Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence

The clinical and cost-effectiveness of drotrecogin alfa (activated) (Xigris™) for the treatment of severe sepsis in adults: a systematic review and economic evaluation (Excluding Commercial in Confidence Data)

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Colin Green, Senior Research Fellow
Jacqueline Dinnes, Senior Research Fellow
Debbie Hartwell, Research Fellow
Andrea Takeda, Research Fellow
Carolyn Cave, Research Fellow
Liz Payne, Information Scientist
Jonathan Shepherd, Senior Researcher
Brian H Cuthbertson, Clinical Senior Lecturer in Anaesthesia and Intensive Care, University of Aberdeen

Correspondence to Colin Green
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
Mailpoint 728, Boldrewood
Southampton
SO16 7PX
Tel: 023 8059 5631 (direct line)
Fax: 023 8059 5639
E-mail: c.green@soton.ac.uk

Date completed December 2003

Expiry date To be confirmed (following NICE Appraisal Committee Meeting)

Note: This document and any associated economic model are protected by intellectual property rights (IPR), which are owned by the University of Southampton. Anyone wishing to modify, adapt, translate, reverse engineer, decompile, dismantle or create derivative work based on the economic model must first seek the agreement of the property owners
Conflicts of interest:
Dr Brian Cuthbertson has undertaken consultancy work for Eli Lilly and Company. Colin Green has undertaken work for Eli Lilly when working as an employee of a research consultancy firm (2000-2001). No other conflicts declared.

Source of funding:
This report was commissioned by the NHS R&D HTA Programme.

Relationship of reviewer(s) with sponsor
No personal or unit pecuniary relationship with sponsors.

Acknowledgements
We are very grateful to the advisory panel which provided expert advice and comments on the protocol and/or draft of this report. The members included:

- Dr Andrew Bodenham, Consultant in Anaesthesia and Intensive Care, Leeds General Infirmary, Leeds
- Professor Jonathan Cohen, Dean, Brighton and Sussex Medical School, University of Sussex, Brighton
- Prof Tim Evans, Professor of Intensive Care, Anaesthetics & Intensive Care, Imperial College School of Medicine, Royal Brompton Hospital, London
- Prof Tom Evans, Reader in Infectious Diseases and Honorary Consultant, Department of Infectious Diseases, Imperial College, Hammersmith Hospital, London
- Dr Robert Heyderman, Senior Lecturer, Department of Pathology & Microbiology, University of Bristol, Bristol
- Ms Karen Hill, Practice Development Lead Nurse, General ITU, Southampton General Hospital, Southampton
- Professor David Leaper, University Hospital of North Tees, Hardwick
- Dr Beryl Oppenheim, West Midlands Public Health Laboratory, Birmingham Heartlands Hospital, Birmingham
- Professor Mervyn Singer, Professor of Intensive Care Medicine, Dept of Medicine and Wolfson Institute of Biomedical Research, University College London, London

We would also like to thank Tony Brady at ICNARC, Dr RA Fowler, University of Toronto (Canada), Dr Peter Davidson, Consultant in Public Health Medicine and Senior Lecturer at NCCHTA, Ms Liz Hodson at the Information Service, Wessex Institute for Health Research and Development, and Dr Jill Colquitt, Southampton Health Technology Assessments Centre.

Contributions of the authors
The report’s authorship is as follows:

- Protocol: J Dinnes, C Green, BH Cuthbertson, C Cave
- Literature Searching: E Payne
- Inclusion criteria: J Dinnes, A Takeda, C Cave
- Data extraction: J Dinnes, C Green, A Takeda, C Cave, D Hartwell
- Drafting of the report: J Dinnes, C Green, BH Cuthbertson, A Takeda, J Shepherd
This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme.

The final report and any errors remain the responsibility of the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton. Jacqueline Dinnes and Colin Green are guarantors.
# TABLE OF CONTENTS

**SUMMARY** .............................................................................................................................. 7  
**LIST OF ABBREVIATIONS** ........................................................................................................ 11  
**DEFINITIONS OF TERMS** ......................................................................................................... 13  
**AIM OF THE REVIEW** ............................................................................................................. 14  

1 **BACKGROUND** .................................................................................................................... 14  
1.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM ..................................................... 14  
1.1.1 Definitions ........................................................................................................... 14  
1.1.2 Aetiology and pathology .................................................................................... 14  
1.1.3 Epidemiology ..................................................................................................... 15  
1.1.4 Prognosis ........................................................................................................... 17  
1.1.5 Significance in terms of ill-health ...................................................................... 19  
1.2 CURRENT SERVICE PROVISION .................................................................................... 19  
1.2.1 Description of standard care ............................................................................. 20  
1.2.2 Variation in outcome ......................................................................................... 21  
1.2.3 Current service cost ........................................................................................... 21  
1.3 DESCRIPTION OF NEW INTERVENTION ....................................................................... 21  
1.3.1 Drotrecogin alfa (activated) (Xigris™) ................................................................ 21  

2 **EFFECTIVENESS** .................................................................................................................. 23  
2.1 METHODS ......................................................................................................................... 23  
2.1.1 Inclusion and exclusion criteria ........................................................................ 23  
2.1.2 Search strategy ..................................................................................................... 23  
2.1.3 Quality assessment and data extraction strategy .............................................. 24  
2.1.4 Methods of analysis/synthesis ............................................................................ 24  
2.2 RESULTS .......................................................................................................................... 24  
2.2.1 Quantity of research available .......................................................................... 24  
2.2.2 Study characteristics .......................................................................................... 26  
2.2.3 Quality of included studies ................................................................................ 30  
2.2.4 Assessment of effectiveness ................................................................................ 33  
2.2.5 Generalisability of results to the UK setting ..................................................... 46  
2.3 SUMMARY OF EFFECTIVENESS RESULTS ................................................................... 50  

3 **ECONOMIC ANALYSIS** ...................................................................................................... 51  
3.1 INTRODUCTION .............................................................................................................. 51  
3.2 SYSTEMATIC REVIEW OF THE LITERATURE ................................................................ 51  
3.2.1 Methods for the systematic review .................................................................. 51  
3.2.2 Results of the systematic review: cost-effectiveness ......................................... 51  
3.2.3 Life-expectancy for survivors of severe sepsis .................................................... 60  
3.2.4 Health related quality of life after survival of severe sepsis ............................... 63  
3.3 SHTAC COST-EFFECTIVENESS ANALYSIS ............................................................ 66  
3.3.1 SHTAC Cost-effectiveness Model ........................................................................ 66  
3.3.2 SHTAC Cost-effectiveness Results ..................................................................... 75  
3.3.3 Sensitivity Analyses ............................................................................................ 77  

4 **IMPLICATIONS FOR OTHER PARTIES** ........................................................................... 80  

5 **FACTORS RELEVANT TO THE NHS** ............................................................................. 80  

6 **DISCUSSION** ...................................................................................................................... 81
6.1 MAIN EFFECTIVENESS RESULTS ................................................................. 81
  6.1.1 Limitations in the evidence ................................................................. 82
  6.1.2 Limitations of the review ................................................................. 83
6.2 COST-EFFECTIVENESS: STATEMENT OF PRINCIPAL FINDINGS........... 83
  6.2.1 Limitations – cost-effectiveness ......................................................... 84
6.3 FURTHER RESEARCH ............................................................................ 85
7 CONCLUSIONS .................................................................................... 86
8 REFERENCES ....................................................................................... 87

LIST OF APPENDICES
Appendix 1. Details of epidemiological studies ............................................. 94
Appendix 2. Description of APACHE II scoring system ................................. 98
Appendix 3. Documentation of search strategy used ....................................... 101
Appendix 4. Quality assessment tool used ...................................................... 102
Appendix 5. Listing of Excluded Studies ....................................................... 104
Appendix 6 Characteristics of included studies ............................................ 112
Appendix 7 Completed data extraction forms .............................................. 115
Appendix 8 ACCP/SCCM definitions of severe sepsis .................................. 124
Appendix 9 Additional PROWESS subgroup analyses: 28-day all cause mortality according
to demographic and other characteristics .............................................. 127
Appendix 10. Internal validity of economic evaluations ................................. 129
Appendix 11. External validity of economic evaluations ............................... 130
Appendix 12. Summary methods and findings from published economic evaluations and
abstracts reporting cost-effectiveness studies ........................................... 131
Appendix 13. Data extraction (CRD Format) of published economic evaluations ........ 137
Appendix 14. SHTAC Estimates for Long-term Cost per Patient .................. 154
Appendix 15. CEACs for selected sensitivity analyses .................................... 155
TABLES
Table 1. Selected details of epidemiological studies ............................................................... 15
Table 2. Summary of included studies .................................................................................. 26
Table 3. Baseline characteristics of participants in included studies .................................... 28
Table 4. Internal validity of included RCTs ......................................................................... 31
Table 5 Overall 28-day mortality results ............................................................................ 33
Table 6. PROWESS subgroup analyses: 28-day all cause mortality according to clinical measures of baseline disease severity and infection site and type .................................................. 37
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 .................................................. 39
Table 8. PROWESS results: impact of drotrecogin alfa (activated) on other outcomes .... 41
Table 9. Number (%) of adverse events (to 28-day follow-up) ........................................... 47
Table 10. Adverse events – combined results from cumulative safety review ................... 48
Table 11. Generalisability of PROWESS results ................................................................. 49
Table 12 Summary findings for published cost effectiveness studies/abstracts .................. 59
Table 13. Estimates of relative risk of dying for patients with sepsis relative to controls by sepsis severity and time interval ................................................................................. 62
Table 14. Survival of critically ill patients compared to an age- and sex-matched normal population ................................................................................................................. 61
Table 15. Health status assessment among sepsis survivors (interim analysis from Drabinski et al) ......................................................................................................................... 62
Table 16. Estimate of mortality/life-expectancy, years 1 to 5, after discharge from intensive care (data on deaths recorded from Wright et al) ............................................................... 67
Table 17. Model inputs / assumptions for SHTAC cost-effectiveness analysis ................. 70
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 .......... 73
Table 19. Non-discounted cost per life-year and cost per QALY for drotrecogin alfa (activated) versus conventional care, using other base case assumptions .................. 73
Table 20. Sensitivity analysis of the cost per life-year gained and cost per QALY, for treatment with drotrecogin alfa (activated) ............................................................... 76

FIGURES
Figure 1. Flowchart of search results .................................................................................. 25
Figure 2. PROWESS – long-term (90 day) mortality follow-up (all patients) .................... 35
Figure 3. PROWESS long-term survival up to 30 months (all patients) ......................... 35
Figure 4. Mortality rates by time from first organ failure to study drug administration ...... 44
Figure 5. Flow Diagram Showing Basic Structure of SHTAC Model .............................. 65
Figure 6. Cost-effectiveness acceptability curve, drotrecogin alfa (activated) ................. 74
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% to 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 debridement, 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 RCTs targeting mediators such as tumour necrosis factor (TNF) alpha, TNF alpha receptor, interleukin 1 (IL-1), the IL-1 receptor, prostaglandins, bradykinins, as well as using large dose corticosteroids. However, randomised controlled trials (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 regime for drotrecogin alfa (activated) is for 24µg per kilogram body weight per minute for a period of 96 hours, and the mean acquisition cost per 70kg patient, for a full 96 hour course, is estimated to be £4,905 excluding VAT.

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

Methods
A systematic review of the literature and an economic evaluation were undertaken. Data on the clinical 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). The results of the phase III RCT (PROWESS) have been published in five subsequent papers. A review on the safety of drotrecogin alfa (activated) is 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 our 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 our quality assessment of
the internal validity of the two RCTs we regard them as being of good quality. It was not possible to quality assess 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 NICE by the manufacturer of drotrecogin alfa (activated) has also been used to inform 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 comes primarily from one large pivotal RCT – the PROWESS study. The PROWESS study demonstrated a statistically significant absolute reduction in 28-day mortality of 6.5% (95%CI: -10.7, -2.2), equivalent to a relative risk of death of 0.79 (95%CI: 0.68, 0.92). Longer-term follow-up of PROWESS patients shows that the survival benefit is maintained to 90 days (p=0.048). By nine months, the trend towards increased median survival is non-significant (log rank p=0.097), although the survival curves do not cross.

A priori subgroup analyses show a progressive reduction in the relative risk of death with increasing number of organ failures, from 0.92 (95%CI: 0.63, 1.35) in patients with one organ failure at baseline to 0.60 (95%CI: 0.33, 1.11) in those with 5 organ failures. Results presented by the number of organ dysfunctions are not statistically significant, but when mortality rates for those with two or more organ failures are combined, the relative risk of death is significantly lower in those treated with drotrecogin alfa (activated) compared to placebo (0.78, 95%CI: 0.66, 0.93). However, our 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 is 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. In order to do this it is 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) estimates an incremental gain of 1.115 life years per treated patient, in patients with severe sepsis and multiple organ dysfunction. The SHTAC analysis estimates 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 which 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, those hospitalisation costs associated with additional survivors of severe sepsis, and where deemed appropriate,
the long term health care costs associated with additional survivors of severe sepsis. There are variations in estimates of cost within the published literature. The three published cost-effectiveness studies report cost for USA and Canadian patient groups; for those patients with severe sepsis they report the additional cost per patient treated in a ranges circa. $10,000 to $16,000.

The manufacturers submission reports analysis for the UK, based on 28-day survival data in patients with severe sepsis and multiple organ dysfunction (the European license indication), with the additional mean cost per treated patient estimated to be £5,106. The analysis undertaken by SHTAC, for a UK patient group of patients with severe sepsis and multiple organ dysfunction, estimates an additional mean cost per patient treated of £6,661.

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

The relevant patient group for European analysis is those patients with severe sepsis and multiple organ failure. The manufacturers submission to NICE presents cost-effectiveness estimates for drotrecogin alfa (activated) in the UK, in patients with severe sepsis and multiple organ dysfunction, at £6,637 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 £8,228 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.

Sensitivity analyses: cost-effectiveness analysis
Published economic evaluations report 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 are made to the base case assumptions in the SHTAC cost-effectiveness model, the cost per QALY increases towards the estimates reported in the published USA/Canadian economic analysis, but the intervention still remains at a level that would be regarded as cost-effective to most decision makers.

Limitations of the review / Generalisability of the findings
The key limitation of the two RCTs is in the generalisability of the findings to the UK. The definition of severe sepsis used in the pivotal RCT (PROWESS) is 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 has generally been 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) is 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 does not apply the exclusion criteria from the PROWESS study. We regard this 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 license indication, is uncertain.

Other important issues regarding implications
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.

Need for 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, 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.
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
CEAC  Cost-effectiveness Acceptability Curve
CCU   Coronary Care Unit
CI    Confidence Interval
CIC   Commercial In Confidence
CPMD  Case Mix Programme Database
CONSORT Consolidated Standards of Reporting Trials
COPD  Chronic Obstructive Pulmonary Disease
DIC   Disseminated Intravascular Coagulation
EMEA  European Agency for the Evaluation of Medicinal Products
EU    European Union
FDA   Food and Drug Administration
HDU   High Dependency Unit
HTA   Health Technology Assessment
ICNARC Intensive Care National Audit and Research Centre
ICH   Intracranial Hemorrhage
ICU   Intensive Care Unit
IL    Interleukin
ITT   Intention To Treat
LOS   Length of Stay
LYG   Life Year Gained
MI    Myocardial Infarction
MODS  Multiple Organ Dysfunction Syndrome
NHS   National Health Service
NICE  National Institute for Clinical Excellence
OD    Organ Dysfunction
OF    Organ Function
OR    Odds Ratio
“PROWESS” The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Study
QALY  Quality Adjusted Life Year
QoL   Quality of Life
QWB   Quality of Well-Being
RCT   Randomised Controlled trial
rhAPC Recombinant Human Activated Protein C
R&D   Research and Development
RR    Relative Risk
SAE   Serious Adverse Event
SBE   Serious Bleeding Event
SCCM  Society of Critical Care Medicine
SD    Standard Deviation
SHTAC Southampton Health Technology Assessments Centre
SICS  Scottish Intensive Care Society
SIRS  Systemic Inflammatory Response Syndrome
SMR   Standardised Mortality Ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD</td>
<td>Single Organ Dysfunction</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ System Failure Score</td>
</tr>
<tr>
<td>TAFI</td>
<td>Thrombin Activatable Fibrinolysis Inhibitor</td>
</tr>
<tr>
<td>TISS</td>
<td>Therapeutic Intervention Scoring System</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to Pay</td>
</tr>
</tbody>
</table>
### Definitions of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>bacteraeemia</td>
<td>the presence of viable bacteria in the blood</td>
</tr>
<tr>
<td>hypoperfusion</td>
<td>reduction in blood flow through a tissue</td>
</tr>
<tr>
<td>hypotension</td>
<td>systolic blood pressure of $&lt; 90$ mm Hg or a reduction of $\geq 40$ mm Hg from baseline</td>
</tr>
<tr>
<td>infection</td>
<td>microbial phenomenon characterised by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by those organisms</td>
</tr>
<tr>
<td>intrahepatic cholestasis</td>
<td>intrahepatic impairment of bile flow. It is usually due to liver cell damage, but may be due to obstruction of intrahepatic bile ducts</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>acidosis caused by accumulation of lactic acid more rapidly than it can be metabolised</td>
</tr>
<tr>
<td>multiple organ dysfunction syndrome (MODS)</td>
<td>presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention</td>
</tr>
<tr>
<td>nosocomial infection</td>
<td>an infection not present or incubating prior to admittance to hospital, but generally occurring 48-72 hours after admittance</td>
</tr>
<tr>
<td>oliguria</td>
<td>excretion of a reduced amount of urine in relation to the fluid intake</td>
</tr>
<tr>
<td>purpura fulminans</td>
<td>a rare fulminating, non-thrombocytopenic purpura that is often secondary to severe infections and is associated with a high mortality</td>
</tr>
<tr>
<td>sepsis</td>
<td>a systemic inflammatory response due to infection</td>
</tr>
<tr>
<td>septic shock</td>
<td>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</td>
</tr>
<tr>
<td>severe sepsis</td>
<td>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</td>
</tr>
<tr>
<td>systemic inflammatory response syndrome (SIRS)</td>
<td>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 $&gt; 38^\circ C$ or $&lt; 36^\circ C$; (2) heart rate $&gt; 90$ beats per minute; (3) respiratory rate $&gt; 20$ breaths per minute or $\text{PaCO}_2 &lt; 4.3$ kPa $(32$ mm Hg$)$; and (4) white blood cell count $&gt; 12,000$ /cu mm, $&lt; 4,000$ /cu mm, or $&gt; 10%$ immature (band) forms</td>
</tr>
<tr>
<td>tachycardia</td>
<td>excessive rapidity in the action of the heart; the term is usually applied to a heart rate above 100 per minute</td>
</tr>
<tr>
<td>tachypnoea</td>
<td>an abnormally rapid (usually shallow) respiratory rate. The normal resting adult respiratory rate is 12-20 breaths/minute</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>a decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting</td>
</tr>
</tbody>
</table>
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 United States and the European Union 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 and cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in adults in a UK context.

1 Background

1.1 Description of underlying health problem

1.1.1 Definitions

Sepsis is a clinical response to infection in the body; patients present with both evidence of infection and clinical manifestations of systemic inflammation1 (i.e. systemic inflammatory response syndrome (SIRS)). SIRS has been defined by the American College of Chest Physicians / Society of Critical Care Medicine2 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 definitions).

1.1.2 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 micro-organisms such as viruses and fungi. The predominate organisms causing community-acquired infections are Gram positive bacteria, while for nosocomial-acquired infections Gram negative organisms previously predominated.1 However, the advent of multi-resistant Gram positive organisms such as methicillin resistant Staphylococcus Aureus are 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
1.1.3 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.

Table 1. Selected details of epidemiological studies

<table>
<thead>
<tr>
<th>Study / Setting</th>
<th>Incidence</th>
<th>No. organ dysfunctions</th>
<th>Length of stay (Los) (days)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberti, et al8 International ICU admissions (&gt;24 hr): n=8353</td>
<td>38.7% sepsis 25.4% severe sepsis or septic shock</td>
<td>1: 73.6% 2: 20.7% 3: 4.7% ≥4: 1.0%</td>
<td>Mean LoS: hospital 19.6d LoS varied little with no. of ODs (range 18.5-22.8 days)</td>
<td>Hospital: 28.6%. By no. acute ODs: 1: 21.2% 2: 44.3% 3: 64.5% ≥4: 76.2%</td>
</tr>
<tr>
<td>Angus, et al6 USA 847 hospitals: over 6 million admissions</td>
<td>192,980 (3 per 1000 population) severe sepsis</td>
<td>1: 73.6% 2: 20.7% 3: 4.7% ≥4: 1.0%</td>
<td>Median LoS: ICU: 8.5 (range 1-87) Hospital: 11</td>
<td>Crude ICU: 56% Crude hospital: 59% 14d: 46% 28d: 56% (95%CI: 52, 60) 42d: 60% (95%CI: 57, 64)</td>
</tr>
<tr>
<td>Brun-Buisson, et al7 France ICU admissions: n=11,828</td>
<td>9% (1052) severe sepsis</td>
<td>Documented infection only (n=742) ≥2: 53%</td>
<td></td>
<td>ICU: 35.6% Hospital: 42.6%</td>
</tr>
<tr>
<td>Moerer et al, 20028 Germany ICU admissions: n=385</td>
<td>All 385 pts had severe sepsis</td>
<td>1: 29% 2: 46% 3: 22%</td>
<td>Mean LoS: ICU 16.6 ± 14.4 Hospital 32.5 ± 25.0 d</td>
<td>ICU: 35.6% Hospital: 42.6%</td>
</tr>
<tr>
<td>Padkin, et al9 UK ICU admissions: n=56,673</td>
<td>27.1% (95%CI: 26.7, 27.5%) severe sepsis in first 24 h</td>
<td>1: 16.4% (15.8, 17.0) 2: 34.4% (33.7, 35.2) 3: 30.8% (30.0, 31.5) 4: 14.7% (14.1, 15.3) 5: 3.7% (3.4, 4.0)</td>
<td>Median (IQR) LoS: ICU 3.59 (1.50, 9.33) Hospital 18 (8, 36)</td>
<td>Hospital: 47.3% By no. ODs (95%CI) 1: 21.8% (20.2, 23.5) 2: 36.0% (34.7, 37.3) 3: 52.5% (51.1, 53.9) 4: 75.1% (73.3, 86.9) 5: 86.1% (83.0, 88.8)</td>
</tr>
</tbody>
</table>
In the US, a large prospective observational cohort study of 847 hospitals found that three per 1,000 population (or 2.26% of hospital discharges) had severe sepsis. This is equivalent to 1,500 cases per 500,000 population per annum with 51% receiving care in an intensive care unit (ICU) at some point during hospitalisation. 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 1,200 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 US10,15 and Europe5,7,16 (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

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Population</th>
<th>Admission Severe Sepsis</th>
<th>Incidence of Severe Sepsis or Septic Shock</th>
<th>Mortality</th>
<th>28d Mortality</th>
<th>5-mo Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rangel-Frausto, et al10</td>
<td>US CCU and wards admissions: n=3708</td>
<td>33% (1226) sepsis 15.6% (577) severe sepsis or septic shock</td>
<td>16.3% (180) sepsis 5.5% (61) severe sepsis 6.1% (67) septic shock</td>
<td>28d mortality Severe sepsis/+ve culture: 20% Severe sepsis/-ve culture: 16% Shock: 46%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvo, et al11</td>
<td>Italy ICU admissions: n=1101</td>
<td>16.3% (180) sepsis 5.5% (61) severe sepsis 6.1% (67) septic shock</td>
<td>16.3% (180) sepsis 5.5% (61) severe sepsis 6.1% (67) septic shock</td>
<td>Mortality by presence of sepsis on admission: Severe sepsis: 52.2% Septic shock: 81.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sands, et al12</td>
<td>US ICU and non-ICU patients: n=12001</td>
<td>8.9% (1063/12001) severe sepsis</td>
<td>8.9% (1063/12001) severe sepsis</td>
<td>Mean (median) LoS: Hospital 29 (20) ICU 17.7 (8)</td>
<td>8.9% (1063/12001) severe sepsis</td>
<td>Mean (median) LoS: Hospital 29 (20) ICU 17.7 (8)</td>
<td>28d mortality: 34% 5-mo mortality: 45.3%</td>
</tr>
<tr>
<td>Scottish Intensive Care Society13,14</td>
<td>UK ICU admissions: n=3442</td>
<td>47% sepsis 20% severe sepsis 18% septic shock</td>
<td>47% sepsis 20% severe sepsis 18% septic shock</td>
<td>2/3 severe sepsis group had ≥1 OD</td>
<td>2/3 severe sepsis group had ≥1 OD</td>
<td>2/3 severe sepsis group had ≥1 OD</td>
<td>ICU mortality Severe sepsis: 21.4% Septic shock: 52%</td>
</tr>
<tr>
<td>Teres, et al15</td>
<td>US ICU admissions: n=21480</td>
<td>11.3% (2,434) severe sepsis at ICU admission</td>
<td>11.3% (2,434) severe sepsis at ICU admission</td>
<td>Mean (SD) LoS ICU 8.48 (10.1) hospital 16.21 (16.7)</td>
<td>Mean (SD) LoS ICU 8.48 (10.1) hospital 16.21 (16.7)</td>
<td>Mean (SD) LoS ICU 8.48 (10.1) hospital 16.21 (16.7)</td>
<td>Overall 36.3%</td>
</tr>
</tbody>
</table>
suffered from severe sepsis during the first 24 hours of their intensive care stay.\textsuperscript{9} The Scottish Intensive Care Society’s prospective audit of Scottish ICUs demonstrated a 38\% incidence of severe sepsis and septic shock at some point during intensive care stay.\textsuperscript{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\textsuperscript{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 \textit{et al},\textsuperscript{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 US.\textsuperscript{4,6}

Age is the major factor to affect incidence. In one of the US studies\textsuperscript{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 age group to 790 per 500,000 per annum in the 75-79 age group, with a higher rate in males than females.\textsuperscript{9}

1.1.4 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.\textsuperscript{17}

Hospital mortality rates in patients with severe sepsis vary from 28.6\% in the US\textsuperscript{6} to 47\% in the England and Wales, with rates from other studies generally lying in between (Table 1).\textsuperscript{8,12,15} The number of acute sepsis-related organ system failures is a major predictor of mortality. For example, Angus \textit{et al}\textsuperscript{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\textsuperscript{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 \textit{et al}.\textsuperscript{6} Other European studies of patients with severe sepsis in intensive care have shown that between 53\%\textsuperscript{7} and 71\%\textsuperscript{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.\textsuperscript{6} In the UK overall mortality ranged from 17\% in the16-19 age group to 64\% in those over 85 years.\textsuperscript{9}

It has been suggested that hospital mortality for severe sepsis is falling over time.\textsuperscript{1} Recent evidence from the US suggests that although percentage mortality may be falling the total number of deaths from sepsis are increasing due to the increasing incidence.\textsuperscript{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 health care systems.18

The APACHE 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 utilises 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 systems’ 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 whilst 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 to a young and otherwise healthy patient.

In the USA the 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 NICE from the Intensive Care Society, the Scottish Intensive Care Society, Royal College of Anaesthetists and Royal College of Physicians21 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 not been developed 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 and scores
them on a scale of 0 to 4 depending on the severity of dysfunction. The SOFA score has now 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, 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.

1.1.5 Significance in terms of ill-health

Severe sepsis represents a major burden of ill-health for the community. This group of patients are 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. 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.

Overall mean hospital length of stay for survivors of severe sepsis is reported to be between 16.2 and 19.6 days in the US, with median stays in Europe reported to be 11 days in France, and 18 days in the UK. 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 to 22.8 days). Further US studies report that in those patients admitted to an ICU, mean length of intensive care stay is 8 days and 18 days, 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, and 8.5 days in France (range 1-87). These differences in relative use of hospital and intensive care stay may reflect the differences in health care provision across countries.

1.2 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. 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. 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. Although the number of general ICUs hardly changed between 1993 and 1998, the median number of beds within them rose from four to six. The total number of beds and total expenditure on intensive care services in the UK is markedly less than in many other developed countries.
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 due 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 due to high bed demand. The high post-discharge mortality seen in intensive care patients in general could be linked to inappropriate early discharge from intensive care due to inadequate bed provision or may be due to lack of appropriate step down facilities. The apparent decline in mortality in some sub-groups 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.

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 have proposed four definitions covering levels of care:

- Level 0 refers to patients whose needs can be met through normal ward care in an acute hospital;
- Level 1 refers to 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 refers to 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 refers to 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 multi-organ failure.

The availability of level 1 and level 2 hospital beds shows marked variation between hospitals. Although the availability of critical care beds has increased since 1999, a large number of hospitals still lack level 1 and 2 beds. 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).

1.2.1 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, however 10% of patients do not receive prompt antibiotic therapy for the causative pathogen resulting in a 10-15% increase in mortality compared to those who do receive appropriate therapy.

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. Up to half may develop acute respiratory distress syndrome (ARDS) which is associated with a high mortality rate. 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 RCTs targeting mediators such as tumour
necrosis factor (TNF) alpha, TNF alpha receptor, interleukin 1 (IL-1), the IL-1 receptor, prostaglandins, 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 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.\(^{31,32}\)

1.2.2 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 when compared to 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.\(^{18}\)

1.2.3 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 costs per patient day in UK intensive care units was £1,232 in 2002,\(^{33}\) and the median total cost of care of patients with sepsis, estimated from a single ICU, was US$10,622 (interquartile range $3,634 to $20,543).\(^{34}\) One US study using charge data found the median cost to be $63,496 (interquartile range 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 health care provided between countries. Further, the ongoing burden of ill-health associated with patients who survive severe sepsis would suggest significant ongoing health care resource utilisation.\(^{24,25}\)

1.3 Description of new intervention

1.3.1 Drotrecogin alfa (activated) (Xigris™)

Recombinant human activated protein C (rhAPC) is a new treatment for patients with severe sepsis. Activated protein C 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, intra-vascular 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 which limit the microvascular injury seen in severe sepsis. 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 acitvatable fibrinolysis inhibitor (TAFI), thereby increasing thrombolysis. Finally by blocking leukocyte adhesion to selectins, pro-inflammatory cytokine release is inhibited.

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. 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)’. The drug is contraindicated in patients at increased risk of bleeding, for example, those with active internal bleeding, 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 regime for drotrecogin alfa (activated) is for 24 µg per kilogram body weight per minute for a period of 96 hours. Delivery of the drug is by standard intravenous infusion methods using standard delivery equipment and 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 5mg and 20 mg vial, excluding VAT. The mean acquisition cost per 70kg patient, for a full 96 hour course, is estimated to be £4,905 excluding VAT. (Commercial in Confidence data removed.) 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 might be eligible to receive it.
2 Effectiveness

2.1 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

2.1.1 Inclusion and exclusion criteria
Participants: 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 American College of Chest Physicians/Society of Critical Care Medicine 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 compared to conventional care alone.
Study design: In order to establish the effectiveness of the intervention, only randomised controlled trials 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 were estimated by comparing the participants and care used in the available RCT(s) to that 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 were consulted to determine the most appropriate outcome measures for the review.

2.1.2 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 sponsor’s submission has been clearly marked (underlined) in the report submitted to the HTA programme and to NICE. A separate version with any such data removed has also been submitted.

2.1.3 Quality assessment and data extraction strategy

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

Data extraction and quality assessment were conducted independently by two reviewers using pre-designed forms. Any disagreements were resolved through discussion, with referral to a third reviewer if necessary.

2.1.4 Methods of analysis/synthesis

For the primary endpoint, trial data are presented as relative risks and 95% confidence intervals (CI). 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; source and site of infection, e.g. hospital vs. community acquired.

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

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

2.2 Results

2.2.1 Quantity of research available

A total of 1,016 titles and abstracts were retrieved from the literature searches and from screening the reference lists. We obtained 108 full papers and from these 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 at Figure 1, and a list of excluded studies is provided in Appendix 5.

Two randomised controlled trials assessing the effectiveness of drotrecogin alfa (activated) were identified (EVAA and PROWESS) results for the latter (the PROWESS trial) having been published in five subsequent papers. The US Food and Drug Administration (FDA) have also published a clinical review of rhAPC to support their licensing decision. This includes data not available in the other trial publications and also reports some exploratory analyses of the trial data. A cumulative safety review 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.

Figure 1. Flowchart of search results

Abstracts retrieved from searches
n = 1009

Full papers retrieved
n = 108

Excluded full papers (not primary studies of rhAPC)
n = 69

Primary clinical studies of efficacy of rhAPC in severe sepsis
n = 39

Included studies (6 RCT reports, 2 reviews, 3 abstracts):
- 2 RCTs
- 4 unpublished open-label studies

Excluded clinical studies (data published elsewhere; outcomes presented not relevant; abstracts only):
Full papers
- 2 PROWESS publications
- 1 report of 3 case studies
Abstracts
- 1 EVAA
- 9 PROWESS
- 15 open label post-licensing studies

RCTs
1. EVAA (phase II): 1 paper
2. PROWESS (phase III): 5 papers; FDA clinical review; 2 abstracts (long term FU data)
Open-label studies
3. ENHANCE: 1 paper (safety review); 1 abstract
4. EVAS: 1 paper (safety review as above)
5. EVAD: 1 paper (safety review as above)
(6. MERCURY: sponsor’s submission only)
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. 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.

2.2.2 Study characteristics

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

Table 2. Summary of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Data meeting review inclusion criteria reported in published papers</th>
<th>Additional unpublished data included from sponsor’s submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAA</td>
<td>Phase II RCT</td>
<td>28-d mortality, safety data</td>
<td></td>
</tr>
<tr>
<td>PROWESS (EVAD)</td>
<td>Phase III RCT</td>
<td>28-d mortality, safety data, Pivotal trial publication, Prospective subgroup analyses, Retrospective subgroup analyses for multiple organ dysfunction subgroup, Impact on organ dysfunction organ dysfunction, Long-term mortality and safety data (abstract only), Additional safety data in cumulative safety review, Additional FDA analyses</td>
<td>Long-term mortality, Analyses relating to drug timing</td>
</tr>
<tr>
<td>ENHANCE (EVBE, EVBF, EVBG)</td>
<td>Phase IV, open-label</td>
<td>28-d safety data for US subgroup (EVBE) published in abstract format, EVBF, EVBG unpublished, Safety data for all three studies provided in cumulative safety review</td>
<td>28-d safety data</td>
</tr>
<tr>
<td>EVAS</td>
<td>Open-label</td>
<td>Unpublished; safety data provided in cumulative safety review</td>
<td>28-d safety data</td>
</tr>
<tr>
<td>EVBC</td>
<td>Open-label</td>
<td>Unpublished; safety data provided in cumulative safety review</td>
<td>28-d safety data</td>
</tr>
<tr>
<td>MERCURY</td>
<td>Retrospective uncontrolled</td>
<td>Unpublished</td>
<td>Analyses relating to drug timing</td>
</tr>
</tbody>
</table>

Interventions

The first RCT (study id: EVAA) was a phase II dose-ranging study, randomising 135 patients to one of seven drotrecogin alfa (activated) regimes or placebo (four regimes/doses for 48 hours, 3 for 96 hours). The second RCT was the pivotal PROWESS trial, 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/hr 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) regime was used in each of the open-label studies.\textsuperscript{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), though it appears that all studies were conducted exclusively on patients admitted to intensive care units.

\textbf{Participants}

The eligibility criteria for the two RCTs were very similar. Both studies included patients aged 18 or over, with known or suspected infection and with at least three signs of systemic inflammation and for PROWESS,\textsuperscript{39} sepsis-induced dysfunction of at least one organ or system lasting no longer than 24hrs. For the EVAA study patients had to show evidence of cardiovascular, renal or respiratory organ failure.\textsuperscript{43} These are a modification of the ‘Bone criteria’ for severe sepsis as laid out by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference in 1992\textsuperscript{2} (Appendix 8). The modification produces a more stringent definition of severe sepsis compared to 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)\textsuperscript{39} or 36 hours (EVAA)\textsuperscript{13} of meeting the inclusion criteria.

The main exclusion criteria for both studies were: presence of conditions that increased the risk of bleeding; known hypercoagulable conditions; or patient not expected to survive 28-days due to a co-morbid condition.

The open-label ENHANCE study\textsuperscript{51} used identical inclusion and exclusion criteria to that of the PROWESS trial, but also included paediatric patients.\textsuperscript{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.\textsuperscript{49} The other (EVAS), required only the clinical diagnosis of purpura fulminans and did not have the presence of thrombocytopenia as an exclusion criterion.\textsuperscript{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 a half to two-thirds were male. Over half of the patients in PROWESS came from the US or Canada, and none of the centres were based in the UK.\textsuperscript{39} In comparison, 69% of patients in ENHANCE were from Europe and 20% of the total (n=470) originated in the UK.\textsuperscript{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 to 40% in the latter. The mean APACHE II score was considerably higher in PROWESS than in the EVAA study, though 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 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.
## Table 3. Baseline characteristics of participants in included studies

<table>
<thead>
<tr>
<th></th>
<th>EVAA 43</th>
<th>PROWESS (EVAD) 39</th>
<th>ENHANCE 11 (EVBE 51, EVBF, EVBG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rhAPC / placebo n=90 / n=41</td>
<td>rhAPC / placebo n=850 / n=840</td>
<td>rhAPC n=2378</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>58 ± 14 / 62 ± 16</td>
<td>60.5 ± 17.2 / 60.6 ± 16.5</td>
<td>59.1</td>
</tr>
<tr>
<td>Age (%)</td>
<td>not reported</td>
<td>44.1 / 43.6</td>
<td>51.4 / 53.5</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>63 / 66</td>
<td>56.1 / 58.0</td>
<td>58.2</td>
</tr>
<tr>
<td>Race (%)</td>
<td>Caucasian</td>
<td>81.8 / 82.0</td>
<td>(Academic in confidence)</td>
</tr>
<tr>
<td>Region</td>
<td>not reported</td>
<td>rhAPC (total %)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td>54.4 (54.7)</td>
<td>30.1 (30)</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td>30.1 (30)</td>
<td></td>
</tr>
<tr>
<td>Intercontinental</td>
<td></td>
<td>15.5 (15.3)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>16.8 ± 5.2 / 18.4 ± 6.9 (Modified AII)</td>
<td>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)</td>
<td>22.0 (7.4)</td>
</tr>
<tr>
<td>Organ failures (%)</td>
<td>61 / 59</td>
<td>25.3 / 24.2</td>
<td>31.8 / 32.5</td>
</tr>
<tr>
<td></td>
<td>32 / 34</td>
<td>25.3 / 24.2</td>
<td>31.8 / 32.5</td>
</tr>
<tr>
<td></td>
<td>7 / 7</td>
<td>25.3 / 24.2</td>
<td>31.8 / 32.5</td>
</tr>
<tr>
<td></td>
<td>25.3 / 24.2</td>
<td>31.8 / 32.5</td>
<td>25.2 / 26.0</td>
</tr>
<tr>
<td></td>
<td>14.0 / 13.8</td>
<td>3.6 / 3.6</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 2 systems 75%</td>
<td>≥ 2 systems 84.4%</td>
<td>≥ 3 systems 43%</td>
</tr>
<tr>
<td>Mean (SD) no. OF at</td>
<td>2.39 (1.12) / 2.40 (1.10)</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>baseline42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ-system failure</td>
<td>rhAPC 11</td>
<td>SOFA = 3 or 448 (Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>cardiovascular</td>
<td>70.8 ( Academic in confidence)</td>
<td>60.7 / 64.4</td>
</tr>
<tr>
<td></td>
<td>respiratory</td>
<td>74.4</td>
<td>55.5 / 60.4</td>
</tr>
<tr>
<td></td>
<td>renal</td>
<td>42.0</td>
<td>12.1 / 11.6</td>
</tr>
<tr>
<td></td>
<td>haematological</td>
<td>16.2</td>
<td>5.3 / 6.0</td>
</tr>
<tr>
<td></td>
<td>hepatic</td>
<td>not reported</td>
<td>2.7 / 2.8</td>
</tr>
<tr>
<td>Mean SOFA score</td>
<td>rhAPC 11</td>
<td>SOFA = 3 or 448 (Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>(SD)48</td>
<td>cardiovascular</td>
<td>2.6 ± 1.5 / 2.7 ± 1.5</td>
<td>2.7 ± 1.0 / 2.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>respiratory</td>
<td>2.6 ± 1.5 / 2.7 ± 1.5</td>
<td>2.7 ± 1.0 / 2.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>renal</td>
<td>2.6 ± 1.5 / 2.7 ± 1.5</td>
<td>2.7 ± 1.0 / 2.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>haematological</td>
<td>2.6 ± 1.5 / 2.7 ± 1.5</td>
<td>2.7 ± 1.0 / 2.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>hepatic</td>
<td>2.6 ± 1.5 / 2.7 ± 1.5</td>
<td>2.7 ± 1.0 / 2.7 ± 1.1</td>
</tr>
<tr>
<td>Time from first OF to</td>
<td>not reported</td>
<td>17.5 ± 12.8 / 17.4 ± 9.1</td>
<td></td>
</tr>
<tr>
<td>start of drug infusion (hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock:</td>
<td>70 / 68</td>
<td>70.4 / 71.7</td>
<td>75.7</td>
</tr>
<tr>
<td>Use of (%):</td>
<td>vasopressors</td>
<td>not reported</td>
<td>71.8 / 75.5</td>
</tr>
</tbody>
</table>
In PROWESS, the proportion of patients with hypertension at baseline was slightly lower in the placebo than control group, but the proportions of those with previous MI, congestive cardiomyopathy and diabetes was slightly higher. A higher proportion of patients in the placebo group also had septic shock (as defined by the sponsor), were being treated with vasopressors, and were receiving mechanical ventilation. The FDA concluded that these differences could slightly favour the drotrecogin alfa (activated) group.

The CIC data for the ENHANCE study indicate that there may be differences in severity of illness for patients in that study compared to those patients recruited into the PROWESS study. Although the mean APACHE II score in ENHANCE was lower than that in PROWESS, a much higher proportion of patients had three or more organ failures at baseline (55% vs 43%). This was also reflected in the higher proportions of patients with each underlying organ system failure (Table 3). Furthermore, although the proportion of patients with prior or pre-existing conditions was generally lower

---

<table>
<thead>
<tr>
<th>dobutamine</th>
<th>not reported</th>
<th>13.9 / 13.5</th>
<th>not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation (%)</td>
<td>74 / 73</td>
<td>73.3 / 77.6</td>
<td>82.0</td>
</tr>
<tr>
<td>Pre-exist conds (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>38.2 / 35.0</td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>12.1 / 14.4</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>Cong. cardiomyop</td>
<td>6.4 / 9.0</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.7 / 22.4</td>
<td>(Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3.4 / 3.9</td>
<td>(Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>3.1 / 2.6</td>
<td>(Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>22.2 / 26.1</td>
<td>(Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>17.1 / 18.8</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Recent trauma</td>
<td>3.3 / 5.1</td>
<td>(Academic in confidence)</td>
<td></td>
</tr>
<tr>
<td>Recent surgery (%)</td>
<td>not reported</td>
<td>5.8 / 6.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Elective</td>
<td>20.7 / 21.2</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>73.5 / 72.6</td>
<td>63.2</td>
<td></td>
</tr>
<tr>
<td>Infections (%)</td>
<td>not reported</td>
<td>32.7 / 32.5</td>
<td>(Academic in confidence)</td>
</tr>
<tr>
<td>+ve blood culture</td>
<td>21.8 / 23.3</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Gram staining of culture: purely Gram -ve</td>
<td>25.8 / 25.1</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td>purely Gram +ve</td>
<td>15.6 / 13.9</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>mixed</td>
<td>3.3 / 5.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>unconfirmed</td>
<td>33.5 / 32.3</td>
<td>37.2</td>
<td></td>
</tr>
<tr>
<td>-ve culture or not obtained</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of infection (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>39 / 49</td>
<td>53.6 / 53.6</td>
<td>46.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>16 / 17</td>
<td>20.0 / 19.9</td>
<td>24.4</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>14 / 12</td>
<td>10.0 / 10.2</td>
<td>(Academic in confidence)</td>
</tr>
<tr>
<td>Blood</td>
<td>18 / 10</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>not reported</td>
<td>16.4 / 16.3</td>
<td>(Academic in confidence)</td>
</tr>
</tbody>
</table>

---

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
(Academic in confidence information removed from Table 3)

---

i Note that Lilly’s definition of shock (arterial SBP <= 90mm Hg or mean arterial pressure <= 70mm Hg) is not consistent with more usual definitions
than in either group in the PROWESS study (particularly so with respect to MI, congestive cardiomyopathy (Academic in confidence information removed) and cancer), relatively more patients had undergone recent surgery, were in septic shock or were receiving mechanical ventilation.\textsuperscript{11}

Very limited details of the patients included in the compassionate use studies are available from the sponsor submission.\textsuperscript{11} (Commercial in confidence information removed)

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

**Outcomes**

The primary outcome in the PROWESS and ENHANCE studies was 28-day all cause mortality,\textsuperscript{39,51} though the PROWESS trial initially had two primary outcomes\textsuperscript{39} (see ‘PROWESS protocol changes’ in section 2.2.3 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 one year.\textsuperscript{11} Survival status was known for 94% of patients at 90 days and 93% at one year.\textsuperscript{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\textsuperscript{39} and safety-related outcomes were assessed in all of the open-label studies.\textsuperscript{49} The cumulative safety update provides combined safety data for all studies plus data on the commercial use of drotrecogin alfa (activated).\textsuperscript{49}

2.2.3 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 (section 2.2.5).

**Randomisation and allocation concealment**

For the PROWESS study patient assignments were made through a central randomisation centre, stratified according to site.\textsuperscript{39} The method and details of the randomisation procedure used for the EVAA study was not reported, therefore both of these items were scored as ‘unclear’.\textsuperscript{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,\textsuperscript{39} though EVAA was described only as double-blind.\textsuperscript{43} Neither study mentioned blinding of outcome assessors.
Intention-to-treat analysis

Intention-to-treat 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), 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 intention-to-treat 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.

Table 4. Internal validity of included RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Random Allocation concealment</th>
<th>Blinding ITT analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAA43</td>
<td>Unclear</td>
<td>‘Double-blind’</td>
</tr>
<tr>
<td>PROWESS39</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
</tbody>
</table>

PROWESS methods of analysis

As discussed below, a very large number of subgroup analyses of the PROWESS mortality data have been conducted, some prospective and many retrospective in nature. Two points need to be emphasised regarding these analyses. In the first place, 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 et al.46 That paper describes all of the subgroup analyses presented in it as ‘prospectively defined’ except for two (related to presence of DIC and SOFA scores at baseline). The paper by Dhainaut et al45 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 have been identified as far as possible in the sections below.

Secondly, 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. 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 and 95% CI 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% CI 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 CONSORT guidelines, using the Breslow-Day test for homogeneity of odds ratios across strata. This is a reasonable approach, as the odds ratio 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. It should be noted that qualitative interactions are thought to be unreliable estimates of direction of effect due to inconsistent replication, 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
- who were moribund and death imminent
- whose family had not committed to aggressive management of the patient
- 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’. 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 made 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 in fact a larger effect from treatment was actually seen in these patients,46 it is unlikely that this decision was made in order to increase the chance of demonstrating a significant benefit.

2.2.4 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, 0.11)43 and 6.5% (95%CI: -10.7, -2.2)39 for a relative risk of death of 0.85 (95%CI: 0.50, 1.44) and 0.79 (95%CI: 0.68, 0.92) respectively. The latter is the intention-to-treat result; when the analysis is restricted to treated patients only the relative risk is 0.80 (95%CI: 0.69, 0.94). For the dose-ranging study43 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.

Table 5 Overall 28-day mortality results

<table>
<thead>
<tr>
<th>Study</th>
<th>rhAPC / Placebo</th>
<th>ARR % (95%CI)</th>
<th>Relative risk of death (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAA43</td>
<td>28.9% / 34.1%</td>
<td>-5.2 (-23.0, 0.11)</td>
<td>0.85 (0.50, 1.44)</td>
</tr>
<tr>
<td></td>
<td>low-dose rhAPC: 35.3%</td>
<td>+1.2 (-1.9, 20.3)</td>
<td>1.03 (0.59, 1.82)</td>
</tr>
<tr>
<td></td>
<td>high-dose rhAPC: 20.5%</td>
<td>-13.6 (-32.5, 6.2)</td>
<td>0.60 (0.28, 1.27)</td>
</tr>
<tr>
<td>PROWESS39</td>
<td>ITT results</td>
<td>-6.5 (-10.7, -2.2)*</td>
<td>0.79 (0.68, 0.92)*</td>
</tr>
<tr>
<td></td>
<td>Treated pts</td>
<td>-6.1 (-10.4, -1.9)*</td>
<td>0.80 (0.69, 0.94)*</td>
</tr>
<tr>
<td></td>
<td>Combined result49</td>
<td>-5.9 (-10.0, -3.1)*</td>
<td>0.81 (0.70, 0.94)*</td>
</tr>
</tbody>
</table>

* denotes statistically significant result

ITT: intention-to-treat

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, ARR 5.2%, (p=0.023), (95%CI: -9.6, -0.8),11 and at 90 days (p=0.048, see

Technology assessment report
NICE AC-nonCIC December 2003
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 to 1,113 days in the drotrecogin alfa (activated) group (log rank p=0.097). Survival status was known for 94% of patients at 90 days and 93% at one year. Given that the sponsor’s submission states that between 5,800 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.
**Figure 2. PROWESS – long-term (90 day) mortality follow-up (all patients)**

![Graph](image1)

* Accounting for other predictors of 90 day outcome

**Figure 3. PROWESS long-term survival up to 30 months (all patients)**

![Graph](image2)

Log rank P = 0.048

Log rank P = 0.097
Placebo Median Survival = 846 days
Xigris Median Survival = 1113 days

**Mortality - subgroup analyses**

A multitude of subgroup analyses of mortality for the PROWESS trial have been reported in several publications by the trial investigators and the FDA. We designated *a priori* in our 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 Table 6 and Table 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, 1.35) in patients with one organ failure at baseline to 0.60 (95%CI: 0.33, 1.11) in those with 5 organ failures. Results for the individual subgroups were not significant, however when mortality 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 to placebo (0.78, 95%CI: 0.66, 0.93).45

Results were also presented according to APACHE II and SOFA scores at baseline. As discussed in section 1.1.4 above, 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. Also 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. 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 compared to placebo (relative risk 1.25, 95%CI: 0.78, 2.02). Those in the highest two quartiles at baseline experienced significantly lower mortality when treated with drotrecogin alfa (activated) compared to 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), though the relative benefit was greatest in those in the first and fourth quartiles and was only statistically significant in the fourth quartile. 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.

---

i 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 *et al*46 shows the relative risks and 95% confidence intervals in a forest plot.
Table 6. PROWESS subgroup analyses: 28-day all cause mortality according to clinical measures of baseline disease severity and infection site and type\(^{46}\)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mortality (%) rhAPC / placebo (n=850)/(n=840)</th>
<th>ARR (% 95% CI)(^{a}) Relative risk of death (95%CI)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall result</td>
<td>1690</td>
<td>31.3 / 24.8</td>
<td>-6.5 (-10.9, -2.3)*</td>
</tr>
<tr>
<td>No. organ failures at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2(^{ts})</td>
<td>1272</td>
<td>26.5 / 33.9</td>
<td>-7.4 (-12.1, -2.0)*</td>
</tr>
<tr>
<td>APACHE II quartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (3-19)</td>
<td>433</td>
<td>15.1 / 12.1</td>
<td>+3.0 (-3.5, 9.6)</td>
</tr>
<tr>
<td>2nd (20-24)</td>
<td>440</td>
<td>22.5 / 25.7</td>
<td>-3.2 (-11.2, 4.8)</td>
</tr>
<tr>
<td>3rd (25-29)</td>
<td>366</td>
<td>23.5 / 35.8</td>
<td>-12.3 (-21.7, -2.9)*</td>
</tr>
<tr>
<td>4th (30-53)</td>
<td>451</td>
<td>38.1 / 49.0</td>
<td>-10.9 (-19.8, -1.7)*</td>
</tr>
<tr>
<td>SOFA quartile(**)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (0-7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd (8-9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd (10-11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th (&gt;11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS (FDA analysis(^{38}))**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1431</td>
<td>23.9 / 30.6</td>
<td>-6.7 (-11.3, -2.1)*</td>
</tr>
<tr>
<td>Yes</td>
<td>259</td>
<td>29.6 / 32.1</td>
<td>-2.5 (-13.7, 8.8)</td>
</tr>
<tr>
<td>Presence of shock (PROWESS definition)((b))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>490</td>
<td>21.0 / 22.3</td>
<td>-1.3 (-8.6, 6.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>1200</td>
<td>26.3 / 34.2</td>
<td>-7.9 (-13.1, -2.8)*</td>
</tr>
<tr>
<td>Presence of shock (FDA definition(^{38}))((c))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>633</td>
<td>21.0 / 26.1</td>
<td>-5.1 (-11.8, 1.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>1057</td>
<td>27.1 / 33.5</td>
<td>-6.4 (-11.8, -0.8)*</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>415</td>
<td>17.6 / 22.9</td>
<td>-5.3 (-12.4, 1.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>1275</td>
<td>27.3 / 33.1</td>
<td>-5.8 (-10.9, -0.8)*</td>
</tr>
<tr>
<td>Vasopressor support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>633</td>
<td>17.9 / 25.2</td>
<td>-7.3 (-15.1, 0.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>1057</td>
<td>27.4 / 32.7</td>
<td>-5.3 (-10.3, -0.2)*</td>
</tr>
<tr>
<td>Presence of pneumonia(^{i})**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia - CAP</td>
<td>882</td>
<td>24.7 / 32.0</td>
<td>-7.3 (-13.3, -1.4)*</td>
</tr>
<tr>
<td>- Nosocom pneum(^{d})</td>
<td>602</td>
<td>22.5 / 31.3</td>
<td>-8.8 (-15.8, -1.7)*</td>
</tr>
<tr>
<td>- Non-pulm infection</td>
<td>280</td>
<td>30.0 / 33.3</td>
<td>-3.3 (-14.3, 7.3)</td>
</tr>
<tr>
<td>Infection site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>906</td>
<td>24.0 / 33.6</td>
<td>-8.6 (-14.4, -2.6)*</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>337</td>
<td>27.6 / 30.5</td>
<td>-2.9 (-12.6, 6.8)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>171</td>
<td>21.2 / 20.9</td>
<td>+0.1 (-12.1, 12.6)</td>
</tr>
<tr>
<td>Other</td>
<td>276</td>
<td>22.3 / 28.5</td>
<td>-6.2 (-16.4, 4.1)</td>
</tr>
<tr>
<td>Infection type(^{44})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial - Pure Gram+</td>
<td>1016</td>
<td>22.6 / 28.6</td>
<td>-6.0 (-11.3, -0.6)*</td>
</tr>
<tr>
<td>- Pure Gram-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mixed Gram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fungus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other org</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* denotes statistically significant result
** denotes retrospective subgroup analysis; all others are reported by the investigator as prospective in nature
ARR confidence intervals and RRs and confidence intervals, or data to estimate them, provided in FDA report or estimated by SHTAC using data provided in paper. Where CIs are not provided, insufficient data was available with which to estimate them.

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.

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 vaspressors), were included in the ‘no shock’ group.

241/280 had ventilator associated pneumonia.

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 us to reliably discriminate 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 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 though 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 (ACCP/SCCM definition requires both hypotension and evidence of perfusion abnormalities), those in shock at baseline (i.e. more severely ill) experienced a larger and statistically significant reduction in mortality compared to those not in shock: relative risks 0.77 (95%CI: 0.64, 0.91) compared to 0.94 (95%CI: 0.67, 1.32). It is notable that when the FDA 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).

Unpublished data relating to an assumed retrospective subgroup analysis by presence/absence of various forms of pneumonia is also available. Those patients with pneumonia experienced a larger and statistically significant relative risk reduction from drotrecogin alfa (activated) compared to those with non-pulmonary infections (relative risks 0.77 (95% CI: 0.62, 0.95) versus 0.84 (95%CI: 0.67, 1.05) respectively) though the confidence intervals for the two estimates overlap considerably. In those with pneumonia, the benefit may occur in those with community-acquired pneumonia rather than nosocomial pneumonia (defined as those in hospital for less than or longer than four days [usually 72 hours] prior to study enrolment respectively), see Table 6.

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.
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). Although insufficient data is 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.

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

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

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

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 or over in the drotrecogin alfa (activated) compared to the placebo group.

The impact of three other indicators of disease severity were 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 compared to those without overt DIC, with a larger reduction in all cause mortality; relative risks 0.64 (95%CI: 0.48, 0.83) and 0.85 (95%CI: 0.69, 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. On the other hand, 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
(Academic 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 mortality49 (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 colleagues44 have presented results according to type of infection, i.e. causative micro-organism 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, though neither result was statistically significant.iv

Reported retrospective analyses for patients with multiple organ dysfunction according to these categories show similar or smaller differences between groups according to these categories48 (Table 7). In particular, patients with Gram positive and Gram negative infections had relative risks of death of 0.67 and 0.71 respectively. We have been unable to calculate the confidence intervals for these estimates due to lack of data, however the paper by Dhainaut and colleagues45 shows the confidence intervals for both to be very similar, though results are only statistically for the Gram positive group.

iv Data for these subgroups were also reported by Ely and colleagues46, but the differences between the subgroups was greater. We can find no reason for this discrepancy.
Mortality – result of logistic regression analysis

A multivariable logistic regression model of predicted risk of mortality in the PROWESS study\textsuperscript{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.\textsuperscript{39}

Additional outcomes (excluding safety)

Death from septic shock

The published cumulative safety review\textsuperscript{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, 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, 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 organ-failure free days, though there were non-significant trends in favour of high-dose drotrecogin alfa (activated) in the number of SIRS-, respiratory-, central nervous system- and circulatory failure-free days.\textsuperscript{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 to 7\textsuperscript{48} (Table 8). Overall there were reported to be no significant differences in mean total SOFA scores between groups either over days 1 to 7 (p=0.463) or days 1 to 28 (p=0.329) though 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 to placebo when SOFA scores were averaged over both 1-7 days and 1-28 days.

Table 8. PROWESS results: impact of drotrecogin alfa (activated) on other outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patient group</th>
<th>N</th>
<th>rhAPC / placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from septic shock (%) (for both RCTs)</td>
<td>MOD</td>
<td>509 (1821)</td>
<td>47.9 / 39.2 (12.0 / 12.1)\textsuperscript{a}</td>
</tr>
</tbody>
</table>
### Impact on organ dysfunction

#### Mean SOFA score, overall and for individual organ systems

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Cardio</th>
<th>Hepatic</th>
<th>Respir</th>
<th>Haem</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-7</td>
<td>1690</td>
<td>1482</td>
<td>1598</td>
<td>1040</td>
<td>681</td>
<td>590</td>
</tr>
<tr>
<td>% resolving</td>
<td></td>
<td>63.3%</td>
<td>17.5%</td>
<td>56.8%</td>
<td>56.4%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.19 (1.04, 1.36)*</td>
<td>1.41 (1.09, 1.82)*</td>
<td>1.08 (0.92, 1.27)</td>
<td>1.01 (0.83, 1.24)</td>
<td>0.86 (0.68, 1.09)</td>
<td></td>
</tr>
</tbody>
</table>

#### Resolution of organ dysfunction from baseline (during days 1-7)<sup>b</sup>

<table>
<thead>
<tr>
<th>OD present:</th>
<th>Cardio</th>
<th>Hepatic</th>
<th>Respir</th>
<th>Haem</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% resolving</td>
<td>63.3%</td>
<td>17.5%</td>
<td>56.8%</td>
<td>56.4%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.19 (1.04, 1.36)*</td>
<td>1.41 (1.09, 1.82)*</td>
<td>1.08 (0.92, 1.27)</td>
<td>1.01 (0.83, 1.24)</td>
<td>0.86 (0.68, 1.09)</td>
</tr>
</tbody>
</table>

#### Development of organ dysfunction in those without the relevant OD at baseline (days 1-7)

<table>
<thead>
<tr>
<th>OD present:</th>
<th>Cardio</th>
<th>Hepatic</th>
<th>Respir</th>
<th>Haem</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% new dysfunction</td>
<td>64.4%</td>
<td>92.6%</td>
<td>20.4%</td>
<td>37.2%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.19 (1.04, 1.36)*</td>
<td>0.93 (0.55, 1.56)</td>
<td>1.23 (0.86, 1.76)</td>
<td>0.82 (0.67, 0.99)*</td>
<td>1.01 (0.78, 1.32)</td>
</tr>
</tbody>
</table>

### Impact on other outcomes

#### Length of hospital stay (mean days)<sup>c</sup>

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1221</td>
<td>469</td>
</tr>
<tr>
<td>20.7 / 20.9</td>
<td></td>
<td>8.3 / 8.5</td>
</tr>
</tbody>
</table>

#### Length of ICU stay (mean days)<sup>c</sup>

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1221</td>
<td>469</td>
</tr>
<tr>
<td>12.9 / 12.7</td>
<td></td>
<td>7.6 / 7.7</td>
</tr>
</tbody>
</table>

#### Functional status at day 28

<table>
<thead>
<tr>
<th>ADL score&lt;sup&gt;d&lt;/sup&gt;</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>mean score at day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>47%</td>
<td>5%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>10%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/ 44%</td>
<td>/ 6%</td>
<td>/ 4%</td>
<td>/ 5%</td>
<td>/ 8%</td>
<td>/ 8%</td>
<td>/ 25%</td>
<td>/ 2.44</td>
</tr>
</tbody>
</table>

#### Effect of drug timing<sup>11</sup>

<table>
<thead>
<tr>
<th>rhAPC admin (h):</th>
<th>ARR (95%CI)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;Q (&lt;11.07)</td>
<td>-6.5 (-15.1, 2.2)</td>
<td>0.80 (1.59, 1.08)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;Q (11.08-17.75)</td>
<td>-5.5 (-14.0, 3.2)</td>
<td>0.83 (0.61, 1.12)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;Q (17.8-22.5)</td>
<td>-3.5 (-11.9, 4.9)</td>
<td>0.88 (0.64, 1.20)</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;Q (&gt;22.52)</td>
<td>-9.0 (-17.2, -0.6)</td>
<td>0.70 (0.51, 0.98)</td>
</tr>
</tbody>
</table>

---

MODS – multiple organ dysfunction (sepsis-induced) syndrome; ARR – absolute risk reduction; RRR – relative risk reduction; Cardio – cardiovascular; Respir – respiratory; Haem – haematologic; ADL – Activities of Daily Living

<sup>a</sup> data in brackets, ARRs and RRs relate to number of deaths from each cause out of total number of patients in the trials

<sup>b</sup> the percentage of patients whose organ dysfunction resolved during days 1-7 was lower for those with APACHE II ≥ 25 compared to those with lower APII scores. No significant interactions between treatment and disease severity were found for any organ system (all p ≥ 0.206)

<sup>c</sup> standard deviations not provided
ADL scale assesses functional dependence in 6 domains – bathing, dressing, toileting, transferring, feeding, and continence; a score of 6 indicates full dependence while 0 indicates fully independent.

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 to placebo for all organ systems except for hepatic organ dysfunction. Results were significant only for those with cardiovascular or respiratory dysfunction at baseline, 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 haematologic organ dysfunction during days 1-7 compared to placebo (hazard ratio 0.82 (95%CI: 0.67, 0.99)). The likelihood of developing other new organ system dysfunctions did not differ significantly between treatment groups though 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 the mean Activities of Daily Living (ADL) score in the drotrecogin alfa (activated) group at day 28 was slightly higher than that in the placebo group (2.50 vs. 2.44) and a slightly higher proportion of patients in the drotrecogin alfa (activated) group were fully independent (ADL score of 0) though 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.

For the PROWESS trial, 46.8% of drotrecogin alfa (activated) survivors were discharged to home compared to 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. skilled nursing home or other hospital. 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.

Length of stay

The phase II RCT (EVAA) 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 indicate that drotrecogin alfa (activated) did not appear to have any impact on overall length of hospital or intensive care stay. Hospital stay in both groups was almost 21 days for survivors and just over 8 days for non-survivors and intensive care stay almost 13 days and just under 8 days respectively (Table 8).

Assessed by the need for vasopressors and mechanical ventilation respectively

Assessed by platelet count
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 et al (2003) as reported in the sponsor’s submission\(^{11}\) have 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 below demonstrates results for cardiovascular dysfunction. Continued improvement in cardiovascular function the next day was also reported to improve odds of survival. Improvement in other organ systems or beyond first study day was not associated with improved survival.\(^{11}\)

Figure 4 Mortality trend in vasopressors\(^{11}\)

![Mortality by Trend in Vasopressors](image)

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) is administered in the first to third quartiles the relative risks of death lie 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, 0.98). The importance of this result is difficult to interpret given the retrospective nature of the subgroup analyses.

Figure 5. Mortality rates by time from first organ failure to study drug administration\(^{11}\)
Limited results from the retrospective MERCURY study were also provided in the sponsor’s submission (Wheeler et al 2004 and Schmidt et al 2003, as reported in submission). 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 – 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 between drotrecogin alfa (activated) and placebo in either RCT (Table 9). 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). The incidence of SBEs was higher in the ENHANCE study (Commercial in confidence information removed) when compared to the RCTs. The incidence of intracranial haemorrhage (ICH) was also higher than in PROWESS, though fatal ICHs were similar between ENHANCE and PROWESS.

Data on adverse events in all of the studies have been published in the cumulative safety review, though it appears that data for all of the patients in the open-label studies were not available at the time of that review (Table 10). There are also slight discrepancies in number of SBEs reported in the individual trials compared to 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 to 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 to 69 post-
infusion). 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%).

When data for intracranial haemorrhage were pooled, no patients receiving placebo experienced an ICH compared to 16 (0.6%) of drotrecogin alfa (activated) treated patients; approximately half of these (9) were fatal (Table 10), and most were drug-related (12/16).

2.2.5 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, both in terms of 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). This provides as close a picture as possible of those UK patients that 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, and we have obtained further information related to this 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 have a higher disease severity in terms of number of organ failures compared to those included in the PROWESS study. Nevertheless, when the PROWESS inclusion and exclusion criteria are applied, the 28-day mortality is similar to the placebo group of PROWESS although hospital mortality is 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 highest risk of death were excluded from the clinical studies and that patients in the UK tend to be admitted to ICU at a later stage in their disease.

The implications of these data are covered further in the discussion (Section 6).
### Table 9. Number (%) of adverse events (to 28-day follow-up)

<table>
<thead>
<tr>
<th></th>
<th>At least 1 SAE&lt;sup&gt;a&lt;/sup&gt;</th>
<th>At least 1 bleeding event</th>
<th>SBE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ICH during infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rhAPC</td>
<td>placebo</td>
<td>p-val</td>
<td>rhAPC</td>
</tr>
<tr>
<td>EVAA&lt;sup&gt;43&lt;/sup&gt;</td>
<td>rhAPC: 90</td>
<td>placebo: 41</td>
<td></td>
<td>rhAPC</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>19</td>
<td>.42</td>
<td>4 (2)</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>46%</td>
<td></td>
<td>4% (2%)</td>
</tr>
<tr>
<td>PROWESS&lt;sup&gt;11,39&lt;/sup&gt;</td>
<td>rhAPC: 850</td>
<td>placebo: 840</td>
<td></td>
<td>212 (160)</td>
</tr>
<tr>
<td></td>
<td>106</td>
<td>102</td>
<td>.84</td>
<td>24.9% (18.8%)</td>
</tr>
<tr>
<td></td>
<td>12.5%</td>
<td>12.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENHANCE&lt;sup&gt;11&lt;/sup&gt;</td>
<td>rhAPC: 2378</td>
<td></td>
<td></td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nr (91)</td>
</tr>
</tbody>
</table>

(Commercial in confidence information removed)

SAE – serious adverse event; SBE – serious bleeding event; ICH – intracranial haemorrhage; nr = not reported
<sup>a</sup> serious adverse events: 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
<sup>b</sup> serious bleeding events: those serious adverse events that involved bleeding, including 1) any intracranial haemorrhage, 2) a need for transfusion of two or more units of packed red blood cells on two consecutive days, 3) life threatening bleeding (an event in which the patient was at risk of death at the time of the event)
Table 10. Adverse events – combined results from cumulative safety review\textsuperscript{49}

<table>
<thead>
<tr>
<th></th>
<th>SBEs</th>
<th>During infusion</th>
<th>Post-infusion</th>
<th>ICH during infusion All (fatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N</td>
<td>n (%)</td>
<td>n</td>
<td>% (95%CI)</td>
</tr>
<tr>
<td>Placebo</td>
<td>881</td>
<td>20 (2.3%)</td>
<td>6</td>
<td>0.7 (0.3, 1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.6 (0.8, 2.7)</td>
</tr>
<tr>
<td>rhAPC - all clinical studies</td>
<td>2786</td>
<td>148 (5.3%)</td>
<td>79</td>
<td>2.8 (2.3, 3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5 (1.9, 3.1)</td>
</tr>
<tr>
<td>RCTs\textsuperscript{b} (EVAA, PROWESS)</td>
<td>940</td>
<td>35 (3.7%)</td>
<td>20</td>
<td>2.0 (1.3, 3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.6 (0.9, 2.6)</td>
</tr>
<tr>
<td>Open-label studies (ENHANCE)</td>
<td>1578</td>
<td>94 (6.0%)</td>
<td>49</td>
<td>3.1 (2.3, 4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.9 (2.1, 3.8)</td>
</tr>
<tr>
<td>Comp. use studies (EVAS, EVBC)</td>
<td>268</td>
<td>19 (7.1%)</td>
<td>10</td>
<td>3.7 (1.8, 6.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4 (1.6, 6.3)</td>
</tr>
<tr>
<td>rhAPC - commercial use</td>
<td>3991</td>
<td>34 (0.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} defined as any intracranial haemorrhage, 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.

\textsuperscript{b} Note: numbers do not add up to those reported in original trial publications.\textsuperscript{39,43}
Table 11. Generalisability of PROWESS results

<table>
<thead>
<tr>
<th></th>
<th>UK 1 (n=17025)(^a)</th>
<th>UK 2 (n=15362)(^b)</th>
<th>PROWESS (EVAD)(^39) rhAPC/placebo</th>
<th>ENHANCE(^11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean±SD)</strong></td>
<td>61.9</td>
<td>60.8 (16.9)</td>
<td>60.5 ± 17.2 / 60.6 ± 16.5</td>
<td>59.1</td>
</tr>
<tr>
<td><strong>Mean APACHE II score</strong></td>
<td>18.9</td>
<td>24.6 / 25.0</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td><strong>OF incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 system</td>
<td>19.8</td>
<td>16.4</td>
<td>25.3 / 24.2</td>
<td>15.6</td>
</tr>
<tr>
<td>2 systems</td>
<td>41.0</td>
<td>34.4</td>
<td>31.8 / 32.5</td>
<td>29.7</td>
</tr>
<tr>
<td>3 systems</td>
<td>28.8</td>
<td>30.8</td>
<td>25.2 / 26.0</td>
<td>29.6</td>
</tr>
<tr>
<td>4 systems</td>
<td>9.0</td>
<td>14.7</td>
<td>14.0 / 13.8</td>
<td>18.3</td>
</tr>
<tr>
<td>5 systems</td>
<td>1.3</td>
<td>3.7</td>
<td>3.6 / 3.6</td>
<td>6.7</td>
</tr>
<tr>
<td>≥ 2 systems</td>
<td></td>
<td>83.6%</td>
<td>75%</td>
<td>84.4% (72.9%)</td>
</tr>
<tr>
<td>≥ 3 systems</td>
<td></td>
<td>49.2%</td>
<td>43%</td>
<td>54.7% (39.9%)</td>
</tr>
<tr>
<td>≥ 4 systems</td>
<td></td>
<td>18.4%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td><strong>28-d mortality % (95%CI)</strong></td>
<td>32.7</td>
<td>41.5 (40.8, 42.3)</td>
<td>24.8 / 31.3</td>
<td>25.3 (23.5, 27.0)</td>
</tr>
<tr>
<td><strong>Hospital mortality % (95%CI)</strong></td>
<td>39.2</td>
<td>47.3 (46.5, 48.1)</td>
<td>29.4 / 34.6</td>
<td></td>
</tr>
<tr>
<td><strong>28-d mortality by no. ODs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 system</td>
<td></td>
<td>17.8 (16.3, 19.4)</td>
<td>19.5 / 21.2</td>
<td></td>
</tr>
<tr>
<td>2 systems</td>
<td></td>
<td>30.2 (29.0, 31.5)</td>
<td>20.7 / 26.0</td>
<td></td>
</tr>
<tr>
<td>3 systems</td>
<td></td>
<td>47.3 (45.9, 48.8)</td>
<td>26.2 / 34.4</td>
<td></td>
</tr>
<tr>
<td>4 systems</td>
<td></td>
<td>71.8 (69.9, 73.6)</td>
<td>38.7 / 46.6</td>
<td></td>
</tr>
<tr>
<td>5 systems</td>
<td></td>
<td>83.3 (79.9, 86.3)</td>
<td>32.3 / 53.3</td>
<td></td>
</tr>
<tr>
<td>≥ 2 systems</td>
<td></td>
<td>46.2 (45.3, 47.1)</td>
<td>26.5 / 33.9</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital mortality by no. ODs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 system</td>
<td></td>
<td>18.0</td>
<td>21.8 (20.2, 23.5)</td>
<td></td>
</tr>
<tr>
<td>2 systems</td>
<td></td>
<td>32.7</td>
<td>36.0 (34.7, 37.3)</td>
<td></td>
</tr>
<tr>
<td>3 systems</td>
<td></td>
<td>46.2</td>
<td>52.5 (51.1, 53.9)</td>
<td></td>
</tr>
<tr>
<td>4 systems</td>
<td></td>
<td>71.5</td>
<td>75.1 (73.3, 76.9)</td>
<td></td>
</tr>
<tr>
<td>5 systems</td>
<td></td>
<td>77.6</td>
<td>86.1 (83.0, 88.8)</td>
<td></td>
</tr>
<tr>
<td>≥ 2 systems</td>
<td></td>
<td>44.0</td>
<td>51 (50.1, 51.9)</td>
<td>32.0 / 36.6</td>
</tr>
</tbody>
</table>

UK 1 – UK admissions with PROWESS inclusion and exclusion criteria applied
UK 2 - UK admissions with only PROWESS inclusion criteria applied
\(^a\) ICNARC analyses done for Lilly based on 61458 admissions between 1996 and 2000; analyses for ICNARC CCM 2003 paper based on 56673 admissions between Dec 1995 to and Feb 2000.
\(^b\) 6983/15362 (45.5%) would have met PROWESS exclusion criteria.
2.3 **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, -2.2) for a relative risk of death of 0.79 (95%CI: 0.68, 0.92) (intention-to-treat 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, -2.4) and 0.78 (95%CI: 0.66, 0.93).

A large number of further subgroup analyses have been conducted and we have highlighted our 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 when compared to those with higher scores. As discussed above, 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), we can see that some indicators show a greater effect in the more severely ill, whilst others show less effect.
3 Economic analysis

3.1 Introduction

The aim of this section 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 SHTAC.

3.2 Systematic review of the literature

3.2.1 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 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.

3.2.2 Results of the systematic review: cost-effectiveness

The literature search identified three published cost-effectiveness studies (Angus et al,52 Manns et al58 and Fowler et al59), and six published abstracts (Davies et al,60 Neilson et al,61,62 Lucioni et al,63 Sacristan et al,64 Launois et al65). Two further unpublished abstracts were identified by the review team (Coyle et al66, Riou Franca et al67). Additionally, the Eli Lilly submission to the NICE Technology Appraisal Programme 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 checklist68 (see Appendix 10), and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions (see Appendix 11).

Our review of the cost-effectiveness literature places emphasis on the published economic evaluations, and the Eli Lilly submission to NICE. We offer outline detail on 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/saved, and a cost per QALY. The cost-effectiveness analysis from the PROWESS investigators, and from Fowler et al, also show an estimate of the cost per life saved. Below we discuss the methods used in the studies to estimate costs and benefits, and thereafter we consider the cost-effectiveness findings.

**Economic Evaluations: Estimation of Benefits**

**Summary of Methods**

In order 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 intent-to-treat 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 absolute risk reduction (ARR) associated with drotrecogin alfa (activated). Where cost-effectiveness has been determined through the comparison of a country specific baseline cohort of severe sepsis patients, studies have used relative risk (RR) data from the PROWESS analysis (and from the posthoc analysis of PROWESS reported by the FDA). Effectiveness data reported from PROWESS, and from the posthoc 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, i.e. those patients with two or more organ dysfunctions, and/or those patients with higher APACHE II scores.

**Published Economic Evaluations**

The cost-effectiveness analysis from the PROWESS investigators\(^5^2\) used the primary clinical endpoint from the trial, where observed mortality was 30.8% for placebo and 24.7% for drotrecogin alfa (activated) (p=0.005). Angus et al 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 et al,\(^2^3\) 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 elder 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 an additional 12.3 years at an average utility of 0.68, resulting in 8.5 QALYs. The incremental life-years gained were $0.48 \pm 0.29$, and the incremental QALYs gained were $0.33 \pm 0.21$ per treated patient.

The cost-effectiveness analysis from Manns et al$^{58}$ applies 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 $\leq 24$ and those $\geq 25$). 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 estimates life-expectancy using data from the cohort study on subsequent risk of death amongst survivors of severe sepsis, and mortality rates for the Canadian population. Again, the data on subsequent risk of death was available by age group and APACHE II score. The authors report only cost per life-year gained in their baseline analysis, but adjust life-expectancy for quality of life to estimate cost-per QALY in further analyses. They use 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 one year after discharge in a group of patients admitted to intensive care with acute respiratory distress syndrome (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, 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 $\leq 24$, and 0.76 years for those with a score $\geq 25$.

The analysis from Fowler et al$^{59}$ considers a cohort of severe sepsis patients 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 uses data on ARR from PROWESS, and from FDA analysis of PROWESS data by disease severity (using APACHE II scores). Analysis is undertaken for patients matching the PROWESS criteria (i.e. all patients), and according to disease severity, as measured by an APACHE II score of $\geq 25$, and less than 25.

Life-expectancy is estimated using US life tables, and an adjustment to life expectancy over an eight year period to allow for the effects of severe sepsis on rates of mortality. The authors also cite the study by Quartin et al$^{23}$ as a source for data on the adjustment of life expectancy, but they do not report the exact methods used. Utilities/values for the health states in the Markov process are stated to be from published estimates of health related quality of life that are similar to the states describing the transitions for patients with severe sepsis. The study assumes 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 are used respectively for acute severe sepsis with and without treatment complications). A health state value of 0.64 is used for subacute septic illness beyond the treatment period, and a value of 0.80 was used to represent post-sepsis survival. These values, for survival after the acute septic illness are assumed to be similar to those for long-term survival following similar acute illnesses. No supporting data or arguments for this are presented.

Fowler et al estimate 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 ≥ 25, and were 0.02 life years (0.017 QALYs) for those with a score < 25.

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

The abstracts from Neilson et al and Lucioni et al 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 et al and Neilson et al 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 et al report an adjusted life-expectancy of 9.9 years per survivor, or a gain of 0.59 years per patient treated. Sacristan et al report that hospital survivors were estimated to live 12.2 years.

Davies et al 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. Firstly, as above, they use an adjustment factor of 0.51, from a published study (i.e. Quartin et al), across all patients. Secondly, a patient specific five year survival was estimated using data from a published cohort study reporting on adult patients admitted to intensive care. Using this second method, following a period of five 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. 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 et al,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 is based on patient level data from the PROWESS placebo and treatment group, for patients meeting PROWESS criteria and having multiple organ failure. The analysis applies data on 28-day all cause mortality for PROWESS for patients with multiple organ failure (ARR of 7.4%), with an adjustment made in order to guard against double counting hospital mortality (mortality in hospital but after day 28) and mortality in year one following survival at day 28; an adjusted ARR of 7.26% is used in the cost-effectiveness model. Further survival analysis is undertaken using ARR data from longer follow-up of PROWESS patients. (Academic in confidence information removed). The analysis uses age-gender patient profiles from the PROWESS placebo and treatment arms, and attributes an expected life-expectancy using data from UK life tables, to estimate future survival benefits. Future life-expectancy is adjusted over years one to four, following survival of severe sepsis, using data from an observational study by Wright et al (discussed below). The data are 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 is 15.37 years, using data on 28-day survivors. The estimated life year gains per patient treated are 1.115 years (based on 28-day survivors). Where data are used from longer-term follow up studies the life expectancy per extra survivor is 15.25 years, and the incremental gain is 0.706 years.

The cost-effectiveness analysis from Eli Lilly uses a single point estimate of 0.69 as a health state utility to weight future life year gains, i.e. to calculate QALYs. This point estimate is from an abstract published by Drabinski et al,70 (discussed below).

**Economic Evaluations: Estimation of Costs**

**Summary of methods**

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

Published Economic Evaluations

Angus et al\textsuperscript{52} measure costs for their base case analysis (i.e. cost per life saved) as the differences in health care costs (hospital, physician, study-drug, and post-discharge 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. Post discharge costs (up to 28 days) were estimated by assigning each day a cost depending on patient location, and summing over total days (using $1,170 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. life-time analysis), the costs were as the base case plus life-time costs post day 28, which were calculated using age-specific annual health care costs for the US (US database costs, from 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. Due to the use of a cost cohort in the calculation of overall patient costs the authors correct 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 $9,800 ± $2,900 per patient treated. For the life time reference case analysis the costs increased by $16,000 ± $4,200 per patient treated.

Manns et al\textsuperscript{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 health care costs were based on estimates derived from the cohort study, which provided costs for years one to three, with costs assumed to remain constant over time, after year three (mean cost following discharge in year one was $14,181, year 2 was $4,698, with year three and thereafter at $4,579). 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 $6,800 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 et al used a published estimate of cost related to treatment of serious bleeds ($8,306 per episode), and estimated the additional cost per patient for treatment of serious bleeds to be $122. Manns et al do not report the incremental costs per patient, but they can be estimated from their cost-effectiveness results to be circa $10,615.

Fowler et al estimate intervention costs, hospitalisation costs and longer term health care costs associated with survivors of severe sepsis. They use a modelling approach and present findings for patient defined using PROWESS characteristics (all patients), and for patients defined using the APACHE II score (group with a score ≥25, and the group with a score <25). The authors employed a life time 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 $6,800. The analysis included costs associated with serious bleeding (cost estimate of $1,237 per event used), and a cost associated with all cause death ($5,310). 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 health care costs for survivors were estimated using age adjusted US medical expenditure data. Fowler and colleagues estimate 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 ≥25 were $15,166, and $6,851 for those with an APACHE II score of <25.

Abstracts

Abstracts from Neilson et al, Lucioni et al, and Sacristan et al apply PROWESS data on resource use with country specific unit costs, generally covering drug costs, costs to day 28, and to final hospital discharge. Riou Franca and colleagues estimate costs using PROWESS trial data, the French CubRea database and a literature review, and estimate an incremental cost per patient treated of $7,545. The authors include treatment and initial hospitalisation in their cost estimate, and surprisingly their incremental cost per patient is 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 et al do not report methods for cost calculations, but report the incremental cost per patient (all patient group) treated with drotrecogin alfa (activated) to be 7,623 Euros.

Davies et al calculate cost per hospital stay, using UK specific data on resource use, and cost for drotrecogin alfa (£4,496) from the PROWESS study data. They report the mean additional cost of caring for an extra survivor, excluding drotrecogin alfa (activated), at £2,433, with total incremental cost per patient at £4,642 (this estimate is based on drug cost plus a 6% chance of incurring additional health care costs for extra survivors).

Coyle et al used resource use data from PROWESS and apply 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 uses an estimate of the intervention cost based on findings from PROWESS, where the mean cost for drotrecogin alfa (activated) was £4,717 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 £1,337 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 estimate that the total additional cost per patient treated is £5,106. Using data from the longer term follow up study the additional cost per patient treated was £5,331. No allowance is made for additional risks associated with serious bleeding events. Eli Lilly do not include health care 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, section 3.3).

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 et al reporting $33,000 and $27,936 respectively per life year gained, with estimates of $48,800 and $46,560 respectively per QALY. Estimates from Fowler et al are slightly lower with cost per life year 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 et al the cost per life year for this group is $575,054, with Fowler and colleagues reporting 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 license 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% to 7.4% versus ARR of 6.1%), hence the cost-effectiveness profile is more attractive.

Davies et al, in a UK study, report cost per life year for the PROWESS patient group between £7,037 and £9,519, 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 per QALY for the patient group with multiple organ dysfunction are £4,716 and £6,385, 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,\textsuperscript{11} reports a cost per QALY of £6,637 (£4,580 per life year gained) in those patients with multiple organ dysfunction, based on PROWESS 28-day all cause mortality data. A further cost per QALY of £10,937 (£7,547) is estimated based on all-cause mortality data observed at a longer term follow-up (based on hospital mortality at final patient discharge day 297).\textsuperscript{11}

Table 12 Summary findings for published cost effectiveness studies/abstracts

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost-Effectiveness Estimates – Summary findings</th>
</tr>
</thead>
</table>
| Angus et al 2003\textsuperscript{52}  
(for the PROWESS Investigators) | Reference case: $33,000 per life-year gained  
Reference case: $48,800 per QALY gained  
Reference case: By severity,  
Base case analysis: $160,000 per life saved  
Base case, cost per life saved, by severity, APACHE II quartiles:  
| Manns et al 2002\textsuperscript{58} | All patients: (with relative risk of death reported in PROWESS study)  
Cost per life year gained $27,936  
Cost per QALY $46,560  
By severity: (with relative risk of death reported in FDA reanalysis)  
APACHE II $\geq$ 25: $19,723 per life year gained ($32,872 per QALY)  
APACHE II $<$ 25: $575,054 per life year gained ($958,423 per QALY) |
| Fowler et al 2003\textsuperscript{59} | For ‘all patient’ analysis:  
Cost per Life year gained $15,801  
Cost per QALY £20,047  
For patients with APACHE II $\geq$ 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\textsuperscript{60}  
[Abstract] | For severe sepsis patients defined according to PROWESS:  
Cost per life year saved is £7,037 - £9,519, 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 $\geq$2 organ dysfunctions, cost per life year saved is £4,716, and cost per QALY is £6,385 |
| Launois et al 2002\textsuperscript{55}  
[Abstract] | Cost per additional life year saved reported at 18,446 Euros.  
Other results reported for sub-groups ranged from 10,005 Euros to 31,833 euros. |
| Neilson et al (1) 2002\textsuperscript{61}  
[Abstract] | Incremental cost per life year gained reported at 14,400 Euros. |
| Neilson et al 2002 (2)\textsuperscript{62}  
[Abstract] | Germany: 14,400 Euros per life year gained  
Austria: 15,400 Euros per life year gained  
For high risk patients, with $\geq$ 2 or more organ dysfunctions, cost per life year reported at 10,400 Euros for Germany and 11,300 or Austria |
| Lucioni et al 2002\textsuperscript{63}  
[Abstract] | Cost per life year gained:  
13,436 Euros for the severe sepsis patient group  
9,660 Euros for severe sepsis patients with multiple organ failure |
| Sacristan et al 2002\textsuperscript{64}  
[Abstract] | Base case: cost per life year gained reported at 9,799 Euros, for patients with multiple organ failure,  
(13,594 euros for patients with severe sepsis population) |
| Coyle et al 2002\textsuperscript{65} | Incremental cost per QALY reported at $15,500. |


<table>
<thead>
<tr>
<th>Study</th>
<th>Cost-Effectiveness Estimates – Summary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Abstract,]</td>
<td></td>
</tr>
<tr>
<td>Riou Franca 200367</td>
<td>Incremental cost per QALY reported at $19,685 for patients with severe sepsis and multiple organ failure</td>
</tr>
<tr>
<td>Eli Lilly Submission11</td>
<td>PROWESS patients with multiple organ dysfunction:</td>
</tr>
<tr>
<td></td>
<td>28-d survival data:  Cost per Life year gained £4,580</td>
</tr>
<tr>
<td></td>
<td>Cost per QALY £6,637</td>
</tr>
<tr>
<td></td>
<td>Longer term follow up data:</td>
</tr>
<tr>
<td></td>
<td>Cost per life year gained £7,547</td>
</tr>
<tr>
<td></td>
<td>Cost per QALY £10,937</td>
</tr>
</tbody>
</table>

**Generalisability**

The cost-effectiveness findings from the published economic evaluations are based on non-UK populations, with Angus et al and Fowler et al using US resource use and cost data, and Manns et al 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 et al. Furthermore, the licence indication in North America is different to that in Europe, where the indicated patient group are those patients with severe sepsis and multiple organ dysfunction.

European abstracts present country 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 are limited in the context of the relevant patient group in England and Wales. Davies and colleagues present analyses for the UK, with UK specific data on resource use and life-expectancy, therefore the findings are relevant to the UK population, however, they do use 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 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, i.e. 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 was 30.8%, the controls used in the Eli Lilly analysis (ICNARC matched data) have 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), 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.

3.2.3 *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. We discuss below 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.

**Quartin and Colleagues**

Quartin *et al*\textsuperscript{23} report findings from a US cohort study examining the magnitude and duration of the effects of sepsis on survival. The study compares survival of 1,505 patients screened for a controlled trial (conducted in the 1980’s) of corticosteroids in the treatment of sepsis (the VACSSS trial\textsuperscript{71}), with 91,830 nonseptic 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 ICD-9 codes in patient treatment notes. Septic patients and controls were of a similar age, with both populations almost entirely male. Data on a range of comorbidities 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 eight 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 to controls) through five years after the septic episode. Survivors of uncomplicated sepsis appeared at increased risk of dying compared to controls beyond five years, in analysis of all cause mortality data. However, where analysis adjusted for death from nonseptic 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 *et al* report that after eight years 1,229 of the 1,505 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 life span from 8.03 years to 4.08 years in 30-day survivors.

Quartin *et al* 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. Quartin *et al* do not directly report an adjustment factor of 0.51, they report estimates of the relative risk of dying for patients with sepsis relative to controls by sepsis severity and time interval (both adjusted and nonadjusted analysis). We present below (Table 13) the relative risks reported by Quartin *et al* in their analysis of unadjusted mortality. It would appear that their reporting of the reduction of life span 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 *et al*. 

Technology assessment report 61
NICE AC-nonCIC December 2003
Table 13. Estimates of relative risk of dying for patients with sepsis relative to controls by sepsis severity and time interval* (source: Quartin et al23 table 4)

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Uncomplicated sepsis</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30d</td>
<td>5.0 (4.2-5.9)</td>
<td>12.1 (10.8-13.6)</td>
<td>16.8 (14.0-20.0)</td>
</tr>
<tr>
<td>31-90d</td>
<td>4.9 (3.9-6.2)</td>
<td>8.3 (6.8-10.3)</td>
<td>8.5 (5.7-12.8)</td>
</tr>
<tr>
<td>91-180d</td>
<td>3.5 (2.6-4.8)</td>
<td>4.3 (3.1-6.0)</td>
<td>8.7 (5.4-14.2)</td>
</tr>
<tr>
<td>181-365d</td>
<td>1.6 (1.1-2.4)</td>
<td>3.4 (2.4-4.8)</td>
<td>5.2 (2.9-9.6)</td>
</tr>
<tr>
<td>1-2y</td>
<td>2.3 (1.7-3.0)</td>
<td>3.1 (2.3-4.2)</td>
<td></td>
</tr>
<tr>
<td>2-5y</td>
<td>1.7 (1.4-2.1)</td>
<td>2.2 (1.7-2.8)</td>
<td></td>
</tr>
<tr>
<td>5-8y</td>
<td>1.6 (1.2-2.1)</td>
<td>1.2 (0.8-1.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Relative risks were calculated by means of univariate Cox proportional hazards regression.

The finding by Quartin et al of an increased risk of death for survivors of sepsis (by category) compared to controls (certainly over the first year after hospitalisation and probably for as long as five years thereafter), indicates that mortality in severe sepsis patients is a serious concern beyond the typical clinical trial endpoint of 28 days. The study demonstrates that much of the mortality attributable to sepsis occurs after this time-frame. The study does have limitations in that it is based on treatment practice in the mid 1980’s, and both populations are almost entirely male. The study is an observational design so it is not possible to fully adjust for differences between sepsis patients and controls. The authors warn over the use of ICD-9 data and over potential biases in the reporting of comorbidities between groups. Furthermore they warn that there is a possibility that some of the sepsis patients may have suffered from a systemic inflammatory response syndrome but may have not been septic.

Wright and Colleagues

Wright et al25 report a retrospective cohort study on 2,104 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 long-term survival of critically ill patients, who were followed up for a minimum of five years and a maximum of 12 years, with that of an age- and sex-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 five year mortality was 47.1%; for those diagnosed with septic shock ICU mortality was 41.6% and five year mortality was 62.9%. For those patients surviving intensive care the five 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 below; 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.
Table 14. Survival of critically ill patients compared to an age- and sex-matched normal population [source: Wright et al, Table 2]

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

*Year 6 onwards do not include 95% confidence intervals as the patients entering this period represent an incomplete cohort.

Limitations highlighted by the authors are the possibility of missing some deaths due to data matching with registration of death, and loss to follow-up. The sample was from an ICU which 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 four years, after which mortality matched that of the general population.

**Manns and colleagues**

In their cost-effectiveness study Manns et al\(^{58}\) report findings from a cohort study which was undertaken to obtain estimates of mortality and direct health care 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 one, 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.

### 3.2.4 Health related quality of life after survival of severe sepsis

We have undertaken 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; we identified only one published abstract 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 et al\(^{72}\) report that less than two percent 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 et al\textsuperscript{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 (day 30, 60, 90 and 180) using the Euroqol EQ-5D health status instrument, including the use of a visual analogue scale (VAS). Patients completed initial assessments whilst in hospital and follow-up assessments via telephone interviews. The mean age of patients was 60 years (± 17), 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 (Source: interim analysis from Drabinski et al\textsuperscript{70})

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>EQ-5D Value</th>
<th>VAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>0.53</td>
<td>0.61</td>
</tr>
<tr>
<td>60 days</td>
<td>0.62</td>
<td>0.68</td>
</tr>
<tr>
<td>90 days</td>
<td>0.68</td>
<td>0.71</td>
</tr>
<tr>
<td>180 days</td>
<td>0.69</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Drabinski et al report that improvement in health utilities was influenced primarily by improvements in mobility, self-care and usual activities. A number of cost-effectiveness studies have reported the use of data from Drabinski et al\textsuperscript{70}, but the level of detail offered in the abstract does not allow us to consider the quality of the study.

Supporting information on quality of life associated with severe sepsis

A study by Angus et al\textsuperscript{69} which reports on quality-adjusted survival in the first year after ARDS, was used in the economic evaluation from Manns et al\textsuperscript{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 (i.e. using descriptive scales for mobility, physical activity, social activity) and a range of symptoms. Responses to the questionnaire provide a profile which 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.\textsuperscript{73} Angus et al collected QWB data at six and twelve months after study enrolment, via a structured telephone interview. The overall study cohort (n=200) had a mean age of 48.6 years (±17), with 66.2% being male. There was loss to follow-up over both six months (n=32) and twelve months (n=45).
The study reports a mean QWB value of 0.59 (±0.015) at six months and 0.60 (±0.015) at twelve months, the mean scores were both 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 endpoint 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 et al\(^{24}\) 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 to 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 below 65 years. The authors report that patients requiring critical care (ICU) have lower scores than a normal population prior to admission (premorbid quality of life), for all dimensions of the SF-36. Patients admitted to the ICU due 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 prior to ICU admission, and their scores were not significantly different from the population norm values.
3.3 SHTAC Cost-effectiveness Analysis

3.3.1 SHTAC Cost-effectiveness Model

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

SHTAC have 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 severe sepsis patients. 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, i.e. the NHS in England and Wales. Costs associated with patient care from the NHS and the personal social services are included in the analysis, together with all known patient benefits.

Strategies/comparators

Above (Section 1) we have described the use of drotrecogin alfa (activated) in detail, and the relevance of using conventional care alone as the comparator strategy.

Model type and rational for the model structure

Presently 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 5. 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 severe sepsis patients 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 implications of treatment for those patients surviving to day 28. The decision model simulates the experiences of a cohort of 1,000 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 1,000 patient cohort constitutes a trial, and the mean incremental effects per patient are recorded per trial, for a total of 1,000 trials.
Baseline cohort of adult severe sepsis patients

We use 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 (see Table 17). This patient group have been used as they are deemed to represent the in-practice patient group for severe sepsis, and contain the subgroup of patients relevant to the European licence indication for drotrecogin alfa (activated), i.e. 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 have been used as a baseline in the model.

Figure 6. Flow Diagram Showing Basic Structure of SHTAC Model

- Age
- Gender
- Severity
- Baseline risk

Cohort of Severe Sepsis Patients

Conventional care

28 day survivor

Survivor years 1-4

Population Norm Life expectancy

Treatment with rhAPC

28 day survivor

Survivor years 1-4

Population Norm Life expectancy

Death
Effectiveness data

Above we have reported on the findings from a systematic review on the clinical effectiveness of drotrecogina alfa (activated), (Section 2). For the cost-effectiveness analysis we apply data from the PROWESS study on 28-day all cause mortality. We apply data on the relative reduction in all cause mortality at day-28, for all randomised patients (RR 0.79; 0.68-0.92), and for those patients with two or more organ dysfunctions (RR 0.78; 0.66-0.93). 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 serious bleeding events (SBE) between groups, with 3.5% of those patients treated with drotrecogin alfa (activated) experiencing a SBE, and 2% of those in the conventional care cohort experiencing a SBE. This difference (1.5%) was not statistically significant (p = 0.06), however, it is regarded as clinically significant. Furthermore, above (Section 2) we have reported that combined results from a cumulative safety review show 2.3% of patients in placebo groups having SBEs, compared to 5.3% of patients treatment with drotrecogin alfa (activated). In the SHTAC model we apply comparative data from PROWESS, 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, we examine this issue in sensitivity analysis.

Life-expectancy

Above we have discussed the fact that life-expectancy for survivors of severe sepsis is not the same as that of the general population. In the SHTAC model we use 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. A patient level probabilistic model is used to estimate the mean life-expectancy for the patient group (discounted where appropriate). This model is run prior to 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). In the modelling of these data we draw a sample of 1,000 consecutive patients, using data on age and gender from ICNARC, and assign each patient an age-gender specific life-expectancy, and thereafter calculate 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 1,000 iterations. We estimate mean normal life expectancy for the patient group to be 22.56 years (SD 12.98 years); we use this mean value in the cost-effectiveness model, but do not sample probabilistically using the measure of dispersion in the cohort model, as this seems intuitively incorrect (i.e. some of the 1,000 patient cohorts would be attributed a very low, or negative, life-expectancy based on the calculated patient level distribution). However, we feel that 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.
In order 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 four years where they are at increased risk of death (compared to the general population), based on data from Wright et al.,25 (see Figure 6 above). Wright and colleagues show a greater risk of death in critically ill intensive care patients through years one to four following ICU discharge (see Table 16). In sensitivity analyses we also take 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 et al.).52,60,62,63

Table 16. Estimate of mortality/life-expectancy, years 1 to 5, after discharge from intensive care (data on deaths recorded from Wright et al25)

<table>
<thead>
<tr>
<th>Time period / year</th>
<th>Critically ill patients (n) at start</th>
<th>Deaths recorded (n) within period</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>2104</td>
<td>434</td>
<td>20.63%</td>
</tr>
<tr>
<td>Year 1, after ICU*</td>
<td>1711</td>
<td>332</td>
<td>19.40%</td>
</tr>
<tr>
<td>2</td>
<td>1338</td>
<td>76</td>
<td>5.68%</td>
</tr>
<tr>
<td>3</td>
<td>1262</td>
<td>60</td>
<td>4.75%</td>
</tr>
<tr>
<td>4</td>
<td>1202</td>
<td>47</td>
<td>3.91%</td>
</tr>
<tr>
<td>5</td>
<td>1155</td>
<td>43</td>
<td>3.72%</td>
</tr>
</tbody>
</table>

* Following ICU discharge [mean ICU stay was 4.5 days (SD 7.2 days)]

Health state values/utilities

A systematic search of the literature has been undertaken (discussed above) and no published studies have been identified with data on health state utilities for survivors of severe sepsis; one abstract was identified.70 Above we discuss the estimates used to date in published cost-effectiveness studies. We believe this remains an area of uncertainty. Given the limitations in the empirical literature, in the SHTAC model we apply the data (0.60 ±0.015) reported by Angus et al for the quality of life of a sample of ARDS patients (at 12 months), to quality adjust life year gains.69 Data from Drabiniski et al,70 showing an EQ-5D value of 0.69 (at 180 days) is applied in the sensitivity analyses.

Discounting of future benefits

A discount rate of 1.5% has been 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 serious bleeding episodes (SBEs). The list price for drotrecogin alfa (activated), excluding VAT, is £152.05 per 5mg vial, and £608.19 per 20mg vial. Davies et al estimate the mean drug cost to be £4,775 based on the PROWESS trial group, and £4,716 for those patients in the PROWESS trial with 2 or more organ dysfunctions (this data makes some allowance for 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 (£5,610 and £5,541 respectively).

Cost data for serious bleeding episodes has been taken from the NHS reference costs, produced by the Department of Health in the UK. The mean cost associated with very major procedures for gastrointestinal bleeds (HRG code F61) is £3,182 for non-elective inpatient procedures. The cost range across all NHS Trusts is reported at £410 to £9,833, with the range across 50% of Trusts at £1,731 to £3,804. For simplicity, we have calculated the mean cost per patient treated 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 ICU, and days spent in hospital in a non-ICU setting. We estimated costs using data on resource use (length-of-stay) from ICNARC, 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. Length of stay data from ICNARC, by survival status, are from patients with severe sepsis defined according to PROWESS criteria (see Table 17). We estimate the mean hospital cost for severe sepsis survivors to be £15,640 and the mean cost for non-survivors at £10,384. For survivors and non-survivors of severe sepsis and multiple organ failure we estimate mean hospital costs of £16,802 and £10,156 respectively (we do not have data on standard deviations for length of stay in this group, but expect variation to be similar to the broader severe sepsis patient group).

There is considerable uncertainty around both the cost per day and the number of days per hospital stay (see Table 17), we have therefore introduced uncertainty surrounding hospital cost by applying a standard deviation of 20% to the point estimate and allowing it to vary in our probabilistic approach to the modelling of cost-effectiveness.

**Longer term costs**

Above we have discussed the estimates for the hospital stay associated with the episode of severe sepsis, however, where patients survive severe sepsis they will continue to use NHS resources over their life-time regardless of the reason for the resource use. This may be related to the consequences of severe sepsis, or for 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 have included life-time health care costs for survivors of severe sepsis,52,58,59 whilst the studies reported in abstract format have not included such costs. SHTAC believes that there is evidence indicating that survivors of intensive care will incur additional NHS costs compared to age-sex-matched members of the general population,76 but we also feel that it is not possible to disentangle the causes leading to such NHS resource use (i.e. in our patient group long-term costs may be non-sepsis related), therefore it is not possible to say with any certainty whether additional longer-term health care 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. But, 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 Angus77 in their review of methods for the economic evaluation of new therapies for critical illness, argue in favour of including longer-term health care costs (unrelated to the therapy being evaluated) for additional survivors. However, there is no agreement amongst health economists on the inclusion, in economic evaluations, of unrelated health care costs in later years of life.78 Drummond et al79 argue that the inclusion of future unrelated costs should be guided by considerations over (i) the extent to which future health care is a necessary consequence of the programme being evaluated, and (ii) 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 patients underlying morbid condition should be included in the evaluation. Regardless of the rationale for including longer term health care costs, here in the UK we do not have good quality cost data on the long term costs associated with NHS treatment (unlike the USA where billing databases are available to inform on such issues). On this issue, Drummond et al79 suggest that it is often difficult to be more precise than an average annual per capita health expenditure estimate.

In our base case cost-effectiveness analysis we do make some allowance for life-time health care 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 we use are described in Appendix 14. Briefly we have taken the data from the Department of Health for NHS expenditure on hospital community and family health services, hospital episode statistics by patients age (grouped 15-44,45-64, and 65+ years), and estimated the cost per patient per year using population data for England and Wales. Our estimates are shown in Table 17. Where we estimated the long term follow-up
costs for those patients who survive beyond year four we use age-specific costs for each year of survival in our estimates. Where we make allowances for follow-up cost for those patients who do not survive beyond year four, we use the proportions of severe sepsis patients in the respective age bands (from the simulate patient level data) and combine these 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 not. We therefore report cost-effectiveness findings based on both the inclusion and exclusion of longer term health care costs.

**Discounting of future costs**

A discount rate of 6% has been applied to future costs. This is the rate that is 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%).

**Table 17. Model inputs / assumptions for SHTAC cost-effectiveness analysis**

<table>
<thead>
<tr>
<th>Variable/parameter</th>
<th>Description</th>
<th>Data [Distribution]</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline cohort characteristics</strong></td>
<td>Age (mean, SD)</td>
<td>60.8 (16.9) [normal distribution] – bounded by limits of 16 and 100 years</td>
<td>ICNARC74</td>
</tr>
<tr>
<td></td>
<td>Sex (% Male)</td>
<td>54.27% [normal distribution]</td>
<td>ICNARC9</td>
</tr>
<tr>
<td><strong>Baseline risk</strong></td>
<td>28-day mortality for patients with severe sepsis</td>
<td>41.5% (40.8% - 42.3%) [normal distribution]</td>
<td>ICNARC9</td>
</tr>
<tr>
<td></td>
<td>28-day mortality for patients with severe sepsis and multiple organ dysfunction</td>
<td>46.2% (45.3% - 47.1%) [normal distribution]</td>
<td>ICNARC74</td>
</tr>
<tr>
<td><strong>Effectiveness Data</strong></td>
<td>Patients meeting PROWESS criteria</td>
<td>RR 0.79 (0.68-0.92) [normal distribution]</td>
<td>PROWESS39</td>
</tr>
<tr>
<td></td>
<td>Patients meeting PROWESS criteria with 2 or more organ dysfunctions</td>
<td>RR 0.78 (0.66-0.93) [normal distribution]</td>
<td>PROWESS39</td>
</tr>
<tr>
<td></td>
<td>Additional risk of SBE</td>
<td>1.5%</td>
<td>PROWESS39</td>
</tr>
<tr>
<td><strong>Life-expectancy data</strong></td>
<td>Data for life-expectancy by age for the general population of England and Wales</td>
<td>Age specific life expectancy</td>
<td>ONS (Government Actuary’s Department, interim tables, 1999-2001)75</td>
</tr>
<tr>
<td></td>
<td>Mean life-expectancy (years) estimated for the above age-gender patient group (mean, SD)</td>
<td>22.56 (12.98) – No discounting</td>
<td>SHTAC model</td>
</tr>
<tr>
<td><strong>Adjustment of life-expectancy</strong></td>
<td>Following 28-day survival: Risk of death year 1</td>
<td>19.40%</td>
<td>Using Data from Wright et al (2003)25</td>
</tr>
<tr>
<td></td>
<td>Risk of death year 2</td>
<td>5.68%</td>
<td></td>
</tr>
</tbody>
</table>

---

Technology assessment report  NICE AC-nonCIC December 2003

72
<table>
<thead>
<tr>
<th></th>
<th>Risk of death year 3</th>
<th>Risk of death year 4</th>
<th>4.75%</th>
<th>3.91%</th>
<th>Angus et al (2001)\textsuperscript{69}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health state value</td>
<td>Health state value used in the analysis for survivors of severe sepsis</td>
<td>0.60 (±0.015) [Beta distribution]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost for drotrecogin alfa (activated)</td>
<td>Mean cost per patient (Excl. VAT)</td>
<td>£4,775</td>
<td>£4,716 (2 or more org. dysf)</td>
<td>Davies et al 2002\textsuperscript{60}</td>
<td></td>
</tr>
<tr>
<td>Cost for serious bleed</td>
<td>Cost for major bleed - very major procedures for gastrointestinal bleeds (HRG F61)</td>
<td>£3,182</td>
<td></td>
<td>NHS Reference Costs, 2002\textsuperscript{33}</td>
<td></td>
</tr>
<tr>
<td>Hospital resource use</td>
<td>Length of stay in ICU (days): survivors of severe sepsis / severe sepsis plus multiple organ dysfunction</td>
<td>7.8 (10.5) / 8.8&quot;</td>
<td></td>
<td>ICNARC\textsuperscript{74}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of stay in ICU (days): non-survivors of severe sepsis / severe sepsis plus multiple organ dysfunction</td>
<td>6.4 (10.1) / 6.1&quot;</td>
<td></td>
<td>ICNARC\textsuperscript{74}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of overall hospital stay (days): survivors of severe sepsis / severe sepsis plus multiple organ dysfunction</td>
<td>36.6 (36.7) / 38.6&quot;</td>
<td></td>
<td>ICNARC\textsuperscript{74}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of overall hospital stay (days): non-survivors of severe sepsis / severe sepsis plus multiple organ dysfunction</td>
<td>18.9 (26) / 18.3&quot;</td>
<td></td>
<td>ICNARC\textsuperscript{74}</td>
<td></td>
</tr>
<tr>
<td>Hospital Costs</td>
<td>Cost per day in ICU</td>
<td>£1,232 (Range: 50% of NHS Trusts £1,077 - £1,439)</td>
<td></td>
<td>NHS Reference Costs 2002\textsuperscript{33}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cost per day other ward</td>
<td>£200</td>
<td></td>
<td>Davies et al 2002\textsuperscript{60}</td>
<td></td>
</tr>
<tr>
<td>Estimated Hospitalisation Cost</td>
<td>Severe sepsis: Survivors Non-survivors Severe sepsis and multiple organ dysfunction: Survivors Non-survivors</td>
<td>£15,370</td>
<td>£10,384</td>
<td>As above under resource use and hospital costs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>£16,802</td>
<td>£10,156</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model uses above mean estimates with a Gamma distribution, based on an estimated SD of 20% of the mean.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term NHS costs</td>
<td>Annual cost per patient (general population): Aged 16-44 years Aged 45-64 years Aged 65+ years</td>
<td>£708.47</td>
<td>£985.19</td>
<td>£1,807.84</td>
<td>SHTAC Estimate based on DOH Annual Expenditure Data for HCHS,</td>
</tr>
</tbody>
</table>
### Weighted annual cost (weighted using proportions by age group)

- **Hospital Episode Statistics (Dept of Health), and population data for England and Wales (ONS)**

### Mean (SD) estimate of long-term NHS cost (excl. initial intervention/acute care):

- **Base case**
- **Discounting at 3.5%**
- **No-discounting**

<table>
<thead>
<tr>
<th>Discount rate</th>
<th>Future costs</th>
<th>Future benefits (life years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discount rate</td>
<td>£17,062 (£3,294)</td>
<td>£17,062 (£3,294)</td>
</tr>
<tr>
<td>Discount rate</td>
<td>£22,112 (£9,155)</td>
<td>£22,112 (£9,155)</td>
</tr>
<tr>
<td>Discount rate</td>
<td>£35,459 (£17,737)</td>
<td>£35,459 (£17,737)</td>
</tr>
</tbody>
</table>

*SD data not known

### Presentation of results

We report findings on the mean incremental gain in life years (QALYs), and mean incremental cost, per treated patient, based on a cohort analysis of 1,000 patients (trial), and a simulation of 1,000 trials. We estimate the incremental cost per life year gained, and incremental cost per QALY. Using the mean incremental benefits and cost per trial we estimate the ‘net benefit’ associated with treatment, and plot a cost-effectiveness acceptability curve (CEAC), showing the probability of a positive net benefit based on a range of threshold values for the willingness to pay per QALY.

We also report the mean cost per life saved, for base case assumptions, (i.e. the difference in the mean total cost per 1,000 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 1,000 patient cohort).

### Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

We undertake sensitivity analysis to address uncertainty in the cost-effectiveness analysis. We consider methodological and structural uncertainty by addressing the methods for inclusion of long-term health care costs and by considering different methods for the estimation of life-expectancy and life-year gains. We also address heterogeneity in the patient groups, 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 has not been possible in all instances. Therefore, where parameter values have not been varied in a probabilistic manner we have undertaken sensitivity analysis on these parameters by re-running probabilistic analysis with different point estimates.
3.3.2 SHTAC Cost-effectiveness Results

Cost-effectiveness findings are presented for two patient groups (i) UK severe sepsis patients matching the PROWESS inclusion criteria, (ii) UK severe sepsis patients, 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 £5,495 and £9,161 respectively. For patients with severe sepsis and multiple organ dysfunction the cost per life year and cost per QALY are £4,931 and £8,228. Cost-effectiveness findings based on zero discounting of future costs and benefits are presented in Table 19.

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with severe sepsis and 2 or more organ dysfunctions</th>
<th>Patients with severe sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental life years</td>
<td>1.351 (0.43)</td>
<td>1.144 (0.343)</td>
</tr>
<tr>
<td>Incremental QALYS</td>
<td>0.810 (0.258)</td>
<td>0.686 (0.208)</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>£6,661 (£772)</td>
<td>£6,288 (£593)</td>
</tr>
<tr>
<td>Cost per life year</td>
<td>£4,931</td>
<td>£5,495</td>
</tr>
<tr>
<td>Cost per QALY</td>
<td>£8,228</td>
<td>£9,161</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with severe sepsis and 2 or more organ dysfunctions</th>
<th>Patients with severe sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental life years</td>
<td>1.569 (0.513)</td>
<td>1.352 (0.398)</td>
</tr>
<tr>
<td>Incremental QALYS</td>
<td>0.941 (0.308)</td>
<td>0.811 (0.240)</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>£7,958 (£1,783)</td>
<td>£7,398 (£1,368)</td>
</tr>
<tr>
<td>Cost per life year</td>
<td>£5,071</td>
<td>£5,473</td>
</tr>
<tr>
<td>Cost per QALY</td>
<td>£8,462</td>
<td>£9,120</td>
</tr>
</tbody>
</table>

As cost-effectiveness ratios are not suited for the estimation of confidence intervals, we use the net monetary benefit approach 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 willingness to pay for an outcome (e.g. QALY); with the net benefit formula based on the value we are willing to pay per outcome multiplied by the outcomes obtained, less the cost incurred (i.e. WTP per QALY x 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).

Using the net monetary benefit approach in our assessment of the cost-effectiveness of drotrecogin alfa (activated), if we 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 cost-effectiveness acceptability curves (CEACs), which plot the findings for net monetary benefit, for a range of values on the willingness to pay per QALY.

**Figure 7. Cost-effectiveness acceptability curve, drotrecogin alfa (activated)**

![Cost-effectiveness acceptability curve, drotrecogin alfa (activated)](image)

Note: INB = incremental net benefit

**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 1,000 patients treated, divided by the mean difference in 28-day survival per 1,000 patient cohort). The cost per life saved based on including only initial (acute) intervention and hospital costs is estimated at £61,468.

**Sub-groups: Cost-effectiveness**

As discussed above there have been a number of subgroup analyses on the PROWESS effectiveness data. We have warned against conflicting findings across patient groups (i.e. all PROWESS patients, versus those with multiple organ dysfunction), and more importantly we have warned over methodological concerns over the subgroup analyses undertaken. General findings indicate that drotrecogin alfa (activated) is
cost-effective in the license 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 we provide in the sensitivity analyses a range of results by differing effectiveness (relative risk reduction), and guide the reader to consider these in the context of the specific sub-group of interest (we do not have separate data on other model inputs by subgroup).

3.3.3 Sensitivity Analyses

Sensitivity analysis has been 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) we have run separate analyses (i) UK severe sepsis patients meeting the PROWESS inclusion criteria, (ii) UK severe sepsis patients meeting the PROWESS inclusion criteria and have two or more organ dysfunctions.

Methodological and structural uncertainty

We report sensitivity analysis for the use of a different method for the adjustment of life-expectancy for survivors of severe sepsis (see Table 20). The base case method was the use of data from Wright et al., with an increased all cause mortality for survivors of severe sepsis over years one to four. In separate analysis we have adjusted life-expectancy using the parameter of 0.51 commonly cited from the study by Quartin et al. (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 are smaller (subsequently the long term NHS costs are lower) and the cost per life year and cost per QALY increase over the base case findings i.e. cost per QALY increases from £8,228 to £10,439 in the patient group with severe sepsis and multiple organ failure. (In this sensitivity analysis we also make an adjustment to the longer term patient costs calculated and used in the base case analysis, using a factor 0.51. We accept that this will underestimate the true long term costs for the period of life-expectancy in question, but we feel it is sufficiently accurate to help guide the present analysis).
Table 20. Sensitivity analysis of the cost per life-year gained and cost per QALY, for treatment with drotrecogin alfa (activated)

<table>
<thead>
<tr>
<th>Variable used in analyses</th>
<th>Severe sepsis and multiple organ dysfunction</th>
<th>Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost per QALY</td>
<td>Cost per Life Year Gained</td>
</tr>
<tr>
<td>Baseline analysis</td>
<td>£8,228</td>
<td>£4,931</td>
</tr>
<tr>
<td>Discount rate for costs and benefits at 3.5% $^\dagger$</td>
<td>£10,797</td>
<td>£6,475</td>
</tr>
<tr>
<td>Long term costs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Where costs per patient per year are higher in year 1 (£10,000)</td>
<td>£8,962</td>
<td>£5,373</td>
</tr>
<tr>
<td>(b) Where costs per patient per year are higher in year 1 (£20,000)</td>
<td>£9,691</td>
<td>£5,823</td>
</tr>
<tr>
<td>Life-expectancy method:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Where life-expectancy adjusted by factor or 0.51 (l-term costs x 0.51)</td>
<td>£10,439</td>
<td>£6,266</td>
</tr>
<tr>
<td>Excl long term costs</td>
<td>£6,691</td>
<td>£4,020</td>
</tr>
<tr>
<td>QALY weight/Utility value: using estimate of 0.69 from Drabinski et al</td>
<td>£7,145</td>
<td>£4,930</td>
</tr>
<tr>
<td>QALY weight at 0.69 and Exclude l-term costs (similar to Eli Lilly analysis)</td>
<td>£5,826</td>
<td>£4,020</td>
</tr>
<tr>
<td>Probability of SBEs at 15%</td>
<td>£8,812</td>
<td>£5,287</td>
</tr>
<tr>
<td>Cost of drotrecogin alfa Incl. VAT</td>
<td>£9,303</td>
<td>£5,583</td>
</tr>
<tr>
<td>Effectiveness data – using RR of 0.70</td>
<td>£6,778</td>
<td>£4,065</td>
</tr>
<tr>
<td>0.75</td>
<td>£7,486</td>
<td>£4,494</td>
</tr>
<tr>
<td>0.85</td>
<td>£11,142</td>
<td>£6,687</td>
</tr>
<tr>
<td>0.90</td>
<td>£15,637</td>
<td>£9,375</td>
</tr>
<tr>
<td>0.95</td>
<td>£28,868</td>
<td>£17,267</td>
</tr>
<tr>
<td>(assume the same SE as base case)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assuming longer term costs are £20,000 in year one, base case values thereafter, AND life-expectancy is estimated using the parameter value of 0.51 from Quartin et al.</td>
<td>£11,648</td>
<td>£6,986</td>
</tr>
<tr>
<td>Assuming longer term costs are £20,000 in year one, base case values thereafter, AND life-expectancy is estimated using the parameter value of 0.51 from Quartin et al. Plus, baseline all cause mortality (risk) at 33.9% (MODS) and 31.3% (severe sepsis) $^\dagger$</td>
<td>£14,645</td>
<td>£8,801</td>
</tr>
</tbody>
</table>

$^\dagger$ See Appendix 15 for CEACs for analysis at a discount rate of 3.5% for costs and benefits, and multi-way sensitivity analysis

We also report sensitivity analysis to consider different methods for the estimation of longer term NHS costs, for additional survivors of severe sepsis (see Table 20).
Where long term NHS costs are excluded, the cost per life year and cost per QALY estimates are lower than base case values; in patients with severe sepsis and multiple organ dysfunction the cost per QALY falls from £8,288 to £6,691. Where we assume 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 increase; with cost per QALY for patients with severe sepsis and multiple organ dysfunction rising from £8,228 to £8,962 and £9,691 respectively.

We introduce a number of changes to the methods/assumptions in the model simultaneously, with base case assumptions altered to reflect (i) a follow-up NHS cost of £20,000 per survivor in the first year after the severe sepsis episode, (ii) life-expectancy adjusted to 0.51 of the population norm (as in Quartin et al), and (iii) 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), see Table 20. In this analysis we report 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 multi-way 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 has been used to consider uncertainty on parameter values simultaneously. This has been possible for patient age, sex, 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 have not been varied in a probabilistic manner, or where alternate point estimates may be expected, we have undertaken sensitivity analysis on these parameters by re-running probabilistic analysis with different point estimates (see Table 20).

Applying a QALY weight of 0.69 per life year gained (base case is 0.60) results 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 results in an increase in the cost-effectiveness estimates, e.g. to £9,303 per QALY for patients with severe sepsis and multiple organ dysfunction. Where we assume a less favourable effectiveness profile for drotrecogin alfa (activated), using a relative risk of 0.85, or 0.90, the cost per life year / QALY increases substantially e.g. from a base case of £8,288 to £11,142 and £15,637 respectively per QALY in patients with severe sepsis and multiple organ failure.
4 Implications for other parties

Drotrecogin alfa (activated) has demonstrated a significant survival benefit in reported RCTs. However, we do not have 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 health care and other related care needs. As stated previously this patient group are 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. A significant proportion of this burden would be on families and carers.

The increased burden of ill health and associated increased health care 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 health care resource utilisation especially in primary care.

5 Factors relevant to the NHS

In the SHTAC cost-effectiveness analysis we have 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 £6,661. The majority of this cost is the acquisition cost for drotrecogin alfa (activated), which is estimated at £4,905 (excluding VAT) for a full course of treatment in a 70kg 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. 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: 18,800-23,740). Assuming 83.6% of these patients have multiple organ dysfunction, we estimate 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). Obviously not all treatment eligible patients will be prescribed drotrecogin alfa (activated) i.e. due to contraindication where there is risk of serious bleeding, but given that many patients will have severe sepsis outwith 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 persons, similar to a former health authority region, we 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.
6 Discussion

6.1 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.\textsuperscript{39} A much smaller phase II RCT\textsuperscript{43} plus 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, 10.7), equivalent to a relative risk of death of 0.79 (95\% CI: 0.68, 0.92).\textsuperscript{39} Long-term follow-up of these patients shows that the survival benefit is maintained to 90 days (p=0.048) although by nine months, the trend towards increased median survival is non-significant (log rank p=0.097), although the survival curves do not cross.\textsuperscript{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 have been performed. As discussed above (section 2.2.3) 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, we have focused on those related to disease severity. \textit{A priori} analyses show a progressive reduction in the relative risk of death with increasing number of organ failures, from 0.92 (95\%CI: 0.63, 1.35) in patients with one organ failure at baseline to 0.60 (95\%CI: 0.33, 1.11) in those with 5 organ failures. All of the confidence intervals for these subgroups overlapped the overall estimate and none were 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 to placebo (0.78, 95\%CI: 0.66, 0.93).\textsuperscript{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, i.e. benefit could appear to be greatest in those with more severe disease.\textsuperscript{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 to female patients. Subgroup analyses of the entire cohort, which have slightly more patients, though are still underpowered indicate that subgroup effects could be occurring due to any number of factors, including age, race, the presence of comorbidities, and infection site and type among others.\textsuperscript{46}

A number of 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 to placebo for all organ systems except for
hepatic organ dysfunction. The likelihood of developing new organ system dysfunctions was significantly reduced by drotrecogin alfa (activated) only for haematologic organ dysfunction. In terms of functional status at day 28, there was little difference between groups, although a higher proportion of rhAPC survivors were discharged to home compared to 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 serious bleeding events was much higher with drotrecogin alfa (activated) than with placebo, though for PROWESS the difference was not statistically significant. As might be expected, the incidence was higher in the large open-label study than in the treatment arm of PROWESS.

6.1.1 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 intention-to-treat 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) did occur after the protocol changes but it is likely that this was down 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 did state 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 of all, the definition of severe sepsis that was used in the PROWESS trial is more strict than that usually applied in practice. PROWESS required evidence of infection, at least three SIRS criteria plus at least one organ dysfunction. The usual definition requires evidence of infection, at least two SIRS criteria plus at least one organ dysfunction, hypoperfusion or hypotension. Secondly, only patients developing severe sepsis within the first 24 hours of screening (presumably intensive care admission in most cases) were included. As discussed in the section above relating to the epidemiology of sepsis, the incidence of severe sepsis at any stage during intensive care stay may be up to double that on admission and furthermore the same incidence of severe sepsis cases may be found outwith the ICU.

The pragmatic nature of the study (i.e. that it was non-prescriptive regarding supportive care) does increase 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 furthermore 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 license 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.

6.1.2 Limitations of the review
The systematic nature of the review means that we 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 be performed and, if performed, unlikely to yet be in the public domain.

6.2 Cost-effectiveness: Statement of principal findings
Three published economic evaluations and eight abstracts were identified to inform 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 to 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 USA 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 et al\textsuperscript{52} and Manns et al\textsuperscript{58} are regarded by SHTAC as better quality studies than the economic evaluation reported by Fowler et al\textsuperscript{59} due to a greater transparency in the methods used, and it is the latter of these published evaluations which reports the lower of the cost-effectiveness estimates in the range discussed.

All three published economic evaluations report findings for severe sepsis patients 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\textsuperscript{52} report that drotrecogin alfa (activated) was cost
in-effective for those patients with an APACHE II score of less than 25 (there were no incremental QALY benefits). Manns et al and Fowler et al report cost per QALY estimates in excess of $400,000 for severe sepsis patients with and APACHE II score of less than 25.

Cost-effectiveness findings for Europe, reported in abstract form, and in the analysis reported by Eli Lilly, are generally more attractive (i.e. cost per QALY estimates are lower) than those reported in the published US/Canadian studies. This would appear to be due to a combination of factors, mainly relating to (i) 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 to the ‘severe sepsis’ patient group (i.e. ARR of 7.4% compared to 6.1%), (ii) the cost estimates for both hospitalisation and longer term health care costs being much lower in the European analyses, and (iii) methods for the assessment of quality-adjusted life-expectancy also varying between studies.

The estimates of cost per QALY presented by Davies et al and by Eli Lilly, for the UK (severe sepsis with multiple organ dysfunction), are under £11,000. The SHTAC analysis estimates the cost per QALY for UK severe sepsis patients, and patients with severe sepsis and multiple organ dysfunction at £9,161 and £8,288 respectively. The analyses for the UK and for Europe more broadly, report findings for the patient group regarded as more severely affected by disease i.e. severe sepsis and multiple organ failure.

Sensitivity analysis indicates 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 USA/Canadian economic evaluations.

6.2.1 Limitations – cost-effectiveness

The published literature on the cost-effectiveness of drotrecogin alfa (activated) is based on analysis for US/Canadian patients, and its generalisability to Europe and the UK is limited. The literature to inform on cost-effectiveness of treatment in Europe is published in abstract form only. This literature is limited in the detail it offers, and has not been subject to peer-review, therefore we are not able 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 absolute risk reduction 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 severe sepsis patients, and applies effectiveness data on the relative risk reduction in patients treated with drotrecogin alfa (activated). The baseline cohort of UK severe sepsis patients used in the SHTAC cost-effectiveness model, are 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 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 et al23 have been used to estimate mortality post 28-day survival (in order to adjust life-expectancy for survivors of severe sepsis compared to 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 et al are used to estimate risk of death over years one to four, following survival at day 28, however these data are not from a severe sepsis patient group. Furthermore data are only available as mean point estimates (per year) and we do not have a measure of distribution (e.g. standard deviation) around these mean values. Data from Manns et al58 offer some support (i.e. their data are not dissimilar) for the parameters used in the SHTAC model. Results from the SHTAC simulation modelling show that the data used in the model (from Wright et al), with base case assumptions, adjusts 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 inform on the health state values for severe sepsis survivors, following from the methods applied by Manns et al.58

6.3 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), in order to inform on 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. For instance the effect of combining low dose systemic corticosteroid therapy with drotrecogin alfa (activated) in the treatment in adults with severe sepsis.

7 Conclusions

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


Previous publications (inside back cover)
List of unit’s publications to date (most recent ones first, number determined by space).
### Appendix 1. Details of epidemiological studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristics</th>
<th>Disease severity</th>
<th>Length of stay (days)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberti, et al²</td>
<td>47% (3946/8353) of long stay pts (&gt;24 hr in ICU) had sepsis or sepsis-related conditions: 17.9% (707) infection without SIRS 28.3% (1115) sepsis 23.9% (944) severe sepsis 29.9% (1180) septic shock As % of all long-stay ICU patients: 38.7% had sepsis 25.4% severe sepsis or septic shock Source of sepsis infection (severe sepsis/septic shock): 33% community-acquired 30% hospital-acquired 37% ICU-acquired</td>
<td>For long-stay pts Median ICU LoS: 6d (3-34). Median hospital LoS: 16d (3-69)</td>
<td>Crude ICU mortality All pts: 20.4% (95%CI: 19.5, 21.2) Crude hospital mortality All pts: 26.6% (95%CI: 25.6, 27.6)</td>
<td></td>
</tr>
</tbody>
</table>

**International**  
28 ICUs in 8 countries (2 in UK)  
Prospective multicentre cohort study of 14,364 (≥18yo) unselected consecutive pts admitted to ICU over 1-yr. Used ACCP/SCCM criteria  
short stay : < 24 hr in ICU: 6011  
long stay : > 24 hr in ICU: 8353  
Only long stay results reported here
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Patient Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angus, et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>USA</td>
<td>847 hospitals</td>
<td>Prospective cohort study of 192,980 cases of severe sepsis over 1 yr. Severe sepsis defined as acute care hospitalizations with ICD-9-CM codes for both a bacterial or fungal infectious process and a diagnosis of acute organ dysfunction</td>
<td></td>
<td>Number of acute organ dysfunctions (ODs) 1: 73.6% 2: 20.7% 3: 4.7% ≥4: 1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>192,980 or 3% of all hospitalisations had severe sepsis. Of these: 55.5% had underlying comorbidity 51.1% received ICU care 6.2% were ventilated in an intermediate care unit but never received ICU care. 28.6% had surgical conditions; 41.4% were medical</td>
<td></td>
<td>Mean hospital LoS: Overall: 19.6d Non-survivors: 19.9d Survivors: 19.4d ICU: 23.3d No ICU: 15.6d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.6% of all hospitalisations had severe sepsis. Of these: 55.5% had underlying comorbidity 51.1% received ICU care 6.2% were ventilated in an intermediate care unit but never received ICU care. 28.6% had surgical conditions; 41.4% were medical</td>
<td></td>
<td>Hospital mortality Overall: 28.6%. Pts with ICU admission: 34.1% By no. acute ODs: 1: 21.2% 2: 44.3% 3: 64.5% ≥ 4: 76.2%</td>
</tr>
<tr>
<td>Brun-Buisson, et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>France</td>
<td>170 adult ICUs (specialised coronary care units excluded)</td>
<td>Prospective survey of 11,828 consecutive admissions to ICU over 2 mos. ACCP/SCCM definitions</td>
<td></td>
<td>Frequency of severe sepsis in ICU pts: 9% (n=1052) 1. Documented infection (n=742, 6.3% (95%CI: 5.8, 6.7)) mean age 61.4±17 63% male medical admission 64%; emergency surgery/trauma 25%; scheduled surgery 11% infection community-acquired: 48% hospital-acquired: 52% (48% (185) of which were ICU-acquired) 2. highly probable clinical dx (n=310); similar characteristics reported for those with probably sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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=.03)</td>
<td></td>
<td>Crude ICU mortality all ICU pts: 17% documented sepsis: 56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median hospital LoS all sepsis pts: 11 survivors: 34 non-survivors: 4</td>
<td></td>
<td>Crude hospital mortality (documented sepsis only) overall: 59% 14-day: 46% 28-day: 56% (95%CI: 52, 60%) 42-day: 60% (95%CI: 57, 64%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rates for culture-negative sepsis reported to be similar: - 28-day mortality: 60% (95%CI: 55, 66%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Technology assessment report 95 NICE AC-nonCIC December 2003
Moerer et al, 2002 in Germany
2 surgical/medical adult ICUs
Retrospective cohort study of 385 pts with severe sepsis (1997-2000). Used ACCP/SCCM definitions

| 162/385 (42%) infected on admission | Organ failure therapy: |
| 238/385 (62%) acquired infection following admission (overlap between groups) 58% male | 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 d

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

Padkin, et al. in the UK
91 adult general ICUs
Comparative audit of 56,673 adult ICU admissions Dec 1995 to Feb 2000. Selected patients with severe sepsis in first 24h of ICU as defined by inclusion criteria for PROWESS study

| 15,362 of adult ICU admissions had severe sepsis during first 24h: 27.1% (95%CI: 26.7, 27.5%) median age 65 (IQR 51 to 73 yrs) 54.3% male 35.3% non-surgical; 34.5% emergency surgical admissions; 7.4% elective surgical admissions 45.5% (6983) would not have been eligible for PROWESS due to trial exclusion criteria | Number of organ dysfunctions (OD) at baseline (95%CI): 1: 16.4% (15.8, 17.0%) 2: 34.4% (33.7, 35.2%) 3: 30.8% (30.0, 31.5%) 4: 14.7% (14.1, 15.3%) 5: 3.7% (3.4, 4.0%) 47.3% APACHE II score >22 | 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 hospital LoS: Overall: 18 (IQR 8, 36) Survivors: 25 (14, 46) Non-survivors: 11 (4, 23) | Hospital mortality: Overall: 47.3% By no. ODs (95%CI) 1: 21.8% (20.2, 23.5%) 2: 36.0% (34.7, 37.3%) 3: 52.5% (51.1, 53.9) 4: 75.1% (73.3, 86.9) 5: 86.1% (83.0, 88.8) |

Number of organ dysfunctions (OD) at baseline (95%CI): 1: 16.4% (15.8, 17.0%) 2: 34.4% (33.7, 35.2%) 3: 30.8% (30.0, 31.5%) 4: 14.7% (14.1, 15.3%) 5: 3.7% (3.4, 4.0%) 47.3% APACHE II score >22

Median hospital LoS:
Overall: 18 (IQR 8, 36) Survivors: 25 (14, 46) Non-survivors: 11 (4, 23)
Rangel-Frausto, et al. 10

US
3 critical care units and 3 wards of a 900-bed teaching hospital

Prospective, concurrent incidence surveys of adult pts with >12hr in ICU and ≥2 criteria for SIRS over 9-mo period. ACCP/SCCM definitions used

Pts followed-up for 28 days or until hospital discharge.

<table>
<thead>
<tr>
<th>Over 28 day Follow-up</th>
<th>Mean APACHE II score on admission to CCU</th>
<th>Crude 28d mortality rate of pts with SIRS: 9% (224/2527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68% (2527/3708) of all pts admitted had ≥ 2 criteria for SIRS. 60% male Mean age: 54.7±17.2 (men), 55.7±18.1 (women) Surgical procedures: 47% Surgical ICU: 857 Medical ICU: 804 Cardiovascular ICU: 542 Non-ICU: 1486</td>
<td>18.5±9 (range 2 to71). 649 (26%) had sepsis (56% diagnosed on admission) 467 (18%) had severe sepsis (42% diagnosed on admission) 110 (4%) had septic shock (29% diagnosed on admission) further 892 (35%) thought to be clinically septic Of all pts admitted to ICU: 33% (1226) diagnosed with sepsis 15.6% (577) severe sepsis or septic shock</td>
<td>28-d 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 mo FU: 41% from SIRS group 10% sepsis 44% severe sepsis 5% septic shock Additional 115 died between 3 and 6 mo FU: 27% from SIRS group 25% sepsis 44% severe sepsis 5% septic shock</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Setting</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Salvo, et al.</td>
<td>Italy</td>
<td>99 ICUs</td>
</tr>
<tr>
<td>Sands, et al.</td>
<td>US</td>
<td>8 academic tertiary care centres</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Setting</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Scottish Intensive Care Society</td>
<td>UK</td>
<td>25 ICUs</td>
</tr>
<tr>
<td>Teres et al.</td>
<td>USA</td>
<td>50 ICUs: project IMPACT</td>
</tr>
</tbody>
</table>
Appendix 2. Description of APACHE II scoring system

**APACHE = Acute Physiology Age and Chronic Health Evaluation**

**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 has been developed from a prototype APACHE system,\(^{81}\) and is based on the use of basic physiologic principles to stratify patients prognostically by risk of death. The original APACHE system provided weightings for 34 potential physiologic measures, the sum of which represented an acute physiology 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 physiologic 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 upon data available in most hospitals.

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

The physiologic variables included are:
- Temperature (rectal °C)
- Mean arterial pressure (mm Hg)
- Heart rate (ventricular response)
- Respiratory rate (non-ventilated or ventilated)
- Oxygenation A-aDO\(_2\) or PaO\(_2\) (mm Hg)
  a: FIO\(_2\) ≥ 0.5 record A-aDO\(_2\)
  b: FIO\(_2\) < 0.5 record only PaO\(_2\)
- Arterial pH
- Serum sodium (mMol/L)
- Serum potassium (mMol/L)
- Serum creatinine (mg/100ml) (double point score for acute renal failure)
- Hematocrit (%)
- White blood count (total/mm\(^3\) in 1,000s)
- 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 et al, 1985,\(^{19}\) p820).

**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 to 4 points up 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).”(p823) 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%, 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 to actual death rates as a test of therapeutic efficacy for patients in particular diagnostic groups. But, 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 physiologic 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.

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

(see detail on page 828)

**Note:**
(a) Rowan and colleagues (1994)\(^20\) 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.
(b) 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 score.¹⁸
Appendix 3. Documentation of search strategy used

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

1. Cochrane Database of Systematic Reviews (CDSR)
2. Database of Abstracts of Reviews of Effectiveness (DARE)
3. HTA Database
4. MEDLINE and PubMed
5. EMBASE
6. BIOSIS
7. TOXLINE
8. Cochrane Controlled Trials Register (CCTR)
9. Science Citation Index
10. Biomed Central
11. NHS Economic Evaluations database (NHS Eed)
12. EconLit

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

Search strategy (for database Pre-MEDLINE, MEDLINE)

--------------------------------------------------------------------------------
1  sepsis.ti,ab. (30430)
2  Sepsis Syndrome/ (1432)
3  Shock, Septic/ (11940)
4  septic shock.ti,ab. (6452)
5  SEPSIS/ (5356)
6  Septicemia/ (19691)
7  septicemia.ti,ab. (7204)
8  septicaemia.ti,ab. (3755)
9  exp septicemia/ (45752)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (65131)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (76675)
12 drotrecogin.ti,ab. (66)
13 drotrecogin.rw. (75)
14 xigris.mp. [mp=ti, ab, rw, sh] (12)
15 zovant.mp. [mp=ti, ab, rw, sh] (0)
16 activated protein c.ti,ab. (2154)
17 recombinant protein c.ti,ab. (29)
18 12 or 13 or 14 or 16 or 17 (2225)
19 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 et al.82

1. Allocation concealment
   Adequate: 1 if patients an investigators enrolling patients cannot foresee assignment
   Inadequate: if allocation concealment not reported or reported an approach not considered to be adequate
   Unclear: 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; other description that contained convincing elements of concealment

2. Generation of allocation sequence
   Adequate: 1 if sequences are suitable to prevent selection bias and the method used is described
   Inadequate: 2 if sequences could be related to prognosis
   Unclear: 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; or other methods of allocation that appear to be unbiased
   Inadequate methods include case record number, date of birth, day, month or year of admission

3. Blinding
   Report which of the following are aware of the treatment the patient is receiving
   Patient
   Health-care provider
   Outcome assessor

4. Intention-to-treat analysis
   Adequate: if more than 90% of patients randomised in the trial were included in the analyses
   Inadequate: 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 et al.42

5. Definition of sepsis and severe sepsis
   Sepsis is a multi-faceted 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 Group41 recommend that studies should use the criteria set out by the American College of Chest Physicians/Society of Critical Care
Medicine\textsuperscript{2} in 1992 (the Bone criteria) or some modification of them combined with a requirement for:

\begin{itemize}
  \item confirmed infection (e.g. positive blood culture, Gram stain in bronchoalveolar lavage or sputum, bacteriuria, or positive local microbiological culture results), or
  \item 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).
\end{itemize}

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

6. Admission diagnoses and patient characteristics
Distribution of underlying disease and comorbid states, and how these compare to those in the UK

7. Standard care
Was standard care and comorbidity treatment comparable to that routinely given to patients with similar characteristics in the UK? There is known heterogeneity in the treatment of sepsis between centres.
Appendix 5. Listing of Excluded Studies

Excluded clinical studies on rhAPC


   Reason: PROWESS - abstract only. Data published in full in Vincent *et al*, 200348


   Reason: open-label study - abstract only


   Reason: safety data - abstract only. Data published in full in Bernard *et al*, 200339


   Reason: EVAD - abstract only. Data published in full Bernard *et al*, 200143


   Reason: PROWESS - abstract only. Data published in full Bernard *et al*, 200139


   Reason: PROWESS - abstract only. Data published in full Bernard *et al*, 200139


   Reason: open-label study - abstract only


   Reason: open-label study - abstract only


   Reason: PROWESS - abstract only. Data reported in full in Dhainaut *et al*, 200345

Reason: PROWESS – full paper, but only reports outcomes in patients aged 75+. This is not one of our pre-specified subgroups of interest


Reason: open-label study; abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: report of 3 case studies of patients following solid-organ transplant


Reason: open-label study - abstract only


Reason: PROWESS - abstract only.


Reason: PROWESS – full paper; pharmacodynamic outcomes only.


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only


Reason: open-label study - abstract only

**Additional excluded studies (not primary studies on rhAPC)**


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


49. Mathiak G, Neville LF, Grass G. Targeting the coagulation cascade in sepsis: did we find the "magic bullet"? *Critical Care Medicine* 2003;31:310-1.


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

### Appendix 6 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID / Sponsor</th>
<th>Relevant publications</th>
<th>Number of Participants</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAA Eli Lilly Phase II (randomised)</td>
<td>Bernard et al., 2002</td>
<td>135 randomised 131 treated</td>
<td>rhAPC 48h continuous iv infusion: 12 µg/kg/hr, n=11 18 µg/kg/hr, n=11 24 µg/kg/hr, n=12 30 µg/kg/hr, n=12 rhAPC 96h continuous iv infusion: 12 µg/kg/hr, n=14 18 µg/kg/hr, n=15 24 µg/kg/hr, n=15</td>
<td>Saline continuous iv infusion: 48h, n=26 96h, n=15</td>
<td>Primary clinical outcomes: *frequency of serious adverse events, serious bleeding events, and assessment of anti-APC antibody response. Primary pharmacodynamic measures: changes in D-dimer, fibrinogen, platelet and interleukin (IL)-6 levels. Secondary outcomes: 28d all-cause mortality; use of intensive care and hospital resources; organ dysfunction (failure-free day methodology of Bernard et al[ref] used with minor modifications)</td>
<td>Additional interventions except high dose heparin were given at discretion of treating physician and not pre-specified in study protocol *Safety data for all pts also provided in cumulative safety update</td>
</tr>
<tr>
<td>PROWESS (EVAD) Eli Lilly Phase III</td>
<td>Bernard et al. 2002, Vincent et al. 2002, Ely et al., Dhainaut et al, 2003, Angus et al.</td>
<td>1728 randomised; 1690 treated</td>
<td>rhAPC 96h continuous iv infusion: 24 µg/kg/hr, n=850</td>
<td>Saline (0.9% with or w/out 0.1% human serum albumin) continuous i.v. infusion</td>
<td>Primary outcomes: 28d all-cause mortality</td>
<td>Additional interventions as above. Composition of placebo changed after 720pts recruited (Jun 1999) Inclusion/exclusion criteria changed at (Aug 1999) Primary outcome analyses performed on treated patients and ITT. ITT only reported here</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENHANCE (EVBE, EVBF, EVBG)</td>
<td>1578 treated&lt;sup&gt;49&lt;/sup&gt;, 273 reported&lt;sup&gt;51&lt;/sup&gt;</td>
<td>rhAPC 96h continuous iv infusion: 24 µg/kg/hr</td>
<td>No control group</td>
<td>Outcomes: 28-d mortality, safety* (serious bleeding events, intracranial haemorrhage)</td>
<td>Inclusion and exclusion criteria were identical to those of PROWESS. *Safety data for all pts also provided in cumulative safety update&lt;sup&gt;49&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>EVAS</td>
<td>28 treated (compassionate use – purpura fulminans)</td>
<td>rhAPC for minimum of 96h continuous iv infusion: 24 µg/kg/hr</td>
<td>No control group</td>
<td>Outcomes: Safety*</td>
<td>*Safety data for all pts provided in cumulative safety update&lt;sup&gt;49&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>EVBC</td>
<td>240 treated (compassionate use)</td>
<td>rhAPC 96h continuous iv infusion: 24 µg/kg/hr</td>
<td>No control group</td>
<td>Outcomes: Safety*</td>
<td>*Safety data for all pts provided in cumulative safety update&lt;sup&gt;49&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cumulative safety update</td>
<td>Bernard &lt;i&gt;et al&lt;/i&gt; (2003)&lt;sup&gt;49&lt;/sup&gt;</td>
<td>rhAPC 96h continuous iv infusion: 24 µg/kg/hr</td>
<td>2 RCTs (EVAA and EVAD), plus five open label studies, see above for details</td>
<td>Outcomes: 28-day mortality, safety (serious bleeding event rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>commercial use data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) a priori subgroup analyses

\(^b\) post hoc subgroup analyses according to single/multiple organ dysfunction
### Reference and Design

**Author:** Bernard, et al.  
**Recruitment date:**  
**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.

### Interventions

**Recombinant human activated protein C (rhAPC):**  
- **Stage I:**  
  - **Dose:** 12, 18, 24 or 30 µg/kg/hr  
  - **Duration:** 48 hrs continuous i.v. infusion  
- **Stage II:**  
  - **Dose:** 12, 18, or 24 µg/kg/hr  
  - **Duration:** 96 hrs 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 & respiratory support, and surgical intervention were left to the treating physician and not pre-specified in the protocol.

### Subjects

**Total number of patients:** 135 pts randomised of which 131 received rhAPC (n=90) or placebo (n=41).  

**Numbers of patients in each group:**  
- **Stage I:**  
  - rhAPC 12 µg/kg/hr = 11  
  - rhAPC 18 µg/kg/hr = 11  
  - rhAPC 24 µg/kg/hr = 12  
  - rhAPC 30 µg/kg/hr = 12  
  - placebo = 26  
- **Stage II:**  
  - rhAPC 12 µg/kg/hr = 14  
  - rhAPC 18 µg/kg/hr = 15  
  - rhAPC 24 µg/kg/hr = 15  
  - placebo = 15  

**Baseline characteristics:**  
- **Age (yrs):** 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 prior to 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:** Pts ≥18 yrs with

### Outcome measures

**Primary outcomes:** frequency of serious adverse events, serious bleeding events, and assessment of anti-APC antibody response.  
**Primary pharmacodynamic measures:** changes in D-dimer, fibrinogen, platelet and interleukin (IL)-6 levels.  
**Secondary outcomes:** assessments for 28-day all-cause mortality, morbidity markers (utilisation of intensive care and hospital resources), and organ dysfunction (failure-free day methodology of Bernard et al (see refs) was used with minor modifications).  
**Length of follow-up:** 28 days
severe sepsis and known/suspected site of infection. (Criteria for severe sepsis were a modification of systemic inflammatory response syndrome (SIRS) as defined by ACCP/SCCM Consensus Conference with details given in Appendix 1). Briefly, $\geq 3$ signs of SIRS, and cardiovascular, renal or respiratory organ failure – these criteria had to be met within 24hrs. Pts had to begin treatment within 36hrs of meeting inclusion criteria.

*Exclusion criteria:* (details given in Appendix 2). Pts with active or increased risk of bleeding; known hypercoagulable condition; not expected to live $>6$hrs or survive 28-days due to co-morbid condition; known or suspected sustained irreversible cessation of brain function; or pts with ESRD on renal dialysis.
## Technology assessment report

### Reference and Design

**Authors:** Bernard, et al.\(^9\) (efficacy)

Vincent, et al.\(^{28}\) (organ dysfunction)**

Wesley Ely, et al.\(^{36}\) (subgroup analyses)†

Dhainaut et al.\(^ {45}\) (multiple organ dysfunction)‡

**Recruitment date:** July 1998 to June 2000

**Location:** 164 centres in 11 countries

**Setting:** clinical

**Publication status:** published 2001, 2003**\(^2\), 2003†, 2003

**Design:** RCT, double-blind, placebo-controlled, multicentre

**Trial sponsor:** Supported by Eli Lilly

---

### Interventions

**Drotrecogin alfa (activated) (Da):**

- **Dose:** 24µg/kg/h i.v. at a constant rate
- **Duration:** 96 hrs

**Details of placebo:** 0.9% saline with or w/out 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 & placebo pts also received standard supportive care.

---

### Subjects

**Total number of patients:** 1728 pts randomised of which 1690 received Da or placebo.

**Numbers of patients in each group:**

- Da group = 850, placebo group = 840

**Patient numbers not reported separately for centres.**

\(^{†}\) M.O.D n=1271, Da 634, placebo 637.

\(^{‡}\) S.O.D n=419, Da 216, placebo 203

**Baseline characteristics:**

- **Age:** 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%**

**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 (+ve blood culture):** Da 32.7%

---

### Outcome measures

**Primary outcomes:** death from any cause

**Secondary outcomes:** D-dimer levels, interleukin-6 levels, plasma protein C activity level, microbiologic cultures, serious adverse events (serious bleeding or thrombotic event)

\(^{†}\) Univariate 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, interleukin-6 levels, ventilator or vasopressor se,

\(^{‡}\) 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).

\(^{†}\) SOFA scores collected at baseline and daily throughout the 28-d study; presence of DIC was assessed post-hoc; APACHE II scores were recorded as the most extreme values in the 24hrs prior to drug administration.

**Length of follow-up:** 28 days after start of infusion or until death

---

**Note:** Use symbols (**, †, ‡) for reference to specific studies, where not symbol shown study is Bernard et al.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Da</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram -ve bacteria</td>
<td>21.8%</td>
<td>23.3%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Gram +ve bacteria</td>
<td>25.8%</td>
<td>25.1%</td>
<td></td>
</tr>
<tr>
<td>Documented pseudomonad</td>
<td>6.6%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>10.0%</td>
<td>10.2%</td>
<td></td>
</tr>
<tr>
<td>Pneumonia (Streptococcus pneumoniae)</td>
<td>12.5%</td>
<td>11.3%</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>20.0%</td>
<td>19.9%</td>
<td></td>
</tr>
<tr>
<td>Prior or pre-existing conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% COPD</td>
<td>18.6%</td>
<td>18.7%</td>
<td></td>
</tr>
<tr>
<td>% recent trauma</td>
<td>3.2%</td>
<td>6.4%</td>
<td>0.485</td>
</tr>
<tr>
<td>% recent surgery</td>
<td>4.8%</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>21.7±7.2</td>
<td>21.4±7.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>57.5%</td>
<td>61.1%</td>
<td></td>
</tr>
<tr>
<td>% recent surgery</td>
<td>4.0%</td>
<td>4.7%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Use of any vasopressor</td>
<td>72.7%</td>
<td>73.9%</td>
<td></td>
</tr>
<tr>
<td>Overt DIC</td>
<td>12.4%</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>Non-overt DIC</td>
<td>87.6%</td>
<td>85.7%</td>
<td></td>
</tr>
<tr>
<td>Overt DIC</td>
<td>89.4%</td>
<td>84.9%</td>
<td></td>
</tr>
<tr>
<td>Non-overt DIC</td>
<td>74.4%</td>
<td>75.7%</td>
<td></td>
</tr>
</tbody>
</table>

\* Prior or pre-existing conditions listed for many conditions, inc:

% COPD: S.O.D. All 78 (18.6%), Da 40 (18.5%), Pl 38 (18.7%)
M.O.D. All 330 (26.0%), Da 149 (23.5%), Pl 181 (28.4%)  p=0.002
% recent trauma: S.O.D. All 20 (4.8%), Da 7 (3.2%), Pl 13 (6.4%)
M.O.D. All 51 (4.0%), Da 21 (3.3%), Pl 30 (4.7%)  p=0.485
% recent surgery: S.O.D. All 96 (22.9%), Da 49 (22.7%), Pl 47 (23.2%)
M.O.D. All 406 (31.9%), Da 196 (30.9%), Pl 210 (33.0%)  p=0.0005

**APACHE II: S.O.D. All 21.7±7.2, Da 21.4±7.1, Pl 22.0±7.2
M.O.D. All 25.8±7.6, Da 25.7±7.5, Pl 25.9±7.8  p=0.0001
Mechanical ventilation: S.O.D. All 241 (57.5%), Da 117 (54.2%), Pl 124 (61.1%)
M.O.D. All 1034 (81.4%), Da 506 (79.8%), Pl 528 (82.9%)  p=0.0001

**Shock: S.O.D. All 153 (36.5%), Da 83 (34.4%), Pl 70 (34.5%)
M.O.D. All 1047 (82.4%), Da 515 (81.2%), Pl 532 (83.5%)  p<0.0001

**Use of any vasopressor: S.O.D. All 133 (31.7%), Da 63 (29.2%), Pl 70 (34.5%)
M.O.D. All 924 (72.7%), Da 453 (71.5%), Pl 471 (73.9%)  p=0.0001

**Overt DIC: S.O.D. All 52 (12.4%), Da 23 (10.7%), Pl 29 (14.3%)
M.O.D. All 326 (25.6%), Da 171 (27.0%), Pl 155 (24.3%)  p<0.0001
**Non-overt DIC: S.O.D. All 367 (87.6%), Da 193 (89.4%), Pl 174 (85.7%)
M.O.D. All 945 (74.4%), Da 463 (73.0%), Pl 482 (75.7%)
Markers of coagulation and inflammation – median level and interquartile range given as ML(IR):

**Plasma D-dimer (µg/ml):**
- S.O.D. all n=375, ML=3.48(2.02-6.71), Da n=193, ML=3.42(1.88-6.62), pl n=182, ML=3.59(2.11-6.77)
- M.O.D. all n=1175, ML=4.51(2.36-9.07), Da n=599, ML=4.51(2.48-8.93), Pl n=576, ML=4.51(2.24-9.13)

**P=0.0001**

**Serum IL-6(pg/ml):**
- S.O.D. all n=401, ML=245.3(78.3-770), Da n=209, ML=233.6(89.6-591.2), pl n=192, ML=251.6(71.4-1038.5)
- M.O.D. all n=1234, ML=657.2(172.2-3907), Da n=618, ML=734.1(190.1-3960.0), Pl n=616, ML=599.7(162.5-3792.0)

**P=0.0001**

**Plasma protein C activity (%):**
- S.O.D. all n=377, ML=56(39-75), Da n=194, ML=54(38-74), pl n=183, ML=58(40-76)
- M.O.D. all n=1197, ML=45(29-63), Da n=605, ML=44(28-61), Pl n=592, ML=46(30-64)

**P=0.0001**

**Protein C deficiency (<81%):**
- S.O.D. 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%), Pl: deficient 149(73.4%), not deficient 34(16.8%), unknown 20(9.9%)
- M.O.D. 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%), Pl: 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 Bone et al with details given in Appendix 1). Briefly, known or suspected infection present on basis of clinical data at time of screening and met following criteria within 24hrs: (1) ≥3 signs of systemic inflammation; (2) sepsis-induced dysfunction of ≥1 organ or system lasting no longer than 24hrs. Pts had to begin treatment within 24hrs after meeting inclusion criteria.
**Exclusion criteria:** (details given in Appendix 2). Age <18yrs or weight >135kg; conditions that increased the risk of bleeding; known hypercoagulable condition; or not expected to survive 28-days due to co-morbid condition.
### Reference and Design

**Author:** 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 7 completed & ongoing studies (2 RCTs, 3 open-label trials, 2 compassionate-use studies) and data from commercial use. Data obtained from databases.

### Interventions

**Drotrecogin alfa (activated) (Da):**  
- Dose: 24 µg/kg/hr  
- Duration: 96 hrs ± 1hr  

Above regimen used for 5 studies. 1 study gave above dosage for a min of 96hrs. 1 study gave 12, 18, 24, 30µg/kg/hr for 48hrs or 12, 18, 24 µg/kg/hr for 96 hrs. Commercial use studies were expected to give 24 µg/kg/hr for 96 hrs total duration (specific details not available).

**Details of placebo:** saline or 0.1% albumin in saline for RCTs.

### Subjects

**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 1 compassionate-use study* utilised inclusion & 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 organ dysfunctions. Pts 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.  
*This study required only the clinical diagnosis of purpura fulminans and did not exclude those with thrombocytopenia.

### Outcome measures

**Primary outcomes:**  
1. 28-day all-cause mortality (28d after infusion start) was assessed for all but 1 ongoing study (compassionate-use), where 7-d mortality was assessed for a subset of non-US pts and 28d mortality was estimated (method given). Mortality rate for commercial-use pts not available.  
2. Serious bleeding complications, including intracranial haemorrhage, life-threatening bleeding event, requirement for ≥ 3 units of blood transfusion/d for 2 consecutive days, or meeting other criteria defining serious adverse events. Events were recorded for up to 28d from start of Da infusion for all but 1 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 1, where 7-d events were recorded and 28-d events were estimated.
Results (number, rate (95% CI))

- Deaths at follow-up:
  - Controlled trials, Da: 236/940, 25.1% (22.4 – 28.0)
  - Open-label studies, Da: 398/1578, 25.2% (23.1 – 27.4)
  - Compassionate-use studies, Da: 70/268, 26.1% (21.0 – 31.8)
  - Combined mortality rate (all clinical trials), Da: 704/2786, 25.3% (23.7 – 26.9)
  - Commercial use studies: data not available
  - Combined placebo rate: 273/881, 31.0% (28.0 – 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 pts compared to placebo pts, whilst for multiorgan failure, the latter was true.

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

- Serious bleeding events – intracranial haemorrhage (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-d 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 4 events are reported for controlled trials and only 3 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).

Note: ¤Reviewer calculated total by summing bleeding events for infusion period and postinfusion period
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 re blinding during studies.
- **Comparability of treatment groups**: Baseline characteristics not stated. Comparisons between clinical trial types were avoided due 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/drop-out**: Not reported.

General comments

- **Generalisability**: An analysis of all available data on the safety of Da treatment in adult pts with severe sepsis. All studies except 1 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-d 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.
- **Inter-centre 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 & Co.
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 > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) respiratory rate > 20 breaths per minute or PaCO₂ < 32 mm Hg; and (4) white blood cell count > 12,000/cu mm, < 4,000/cu mm, 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 > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) respiratory rate > 20 breaths per minute for PaCO₂ < 32 mm Hg; and white blood cell count > 12,000/cu mm, < 4,000/cu mm, 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 mm Hg or a reduction of ≥ 40 mm Hg 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. This 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.) (p1646).

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) (p1648). 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.” (p1648). 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 that 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 in order 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 physiologic, 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 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

<table>
<thead>
<tr>
<th></th>
<th>Results for all patients (prospective analyses)</th>
<th>Results for patients with ≥ 2 organ dysfunctions (retrospective analyses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N per group</td>
<td>Mortality (%) rhAPC / placebo (n=850) / (n=840)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>886</td>
<td>15.6 / 20.9</td>
</tr>
<tr>
<td>≥65</td>
<td>804</td>
<td>34.4 / 42.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>964</td>
<td>24.3 / 31.0</td>
</tr>
<tr>
<td>Female</td>
<td>726</td>
<td>25.2 / 30.6</td>
</tr>
<tr>
<td>Racial origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1384</td>
<td>24.5 / 31.1</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>306</td>
<td>25.8 / 29.8</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US/Canada</td>
<td>24.9 / 32.3</td>
<td>-7.4</td>
</tr>
<tr>
<td>Europe</td>
<td>25.8 / 30.3</td>
<td>-4.5</td>
</tr>
<tr>
<td>Other</td>
<td>22.0 / 26.8</td>
<td>-4.8</td>
</tr>
<tr>
<td>Recent surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1188</td>
<td>23.5 / 30.9</td>
</tr>
<tr>
<td>Yes</td>
<td>502</td>
<td>27.8 / 30.7</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1387</td>
<td>25.0 / 28.5</td>
</tr>
<tr>
<td>Yes</td>
<td>303</td>
<td>28.3 / 41.1</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1282</td>
<td>24.2 / 27.1</td>
</tr>
<tr>
<td>Yes</td>
<td>408</td>
<td>26.5 / 41.6</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1282</td>
<td>24.2 / 27.1</td>
</tr>
<tr>
<td>Yes</td>
<td>408</td>
<td>26.5 / 41.6</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1534</td>
<td>24.1 / 30.5</td>
</tr>
<tr>
<td>Yes</td>
<td>156</td>
<td>29.9 / 34.8</td>
</tr>
<tr>
<td>Immuno-compromised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unknown</td>
<td>1534</td>
<td>24.1 / 30.5</td>
</tr>
<tr>
<td>Yes</td>
<td>156</td>
<td>29.9 / 34.8</td>
</tr>
</tbody>
</table>
ARR confidence intervals and RRs and confidence intervals, or data to estimate them, provided in FDA report or estimated by SHTAC using data provided in paper. Where CIs are not provided, insufficient data was available with which to estimate them. nr = not reported.

age subgroups: 50, 51-65, 66-75, >75
### Appendix 10. Internal validity of economic evaluations

<table>
<thead>
<tr>
<th>Item</th>
<th>Angus et al</th>
<th>Manns et al</th>
<th>Fowler et al</th>
<th>Eli Lilly Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Well defined question</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2. Clear description alternatives</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3. Reasonable study type</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4. Effectiveness established</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5. Estimates related to population risks</td>
<td>? Trial population assumed to reflect population</td>
<td>✓</td>
<td>? Trial population assumed to reflect population</td>
<td>? Trial population assumed to reflect population</td>
</tr>
<tr>
<td>7. Costs and consequences measured accurately</td>
<td>✓ Trial data used to measure costs and consequences</td>
<td>✓ Specific Canadian cohort study used for baseline risk and resource use</td>
<td>✓ - ? PROWESS effectiveness data and patient groups. Hospital cost data were from an observational cohort study</td>
<td>✓ - ? Apply UK life expectancy and cost data to PROWESS effectiveness profiles</td>
</tr>
<tr>
<td>8. Costs and consequences valued credibly</td>
<td>✓ - ? Health state utilities from US tariff values. Cost data based on US cost cohort. Long-term costs from US database information.</td>
<td>✓ - ? Utility data from a study on ARDS, not severe sepsis.</td>
<td>? Utility values used were not for severe sepsis, but deemed to be similar by authors</td>
<td>✓ UK cost data used ? - Utility data from an unpublished study, cited as abstract</td>
</tr>
<tr>
<td>9. Differential timing considered</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>10. Incremental analysis performed</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>11. Sensitivity analysis performed</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Note: ? means unclear or unknown  
✓ means item included or judged as acceptable to be internally valid.  
X means factor not included or judged to be unacceptable to be internally valid.
### Appendix 11. External validity of economic evaluations

<table>
<thead>
<tr>
<th>Item</th>
<th>Angus et al(^2)</th>
<th>Manns et al(^8)</th>
<th>Fowler et al(^9)</th>
<th>Eli Lilly Submission(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient group – are the patients in the study similar to those of interest in England and Wales?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>2. Health care system/setting – comparability of available alternatives?; similar levels of resources?; no untoward supply constraints?; institutional arrangements comparable?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>?</td>
</tr>
<tr>
<td>4. Resource costs - comparability between study and setting/population of interest?</td>
<td>Intervention cost only</td>
<td>Intervention cost only</td>
<td>Intervention cost only</td>
<td>✓ - ?</td>
</tr>
<tr>
<td>5. Marginal versus average costs - what difference does this make?</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: ? means unclear or unknown  
✓ means judged item suitable to generalise to England and Wales with or without some re-adjustment.  
X means factor judged 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Cost-Effectiveness</th>
<th>Sub-Group analyses</th>
<th>Sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angus <em>et al</em> 2003</td>
<td>Base case analysis ($CE_{base}$), presents cost per life saved: based on, (i) incremental costs as the difference in health care costs (hospital, physician, study-drug and postdischarge costs up to day 28) between treatment and placebo during the first 28 days, and (ii) incremental effects as difference in 28-day all cause mortality</td>
<td>$CE_{base}$: $160,000 per life saved (with 84.7% and 97.9% probabilities that the ratio was &lt;$250,000 and &lt;$500,000 per life saved)</td>
<td>$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</td>
<td>Authors state that $CE_{base}$ was generally robust to assumptions and estimates of costs and effects. (but authors do not present any results of sensitivity analyses on the estimate of effect)</td>
</tr>
<tr>
<td></td>
<td>Reference case analysis ($CE_{reference}$), presents cost per life year gained and cost per QALY gained: based on, (i) 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, (ii) incremental effect as the number of life-years and QALYs gained. Costs and effects discounted at 3%.</td>
<td>$CE_{reference}$: $33,000 per life-year gained (with a 89.1% probability that the ratio was &lt;$100,000 per life-year gained)</td>
<td>$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 &lt;60&gt;, prior location, infection site, etc.)</td>
<td>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 $100,000/QALY.</td>
</tr>
<tr>
<td>Manns <em>et al</em> 2002</td>
<td>Base line analysis presents cost per life year gained for a Canadian cohort of patients. Results presented in US dollars ($), based</td>
<td>All patients: (with relative risk of death reported in PROWESS study)</td>
<td>By severity: (with relative risk of death reported in FDA reanalysis)</td>
<td>Authors state that analysis was not sensitive to plausible variations in estimates of the</td>
</tr>
</tbody>
</table>
Study Methods Cost-Effectiveness Sub-Group analyses Sensitivity analyses

Fowler et al 200359

Cost-effectiveness of rhAPC [drotrecogin alfa (activated)] in severe sepsis patients (USA analysis), compared to usual care

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 or less = 18.5%, for a score of 25 or more 54.5%.

Costs and outcomes discounted at an annual rate of 5%

Cost per LYG $27,936
Cost per QALY $46,560

For ‘all patients’ the incremental gain in life years per patients was 0.38 years
Incremental costs circa. circa $10,615.

APACHE II score of 25 or more = $19,723 per LYG ($32,872 per QALY)
APACHE II score of 24 or less = $575,054 per LYG ($958,423 per QALY)

For ‘all patient’ analysis:
Cost per LYG $15,801
Cost per QALY £20,047

For patients with APACHE II score ≥ 25:
Cost per LYG $10,833
Cost per QALY $13,493

For patients with APACHE II

Abstract states that over a broad range of parameter changes the cost per QALY remained under $30,000. A probabilistic sensitivity analyses is reported showing a less than 1% chance of simulations having a cost per QALY greater than $50,000.

cost of hospital stay, the subsequent cost of health care, 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 life-year gained increased to $74,612.

Where APACHE II subgroups were re-analysed 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 or less was $35,652 ($24,484, for those with a score of 25 or more).
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Cost-Effectiveness</th>
<th>Sub-Group analyses</th>
<th>Sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al 2002&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Cost-effectiveness analysis based on clinical-effectiveness shown in PROWESS, using absolute risk reduction (ARR) for mortality difference. Analysis presented for two patient groups (a) for the overall PROWESS patient population (b) for the 75% of patients in PROWESS who had ≥ 2 organ dysfunctions. Life years discounted at 1.5% QALY value of 0.69 used.</td>
<td>Method (i): PROWESS overall Cost per life year saved is £9,519 Cost per QALY is £13,796 Method (ii): PROWESS ≥ 2 organ dysfunctions Cost per life year saved is £7,037 Cost per QALY is £10,199</td>
<td>For patients with ≥2 organ dysfunctions, cost per life year saved is £4,716, and cost per QALY is £6,385</td>
<td>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.</td>
</tr>
<tr>
<td>Launois et al 2002&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Cost-effectiveness analysis, using a baseline population form the Cub-Rea database (Paris, France), which show 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.</td>
<td>Cost per additional life year saved reported at 18,446 Euros.</td>
<td>Other results reported for sub-groups ranged from 10,005 euros to 31,833 euros.</td>
<td>Monte Carlo bootstrap methods showed 96.3% of results were cost-effective against a threshold willingness to pay of 53,357 Euros.</td>
</tr>
<tr>
<td>Neilson et al (1) 2002&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Cost-effectiveness study, comparing drotrecogin αf (activated) with conventional therapy for patients with severe sepsis in Germany. Combine data from PROWESS on resource use and outcomes with Germany-specific unit costs.</td>
<td>Incremental cost per life year gained reported at 14,400 Euros. Additional analyses reported against modifications to the costing structure, for European and German data, with cost per</td>
<td>No further results reported.</td>
<td>Sensitivity reported to have been undertaken on several parameters, producing cost-effectiveness estimates within the published ranges for other life saving interventions in Germany.</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Cost-Effectiveness</td>
<td>Sub-Group analyses</td>
<td>Sensitivity analyses</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neilson et al 2002 (2)⁶²</td>
<td>Cost-effectiveness of drotrecogin alfa (activated) in Germany (GM), Austria (AS) and Switzerland (CH). Decision analytic model, with results from perspective of health service payer. PROWESS data on absolute risk reduction used.</td>
<td>Life year gained at 14,800 Euros and 13,000 Euros.</td>
<td>Results presented for GM and AS, as 14,400 Euros and 15,400 euros per life year gained respectively (where life years gained were discounted at 3% results were 22,400 euros and 24,700 euros).</td>
<td>For high risk patients, with ≥ 2 or more organ dysfunctions, results were 10,400 euros for GM, and 11,300 or AS (discounting benefits at 3% results were 13,500 and 15,100 euros 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.</td>
</tr>
<tr>
<td>Lucioni et al 2002⁶³</td>
<td>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.</td>
<td>Incremental cost per life year gained reported at 13,436 euros for the severe sepsis patient group. For severe sepsis patients with multiple organ failure the cost per life year gained is reported at 9,660 euros.</td>
<td>For severe sepsis patients with multiple organ failure the cost per life year gained is reported at 9,660 euros.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Sacristan et al 2002⁶⁴</td>
<td>Cost-effectiveness of drotrecogin alfa (activated) in severe sepsis patients with multiple organ failure, in Spain. Decision analytical model approach, with a NHS perspective. Effectiveness data and resource use data from the PROWESS trial, with Spanish unit costs. Base case analysis did not apply any discounting.</td>
<td>Base case: cost per life year gained reported at 9,799 euros, for patients with multiple organ failure, (13,594 Euros for patients with severe sepsis population)</td>
<td>Base case analysis was on those with multiple organ failure.</td>
<td>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.</td>
</tr>
<tr>
<td>Coyle et al 2002⁶⁶</td>
<td>Cost-effectiveness analysis of drotrecogin alfa (activated) in the treatment of severe</td>
<td>Incremental cost per QALY reported at $15,500.</td>
<td>No subgroup analysis. Main analyses refers to</td>
<td>No details of sensitivity analyses reported.</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Cost-Effectiveness</td>
<td>Sub-Group analyses</td>
<td>Sensitivity analyses</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>sepsis in Canada.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with severe sepsis at an increased risk of death (defined as an APACHE II score ≥ 25).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decision analytic model, using Monte Carlo simulation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effectiveness data and resource use data were from the PROWESS trial.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using a threshold willingness to pay of $50,000 per QALY, the net benefit of drotrecogin alfa is estimated to be $8,800 (95% CI: -$9,000 to $38,000)</td>
<td>those patients with APACHE II score of ≥ 25.</td>
<td>Abstract states that variables contributing most to the uncertainty were length of initial hospitalisation, mortality during hospitalisation, and the utility of survivors.</td>
</tr>
<tr>
<td>Riou Franca et al [Abstract]</td>
<td>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 used (CubRea database, Paris). Life-expectancy estimated using database, incl. data on comorbidities. Life-expectancy of survivors adjusted by half. Utility weight of 0.60 used.</td>
<td>Cost per life year gained US $11,812 Cost per QALY US $19,685 (presume this is non-discounted future costs and benefits)</td>
<td>No subgroup analyses reported other than sensitivity analyses.</td>
<td>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.</td>
</tr>
<tr>
<td>Eli Lilly Submission</td>
<td>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 case mortality data at final patient discharge – day 297). Patient group defined according to PROWESS criteria, with multiple organ dysfunction - Based on 28-d survival data: Cost per LYG £4,580 Cost per QALY £6,637 The estimated life year gains per patient treated were 1.115 years (based on 28-day survivors). Additional cost per patient</td>
<td>PROWESS patients with multiple organ dysfunction - Based on 28-d survival data: Cost per LYG £4,580 Cost per QALY £6,637 The estimated life year gains per patient treated were 1.115 years (based on 28-day survivors). Additional cost per patient</td>
<td>No subgroup analyses reported outside of the sensitivity analyses.</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Cost-Effectiveness</td>
<td>Sub-Group analyses</td>
<td>Sensitivity analyses</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>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 to 5 after episode of severe sepsis</td>
<td>treated estimated at £5,106. Using data from longer term follow-up: Cost per LYG £7,547 Cost per QALY £10,937</td>
<td></td>
<td>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 or the two CEA analyses increases by 53% to £10,178 and £16,770 respectively.</td>
</tr>
</tbody>
</table>
Appendix 13. Data extraction (CRD Format) of published economic evaluations

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

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) as 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)
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 (3 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 75kg, 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>135Kg, if patients were expected to die of a non-sepsis-related disease within one month, if severe HIV (see section 2 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-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 et al (2001) and detail of this study can be found in the main body of the review (see Section 2 of the SHTAC report for detail).

Modelling
A model was used to estimate life time 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. 1,728 patients underwent randomisation (1:1), of which 1,690 received the study drug or placebo (840 placebo, 850 in the treatment group). See section 2 of the SHTAC report for detail on the study inclusion/exclusion criteria.

Study design
Randomised controlled trial, 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 endpoint was 28-day all cause mortality. At base line, the demographic characteristics and severity of disease were similar in the placebo and treatment group.

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 endpoint 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 to general population norms.

**Direct costs**

Differences in health care 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 prior to 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 health care costs form 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 to 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 nonsurvivors, and proportions of surgical and nonsurgical 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**


**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, post discharge 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 $9,800 ± $2,900
In the lifetime reference case analysis drotrecogin alfa (activated) increased costs by $16,000 ± $4,200 per treated patient, $6,200 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. Authors report that the cost per QALY remained below $100,000 if average survival decreased to 4.6 yrs (reference case =12.3 yrs). Where average utility was assumed to be 0.51 (reference case = 0.68) the cost per QALY remained below $100,000 until the average years of survival decreased to 6.6 yrs.
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, due 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

Author's 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 trials' clinical endpoints 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 to matched population norms. Such assumptions may be valid, but there are methodological issues which 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 health care costs for survivors of severe sepsis, and this issue may be open to some methodological debate; although 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

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 ICU for severe sepsis

Disease
Severe Sepsis

Type of intervention
Treatment.

Hypothesis/study question
Estimated cost-effectiveness of activated protein C as 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 health care 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, intensive care unit.
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-June 2000). A cohort study was undertaken as part of the analysis to estimate mortality and direct health care 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 April 1, 1996 and March 31, 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 United States 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 Section 2 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 to 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 i.e. 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 et al (see detailed review, Section 2 of the SHTAC report). 1,728 patients underwent randomisation (1:1), of which 1,690 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 multi-national, 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 base line, the demographic characteristics and severity of disease were similar in the placebo and treatment group.

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 (CI:0.59-0.85), and those with a score of ≤ 24 had a relative risk of 0.99 (CI:0.75-1.30).

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. Base-line 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 to conventional care. The model estimated life-years gained. The model considered weekly transitions between 4 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 cost of care per week for ICU and on the hospital ward were calculated. Follow-up cost 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 ($6,800) 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 ($8,306 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 ICU and were subsequently employed, and multiplied it by the average gross annual salary for a full-time Canadian worker (33,384 Canadian dollars).

Currency
United States 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 one 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 health care, 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 simultaneously consider 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
< 40yrs, 0.40 for 40-59 yrs, 0.40 for 60-79 yrs and 0.32 for ≥80 yrs. 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. 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 ($6,800 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, assumed 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 health care costs after hospital discharge for all patients are reported at $14,181 per patient in year 1, $4,698 year 2 and $4,579 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 $27,936 (USD), 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. Results shown above indicate the differences in sub-groups by APACHE II score.

Monte Carlo simulation indicated there was an 86 percent 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**

**Author's 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 (US). 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 acute respiratory distress syndrome. 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, 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 health care 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 health care 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 has 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 sub group 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

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 to usual therapy for patients with severe sepsis. The comparator used is usual therapy (usual anti-infective therapy and supportive care) for patients admitted to 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 comorbidities 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 USA hospital setting, with initial phase of treatment (at least) in an intensive care unit.

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 are 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 to 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 et al (2001) and detail of this study can be found in the main body of the present review (see Section 2 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 Section 2 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 et al (see detailed review, Section 2). 1,728 patients underwent randomisation (1:1), of which 1,690 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 multi-national, 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 base line, the demographic characteristics and severity of disease were similar in the placebo and treatment group.

**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 quality-adjusted life-years). 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 life-time 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 eight 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 health care costs for survivors of severe sepsis. The model also included a cost for death ($5,310), which was from a published estimate. Cost data for serious GI bleeds were from US Medicare (estimate of $1,237 per event). Cost for rhAPC was determined using estimate for a person weighing 70kg ($6,700). Cost data for hospitalisation were from an observational cohort study of hospital discharge records (1995) for severe large US states; hospitalisation cost (acute sepsis care) was estimated to be $24,332 (in 2001 US dollars). Future health care costs were from age specific medical expenditure data for the US (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**
United States 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 undertaken. Where pairs of variable regarded as influential multi-way sensitivity undertaken. Authors state that Monte Carlo methods used for model variables (assuming log normal distributions for cost inputs, and norm or logistic distributions for probabilities and health state utilities).

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

The report runs analyses for various patient groups – by severity of illness (according to APACHE II score ≥ 25 <), also 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 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 $6,851.

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 discounted at 3%.

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

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

The study reports cost per QALY $7,503 for the treatment of those patients with protein C deficiency with rhAPC.

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

The authors report 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 $9,400 and $25,400 per QALY.

Conclusions and critical comment

Author's 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 (US). 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 eight year period, citing a study by Quartin et al (1997) for parameter inputs. The authors do not report how they used the data reported by Quartin et al, and this raises uncertainty over the methods applied, especially as Quartin et al report differences between severe sepsis patients and controls over years 1 to 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 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 were similar to PROWESS patients.

The authors use long term health care 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 has 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

In order to estimate the mean NHS costs per person (adult) per year, we combined aggregate data on NHS expenditure (hospital and community health services), data on NHS activity, and population data by age. 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 cost 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 we used data from the Department of Health, Hospital Episode Statistics 2001-2002 (www.doh.gov.uk/hes, accessed August 2003). The headline figures for 2001-02 for NHS hospital admitted patients for the period 1st April 2001 to 31st March 2002, were used, as listed below.

Hospital episode statistics / Finished Consultant Episodes (FCEs):

<table>
<thead>
<tr>
<th>Age Range</th>
<th>FCEs (in 1000s)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-44 years</td>
<td>3,606,385</td>
<td>34.10%</td>
</tr>
<tr>
<td>45-64 years</td>
<td>2,671,229</td>
<td>25.25%</td>
</tr>
<tr>
<td>65-74 years</td>
<td>1,759,663</td>
<td>16.64%</td>
</tr>
<tr>
<td>75-84 years</td>
<td>1,703,699</td>
<td>16.11%</td>
</tr>
<tr>
<td>85+ years</td>
<td>779,772</td>
<td>7.37%</td>
</tr>
<tr>
<td>Not known</td>
<td>56,651</td>
<td>0.54%</td>
</tr>
</tbody>
</table>

Total NHS expenditure on hospital and community health services (HCHS) for 2002/3 was obtained from Department of Health statistics (www.doh.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 & Wales)*

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Expenditure (in £)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-44 years</td>
<td>£14,762,196,169</td>
<td>20,836,812</td>
</tr>
<tr>
<td>45-64 years</td>
<td>£10,934,275,323</td>
<td>11,098,689</td>
</tr>
<tr>
<td>65-74 years</td>
<td>£7,202,916,604</td>
<td>9,607,385 (aged 65+)</td>
</tr>
<tr>
<td>75-84 years</td>
<td>£6,973,836,363</td>
<td></td>
</tr>
<tr>
<td>85+ years</td>
<td>£3,191,879,744</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combining the above data we estimate the annual NHS HCHS expenditure per adult by age range to be:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Expenditure (in £)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-44 years</td>
<td>£708.47</td>
</tr>
<tr>
<td>45-64 years</td>
<td>£985.19</td>
</tr>
<tr>
<td>65+ years</td>
<td>£1,807.84</td>
</tr>
</tbody>
</table>

For example, age group 45-64 years comprise 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 we estimate an average cost per person at £985.18 each per year.

Appendix 15. CEACs for selected sensitivity analyses

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

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