiveness data was placebo.

Economic study type

Cost-effectiveness/cost–utility analysis (concurrent with the PROWESS clinical trial). The study states that it is from the US societal perspective, limited to healthcare costs.

Study population

Adults presenting with severe sepsis. Severe sepsis defined as suspected or proven infection, evidence of systematic inflammation (three or more systemic inflammatory response syndrome criteria) and sepsis-induced dysfunction of one or more organ systems.

Baseline characteristics: mean age 60.6 years (SD:16.5), 58% male, mean weight 75 kg, 72.6% medical admissions, 27.4% surgical admissions, mean APACHE II score of 25, mean organ system failure 2.4, 71.7% in shock at enrolment.

Excluded: patients at high risk of bleeding, pregnant/breast-feeding patients, weighed >135 kg, if patients were expected to die of a non-sepsis-related disease within 1 month, if severe HIV (see Chapter 3 of the SHTAC report for more detail).

Setting

Hospital setting. The clinical trial data are from a multinational RCT. The economic analyses presented were carried out in USA.

Dates to which data relate

The economic evaluation is performed alongside the clinical trial, which reported results in 2001 (study enrolment July 1998 to June 2000). Costs are reported in US dollars for the year 2000.

Source of effectiveness data

The effectiveness data are from the related clinical trial, the PROWESS study. The trial methods and results are reported by Bernard and colleagues (2001) and detail of this study can be found in the main body of the review (see Chapter 3, of the SHTAC report for detail).

Modelling

A model was used to estimate lifetime benefits and costs, related to the outcomes of the clinical trial. Model type not specified.

Link between effectiveness and cost data

Effectiveness parameters on mortality are from the associated clinical trial, and these data are used to model long-term mortality/survival effects. Differences in cost over the first 28 days are from the clinical trial data. The study uses a cost cohort which is a subset of the trial patients, comprising 552 of the 705 US patients. Other sources of cost data are used for the cost-effectiveness analysis.

Single study

Study sample

The clinical trial enrolled patients with known or suspected infection on the basis of clinical data at the time of screening. Of the 1728 patients who underwent randomisation (1:1), 1690 received the study drug or placebo (840 placebo, 850 in the treatment group). See Chapter 3 of the SHTAC report for detail on the study inclusion/exclusion criteria.

Study design

RCT, placebo-controlled, multicentre, Phase III study, including 164 centres, across 11 countries. Clinical data collection in the trial was limited to 28 days after randomisation.

Analysis of effectiveness

Analysis was based on intention to treat. The primary clinical end-point was 28-day all-cause mortality. At baseline, the demographic characteristics and severity of disease were similar in the placebo and treatment groups.

Effectiveness results

Treatment with drotrecogin alfa (activated) was associated with a reduction in the relative risk of death of 19.4% (6.6 to 30.5%) and an absolute reduction in the risk of death of 6.1% ($p = 0.005$). The incidence of serious bleeding was higher in the treatment group than in the placebo group (3.5% versus 2.0%, $p = 0.06$).

The PROWESS study did not report differences in effectiveness across subgroups.

Clinical conclusions

Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding.

Economic analysis

Measure of benefits used in the economic analysis

The base-case analysis reports incremental effect as the difference in the primary clinical end-point of 28-day all-cause mortality, and estimates cost per life saved.

The reference-case analysis estimates incremental effect as the number of life-years and quality-adjusted life-years (QALYs) gained. A model is used to calculate the number of life-years gained, generating an age- and gender-specific life expectancy for each 28-day survivor, from US life tables, with an adjustment of life expectancy to allow for increased risk of death for survivors of severe sepsis.

QALYS are estimated using general population values from the Beaver Dam Health Outcomes Study, a longitudinal cohort study. Adjustment is made to these values to allow for reduced quality of life in survivors of severe sepsis compared with general population norms.

Direct costs

Differences in healthcare costs between treatment and placebo groups were estimated using a cost cohort of trial patients, comprising 552 of the 705 US patients (those patients for whom billing data were available before unblinding of the dataset). Base-case analyses used institution-specific charges, and cost estimates were adjusted to year 2000 US dollars, using the Consumer Price Index, with adjustment for physician costs. Study drug costs were estimated using trial dose data and the price per vial (assuming $210 per 5-mg vial and $840 per 20-mg vial). Post discharge costs up to 28 days were estimated by assigning a daily rate ($1.170 for acute care, $270 for nursing home care, $200 for supportive care at home) and summing depending on location. Daily rate data were from published sources. Hospital stay and cost data are reported separately.

Reference case analysis used day 1–28 costs (base-case costs) plus post-day-28 lifetime costs for survivors. Post-day 28 costs were estimated using age-specific annual healthcare costs from the 1987 National Medical Expenditure Survey projected to year 2000 costs by the National Centre for Health Statistics (with some additional adjustment to allow for nursing-home costs, using a published source). An age-specific cost was estimated based on predicted remaining years of life, making an allowance for the fact that sepsis survivors incurred higher costs compared with age-matched general population data.

Future costs were discounted at 3%.

In the cost-effectiveness analysis the study adjusts cost estimates to correct for imbalances between the make-up of the cost cohort and the overall trial cohort by deriving an average cost adjusted to the proportions of survivors and non-survivors, and proportions of surgical and non-surgical patients.

Indirect costs

The study does not refer to indirect costs. Where daily $ rates were used for post-day-28 care,

nursing-home care was costed, as was formal or informal supportive care at home; these are referred to above under 'Direct costs'.

Currency
US dollars, year 2000.

Statistical analysis of quantities/costs
To estimate distributions around the mean cost-effectiveness findings the study generated simulations using bootstrapping with replacement. Simulations were conducted using Datadesk software and SAS.

Sensitivity analysis
Various sensitivity analyses were undertaken. One-way sensitivity analysis was undertaken on base-case estimates of hospital costs, postdischarge to day-28 costs, intervention drug costs, lifetime survival and utilities (all ± 25%). Physician costs were varied from half to double the original estimate. The reference cost-effectiveness analysis was undertaken without long-term costs, and all parameters were varied and presented in a tornado diagram. For the reference case two-way sensitivity was undertaken on life expectancy estimates and average annual utility estimates. Analysis was undertaken on US patients only, and sensitivity analysis was undertaken on the discount rates, and adjustment to the risk of death in survivors of severe sepsis.

Subgroup analysis was also undertaken, for a wide range of groupings, with cost-effectiveness results presented using confidence ellipses.

Results
Estimated benefits used in the economic analysis
The PROWESS clinical trial reported mortality rates of 30.8% for placebo and 24.7% for drotrecogin alfa (activated) ($p = 0.005$); this survival benefit was used for base-case cost-effectiveness analysis. Survival effect is reported at 0.061 ± 0.022 lives saved per treated patient.

For reference-case analysis the average 28-day survivor was 58.1 years old and projected to live an additional 12.3 years at an average utility of 0.68, yielding 8.5 QALYs. The incremental life-years gained were 0.48 ± 0.29, and incremental QALYs were 0.33 ± 0.21 per treated patient.

Future benefits were discounted at 3%.

Cost results
In the short-term base-case analysis drotrecogin alfa (activated) increased costs by $9800 ± 2900. In the lifetime reference case analysis drotrecogin alfa (activated) increased costs by $16,000 ± 4200 per treated patient; $6200 of this cost was attributed to long-term post-day-28 costs.

Total intervention costs and comparator costs are reported for all patients (mean per patient costs, without a measure of distribution), but these do not reflect the costs used in the cost-effectiveness ratios; costs used in the ratios were adjusted cost estimates to correct for imbalances between the cost cohort and the overall trial cohort.
Future costs were discounted at 3%.

Synthesis of costs and benefits
A synthesis of cost and benefits was carried out by calculating a cost-effectiveness ratio for cost per life saved (base-case analysis) and cost per life-year gained, plus cost per QALY gained, in the reference-case analysis.

Base-case analysis reports a cost of $160,000 per life saved, with 84.7% and 97.9% probabilities that the ratio was <$250,000 and < $500,000 per life-saved.

Under lifetime reference-cost analysis the cost per life year-gained is $33,300, with 89.1% probability that the ratio was < $100,000. The cost per QALY is $48,800, with 82% probability that the ratio was < $100,000.

The study reports that base-case and reference-case cost-effectiveness results were generally robust to assumptions and estimates of costs and effects.

The reference-case cost-effectiveness was most sensitive to changes in effects. The authors report that the cost per QALY remained below $100,000 if average survival decreased to 4.6 years (reference case = 12.3 years). Where average utility was assumed to be 0.51 (reference case = 0.68) the cost per QALY remained below $100,000 until the average survival decreased to 6.6 years.

Where the average annual utility reduced to 0.33, all else held constant, the cost per QALY reached $100,000.

Results for the US-only analysis were better than for the overall trial cohort.

Where long-term costs were not included in the analysis the cost per QALY was $29,800.

The reference-case cost effectiveness reduced to $41,600 per QALY where cost and effects had a 0% discount rate.

In the subgroup analyses, cost-effectiveness ellipses tended to overlap, indicating no difference. However, older patients had worse cost-effectiveness findings, owing to fewer projected life-years, and drotrecogin alfa (activated) was indicated to be more cost-effective in patients with higher APACHE II scores, at $27,400 per QALY for the upper two APACHE II quartiles (score > 25). Treatment with drotrecogin alfa (activated) appeared cost-ineffective in the lower two APACHE II quartiles (< 25), negative QALY findings.

Conclusions and critical comment

Authors' conclusions

The study concludes that the use of drotrecogin alfa (activated) in patients with severe sepsis is associated with a favourable cost-effectiveness profile, especially if restricted to the FDA-approved use (i.e. in more severe patient groups, such as those with an APACHE II score of 25 or more).

SHTAC commentary

Selection of comparators

The comparator was placebo, as detailed in the clinical trial (PROWESS), and the rationale for this is clear.

Validity of estimate of measure of benefit

The measure of effect is lives saved in the base-case analysis and life-years/QALYs gained in the reference case. The base case directly applies the mortality results from the clinical trial; therefore, the validity of the estimate is robust. The reference-case estimate of life-years gained is influenced by the life expectancy of survivors of severe sepsis and the additional number of survivors in the drotrecogin alfa (activated) group. The input parameters for the mortality estimates were from the associated PROWESS study, a well-designed RCT, but the methods used to model life expectancy from the trial's clinical end-points are more uncertain, as the estimate of longer term survival for survivors of severe sepsis, and the estimates used for the quality adjustment of life-years gained, are based on findings from other experimental studies. Data on health-state values applicable to survivors of severe sepsis are not available and the study uses values from an earlier experimental exercise which modelled values for the USA general population, and some methodological questions remain over this exercise. The analysis then makes certain assumptions over which values to use in the derivation of QALYs gained, making allowances for the expected reduced quality of life and survival in survivors of severe sepsis, compared with matched population norms. Such assumptions may be valid, but there are methodological issues that remain uncertain in this approach.

Validity of estimate of costs

Base-case costs were limited to a 28-day cost estimate, using trial data for the intervention and a cost cohort for hospital cost estimates. The cost cohort comprised US patients with billing data. The methods used in the cost-effectiveness analysis indicate that the cost cohort had a different clinical profile to the broader trial population, and this may lead to some uncertainty over the validity of the cost estimates.

Reference-cost analysis used the base-case 28-day cost estimate; therefore, the above applies equally to reference-case analysis. Furthermore, for reference-cost analysis assumptions were made concerning the make-up over longer term costs for survivors of severe sepsis, and these assumptions lead to uncertainty over the cost estimates used, especially as post-day-28 costs constitute around 70% or more of the total cost for treatment and placebo groups.

The study does not report the actual disaggregated total costs for each group that are used in the cost-effectiveness findings. Adjustment is made in the cost-effectiveness analysis to correct for imbalances between the cost cohort and the trial population.

The reference-case cost-effectiveness analysis uses long-term healthcare costs for survivors of severe sepsis, and this issue may be open to some methodological debate, although the authors do report cost-effectiveness findings excluding long-term costs.

Other issues

Costs associated with additional risk of serious bleeding, assumed to be captured in the trial data used for cost estimates up to day 28.

Implications of the study

The findings from this study suggest that drotrecogin alfa (activated) is cost-effective. However, it may be reasonable to restrict the use of drotrecogin alfa (activated) to patients with APACHE II scores of 25 or more.

The study indicates that treatment may best be targeted to patients with greater severity of illness (APACHE II score of 25 or more) and a reasonable

life expectancy if they survive the episode of severe sepsis; this may have equity implications related to age and severity of illness.

An economic evaluation of activated protein C treatment for severe sepsis

Manns BJ, Lee H, Doig CJ, Johnsen D, Donaldson C. ***N Engl J Med*** **2002;347:993–1000**
This record was compiled by SHTAC following the format used by the NHS CRD Economic Evaluation Database.

Health technology
Recombinant human activated protein C (Xigris®, Eli Lilly), for patients admitted to the ICU for severe sepsis.

Disease
Severe sepsis.

Type of intervention
Treatment.

Hypothesis/study question
Estimated cost-effectiveness of activated protein C compared with conventional care for patients with severe sepsis. The comparator used is conventional care for patients admitted to ICU with severe sepsis. The comparator in the trial used for the clinical effectiveness data was placebo.

Economic study type
Cost-effectiveness/cost–utility analysis. The baseline perspective used was that of the purchase of healthcare services.

Study population
Adult patients admitted to ICU with severe sepsis. Baseline characteristics: mean APACHE II score 20.9, 55.8% male, 30.7% 28-day mortality, 36% mortality before hospital discharge.

Setting
Hospital, ICU. The clinical trial data are from a multinational RCT. The economic analyses presented were carried out in Canada.

Dates to which data relate
The PROWESS clinical trial reported results in 2001 (study enrolment July 1998 to June 2000). A cohort study was undertaken as part of the analysis to estimate mortality and direct healthcare costs for survivors who had been hospitalised with severe sepsis. The authors use a database from the Calgary Health Region, Canada, of patients admitted to ICUs with suspected or known infection between 1 April 1996 and 31 March 1999.

Quality of life is not used in baseline analysis. Estimates of quality of life used in sensitivity analyses are from published estimates in a different/related patient group (acute respiratory distress syndrome).

Cost data were calculated on the basis of 2001 Canadian dollars and were converted to US currency at a rate of 1 US dollar to 1.47 Canadian dollars.

Source of effectiveness data
The effectiveness data were taken from a single trial, the PROWESS study, and the authors used data reported from the trial and also data reported via a post hoc analysis of the trial data undertaken by the FDA. The trial methods and results are reported by Bernard *et al.* (2001) and detail of this study, together with detail on the FDA analysis, can be found in the main body of the review (see Chapter 3 of the SHTAC report for detail).

Modelling
This study involved the construction of a cost-effectiveness model to estimate the costs and benefits associated with treatment, compared with conventional care.

Link between effectiveness and cost data
Effectiveness data are from a single trial (as above), but cost data are provided from other secondary sources, that is, via the specific cohort study undertaken (long-term costs, from retrospective study) and from published sources (bleed costs and intervention cost).

Single study
Study sample
The clinical trial enrolled patients with known or suspected infection on the basis of clinical data at the time of screening. The criteria for severe sepsis were stated as a modification of those defined by Bone and colleagues (see detailed review in Chapter 3 of the SHTAC report). Of the 1728 patients who underwent randomisation (1:1), 1690 received the study drug or placebo (840 placebo, 850 in the treatment group).

Study design
The study was a randomised double-blind, placebo-controlled, multicentre trial. The study was multinational, including 164 centres, across 11 countries.

Analysis of effectiveness
Analysis was based on intention to treat. The primary health outcome was 28-day mortality. At baseline, the demographic characteristics and severity of disease were similar in the placebo and treatment groups.

Effectiveness results
Treatment with drotrecogin alfa (activated) was associated with a reduction in the relative risk of death of 19.4% (6.6 to 30.5%) and an absolute reduction in the risk of death of 6.1% ($p = 0.005$). The incidence of serious bleeding was higher in the treatment group than in the placebo group (3.5% versus 2.0%, $p = 0.06$).

The PROWESS study did not originally report differences in effectiveness across subgroups.

Clinical conclusions
Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding.

FDA post hoc analysis
Post hoc analysis of the PROWESS study by the FDA reported differential benefits according to APACHE II score: those with a score ≥ 25 had a relative risk of death of 0.71 (95% CI 0.59 to 0.85), and those with a score of ≤ 24 had a relative risk of 0.99 (95% CI 0.75 to 1.30).

Economic analysis

Measure of benefits used in the economic analysis
The measure of benefit is life-years gained. The difference in mortality at 28 days from the trial results is used to model the difference in life-years gained. Baseline analysis reports life-year gained as the measure of benefit, thereafter sensitivity analysis uses QALYs.

A Markov model, using an analytical horizon of a lifetime, is used to calculate the cost per life-year gained with recombinant human activated protein C, compared with conventional care. The model estimates life-years gained. The model considers weekly transitions between four clinical states; alive in ICU, alive on the hospital ward, alive at home and dead. The analysis considers a cohort of patients with severe sepsis. Transition probabilities for conventional care were based on observed hazard rates in a cohort study undertaken as part of the evaluation. For survivors death rates were applied using Canadian data; years 1–3 from hospital discharge data, thereafter adjusted age-related mortality data were used.

Life-years gained were discounted at an annual rate of 5%.

Direct costs
Costs for conventional care were estimated by the authors using the cohort study and available costing data for the Calgary Health Region, Canada. The costs of care per week for ICU and on the hospital ward were calculated. Follow-up costs for years 1–3 were also calculated. After year 3 it was assumed that these costs remained constant. Resource use and costs were not reported separately.

Costs for treatment with activated protein C comprised acquisition cost per therapeutic course ($6800) and a small cost attributed to the increased risk of serious bleeding. The cost for the management of bleeding was calculated using a published cost for the management of clinically important gastrointestinal bleeding in the ICU ($8306 per episode) multiplied by the excess risk of 1.5%, with bleed cost stated at $122 per patient treated. Otherwise, costs for the two groups were assumed to be equal.

Costs were discounted at an annual rate of 5%.

Indirect costs
Indirect costs were calculated for use in sensitivity analyses. The authors used a published employment rate of 16.9% for patients under 61 years who were discharged from the ICU and were subsequently employed, and multiplied it by the average gross annual salary for a full-time Canadian worker (Can$33,384).

Currency
US dollars, converted from Canadian dollars; 1 US dollar to 1.47 Canadian dollars.

Statistical analysis of quantities/costs
Costs were treated in a stochastic way as part of the sensitivity analyses.

Sensitivity analysis
Sensitivity analyses were reported presenting supplementary cost–utility estimates of cost per QALY. The authors use 0.6 as the utility value for the cost–utility analysis. This estimate is a published estimate of the overall health-related quality of life 1 year after hospital discharge in a group of patients admitted to the ICU with acute respiratory distress syndrome. This estimate was varied in further sensitivity analyses.

Various other sensitivity analyses were performed, addressing relative risk estimates, in-hospital and

subsequent death rates. Sensitivity analyses were undertaken on the estimate of cost of hospital care and subsequent healthcare, as well as on the cost for activated protein C treatment. Discount rates were varied in sensitivity analyses. As well as these univariate sensitivity analyses, a Monte Carlo simulation was performed to consider simultaneously the sensitivity of all variables for which estimates were uncertain.

Results

Estimated benefits used in the economic analysis

The incremental gain in life-years per patient for all patients is reported at 0.38. Incremental gains in life-years per patient by APACHE II score are reported at 0.01 for scores ≤ 24, and 0.76 for scores ≥ 25. Incremental gains in life-years per patient by age are reported at 0.30 for <40 years, 0.40 for 40–59 years, 0.40 for 60–79 years and 0.32 for ≥ 80 years. When calculating QALYS the study uses a QALY value of 0.6 in the baseline analysis. This QALY estimate is based on a study reporting quality of life (1 year after discharge) in a group of patients admitted to the ICU with acute respiratory distress syndrome (ARDS). Discounted benefits (5%) are reported.

Cost results

Total intervention and total comparator costs are not reported separately. Baseline resource use and hospital (ICU/ward) costs are reported for all patients. In the calculation of the baseline cost per life-year gained only direct costs were considered. The study states that the acquisition cost of activated protein C ($6800 per therapeutic course) and an additional cost to manage bleeding in patients treated with activated protein C ($122 per patient treated) were the only additional costs for those treated with activated protein C, assuming all others to be equal for patients treated and those receiving conventional care. Costs are discounted at 5%.

Analysis is lifetime, and additional costs associated with caring for survivors over their remaining life expectancy are included in the analysis. Mean healthcare costs after hospital discharge for all patients are reported at $14,181 per patient in year 1, $4698 in year 2 and $4579 in year 3 (year 3 costs were used for subsequent years). These costs are all presented by age group and APACHE II score groupings ≤ 24 and ≥ 25.

Synthesis of costs and benefits

A synthesis of cost and benefits was carried out by calculating a cost-effectiveness ratio for cost per life-year gained in the baseline analysis and a cost per QALY in the sensitivity analyses.

The incremental cost per life-year gained (LYG) for all patients is US$27,936, discounting of costs and benefits at 5%, using data reported in the PROWESS study. The cost per QALY is $46,560. Cost per LYG varied between $25,991 and $32,393 among age groups.

Where the study used data from the FDA analysis of the PROWESS study it reports cost per LYG at $19,723 for those patients with an APACHE II score of ≥ 25, and a cost per LYG of $575,054 for those with a score of £ 24. Cost per QALY results were $32,872 and $958,423, respectively.

Various sensitivity analyses were performed, including Monte Carlo simulations. Results were sensitive to estimates of the relative risk of death associated with activated protein C. The results shown above indicate the differences in subgroups by APACHE II score.

Monte Carlo simulation indicated that there was an 86% probability that the use of activated protein C for all patients with severe sepsis would be cost-effective if one were willing to pay $50,000 per QALY.

Conclusions and critical comment

Authors' conclusions

Activated protein C is relatively cost-effective when targeted to patients with severe sepsis, greater severity of illness (APACHE II score of 25 or more) and a reasonable life expectancy if they survive the episode of severe sepsis.

SHTAC Commentary

Selection of comparators

The comparator was conventional care, and the rationale for this is clear.

Validity of estimate of measure of benefit

The measure of benefit is life-years gained, and this is influenced by the life expectancy of survivors of severe sepsis and the additional number of survivors in the treatment (activated protein C) group. The input parameters for the mortality estimates were from the PROWESS study, a well-designed RCT, and from subsequent analysis of the PROWESS data by the FDA (USA). Baseline risks, and subsequent survival data for survivors, were based on a study specific cohort study detailing a Canadian patient group. The cohort study was used to include differences in mortality and longer term survival by age and severity groups.

Quality of life estimates used in the sensitivity analysis were from published estimates of quality of life in a patient group with ARDS. The authors cite a reference which draws similarities between this patient group and the severe sepsis patient group. There is an absence of data on QALY values for severe sepsis; therefore, there will remain some uncertainty over the validity of the QALY estimate used in this study. However, the authors do report sensitivity analysis on the QALY value used.

Validity of estimate of costs
Baseline analysis was limited to direct costs, with other indirect cost considered in the sensitivity analyses. The study does not report disaggregated total costs for each group, and it is not clear as to the exact costing methodology used in the analysis. The study states the additional costs (activated protein C and bleed costs) in the treatment group, but the model structure indicates that hospital (ICU/ward) costs formed part of the model structure also.

The cost-effectiveness analysis uses long-term healthcare costs for survivors of severe sepsis, and this issue may be open to some methodological debate. The study provides sensitivity analyses with some alterations to these costs, but does not provide cost-effectiveness estimates which exclude the long-term healthcare costs for survivors.

Other issues
The issue of generalisability to other patient groups should be considered in the context of the baseline risks of the group. This study used Canadian data with 28-day mortality at 30.7% for all patients with severe sepsis; this varied from 12.4 to 43.1% by age group, and from 18.5 to 54.5% according to APACHE II scores of ≥ 24 or ≥ 25, respectively.

FDA data from a post hoc analysis of the PROWESS study have been used in this economic evaluation to consider differential benefits according to APACHE II score. The authors of this study state that the results of the subgroup analyses by APACHE II score are dependent on the validity of the analysis performed by the FDA.

Implications of the study
The findings from this study suggest that it may be reasonable to restrict the use of activated protein C to patients (in Canada and the USA) with APACHE II scores of 25 or more, until further evidence is available.

The study indicates that treatment may best be targeted to patients with greater severity of illness (APACHE II score of 25 or more) and a reasonable life expectancy if they survive the episode of severe sepsis; this may have equity implications related to age and severity of illness.

Cost-effectiveness of recombinant human activated protein C and the influence of severity of illness in the treatment of patients with severe sepsis

Fowler RA, Hill-popper M, Stasinos J, Petrou C, Sanders GD, Garber AM. *J Crit Care* 2003; 18:181–91
This record was compiled by SHTAC following the format used by the NHS CRD Economic Evaluation Database.

Health technology
Recombinant human activated protein C (drotrecogin alfa) for patients with severe sepsis, treated in an ICU.

Disease
Severe sepsis

Type of intervention
Treatment.

Hypothesis/study question
Estimated cost-effectiveness of recombinant human activated protein C (rhAPC, drotrecogin alfa) compared with usual therapy for patients with severe sepsis. The comparator used is usual therapy (usual anti-infective therapy and supportive care) for patients admitted to the ICU with severe sepsis. The study considers cost-effectiveness by severity of severe sepsis.

Economic study type
Cost-effectiveness/cost–utility analysis

Study population
The study models the effects of treatment in a hypothetical cohort of patients matching the PROWESS trial patient characteristics; mean age 61 years, 57% male, 82% white, same prevalence of co-morbidities as PROWESS patients, with other baseline characteristics similar to PROWESS data. The study considers patients by severity, considering those patients with an APACHE II score of ≥ 25, regarded as having very severe sepsis, and those patients with an APACHE II score of <25, regarded as having less severe sepsis.

Setting
A US hospital setting, with initial phase of treatment (at least) in an ICU.

Dates to which data relate
Effectiveness data were taken from the PROWESS trial, which reported in 2001.

Data on hospitalisation costs associated with severe sepsis were taken from an observational cohort study reporting 1995 data (Angus *et al.*, 2001).

Cost data were converted to 2001 US dollars.

Quality of life data for the calculation of QALYs were from published estimates on health states deemed to be similar to those in the reported cost-effectiveness analysis.

Source of effectiveness data
The effectiveness data were taken from a single trial, with a post hoc analysis of the trial data also used in the cost-effectiveness analysis.

Modelling
The study involved the construction of a cost-effectiveness model to estimate the costs and benefits associated with treatment, compared with usual care.

Link between effectiveness and cost data
The study uses effectiveness data from the PROWESS trial, and applies resource use data from a separate study, an observational cohort study of hospital discharge records.

Details about clinical evidence
Clinical effectiveness is from a single trial, the PROWESS trial, published elsewhere. The trial methods and results are reported by Bernard and colleagues (2001) and detail of this study can be found in the main body of the present review (see Chapter 3 of the SHTAC report).

The economic evaluation also uses a post hoc analysis of the single study data performed by the FDA; detail on this can be found in the main body of the review (see Chapter 3 of the SHTAC report).

Single study

Study sample
The clinical trial enrolled patients with known or suspected infection on the basis of clinical data at the time of screening. The criteria for severe sepsis were stated as a modification of those defined by Bone and colleagues (see detailed review in Chapter 3 of the SHTAC report). Of the 1728 patients who underwent randomisation (1:1), 1690 received the study drug or placebo (840 placebo, 850 in the treatment group).

Study design
The study was a randomised, double-blind, placebo-controlled, multicentre trial. The study was multinational, including 164 centres, across 11 countries.

Analysis of effectiveness
Analysis was based on intention to treat (with a treatment analysis also presented). The primary health outcome was 28-day mortality. At baseline, the demographic characteristics and severity of disease were similar in the placebo and treatment groups.

Effectiveness results
Treatment with drotrecogin alfa (activated) was associated with a reduction in the relative risk of death of 19.4% (6.6 to 30.5%) and an absolute reduction in the risk of death of 6.1% ($p = 0.005$). The incidence of serious bleeding was higher in the treatment group than in the placebo group (3.5% versus 2.0%, $p = 0.06$).

Clinical conclusions
Treatment with drotrecogin alfa (activated) significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding.

Economic analysis

Measure of benefits used in the economic analysis
A decision-analytic framework was used to assess cost-effectiveness. The measure of benefit was life-years gained (and QALYs). The model covers the acute phase of septic illness and survivors of severe sepsis are cycled through a Markov modelling process to estimate benefits and costs associated with rhAPC treatment. The model takes a lifetime time-horizon. It applies effectiveness data from the PROWESS trial on absolute risk reduction at 28 days, using data from PROWESS on the placebo and treatment groups. The model also uses effectiveness data from PROWESS on early complications (serious bleeding events). Survival over time is modelled to estimate life expectancy and life-year gains with rhAPC treatment. The authors state that risk of death may be greater for patients suffering early complications (i.e. serious bleeds), but it is not clear from the description of the model how this was done. Authors state that they adjust life expectancy for survivors of severe sepsis for 8 years, citing a study by Quartin and colleagues (1997), but specific detail is not offered in the paper.

Health-state utilities used in the model are for health states deemed by the authors to be similar to those found in severe sepsis. Acute severe sepsis with treatment complications is valued at 0.44; without complications it is 0.50. Subacute severe sepsis is valued at 0.64, with post-sepsis survival valued at 0.80. These values are from published estimates for health states unrelated to severe sepsis, but deemed by the authors to be similar (e.g. acute severe sepsis regarded as similar to neutropenia or leukaemia).

Life-years gained were discounted at an annual rate of 3%.

Direct costs

The study includes costs for initial treatment with rhAPC, acute complications (serious bleeds), hospitalisation cost and future healthcare costs for survivors of severe sepsis. The model also included a cost for death ($5310), which was from a published estimate. Cost data for serious gastrointestinal bleeds were from US Medicare (estimate of $1237 per event). Cost for an rhAPC was determined using an estimate for a person weighing 70 kg ($6700). Cost data for hospitalisation were from an observational cohort study of hospital discharge records (1995) for several large US states; hospitalisation cost (acute sepsis care) was estimated to be $24,332 (in 2001 US dollars). Future healthcare costs were from age-specific medical expenditure data for the USA (1998), for those aged 55–64 years, 65–74 years and ≥ 75 years.

Resource use and costs were not reported separately.

Costs were discounted at an annual rate of 3%.

Indirect costs

The study does not refer to indirect costs.

Currency

US dollars, converted to 2001 values, using a gross domestic product deflator.

Statistical analysis of quantities/costs

Model created and analyses performed using DATA 4.0 and Excel 2000.

Sensitivity analysis

One-way sensitivity analyses were undertaken. Where pairs of variables were regarded as influential multiway sensitivity analysis was undertaken. The authors state that Monte Carlo methods were used for model variables (assuming log-normal distributions for cost inputs, and norm or logistic distributions for probabilities and health-state utilities).

Sensitivity analyses were run on all cost, probability and utility inputs where assumptions were made in the model. Sensitivity analyses were run on discount rates (applying 0% and 5%). One-way sensitivity analyses were undertaken on variables with most clinical relevance.

The report ran analyses for various patient groups, by severity of illness (according to APACHE II score ≥ 25 or <25) and by protein C deficiency (or normal protein C levels).

Results

Estimated benefits used in the economic analysis

For all patients, treatment with rhAPC resulted in 6.63 QALYs (8.31 life-years) and 6.09 QALYs (7.63 life-years) for usual care; a net difference of 0.54 QALYs (0.68 life-years). Short-term 28-day survival was 0.061 lives saved per treated patient.

For patients with less severe sepsis (APACHE II < 25), treatment with rhAPC resulted in 7.15 QALYs (8.94 life-years) and 7.13 QALYs (8.92 life-years) for usual care, a net difference of 0.017 QALYs (0.02 life-years). Short-term 28-day survival was 0.002 lives saved per treated patient.

For patients with very severe sepsis (APACHE II ≥ 25), treatment with rhAPC resulted in 6.08 QALYs (7.60 life-years) and 4.96 QALYs (6.20 life-years) for usual care, a net difference of 1.12 QALYs (1.4 life-years). Short-term 28-day survival was 0.128 lives saved per treated patient.

Above future benefits were discounted at 3%.

Cost results

For analysis including all patients, the total costs of treatment with rhAPC were $61,751, with costs for usual care at $51,006, a net difference of $10,745.

For patients with less severe sepsis (APACHE II <25), the total costs of treatment with rhAPC were $65,645, with costs for usual care at $57,794, a net difference of $6851.

For patients with very severe sepsis (APACHE II ≥ 25), the total costs of treatment with rhAPC were $57,659, with costs for usual care at $42,493, a net difference of $15,166.

Above future costs were discounted at 3%.

Synthesis of costs and benefits

For short-term 28-day analysis, the 'all patients' group resulted in a cost per life saved of $129,262, the less severe sepsis group $3,339,000 per life saved, and the very severe sepsis $70,297 per life saved.

Incremental cost-effectiveness analysis was reported. Discounting was as above.

For the 'all patients' analysis the cost per QALY was $20,047; cost per life-year saved was $15,801. For patients with less severe sepsis (APACHE II <25), the cost per QALY was $403,000; cost per life-year saved was $342,550. For patients with very severe sepsis (APACHE II ≥ 25), the cost per QALY was $13,493; cost per life year saved was $10,833.

The study reports costs per QALY of $7503 for the treatment of those patients with protein C deficiency with rhAPC.

No range data were provided in the results. No significant differences were reported when sensitivity analyses were undertaken.

The authors report the results of a probabilistic sensitivity analysis, which suggested that 95% of the 10,000 simulated incremental cost-effectiveness ratios for the use of rhAPC in the treatment of very severe sepsis (APACHE II score ≥ 25) would be between $9400 and $25,400 per QALY.

Conclusions and critical comment

Authors' conclusions

Treatment with rhAPC is cost-effective for the population of patients with very severe sepsis as described by the APACHE II score ≥ 25 in the PROWESS trial. When treating patients with less severe sepsis (APACHE II score < 25) rhAPC does not appear cost-effective by generally accepted standards. Treatment in a pooled population of patients with severe sepsis may appear cost-effective. Patients with less severe sepsis should generally not be treated with rhAPC, as it has negligible effectiveness and is not cost-effective.

SHTAC commentary

Selection of comparators

The comparator was usual care, and the rationale for this is clear.

Validity of estimate of measure of benefit

The measure of benefit is life-years gained, and this is influenced by the life expectancy of survivors of severe sepsis and the additional number of survivors in the treatment (rhAPC) group. Life expectancy has been modelled using a cohort of patients defined using PROWESS patient characteristics; this patient group may not represent the overall in-practice treatment group, as inclusion/exclusion criteria for PROWESS may not be applied in practice. The input parameters for the mortality estimates were from the PROWESS study, a well-designed RCT, and from subsequent analysis of the PROWESS data by the FDA (USA). Baseline risk is from the PROWESS placebo group and absolute risk reductions are used to estimate survival benefit. There is a heavy reliance on PROWESS being generalisable to the US population of severe sepsis patients.

The authors state that survival rates have been adjusted to reflect rates of acute complications, but it is not clear from the description of the model how this has been done.

The authors state that they make adjustments to life expectancy over an 8-year period, citing a study by Quartin and colleagues (1997) for parameter inputs. The authors do not report how they used the data reported by Quartin, and this raises uncertainty over the methods applied, especially as Quartin and colleagues report differences between severe sepsis patients and controls over years 1–4 after severe sepsis, with rates of all-cause mortality after year 4 similar to controls.

Quality of life estimates used in the sensitivity analysis were from published estimates of quality of life in conditions other than severe sepsis, with the authors assuming that severe sepsis health-state values were similar to other conditions. The authors offer little rationale on this issue. However, there is an absence of health-state utility data related to severe. Sensitivity analysis is undertaken on parameter values used to estimate benefits, but specific results are not reported.

Validity of estimate of costs

The methods used to estimate cost data appear reasonable. Cost data for rhAPC have been estimated reasonably and intervention costs reflect those seen in PROWESS. The cost data for hospitalisation are from a US cohort study, and the authors state that this patient group was similar to PROWESS patients.

The authors use long-term healthcare costs in their analysis, and this issue may be open to some methodological debate. The authors do not present findings of sensitivity analyses on the long-term cost inputs.

Other issues
FDA data from a post hoc analysis of the PROWESS study have been used in this economic evaluation to consider differential benefits according to APACHE II score. Findings are dependent on the validity of the post hoc analysis performed by the FDA.

Implications of the study
The findings from this study suggest that it may be reasonable to restrict the use of rhAPC (in the USA) to patients with APACHE II scores of 25 or more, until further evidence is available.

Appendix 14

SHTAC estimates for long-term cost per patient

To estimate the mean NHS costs per person (adult) per year, aggregate data on NHS expenditure (hospital and community health services), data on NHS activity and population data by age were combined. The result is a mean cost per person per year by age categories 16–44 years, 45–64 years and over 65 years of age. These costs can only reflect a rough 'rule of thumb' cost estimate, and they do not make any allowance for factors other than age.

For an estimate of NHS activity data were used from the Department of Health, Hospital Episode Statistics 2001–2002 (www.dh.gov.uk/hes, accessed August 2003). The headline figures for 2001/02 for patients admitted to NHS hospitals for the period 1 April 2001 to 31 March 2002 were used, as listed below.

Hospital episode statistics/finished consultant episodes (FCEs)	
Total FCEs	12,357,360 (100%)
Total FCEs for adults *(including those FCEs where age unknown)*	10,577,399 (85.6% of total FCEs)
FCEs by age range	**FCEs, (proportion of adult FCEs)**
16–44 years	3,606,385 (34.10%)
45–64 years	2,671,229 (25.25%)
65–74 years	1,759,663 (16.64%)
75–84 years	1,703,699 (16.11%)
85+ years	779,772 (7.37%)
Not known	56,651 (0.54%)

Total NHS expenditure on hospital and community health services (HCHS) for 2002/03 was obtained from Department of Health statistics (www.dh.gov.uk/HPSS/TBL_E1.htm. accessed August 2003), with total cost reported at £50,583,000,000, and adult expenditure representing £43,296,996,577 of this.

HCHS expenditure by adult age range		Population statistics (England and Wales)[a]
16–44 years	£14,762,196,169	20,836,812
45–64 years	£10,934,275,323	11,098,689
65–74 years	£7,202,916,604	9,607,385 (aged 65+)
75-84 years	£6,973,836,363	
85+ years	£3,191,879,744	
Not known		

[a] Population Statistics for England and Wales – by Age (from ONS, Census 2001 data: www.statistics.gov.uk/census2001, accessed 29 July 2003).

Combining the above data, the annual NHS HCHS expenditure per adult by age range was estimated to be:

16–44 years	£708.47
45–64 years	£985.19
65+ years	£1,807.84

For example, age group 45–64 years comprises 25.25% of £43.3 billion (circa £10.9 billion), and the population in England and Wales comprises just over 11 million 45–64-year-olds, therefore an average cost per person is estimated at £985.18 per year.

Appendix 15

Cost-effectiveness acceptability curves for selected sensitivity analyses

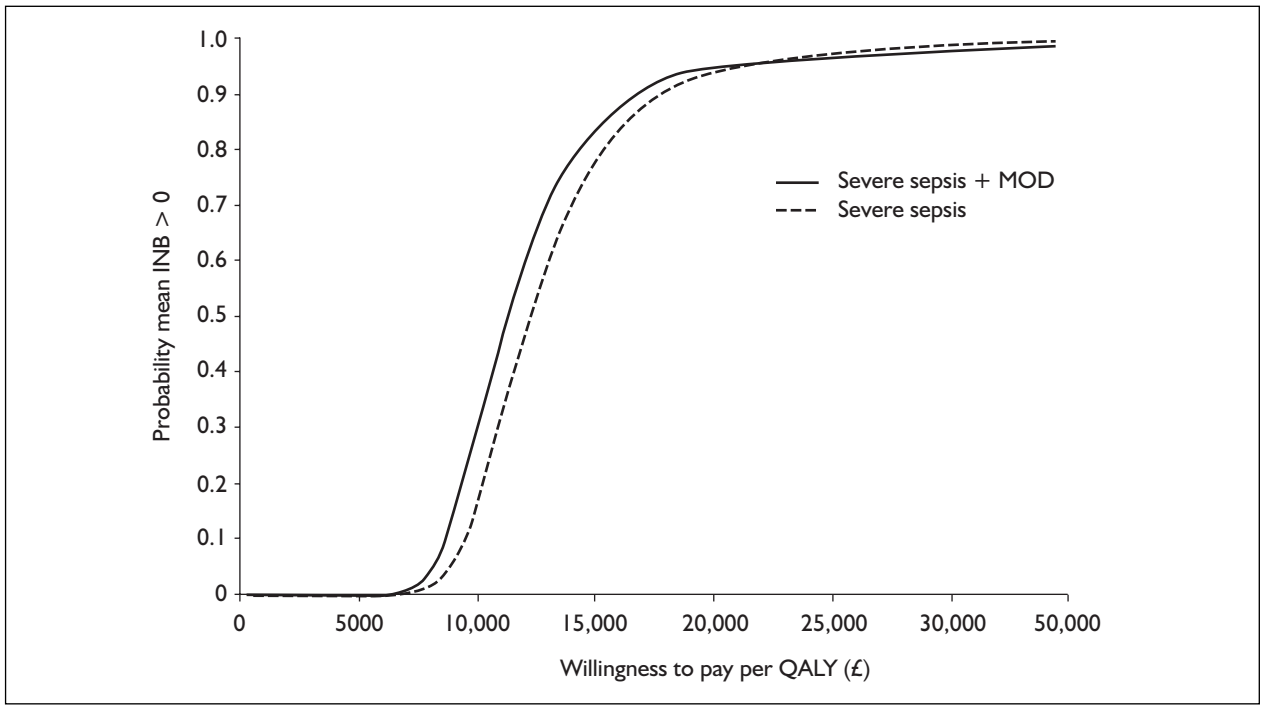

FIGURE 8 *CEACs for sensitivity analysis using base-case assumptions, except with discount rates for future costs and benefits at 3.5%*

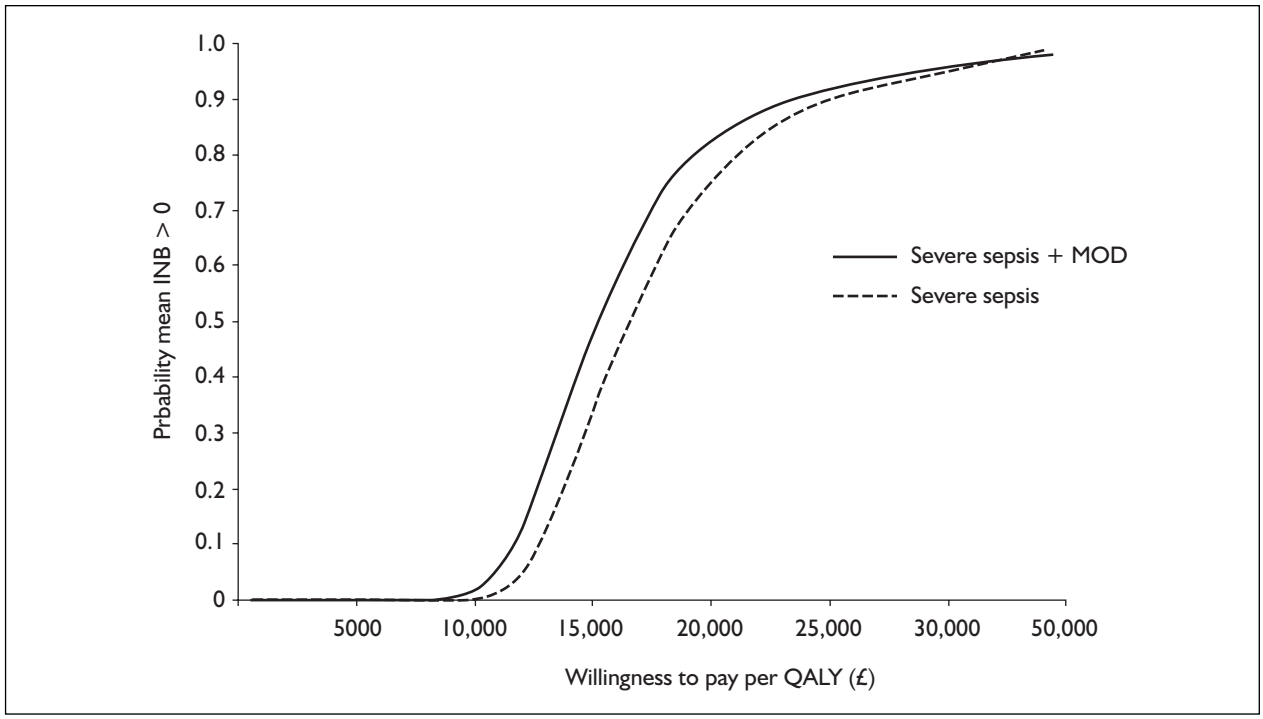

FIGURE 9 *CEACs for sensitivity analysis with base-case assumptions altered to reflect (1) an increased NHS follow-up cost of £20,000 in year 1 (after hospitalisation), (2) adjustment of future life expectancy using a parameter of 0.51, and (3) baseline risk for each group set equal to the respective risk in PROWESS placebo patients*

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We look forward to hearing from you.

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