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DROTRECOGIN ALFA (ACTIVATED) IN SEVERE SEPSIS

DROTRECOGINE ALFA (ACTIVEE) EN SEPSIS SEVERE

An update of the informal TAU report ,(April 2003) entitled, "Drotrecogin alfa (activated) in severe sepsis"

Report available at

www.mcgill.ca/tau/

This report was prepared for the Joint Technology Assessment Unit (TAU) Committee of the

McGill University Health Centre (MUHC) and Centre Hospitalier de l'Université de Montréal (CHUM)

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Drotrécogine alfa (activée) en sepsis sévère

RÉSUMÉ

La sepsis est un syndrome complexe et hétérogène, caractérisée par une réponse inflammatoire et de procoagulation systémique à une infection. La drotrécogine alfa activée est un analogue recombinant de la Protéine C activée endogène et est obtenue par génie génétique à partir d'une lignée cellulaire humaine. Son utilisation thérapeutique a pour but d'améliorer les résultats cliniques en contrant les conséquences inflammatoires et thrombotiques dus à la sepsis sévère.

Compte tenu de la disponibilité d'un grand nombre de publications ainsi que du coût très élevé de la drotrécogine alfa, nous avons décidé de réaliser une évaluation détaillée basée sur l'état actuel des connaissances en examinant son efficacité, sa sécurité et son rapport coût-efficacité. Nous avons identifié, au cours de notre révision systématique de la littérature, deux études contrôlées randomisées, quatre études observationnelles, sept rapports d'évaluations des technologies, neuf évaluations économiques et plusieurs analyses des sous-groupes incluses dans les essais contrôlés randomisés. Une étude contrôlée randomisés pédiatrique a également été identifiée.

Bénéfices cliniques

L'étude contrôlée randomisée PROWESS a démontré une réduction de mortalité dans les 28 premiers jours avec la drotrécogine alfa de 6.1% par rapport au groupe placebo. Cependant, ce bénéfice n'a pas été confirmé dans une deuxième étude (ADDRESS) chez des patients septiques présentant une sévérité moins élevée que dans l'étude PROWESS. Une étude effectuée chez des patients pédiatriques a du être terminée prématurément à cause d'absence de bénéfice clinique chez le groupe recevant de la drotrécogine alfa par rapport au groupe placebo (Mortalité à 28 jours: 17.15% contre 17.45% respectivement p=0.93).

Des analyses des sous-groupes de l'étude PROWESS ont montré un bénéfice, en terme de mortalité à 28 jours, plus prononcé chez les patients à haut risque (score APACHE II ≥ 25, RR 0.71, 95% IC: 0.59, 0.85). Ce résultat a reçu une attention considérable et a influencé la pratique clinique. Cependant, plusieurs analyses de sous-groupes ont été réalisées, ce que pourrait augmenter la possibilité de résultats faux-positifs. De plus, l'analyse des résultats des deux essais contrôlés randomisés n'a pas démontré que la diminution de la mortalité avec drotrécogine alfa est statistiquement significative (ensemble des patients RR: 0.93, IC à 95% : 0.69 , 1.26), même chez

les patients ayant un risque plus élevé de maladie (APACHE II ≥25 RR: 0.90, 95% IC: 0.54 , 1.49, Nombre d'organes défaillants (≥ 2) RR: 0.84, 95% IC: 0.70 , 1.00)

En outre, les résultats du suivi à long terme de PROWESS ont montré que le bénéfice en terme de réduction de mortalité chez les patients atteints d'une sepsis sévère n'était pas aussi évident après 3 mois de traitement. Ainsi, la survie à 3 mois était de 66.1% et 62.4% (p=0.11), à 6 mois elle était de 62.2% et 60.3% (p=0.44) et à 12 mois elle était de 58.9% et 57.2% (p=0.49) chez les groupes de patients utilisant la drotrécogine alfa et placebo respectivement. La survie à long terme des patients présentant un risque élevé (score d'APACHE II >=25) est demeurée statistiquement significative chez les patients traités avec la drotrécogine alpha comparativement aux patients du groupe placebo et ce jusqu'à la fin de la période du suivi de 30 mois (58.9% vs. 48.4% p=0.003 à 3 mois, 52.1% vs. 41.3% p=0.002 à 12 mois, 45.6% vs. 33.8% p= 0.001 à 30 mois). Pourtant, la différence de survie avec drotrécogine alpha par rapport à placebo après 3-6 mois chez une autre groupe ayant un risque plus élevé, nombre d'organes défaillants ≥ 2 n'était pas statistiquement significative (taux de survie non reportés).

Enfin, la seule étude randomisée effectuée sur une population pédiatrique a été achevée prématurément à cause d'une absence de bénéfices cliniques et d'une augmentation des effets indésirables dans le groupe de la drotrécogine alpha par rapport au placebo.

Sécurité

En janvier 2005, le producteur de la drotrécogine a alpha a adressé du courrier aux professionnels de la santé, les mettant en garde d'un risque très élevé de mortalité suite à l'utilisation de la drotrécogine alpha chez des patients présentant un dysfonctionnement d'un organe et à la suite des chirurgies récentes comparativement au groupe de patients placebo. Ce résultat a été basé sur des données des sous-groupes des études PROWESS et ADDRESS.

Chez les adultes, la fréquence d'événements de saignement grave a augmenté substantiellement suite à l'utilisation de la drotrécogine alfa comparativement au placebo. L'utilisation de ce même médicament chez des patients pédiatriques a été la cause de l'augmentation du taux des hémorragies intracrâniennes, ce qui a obligé encore une fois le fabricant à envoyer un autre courrier aux professionnels de la santé en avril 2005 pour les mettre en garde contre ces effets indésirables.

Coût-efficacité

Du fait des incertitudes concernant l'efficacité clinique de drotrécogine alpha rendent l'évaluation de son coût-efficacité exploratoire. Plusieurs études économiques et rapports d'évaluation de technologies sont arrivés à la conclusion que la drotrécogine alpha a un rapport de coût-efficacité acceptable. Ces études ont été basées sur des données à court-terme de l'étude PROWESS et ont supposé que les bénéfices avec drotrécogine alfa seraient soutenus à longue durée, chose qui n'a pas été confirmée par la littérature la plus récente, d'autant que ces études n'ont pas utilisé toute l'évidence clinique disponible à ce jour. Dans le scénario le plus optimiste en réservant le traitement pour les patients à plus haut risque (APACHE II ≥ 25 et coût de traitement de CDN$ 11,000) notre analyse économique a démontré que dans plus de 90% des cas, la drotrécogine alpha avait un rapport de coût-efficacité de ≤ CDN$50,000/années-vie sauvées (LYG), pourtant avec une probabilité de 3% d'être moins efficace et plus chère que le placebo. Cependant, l'instabilité de ce modèle est évidente à une probabilité de moins de 47% d'un rapport de coût-efficacité ≤ CDN$50,000/années de vie sauvées en utilisant une autre mesure de sévérité de la sepsis (en présence de dysfonctionnement de plusieurs organes). En considérant toute la population ayant une sepsis sévère des études randomisées, cette probabilité est de 56%. Des résultats similaires ont été obtenus en utilisant une autre mesure d'efficacité, soit quality adjusted life years (QALYs) au lieu de LYG.

Rapports d'évaluations de technologies

Le National Coordinating Center for HTA au Royaume-Uni a conclu que la drotrécogine alpha lorsque combiné avec une prise en charge conventionnelle optimale avait un rapport de coût-efficacité acceptable chez les patients avec des sepsis graves. Aussi au Royaume-Uni, le National Center for Clinical Excellence (NICE) a recommandé l'utilisation de la drotrécogine alpha comme complément à une prise en charge conventionnelle optimale chez les patients avec un sepsis grave avec deux ou plus défaillances d'organes, si prescrit par un spécialiste en soins intensifs. Par contre, des rapports publiés en Espagne, au Suède, au Canada (CADTH), au Royaume-Uni (University of Birmingham), au Brésil et en Argentine ont considéré que l'évidence disponible sur la drotrécogine alpha est insuffisante ou faible. Ces rapports ont aussi démontré les incertitudes cliniques et économiques de ce médicament. En général, ces analyses économiques ont été basées sur des résultats de recherches à court-terme de l'étude PROWESS dont la véracité a été questionnée dans des publications plus récentes.

Situation actuelle et impact sur le budget du CUSM et du CHUM

Au CUSM en 2004, 11 patients ont reçu la drotrécogine alpha, avec une augmentation à 18 en 2005 et à un coût de CDN$200,000 (soit CDN$11,000 par patient traité). L'utilisation de ce médicament a diminué à 7 patients en 2006.
Au CHUM, on a administré la drotrécogine alpha à 27 patients entre Avril 2005 et Mars 2006 (à un coût approximatif de $295,000 pour cette période). L'impact potentiel sur le budget est donc relativement élevé.

Les cliniciens des deux institutions ont bien compris que le bénéfice clinique de la drotrécogine alpha est limité à une population hautement sélectionnée ce qui a amené a une utilisation plutôt modeste. D'ailleurs, les prescripteurs des deux institutions ont reconnu les problèmes de sécurité et coût de ce médicament et ont préparé des protocoles pour assurer une utilisation optimale de ce médicament. Ainsi, nous espérons que ce rapport servira comme guide qualitatif afin d'assister les médecins dans leurs prises de décision.

RECOMMANDATION

Considérant les incertitudes en termes de bénéfices cliniques, l'évidence de l'augmentation du risque d'hémorragies graves, et de son coût élevé, l'Unité d'Évaluation des Technologies (Technology Assessment Unit, TAU) recommande que la drotrécogine alpha ne soit pas utilisé systématiquement chez les patients adultes présentant une sepsis grave au CUSM et au CHUM.
La totalité de l'évidence suggère que les protocoles du CUSM et du CHUM restreignant l'utilisation de la drotrécogine alpha chez les patients à risque très élevé sont plus appropriés. Les mesures courantes utilisées pour assurer une utilisation optimale de la drotrécogine alpha doivent être maintenues.
Le TAU a aussi conclu qu'actuellement il n'existe aucune indication pour l'utilisation de la drotrécogine alpha chez les patients pédiatriques.

Comme d'habitude, ces recommandations seront mises à jour dès que de nouvelles évidences sur la drotrécogine alpha deviennent disponibles.

DROTRECOGIN ALFA (ACTIVATED) IN SEVERE SEPSIS

EXECUTIVE SUMMARY

Sepsis is a complex and heterogeneous syndrome, characterized by a systemic inflammatory and procoagulant response to an infection. Activated drotrecogin alfa (human activated protein C) is produced by recombinant DNA technology. Its use in therapy aims to improve clinical outcomes by counteracting the inflammatory and thrombotic consequences of severe sepsis.

Given the burgeoning number of publications as well as the high cost of drotrecogin alfa, it was decided to perform a health technology assessment which examined its efficacy, safety and cost-effectiveness based on the most contemporary literature. Our systematic review of the adult literature yielded two randomized controlled trials (RCTs), four observational studies, seven technology assessment reports, nine economic evaluations and multiple secondary analyses of subgroups included in the RCTs. One pediatric RCT was also identified.

Health Benefits.

The PROWESS RCT showed a 6.1% absolute 28-day mortality reduction with drotrecogin alfa compared to placebo. However, this was not confirmed in a second RCT (ADDRESS) of slightly less severely ill sepsis. An RCT carried out in pediatric patients was terminated prematurely due to lack of clinical benefit from drotrecogin alfa compared to placebo (28-day mortality: 17.15% vs. 17.45% respectively p=0.93).

Subgroup analyses in PROWESS found that the 28-day mortality benefit was most pronounced in a subgroup at highest risk (APACHE score ≥ 25, RR 0.71, 95% CI: 0.59 , 0.85), a result that has received considerable attention and has influenced clinical practice. However, it should be noted that multiple subgroup analyses were pre-specified and performed in this study increasing the possibility of a false positive result. Moreover, the pooled analysis of both RCTs **did not show a statistically significant mortality benefit for drotrecogin alfa** (all patients RR: 0.93, 95% CI: 0.69 , 1.26) **even in subgroups with higher disease severity** (APACHE II ≥25 RR: 0.90, 95% CI: 0.54 , 1.49, Multiple organ dysfunction RR: 0.84, 95% CI: 0.70 , 1.00)

Furthermore, the long-term PROWESS follow-up showed that the mortality benefit in the whole severe sepsis cohort was no longer evident by 3 months. Thus, the survival at 3 months was 66.1% and 62.4% (p=0.11) in patients using drotrecogin alfa and placebo respectively, 62.2% vs. 60.3% at 6 months (p=0.44), and 58.9% vs. 57.2% at 12 months (p=0.49) respectively. Long-term survival in the PROWESS patients with APACHE II score >=25 remained statistically significantly higher in patients treated with drotrecogin alfa compared to placebo for the duration of the 30-month follow-up (58.9% vs. 48.4% p=0.003 at 3 months, 52.1% vs. 41.3% p=0.002 at 12 months, 45.6% vs. 33.8% p= 0.001 at 30 months). The robustness of this subgroup analysis is limited by an absence of a statistically significant difference in survival beyond 3-6 months among those classified by another measure of severity, multiple organ dysfunction (survival rates not provided).

Finally the only RCT in a pediatric population was stopped early on grounds of futility and increased adverse events in the drotrecogin alfa group.

Safety.

The drug manufacturer issued a “dear healthcare professional” letter in January 2005 warning of a higher risk of all-cause mortality with drotrecogin alfa compared to placebo in patients with one organ dysfunction and recent surgery, based on the sub-group analysis of the PROWESS and the ADDRESS studies.

In adults the frequency of serious bleeding events was significantly increased with use of drotrecogin alfa. In children treatment with the drug resulted in a higher rate of intracranial hemorrhage, which was the subject of another “dear healthcare professional” letter from the manufacturer in April 2005.

Cost-effectiveness

In view of the uncertain robustness of the clinical effectiveness, estimations of cost-effectiveness must be considered tentative. While several economic studies and a technology assessment report have concluded that this therapy has an acceptable cost-effectiveness profile, all of these studies have been based on the questionable assumption that the PROWESS 28-day mortality benefit is sustained over time, and none included the totality of the published efficacy evidence available from both trials. With this most optimistic scenario and assuming an average treatment cost of CDN$11,000, our economic model showed that in adults with most severe sepsis (APACHE II >=25), there is a higher than 90% probability that the incremental cost-effectiveness ratio (ICER)

per life year gained (LYG) for drotrecogin alfa will be ≤ CDN$50,000, with a nevertheless 3% chance of lower effectiveness and higher cost with the drug compared to placebo. However, the model instability is well demonstrated by a less than 40% probability of an ICER <= CDN$50,000/LYG when severity is measured by the different clinical metric of multiple (≥ 2) organ dysfunction. Economic models including all severe sepsis patients also yielded relatively poor cost-effectiveness (< 47% probability that ICER <= CDN$50,000/LYG). Similar results were obtained using quality adjusted life years (QALYs) as the measure of efficacy instead of LYG.

Technology Assessment Reports

The National Coordinating Center for HTA in the UK concluded that drotrecogin alfa combined with best supportive care is a cost-effective alternative in patients with severe sepsis. Also in the UK the National Center for Clinical Excellence (NICE) recommended the use of the drug in patients with severe sepsis with two or more organ dysfunctions who were already receiving optimum supportive care, if prescribed by an experienced intensive care specialist. Reports from Spain, Sweden, Canada (CADTH), the UK (University of Birmingham), Brazil, and Argentina either considered the available evidence insufficient or weak. These technology assessment reports have also tended to emphasize the clinical and economic uncertainties associated with its use. However, in general these economic evaluations were based only extrapolations of the short-term PROWESS subgroup, whose sustainability has been further questioned by more recent publications.

Present status and budget impact of drotrecogin alfa at the MUHC and CHUM

At the MUHC, in 2004, 11 patients received drotrecogin alfa annually, with an increase to 18 in 2005 at a cost of approximately CDN$200,000 assuming drug costs of CDN$11,000/patient treated. The use of drotrecogin alfa at the MUHC decreased to 7 patients in 2006. At the CHUM, 27 patients have used drotrecogin alfa between April 2005 and March 2006, at a total cost of approximately $295,000 for the period. The potential budget impact for this drug is therefore relatively high.

Clinicians at both institutions appear to have well appreciated the selected patient population who may potentially benefit from this therapy and have targeted the therapy in consequence, which is corroborated by a decrease in drug use. In addition, the prescribing physicians in both institutions (staff intensivists) have explicitly recognized the safety and costs issues and have established protocols to assure optimal drug utilization. Hopefully the present report supplies a quantitative framework to assist physicians in this difficult decision-making process.

RECOMMENDATION

In view of the uncertain clinical benefit, the evidence of increased risk of serious bleeding, and its high acquisition costs, the TAU recommends that drotrecogin alfa should not be used routinely in adult patients with severe sepsis at the MUHC and CHUM. The totality of the evidence suggests that the current MUHC/CHUM policies of restricting use of this medication to those severe sepsis patients at highest risk, is most appropriate. The current clinical measures to assure optimum drug utilization should be continued.

TAU also concluded that there are no current pediatric indications for drotrecogin alfa.

As with all TAU recommendations, they will be reviewed as new evidence becomes available.

ACRONYMS

APACHE – acute physiology and chronic health evaluation
CHUM - Centre Hospitalier de l'Université de Montréal (CHUM)
ICER – incremental cost-effectiveness ratio
ICH – intracranial hemorrhage
LYG – life-years gained
MUHC – McGill University Health Centre
QALY – quality-adjusted life-years
RCT – randomized controlled trial
TAU – Technology Assessment Unit

FOREWORD

In April 2003, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) prepared an informal report on the use of drotrecogin alfa (activated), also known as activated protein C, in patients with severe sepsis[1]. The report concluded that since only one phase III randomized placebo-controlled trial (RCT) had been performed, since several methodological and clinical questions remained, and given its high cost, routine use of drotrecogin alfa for sepsis patients at the MUHC was not recommended. In view of recent publications and the progressive increase in the use of drotrecogin alfa at the MUHC, the TAU has updated its evaluation by incorporating all recent evidence.

INTRODUCTION

Sepsis is a syndrome characterized by a systemic inflammatory and procoagulant response to an infection, and is considered severe in the presence of acute organ dysfunction[2]. Sepsis is a complex syndrome with protean etiologies and manifestations and this heterogeneity complicates clinical research and is an important caveat in the interpretation of study results [2 3 4].

Endogenous protein C activation attempts to counteract the inflammation and thrombosis of severe sepsis, and drotrecogin alfa has been hypothesized to function by correction of the impairment of endogenous activated protein C production [2]. Activated drotrecogin alfa is a form of human activated protein C produced by recombinant DNA techniques[5]. It is administered intravenously at an infusion rate of 24/µg/kg/h for a period of 96 hours[6]. Drotrecogin alfa was approved by the Food and Drug Administration (FDA) on November 21st 2001, based on the PROWESS[7] trial, and contingent on the performance of on-going research [8]. Drotrecogin alfa was approved by Health Canada on January 31st 2003[9] and the European Union in August 2002 [10]. However this approval by regulatory authorities was based on a single RCT and the FDA committee was actually evenly divided (10 for vs. 10 against) for its approval[11 12]. The regulatory authorities in North America and Europe approved the use of the drug in a subset of the severe sepsis patients included in the RCTs, i.e., those with a higher risk of death.

Sepsis is a serious problem, with more than 6,000 cases annually in Québec, half of which are considered severe[13]. Sepsis has a high mortality rate and estimated annual costs to the Province between $36 and $72 million[13]. Treating all potential patients with drotrecogin alfa could increase

costs provincially by approximately $30 million per year. At the MUHC drotrecogin alfa use increased between 2004 and 2005 but decreased in 2006, 11 patients in 2004, 18 in 2005, and 7 in 2006 (Information provided by the Pharmacy, MUHC). At the Centre Hospitalier de l'Université de Montréal (CHUM), 27 patients have used drotrecogin alfa between April 2005 and March 2006 (information provided by Mr. Stephane Roux, CHUM), at a cost of approximately $295,000 (assuming an average cost of $11,000/treated patient).

The treatment protocol followed at the MUHC stipulates that only patients with both an APACHE* II score ≥ 25 **AND** 1 or more organ dysfunctions should receive the drug. The drug can only be dispensed by pharmacy when a signed order from the attending staff physician from the intensive care unit (ICU) is written. Similarly at the CHUM, a protocol stipulates criteria that need to be fulfilled before prescribing the drug to ensure that drotrecogin alfa is only prescribed to patients with severe sepsis with at least 2 organ dysfunctions (cardiovascular, renal, respiratory, hematologic dysfunction or metabolic acidosis), the calculation of the APACHE II score is not mandatory but highly recommended.

Therefore, a systematic review of all published drotrecogin alfa evidence, including cost-effectiveness studies, technology evaluations and our own cost-effectiveness model will be presented to permit up to date informed decision-making regarding its continued use at the MUHC.

METHODS

Literature Search

A systematic literature review of all articles in adult and pediatric patients published in English or French was performed using Medline and Embase databases (search terms: (Drotrecogin OR Activated protein C OR Xigris) AND (Sepsis). Case reports or studies not evaluating clinical outcomes or economic analyses were excluded. Next the International Network of Agencies for Health Technology Assessment (INAHTA) database was searched for health technology assessment reports and other publications on drotrecogin alfa without any restrictions for date or language of publication. Finally, the reference lists of the publications identified were also searched for additional relevant publications. Last search: September 29th 2006.

* The APACHE II (acute physiology and chronic health evaluation) score uses parameters such as age, chronic health, and acute physiology in order to predict the patients' mortality risk[41].

Results of RCTs comparing drotrecogin alfa and placebo were pooled in order to estimate the overall efficacy of the drug. For the pooled analyses, RevMan (the Cochrane Collaboration, Oxford, England, version 4.2 for windows) was used with a random effects model.

Methods for economic analysis

A cost-effectiveness analysis was performed using efficacy and safety data from the PROWESS[7 14] and ADDRESS[15] RCTs, as well as local MUHC costs. We prepared three decision analytic models:

- A lifetime best-case scenario model involving all patients included in the RCTs.
- A lifetime decision model using the results of the **highest risk subgroup** of patients, using the severity criteria employed by the regulatory authorities in the US to approve drotrecogin alfa i.e., the APACHE II severity score†.
- A lifetime decision model using the results of the **highest risk subgroup** of patients, using the severity criteria employed by the regulatory authorities in Europe to approve drotrecogin alfa, i.e. multiple organ dysfunctions.

A Canadian long-term observational study in patients with severe sepsis and the age-specific survival derived from the Statistics Canada life table for the Province of Québec (2000-2002)[16] were applied to our long-term analyses to model survival beyond what was reported in clinical trials.

We have estimated an average age of 61 years at the start of the model as this was the average age in the PROWESS[7] RCT.

Our analyses used a 20-year time horizon, as this is the approximate life-expectancy of a 61 year old individual in Québec[16]. A decision-tree was used to model the treatment outcomes and costs during the first 30 months and a Markov model was used thereafter. One-year cycles with half-cycle correction and 3% discounting were used in the Markov model.

Probabilistic sensitivity analyses were used to estimate the incremental cost-effectiveness ratios (ICERs) and variance for each of the decision analytic models described above. Beta distributions were used for probability variables included in these analyses. The point estimate and variance used to create a distribution for each model variable were obtained from the PROWESS[7 14] and

† The APACHE (acute physiology and chronic health evaluation) II score uses parameters such as age, chronic health, and acute physiology in order to predict the patients' mortality risk[41].

ADDRESS[15] trials for 28-day and hospital survival, and from the PROWESS[14] trial thereafter as this is the only source of long-term RCT available.

As patients with severe sepsis may not have the same life-expectancy as patients in the general population[17], we have tested the robustness of the time horizon used in our models in sensitivity analyses. We varied the time horizon from solely what is reported in RCTs, i.e., 30 months up to 30 years with 5-year increments. Other univariate sensitivity analyses explored the impact of different discount rates, 0 and 5%, and a of different measure of effectiveness, quality-adjusted life years (QALYs), on the results.

Values are shown in 2006 Canadian dollars.

More details on the decision analysis methodology are presented in Appendix 1.

The analyses were done with the TreeAge (TreeAge Pro 2006) software.

RESULTS

Adults

The literature search identified 2 RCTs, PROWESS[7] and ADDRESS[15], a long-term analysis of the PROWESS RCT[14], 4 observational studies[18 19 20 21], 7 technology assessment reports (in addition to the original TAU report[1]) [3 22 23 24 25 26 27], the technology appraisal guidance from the National Insitute of Clinical Excellence (NICE) [28], and 1 position statement from the Critical Care Society of South Africa[29]. Numerous secondary publications of the PROWESS[7] trial often involving subgroup analyses have also been published[30 31 32 33 34 35 36 37 38 39 40 41 42 43 44]. Despite only 2 RCTs, 3 meta-analyses[45 46 47] and 9 economic analyses [3 48 49 50 51 52 53 54 55] were done, one of which was Canadian [54].

Clinical studies

The PROWESS data is presented in Figure 1. At 28 days the mortality was 30.8% (placebo) and 24.7% (drotrecogin alfa) (p=0.005) an absolute risk reduction of 6.1% (95% CI: 1.9% , 10.4%), with a 20% relative risk reduction (Relative risk (RR): 0.80, 95% CI: 0.69 , 0.94) compared to placebo [7]. Whether 28 days is an appropriate time to assess the primary endpoint may be debated as

approximately 30% of the patients remained in hospital at that time[14]. Hospital mortality rates were 29.7% with drotrecogin alfa and 34.9% with placebo (p=0.03)[14].

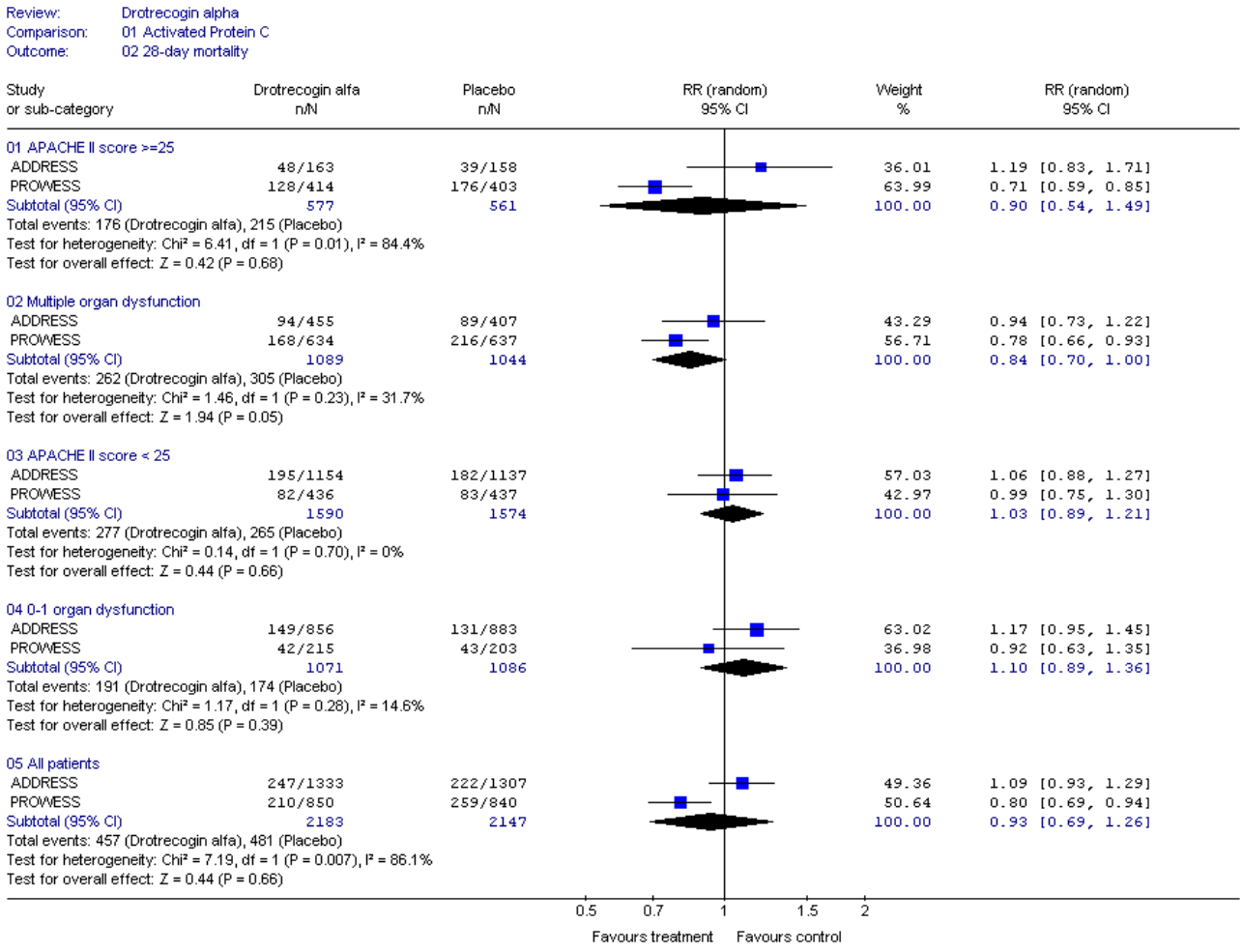
The ADDRESS study[15] was another placebo-controlled randomized study evaluating drotrecogin alfa in patients with severe sepsis and a lower risk of death (placebo mortality rate 17% versus 30.8% in PROWESS). This data is also shown in Figure 1. The trial was stopped early for " futility " with a statistically non-significant trend to a higher 28-day all-cause mortality in the treatment group, (18.5% vs. 17%, p=0.34) [15]. Hospital mortality was 20.6% and 20.5% respectively (p=0.98) [15].

Four observational studies[18] [19] [20] [21] of drotrecogin alfa were identified (see appendix 2). The largest was the ENHANCE study of 2,378 adult patients who all received drotrecogin alfa[18]. The absence of a comparator severely limits the utility of this study. The selection biases in the other observational studies [19] [20] [21] also severely hamper drawing inferences about the safety and efficacy of drotrecogin alfa. Due to the absence of a control group, these non-comparative studies can't contribute to measures of drug efficacy.

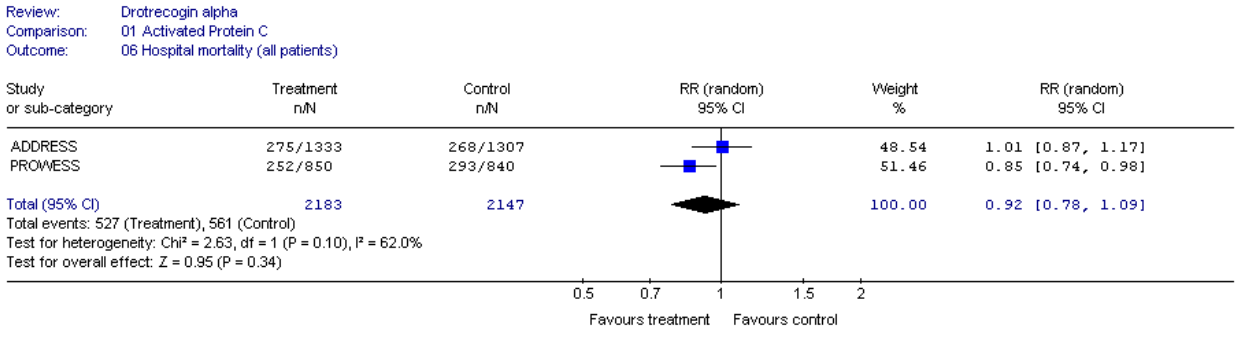
To obtain a summary of drotrecogin alfa effects on 28-day and in-hospital all-cause mortality, we pooled the results of the only adult RCTs available, PROWESS[7] and ADDRESS[15]. Although the entrance criteria for these two trials were slightly different, the pooling of these studies is justified since the same disease entity (sepsis) is being studied with the same research design using the same treatment protocol. Thus, the totality of the available evidence for these two studies, with subgroup analyses taking a secondary role indicate that there is no statistically significant mortality reduction for drotrecogin alfa either at 28 days (RR, 0.93, 95% CI: 0.69 , 1.26) or at hospital discharge (RR 0.92, 95% CI: 0.78 , 1.09) (figure 1). Even the secondary analyses stratifying by baseline APACHE II score or presence of multiple organ dysfunctions show no mortality benefit for drotrecogin alfa if the two RCTs are combined, i.e., APACHE II >=25 RR:0.90, 95% CI: 0.54 , 1.49, multiple (>=2) organ dysfunctions RR: 0.84, 95% CI:0.70 , 1.00) (figure 1).

Figure 1 - Pooled analyses using the 28-day and in-hospital mortality rates from the PROWESS[7] [14] [35] [5] and ADDRESS[15] studies

28-day mortality



Hospital mortality (All patients)

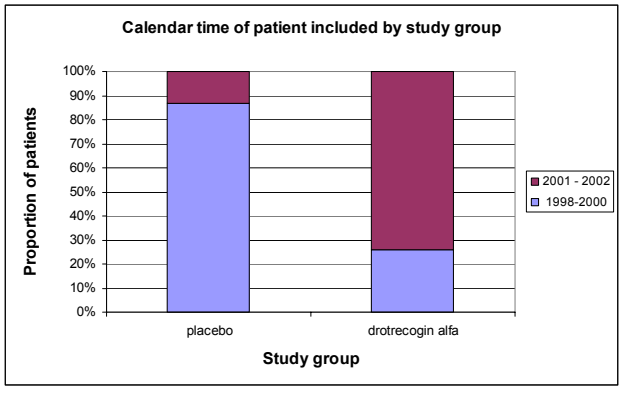


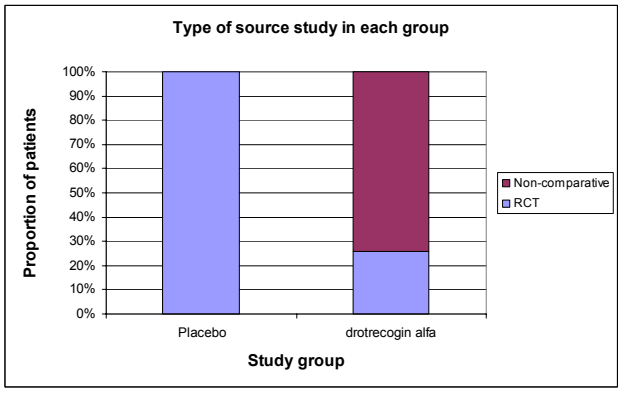
Some of the numbers in the graph are approximations as they were derived from tables in the published studies.

The 28-day mortality results of our pooled subgroup analysis according to APACHE II scores, shown above, are in agreement with the results of Friedrich et al [46]. Moreover, the authors of a second meta-analysis that found a statistically significant benefit in patients at highest Apache II score (RR 0.80, 95% CI 0.68 , 0.94)[45], concluded that their analysis raised doubts about the clinical usefulness of this treatment that could only be resolved by additional clinical trials. These authors' conservative interpretation of their results may be explained by their use of a fixed effects model analysis which assumes no inter-study variation with regards to sampling error due to different sample sizes and treatment effects measured [56]. Recalculating their data accounting for these variations, using a random effects model, gives results identical to ours.

A more controversial, company-sponsored, meta-analysis has used indirect methods to combine 5 sepsis studies (PROWESS, ADDRESS, ENHANCE and two phase 2 studies of secretory phospholipase A2) and reported a statistically significant reduction in the 28-day all-cause mortality (RR 0.84, 95%CI 0.73 , 0.95)[47]. However, this indirect analysis across studies has several clinical and methodological limitations. Variations in patient entry criteria, treatments received, lack of randomization and the potential for calendar time bias (see figure 2) undermines the validity of the results. As shown in figure 2 the trials used in this analysis were not contemporaneous, drotrecogin studies being carried out later than placebo studies. Also, while all the placebo studies were derived from RCTs, the majority of drotrecogin studies were observational.

Figure 2 - Evaluation of the source information used in each study group of the meta-analysis by Sashegyi et al. [47].





In PROWESS multiple sub-analyses (> 30) both pre-specified and not, have been performed[30 31 32 33 34 35 36 37 38 39 40 41 42 43 44]. Caution must be exercised with repeated subgroup analyses as the play of chance may become important. Even the most reported subgroup analyses by patient severity has given conflicting results depending on the metric used to measure severity[4]. For instance an in-hospital mortality benefit was evident when high risk was defined by some variables (mechanical ventilation, dysfunction in 5 organs, APACHE II score between 25 and 29 or ≥25) but not others (need for vasopressor support, ≥ 2 organs dysfunction, APACHE II score between 30 and 53, protein C deficiency) [42]. See table 1 for details.

Table 1 – In-hospital mortality in patient subgroups, data from PROWESS subanalysis[42]

Subgroup	Drotrecogin alfa	Placebo	
Mechanical ventilation			
Yes (N=1249)	32.3%	38.5%	NS
No (N=409)	21.5%	20.8%	Stat. significant
Number of organ dysfunctions			
1 (N=410)	22.1%	28.4%	NS
2 (N=536)	27.3%	27.6%	NS
3 (N=419)	30.5%	37%	NS
4 (N=232)	44.9%	50.1%	NS
5 (N=60)	32.5%	63.3%	Stat. significant
Organ dysfunction			
Single (N=411)	22%	28.4%	NS
Multiple (N=1247)	32%	36.6%	NS
Protein C deficiency			
Yes (N=1353)	30.5%	35.5%	NS
No (N=191)	19%	32.1%	NS
APACHE II quartile			
3-19 (N=423)	19.6%	16.6%	NS
20-24 (N=433)	25.4%	27.7%	NS
25-29 (N=360)	28.8%	39.7%	Stat. Significant
30-53 (N=442)	44.4%	53.4%	NS

NS= not statistically significant

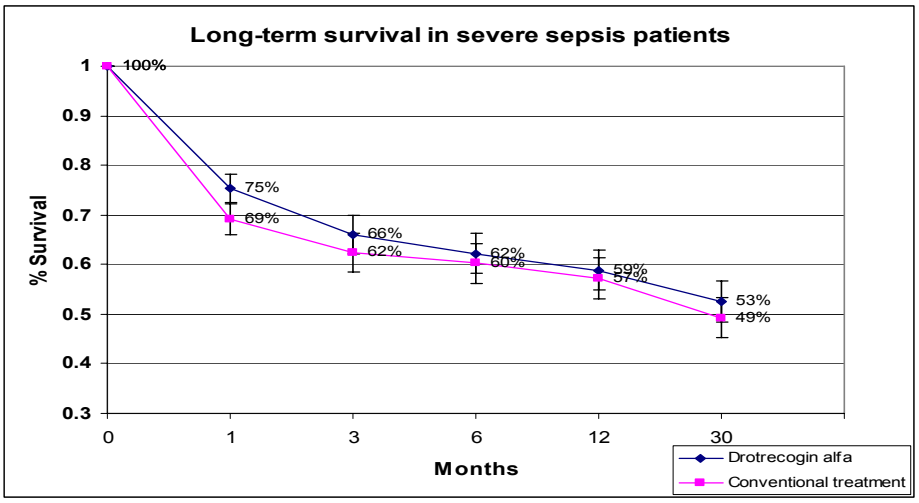
Long-term survival (adults)

Long-term follow-up evaluation of PROWESS patients is now available [14]. Among the 1,220 28-day survivors, 1,127 patients (92.4%) were analysed[14] with non-participation due to patient refusal, unavailability or lack of ethics approval to obtain further hospital information or losses to follow-up[14]. Although hospital survival at 28 days was statistically higher in the patients who received drotrecogin alfa (70.3% vs. 65.1%. (p=0.03), the results at 3 months were no longer statistically significant (66.1% vs. 62.4% (p=0.11) and remained insignificant for up to 2.5 years[14] (figure 3).

Subgroup analyses of long-term survival showed an improved survival in PROWESS patients with APACHE II score >= 25 (figure 4). However, the controversy observed with the subgroup analyses

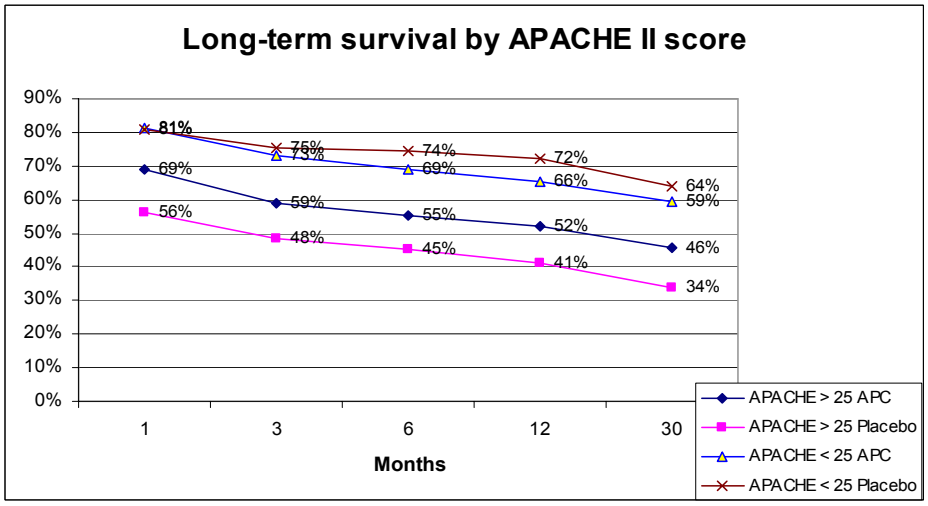
of short-term results continues to occur as, once again, an analysis stratified by another very important measure of severity, multiple organ dysfunction, failed to show a survival benefit with drotrecogin alfa over placebo (p=0.14)[14]. Other long-term subgroup analyses also showed no benefit with drotrecogin alfa, such as functional status, and age[14]. Unfortunately with the exception of the APACHE II subgroup, survival rates with the other subgroups were not provided in the article, only the survival curves[14].

Figure 3 – Long-term survival in all severe sepsis patients – long-term results from the PROWESS study[14]



* Statistically significant at 28 days

Figure 4 – Long-term survival in severe sepsis patients by APACHE II score subgroup – long-term results from the PROWESS study[14]



* The survival difference between drotrecogin alfa and placebo was statistically significant for all points in the APACHE >= 25 subgroup, and at 1 year for the APACHE < 25 subgroup.

Appendix 3 shows the short- and long-term survival in all severe sepsis patients and by APACHE II subgroup.

Results in pediatric patients

One RCT[57], 1 open-label non-comparative study[58], 1 systematic review[59] and 1 phase II safety / pharmacodynamics and pharmacokinetics study were identified in pediatric populations[60].
The RCT (477 patients) was interrupted due to futility (28-day all-cause mortality was 17.15% with drotrecogin alfa and 17.45% with placebo[57]. The previously discussed ENHANCE study also included 188 pediatric patients (term newborns to < 18 years)[58]. The overall 4-day (during-infusion) mortality rate was 7% (n=13, 95% CI: 3.8 , 11.6), and the overall 28-day mortality rate was 13.4% (n=25, 95% CI: 8.8 , 19.1) [58]. Outcomes by age group can be found in Appendix 4.

A Cochrane systematic review on the use of drotrecogin alfa in neonates with severe sepsis was published in April 2006[59]. As no studies that met the pre-specified inclusion criteria were identified in the peer-reviewed literature (RCTs or quasi-RCTs), the authors concluded that there was insufficient evidence for the use of the drug in neonates with severe sepsis[59].

Safety

Adults
Because of its antithrombotic and profibrinolytic effects, bleeding complications may be anticipated with drotrecogin alfa[61] and serious‡ bleeding events were increased compared to placebo [7 15 36 62].
Pooled results observed a 5.3% (148/2786) rate of serious bleeding for the active drug and a 2.3% (20/881) serious bleeding rate with placebo within the first 28 days ($p< 0.001$)[61]. In the ADDRESS study there were 51 (3.9%) and 28 (2.2%) events respectively (p=0.01) [15].

Observational studies showed rates of serious bleeding events varying between 1.7% - 29% [20 63 64].
Different patient populations and the play of chance in small samples may have accounted for these large variations (see Appendix 5).

‡ The definition of serious bleeding events varied from those meeting the regulatory definition for a serious adverse event[61 18] to abnormal bleeding and/or requirement for blood transfusions[64], or life-threatening bleeding requiring ≥ 3 units of packed red blood cells per day for 2-3 consecutive days [62 18].

The drug manufacturer has issued two dear healthcare professional letters, one in January 2005[65], and one in April 2005[66]. The first letter warned of a higher risk of all-cause mortality with drotrecogin alfa compared to placebo in patients with one organ dysfunction and recent surgery, based on a subgroup analysis of the PROWESS and the ADDRESS studies[65]. The second letter reported the higher rate of intracranial hemorrhage (ICH) in pediatric patients treated with drotrecogin alfa [66].

Pediatrics

The 28-day rate of intracranial hemorrhage with drotrecogin alfa was 4% compared to 2% with placebo[66] but other serious bleeding rates were equal (6.7% vs. 6.8% , p=0.97) [67]. In the open-label, non-comparative ENHANCE study there were 52 (27.7%) serious bleeding events in pediatric patients with drotrecogin alfa[58]. A phase II study of 83 patients had 8 (9.6%) deaths and all occurred at the high dose of 24 ug/kg/hr[60]. Four patients (4.8%) also had a serious bleeding event[60] (Appendix 5).

Economic studies

We identified nine cost-effectiveness evaluations of drotrecogin alfa in patients with severe sepsis [3 48 49 50 51 52 53 54 55]. All of these analyses used short-term (28-day mortality) results from the PROWESS study[7]. Most studies [3 48 49 50 53 54 55] modeled long term results by assuming that the PROWESS 28-day mortality results were sustained and durable. One study[68] [51] used long-term results of the PROWESS study published in an abstract format that showed a statistically significant survival benefit with drotrecogin alfa compared to placebo for the duration of the study in patients with APACHE II ≥ 25 and for the first 90 days in all patients[69]. However the long-term results in all patients were not confirmed in the full peer-reviewed publication of the same study[14]. Long-term survival beyond the period covered in RCTs was extrapolated from life-tables adjusted for an estimated higher risk of death in sepsis patients compared to the general population and the calculated cost / life-year gained (LYG) varied between $US 8,500 and $US 33,300 [3 48 49 50 51 53 54 55]. However, as previously shown, the short-term results are not durable putting the validity of these studies in doubt. Moreover, even 28-day mortality is not reduced when the totality of the evidence is considered (see section on clinical studies). One study reported a cost/life saved of $104,000 with drotrecogin alfa compared to placebo in all patients[52]. Another study reported a point estimate of $160,000 / life saved with drotrecogin alfa compared to placebo, with a large variance, the 95% CI limits were above $500,000 and below $100,000 / life saved[55].

More details in Appendix 6.

Technology Assessment Reports

Seven technology assessment reports (in addition to the original TAU report[1]) [3] [22] [23] [24] [25] [26] [27], the technology appraisal guidance from the National Institute of Clinical Excellence (NICE) [28], and 1 position statement from the Critical Care Society of South Africa[29] that were published between July 2001 and November 2006. With the exception of the most recently published report[26], the reports again relied almost exclusively on the PROWESS 28-day mortality results.

The National Coordinating Centre for HTA in the UK concluded that drotrecogin alfa combined with best supportive care is a cost-effective alternative in patients with severe sepsis, although the annual UK drug acquisition cost may reach over CDN$160 million as a consequence of a large number of patients potentially requiring the drug (estimated 16,000 patients) [3]. A guidance from the National Centre for Clinical Excellence (NICE) from the UK recommended the use of the drug in patients with severe sepsis with two or more major organ dysfunctions (in particular cardiovascular, respiratory or renal failure) who were already receiving optimum supportive care and providing that it is prescribed by an experienced intensive care specialist [28]. However as shown earlier, a meta-analysis of the data from PROWESS and ADDRESS for the subgroup with 2 or more organ dysfuntions does not reach statistical significance. NICE excludes the APACHE II score as a marker of severity due to its clinical complexity.

Six reports from Spain[22], Sweden[23], Canada (Canadian Agency for Drugs and Technologies in Health)[24], UK (University of Birmingham)[25], Brazil[26], and Argentina[27] considered the available evidence non-conclusive (weak to moderate) recommending either limited drug use or that its use be closely monitored while awaiting additional information. The reports from Argentina[27], Brazil[26], and the position statement from South Africa[29] also drew attention to the possibility of a significant budget impact of routinely using the drug. In Brazil it was estimated at approximately CDN$450 million if the drug is used in all patients with severe sepsis treated by public health care system [26]. The position statement from the Critical Care Society of South Africa recommends that the drug should be used cautiously and after all other appropriate therapeutic measures have been used due to its high cost impact and possible ethical dilemmas regarding resource allocation in that country [29].

More details in Appendix 7.

TAU ECONOMIC ANALYSIS

The ICER of drotrecogin alfa compared to placebo uses the time-varying results from the RCTs available. In patients with 2 or more organ dysfunctions the long-term data included in our models was derived from the survival curves presented in the publication since specific survival rates were not reported[14]. Long term survival beyond the period covered by the RCTs was extrapolated from a long-term follow-up study and general population data.

The economic analyses were performed from the point of view of the provincial healthcare provider. Number of life-years accumulated and quality-adjusted life-years (QALY) with each treatment group was used as a measure of effectiveness in our models.

In our analyses, negative ICERs represent a lower effectiveness with drotrecogin alfa compared to placebo defined by a smaller number of life-years accumulated, and positive ICERs represent improved effectiveness (the cost is always higher with drotrecogin alfa due to its acquisition costs).

Probabilistic sensitivity analyses were used to estimate the ICERs and variance. Details about the methodology used are provided in Appendix 1.

The RCTs showed that in the groups including all patients or those with 2 or more organ dysfunctions, relatively small and not statistically significant differences in survival were observed after 28 days, therefore the 95% confidence interval of survival in the drotrecogin and placebo groups were frequently overlapping (Appendix 8 shows the point estimate and distributions used in our analyses).

These uncertainties translate into instability in the cost-effectiveness analyses given not only by a wide variation in the results but also resulting in infinitesimally small survival benefit or even lower efficacy with drotrecogin alfa compared to placebo. For instance, in approximately 30% of the simulations drotrecogin alfa presented a lower effectiveness than placebo in the models with all patients. Even using data from patients with a higher severity (>= 2 organ dysfunctions) there was a 16% chance that placebo would be more effective than drotrecogin alfa. In the model including patients with APACHE II >= 25 there was a 3% chance that drotrecogin alfa would be less effective than placebo. The instability in ICERs obtained in the presence of overlapping distributions of outcomes and/or costs between the comparative groups has been previously described in the literature[70 71].

Table 2 shows the incremental effectiveness and cost obtained with the different models for some of the time horizons employed (complete results in Appendix 9). In all models we have observed that the 95% CI includes values where drotrecogin alfa is less effective than placebo.

Table 2 - Incremental effectiveness and cost from the different models evaluated

Effectiveness measure Life-years gained (LYG)						
	All patients			APACHE II ≥ 25		
Time horizon	**LYG, mean (95% CI)**	**Incremental cost, mean (95% CI)**	**% negative effect.* (drotrecogin alfa)**	**LYG (95% CI)**	**Incremental cost (95% CI)**	**% negative effect.* (drotrecogin alfa)**
30 months**	0.067 (-0.176 , 0.314)	$12,502 ($9,831 , $15,130)	29%	0.263 (-0.09 , 0.567)	$16,561 ($11,595 , $21,613)	3%
10 years	0.222 (-0.527 , 0.963)	$12,502 ($9,831 , $15,130)	27%	0.830 (-0.054 , 1.677)	$15,459 ($11,102 , $19,800)	3%
20 years	0.344 (-0.807 , 1.476)	$12,502 ($9,831 , $15,130)	27%	1.191 (-0.082 , 2.417)	$15,459 ($11,102 , $19,800)	3%
30 years	0.381 (-0.891 , 1.632)	$12,502 ($9,831 , $15,130)	27%	1.28 (-0.09 , 2.6)	$15,459 ($11,102 , $19,800)	3%

* Proportion of the simulations where drotrecogin alfa had a lower effectiveness compared to placebo.

Effect. = effectiveness

** 1 year for >= 2 organ dysfunctions / CI= confidence interval

Table 3 shows the probability that the ICER falls below $30,000/LYG, $50,000/LYG and $100,000/LYG in each model for some of the time horizons employed. In the models including only patients with APACHE II ≥ 25, there was a high probability that the ICER would be below $50,000, i.e., > 90% regardless of the time-horizon employed. Nevertheless, in the models with all patients (table 3) and even in models using a different criterion to define higher risk the results were not as favourable for drotrecogin alfa. For instance, in patients with 2 or more organ dysfunctions, which is the criterion used by the European regulatory agency to define higher risk, there was a 47% or less chance that the ICER would fall below $50,000/LYG or 68% or less chance that the ICER will be below $100,000/LYG . More details are given in the acceptability curves reported in Appendix 9.

Using QALY as the measure of efficacy instead of LYG did not change the results considerably (results shown in Appendix 9).

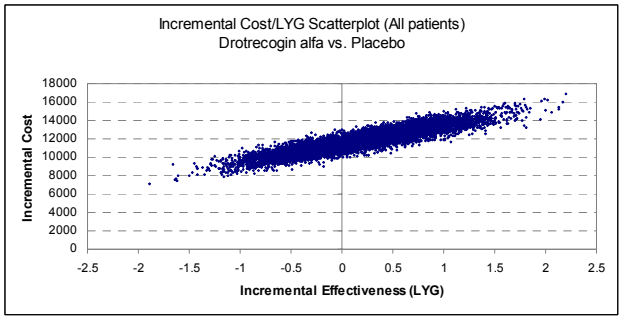
Table 3 – Probability that the ICERs will be under different willingness to pay levels ($30,000/LYG, $50,000/LYG and $100,000/LYG)

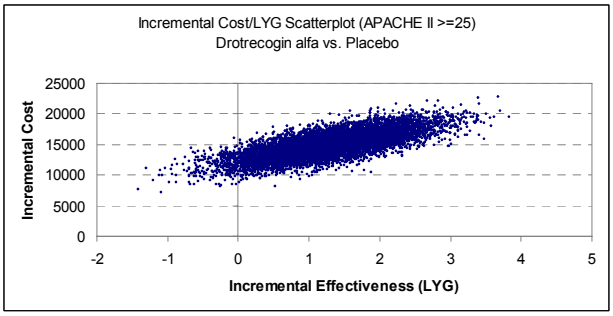
	All patients			APACHE II >=25		
Model	**ICER ≤ $30,000/ LYG**	**ICER ≤ $50,000/ LYG**	**ICER ≤ $100,000/LYG**	**ICER ≤ $30,000/ LYG**	**ICER ≤ $50,000/ LYG**	**ICER ≤ $100,000/LYG**
30 months*	0	3.6%	30%	0.7%	44%	85%
10 years	28%	46%	61%	79%	89%	94%
20 years	44%	56%	66%	87%	92%	95%
30 years	47%	58%	66%	88%	93%	95%

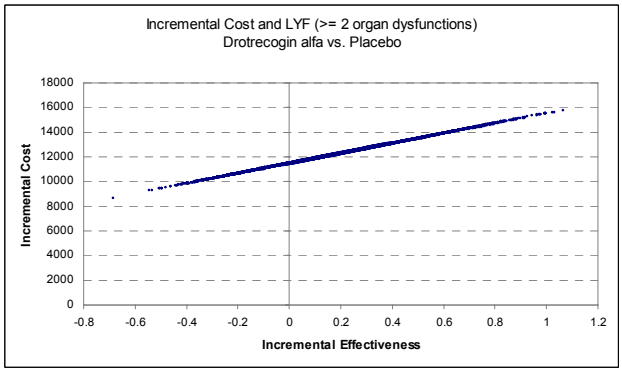
* 1 year for model in 2 or more organ dysfunctions / CI= confidence interval

Figure 5, the scatterplot of the 10,000 Monte-Carlo simulations employed in our probabilistic sensitivity analyses, illustrates the wide variation in the results obtained. The points to the left of the vertical line correspond to the cases where drotrecogin alfa was both less effective and more costly than placebo.

Figure 5 – ICER Scatterplot of drotrecogin alfa compared to placebo (20-year time horizon)







The points to the left of the vertical line correspond to a lower efficacy and higher cost with drotrecogin alfa compared to placebo

DISCUSSION

The adult studies on drotrecogin alfa published in the peer-reviewed literature since the original TAU report do not provide additional evidence of mortality reduction in patients with severe sepsis. Indeed both the overall long-term PROWESS and ADDRESS results are neutral in most subgroups evaluated. Results in pediatric patients do not warrant the adoption of the drug in this patient population due to unproven benefits and concerns about drug safety. The debate on the efficacy of the drug persists, as judged by the numerous recently published editorials and comments coming from several different countries [4 12 72 73 74 75 76 77 78 79 80 81 82 83 84 85].

We have calculated the ICER for drotrecogin alfa compared to placebo based on the best currently available evidence. The immense contrast observed in the results from the different models and the inability to predict with confidence which direction the ICER will take, even under more optimistic conditions further illustrates the uncertainties involved with using drotrecogin alfa. This is in agreement with the current debate in the medical literature regarding the role of the drug in clinical practice. It is important to point out that our results were obtained based solely on the data available from RCTs.

The decision analytic model using one of the criteria to define a higher risk of death (APACHE II ≥ 25) showed very favourable results, (> 90% chance that the ICER would be ≤ $50,000/LYG), although not unequivocally so given the (low) probability of a negative ICER with the drug. This result should be interpreted cautiously as it was based on long-term data from a single RCT[7] and given that the short-term benefits of this RCT were not reproduced in a second RCT[15], even in these patients with increased risk of death. This is further complicated by the difficulties involved in determining the APACHE II score for each patient and as concerns have been expressed regarding its ability to mortality risk[41].

More importantly, the fact that in the same study the same survival benefits and ICER could not be shown with other important measures of severity such as multiple organ dysfunctions (≤ 40% chance of an ICER ≤ $50,000/LYG) is very troublesome and complicates even further the interpretation of these results. Multiple organ dysfunction was preferred to the APACHE II score as a measure of severity in severe sepsis patients by the regulatory authorities of the European Union in the drotrecogin alfa labeling indications [4], other recommendations are that the drug should be used in addition to best standard care and it should be preferably started within 24 hours of the onset of the first organ failure [10]. Health Canada approved drotrecogin alfa to be used in addition to best practice in adult severe sepsis patients with a high risk of death defined by either the APACHE II score or multiple organ dysfuncions[6]. Additionally, Health Canada recommended that the drug should be administered under the supervision of a qualified health professional who is experienced in the use of drugs used in the treatment and in the management of severe sepsis, and that the drug should not be administered in patients with lower risk of death[6].

Our results differ somewhat from the ones obtained in previous publications, due to their assumption that the large 28-day mortality advantage would be sustained over the long-term. The assumption was not confirmed in later trials, except in the subgroup of patients with APACHE II score ≥ 25. Also in the UK the National Center for Clinical Excellence (NICE) recommended the use of the drug in patients with severe sepsis with two or more organ dysfunctions who were already receiving optimum supportive care, if prescribed by an experienced intensive care specialist[28], however their analysis was based on the short-term PROWESS results and assuming that these benefits would be maintained in the long-term. Our conservative estimate, while in contradiction to other published analyses, nevertheless more adequately models the known long-term efficacy data. We have also taken into account the results of the recently published ADDRESS study.

Caution is indicated in attempting to justify treatment only to the subgroup with a higher risk of death. Severe sepsis is a very complex syndrome[3], therefore, even in the RCTs it cannot be ruled out that some of the potential multiple unmeasured baseline confounders may be unequally balanced with repeated subgroup analyses. Therefore group differences may still persist despite matching on one severity measure like the APACHE II score. Basing treatment on disease severity is problematic for several reasons; first the pooled data do not show a statistical benefit according to APACHE II score or for patients with multiple organ failure; second, APACHE II does not take into account important measures of severity in severe sepsis patients such as white blood cell count, number of days in hospital and ICU before the diagnosis of severe sepsis among others [41]; third, analyses based on different markers of disease severity such as need for vasopressor support, multiple organ dysfunction, APACHE II score between 30 and 53, protein C deficiency and interleukin 6 concentration in the 2nd to 4th quartiles (> 143.5 pg/mL) did not demonstrate a benefit for in-hospital mortality[42].

The heterogeneity of sepsis has already been recognized as a difficulty to the undertaking of clinical trials[86]. Its complexity has been considered as one of the possible explanations for the failure of previous clinical trials to show benefits with new sepsis treatments despite promising results in previous animal studies[86].

The limitations of the APACHE II score were well recognized by the regulatory authority of the European Union (European Agency for the Evaluation of Medicinal Products, EMEA) [10 4], who concluded "The selection of appropriate patients for rhDRT treatment based on APACHE II disease severity scores would not be clinically manageable" [87]. Researchers have also expressed concerns about the ability of the APACHE II score to predict the risk in patients with severe sepsis[41]. Most importantly, subgroup analyses should not dominate the overall combined results as pooled analyses from PROWESS and ADDRESS showed no benefit. Even subgroup analyses according to disease severity do not show consistent benefits. Finally the durability of any potential benefits is uncertain and would only be realized at a very high cost. Others have also concluded that additional studies are required to justify clinical benefit[4 72].

RECOMMENDATION

In view of the uncertain clinical benefit, the evidence of increased risk of serious bleeding, and its high acquisition costs, the TAU recommends that drotrecogin alfa should not be

used routinely in adult patients with severe sepsis at the MUHC and CHUM. The totality of the evidence suggests that the current MUHC/CHUM policies of restricting use of this medication to those severe sepsis patients at highest risk, is most appropriate. The current clinical measures to assure optimum drug utilization should be continued.

TAU also concluded that there are no current pediatric indications for drotrecogin alfa.

As with all TAU recommendations, they will be reviewed as new evidence becomes available.

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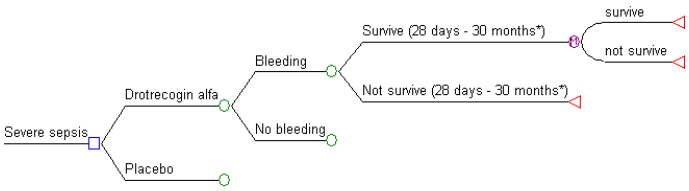
APPENDIX 1 – DECISION ANALYSES METHODOLOGY

Three decision analytic models were employed in our cost-effectiveness analyses:

- A long-term model evaluated the lifetime effects of drotrecogin alfa in all patients.
- A lifetime decision model using the results of the **highest risk subgroup** of patients, using the severity criteria employed by the regulatory authorities in the US to approve drotrecogin alfa i.e., the APACHE II severity score[§].
- A lifetime decision model using the results of the **highest risk subgroup** of patients, using the severity criteria employed by the regulatory authorities in Europe to approve drotrecogin alfa, i.e. the multiple organ dysfunctions.

The decision tree used in our cost-effectiveness analyses is shown below.



*The individual survival probabilities between 28 days and 30 months were included in the model but are not shown in this figure.

A similar tree was used in the bleeding and non-bleeding arms (not shown in the picture), and for the drotrecogin alfa and conventional treatment (placebo) arms (not shown). After the 30 months a Markov model was employed (determined by the node M).

Our analyses used a 20-year time horizon, as this is the approximate life-expectancy of a 61 year old individual in Québec[16]. A decision-tree was used to model the treatment outcomes and costs during the first 30 months and a Markov model was used thereafter. One-year cycles with half-cycle correction and 3% discounting were used in the Markov model.

We have estimated an average age of 61 years at the start of the model as this was the average age in the PROWESS RCT.

[§] The APACHE II score uses parameters such as age, chronic health, and acute physiology in order to predict the patients' mortality risk[41].

Probabilistic sensitivity analyses were used to estimate the ICERs and variance for each of the decision analytic models described above. Beta distributions were used for probability variables used in these analyses. The point estimate and variance used to create a distribution for each model variable were obtained from the PROWESS[7 14] and ADDRESS[15] trials for 28-day and hospital survival, and from the PROWESS[14] trial thereafter as this is the only source of long-term RCT available.

As patients with severe sepsis (average age 61) may not have the same life-expectancy as patients in the general population[17], we have tested the robustness of time horizon used in our models in sensitivity analyses. We varied the time horizon from solely what is reported in RCTs, i.e., from 30 months up to of 30 years with 5-year increments. In other univariate sensitivity analyses we have varied the discount rate employed, 0 and 5%, and we have used quality-adjusted life-years (QALY) as a measure of effectiveness.

Effectiveness

The number of life-years accumulated in each treatment group was the measure of effectiveness used in our base-case analyses and life-years gained (LYG) was the measure of incremental effectiveness used.

Treatment complications during the first 28 days with drotrecogin alfa and placebo reported in the RCTs identified were also included in our analyses.

Survival

Survival data derived from RCTs

Survival rates were taken from the RCTs identified according to data availability,as described below.

Model including all patients

Survival rate at 28 days and hospital discharge were taken from the meta-analysis that included the PROWESS[7] and ADDRESS[15] RCTs. Long-term PROWESS[14] data was used after hospital discharge (up to 30 months) as this was the only trial providing such information.

Model including patients with APACHE II score >= 25

The 28-day pooled survival rate from the PROWESS[5,14] and ADDRESS[15] trials and PROWESS[14] long-term (up to 30 months) survival data were used in this patient subgroup.

Model including patients with 2 or more organ dysfunctions

We have attempted to calculate the cost-effectiveness of drotrecogin alfa compared to placebo in this patient population using the information available. The short-term 28-day survival was taken from the PROWESS[7] and ADDRESS[15] studies. The long-term PROWESS study showed that in this subgroup the long-term survival was not statistically significantly different between drotrecogin alfa and placebo, moreover, the authors reported that the survival curves beyond 3-6 months were very similar to each other[14] suggesting a

very small if any numerical advantage with drotrecogin alfa, however the actual survival rates were not provided. In our cost-effectiveness we have assumed that the 28-day pooled absolute survival advantage of 4.6% (meta-analysis, Figure 1) with drotrecogin alfa would be maintained for the first 6 months. This overestimates the survival advantage of drotrecogin alfa compared to placebo since according to the survival curves from the long-term PROWESS study[14] the survival advantage in the drotrecogin alfa starts to decrease somewhere between 3-6 months. Also for this reason we have assumed different scenarios beyond 6 months in which the difference in survival between the two groups was varied from zero to 3%, 2% was used in the base-case analyses. This numerical difference was maintained for the patient's lifetime. We have assumed that the 6-month survival in the drotrecogin alfa group would be 60% according to the survival curve in the long term PROWESS study[14].

Survival data beyond RCTs

Beyond the follow-up period covered in the RCTs, yearly survival rates were assumed to be identical for both groups as there was no evidence of the contrary.

Survival rates up to 30 months for the models including all patients and those with APACHE II ≥ 25 subgroup were taken from the long-term PROWESS[14] study. For the model in patients with 2 or more organ dysfunctions survival rates in years 2 and 3 were derived from a 3-year follow-up study conducted in Canada in patients hospitalized for severe sepsis[54].

Beyond year 3, the age-specific annual survival was derived from the life table provided by Statistics Canada for the Province of Québec (2000-2002)[16]. The lifetime annual survival rates in the general population were adjusted for a higher severity in severe sepsis patients according to the absolute difference in survival at 3 years between severe sepsis patients (as reported in the 3-year study[54]) and the age-specific survival in the general population[16].

The age at the start of the model was assumed to be 61 years as this was the mean age in the clinical studies included in the report.

Utilities

Utilities were derived from a 6-month study in patients with severe sepsis[88]. The utility values were measured through the EuroQoL-5D questionnaire[88]. Beyond this point, the utility values in patients with severe sepsis were not available in the literature, therefore, we have assumed that the value reported at the end of the 6-month would be maintained constant until year 3, thereafter, patients were assumed to have full quality of life (utility=1).

We have decided to maintain the decreased first year utility value (representing a decreased quality of life) during the first 3 years as a 3-year follow-up study in severe sepsis patients indicated that patients still required treatment during this period (i.e., high health care costs)[54]. We have assumed that these complications would affect the patients' quality of life. After 3 years, although the patients may still not immediately return to a full quality of life, the lack of information available does not permit the extrapolation of utility values and we have therefore decided to use a conservative utility estimate of 1 (full quality of life).

Costs

Our analysis included the following costs :

- Drug acquisition costs (drotrecogin alfa).
- Treatment complications costs, such as bleeding.
- Costs incurred in the hospitalization for the severe sepsis episode.
- Healthcare treatment costs after hospital discharge for years 1, 2, and 3. Consisting of direct health cared costs for all hospitalizations, emergency visits, day surgeries, and physicians' costs.

Drug cost data were provided by the pharmacy department of the MUHC. Unit costs of treating bleeding events, hospitalization costs and healthcare costs after hospital discharge were taken from a previously published Canadian economic analysis and were applied to both groups [54]. Costs beyond three years were not available and were considered identical for the two groups.

Costs are reported in 2006 Canadian dollars. Costs from other years were corrected for inflation according to the Bank of Canada inflation rates.

APPENDIX 2 – RESULTS OF RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES IN ADULT PATIENTS WITH SEVERE SEPSIS

RCTs

Study (year)	Patient characteristics (DRT)	Mortality
Prowess (2001) N=1690 (DRT: 850 / Pl: 840)[7]	Age: 60.5 ±17.2 (>=75: 24.1%) Apache II (mean, SD): 24.6 ±7.6 > 1 organ dysfunction: 74.6% >= 3 signs of systemic inflammation At least 3 signs of SIRS	28 days DRT: 210 (24.7%) / Pl. 259 (30.8%) AR: -6.1% (1.9 , 10.4) RR: 0.80 (95% CI: 0.69 , 0.94)
Address (2005) N=2640 (DRT: 1333 / Pl.: 1307)[15]	Age: 58.8±16.8 Apache II (mean,SD): 18.2±5.8 Apache II >=25: 165 (12.4%) > 1 organ dysfunction: 460 (34.5%)	28 days DRT: 18.5% / Pl.:17% p=0.34 RR: 1.08 (95% CI: 0.92 , 1.28)

DRT: drotrecogin alfa / Pl.: placebo / SIRS: systemic inflammatory response syndrome / RCT: randomized controlled trial

Observational studies

Study (year)	Patient characteristics		Mortality
Enhance[18] (2005) N=2,378 (adults)	Age: 59.1±16.9 Apache II (mean, SD): 22±7.4 > 1 organ dysfunction: 84.4% At least 3 signs of SIRS		28 days DRT: 25.3% (95% CI: 23.5 , 27.1)
Enhance US[89] (2004) N=273	Age: 59.1±17.4 Age >= 75: 17% APACHE II (mean, SD): 23.4±7.4 > 1 organ failure: 72.9% Protein C deficiency: 75.5%		28 days DRT: 26.4% (21.1 , 31.6) Subgroup analyses – some results similar to the ones from PROWESS
Higgins et al.[19] (2005) N=44 Not comparative	Age: 54.3 ±17.3 Apache II on admission (mean, SD): 21.95±7.28 Concurrent acute respiratory distress syndrome: 73% > 1 organ dysfunction: 100% (DRT) / Pl. 96.2%		28 days DRT: 16 (36.4%, 95% CI: 22.2 , 50.6) 33.3% among 36 patients who met eligibility criteria for PROWESS In-hospital DRT: 19 (43%)
Kuebler et al.[20] (2006) N= 3,233 DRT (n=302) / no DRT (n=2931)	DRT Age:44.7±18.2 >1 organ d.: 100% APACHE II: 25.3±9.5	No DRT Age: 55.1±20.4 >1 organ d.: 96.2% APACHE II: 25.4±8.9	Unadjusted RR: 0.31 (95% CI or mortality rate for each group not given. Adjusted RR: approximately 0.45 (95% CI: 0.3 , 0.6) – approximate values derived from a graph
Nguyen et al. [21](2006) N=24 (DRT: 8 / not DRT: 16)	All patients Age: 79.5 APACHE II : 31.5 (29.8 , 97.3) 8 (33.3%) received DRT		In-hospital mortality DRT users 25% (3.2% , 65.1%) Overall: 45.8% (25.6% , 67.2%), predicted mortality: 76.7% (71.9% , 86.4%)

DRT: drotrecogin alfa / Pl.: placebo / SIRS: systemic inflammatory response syndrome

APPENDIX 3 – SUMMARY OF SURVIVAL IN SEVERE SEPSIS PATIENTS

Short and long-term survival in all severe sepsis patients

Drotrecogin alfa				
Cumulative survival	**PROWESS**	**ADDRESS**	**Point estimate Pooled results (±SD)**	**Distribution used**
28-day	75.3%[7]	81.5%[15]	79.4% (±1.06)	Beta distribution
Hospital discharge	70.3%[14]	79.4%[15]	76.4% (±1.11)	Beta distribution
3-month	66.1%[14]	NA	66.1% (±1.86)	Beta distribution
6-month	62.2%[14]	NA	62.2% (±1.97)	Beta distribution
12-month	58.9%[14]	NA	58.9% (±2.05)	Beta distribution
30-month	52.6%[14]	NA	52.6%(±2.10)	Beta distribution
Placebo				
Cumulative survival	**PROWESS**	**ADDRESS**	**Pooled results (±SD)**	**Distribution used**
28-day	69.2%[7]	83%[15]	78.8% (±1.04)	Beta distribution
Hospital discharge	65.1%[14]	79.5%[15]	74.95% (±1.12)	Beta distribution
3-month	62.4%[14]	NA	62.4% (±1.93)	Beta distribution
6-month	60.3%[14]	NA	60.3% (±1.98)	Beta distribution
12-month	57.2%[14]	NA	57.2% (±2.06)	Beta distribution
30-month	49.3%[14]	NA	49.3 (±2.10)	Beta distribution

CI= confidence interval / NA= not available / SD= standard deviation

Short and long-term survival in severe sepsis patients with APACHE II >= 25

Drotrecogin alfa					
Variable	**PROWESS**	**ADDRESS**	**Pooled results (±SD)**	**95% CI (pooled results)**	**Distribution used**
28-day	69.1%[5]	70.5%[15]	69.45% (±3.55)	62.49% , 76.41%	Beta distribution
3-month	58.9% [14]	NA	58.9% (±2.42)	54.16% , 63.64%	Beta distribution
6-month	55.2% [14]	NA	55.2% (±2.44)	50.41% , 60.00%	Beta distribution
12-month	52.1% [14]	NA	52.1% (±2.46)	47.29% , 56.91%	Beta distribution
30-month	45.6% [14]	NA	45.6% (±2.45)	40.80% , 50.40%	Beta distribution
Placebo					
Variable	**PROWESS**	**ADDRESS**	**Pooled results (±SD)**	**95% CI (pooled results)**	**Distribution used**
28-day	56.3%[5]	75.3% [15]	62.93% (±3.40)	56.27% , 69.59%	Beta distribution
3-month	48.4% [14]	NA	48.4% (±2.49)	43.52% , 53.28%	Beta distribution
6-month	45.3% [14]	NA	45.3% (±2.48)	40.44% , 50.16%	Beta distribution
12-month	41.3% [14]	NA	41.3% (±2.45)	36.50% , 46.11%	Beta distribution
30-month	33.8%[14]	NA	33.8% (±2.36)	29.19% , 38.42%	Beta distribution

CI= confidence interval / NA= not available / SD= standard deviation
* Calculated according to the information provided in the studies

Short and long-term survival in severe sepsis patients with 2 or more organ dysfunctions

Drotrecogin alfa				
Variable	**PROWESS**	**ADDRESS**	**Pooled results (±SD)**	**95% CI (pooled results)**
28-day	73.5%[5]	79.3%[15]	76.2% (±1.75)	72.77% , 79.63%
Placebo				
Variable	**PROWESS**	**ADDRESS**	**Pooled results (±SD)**	**95% CI (pooled results)**
28-day	66.1%[5]	78.1%[15]	71.6% (±1.88)	67.92% , 75.28%

CI= confidence interval / NA= not available / SD = standard deviation

APPENDIX 4 – RESULTS OF STUDIES IN PEDIATRIC PATIENTS WITH SEVERE SEPSIS

Study	Baseline characteristics DRT	Mortality DRT	28-day Mortality (placebo)
RESOLVE* (RCT) N=477 (DRT: 240 / Pl.: 237)[57]	NA	41 (17.15%) p=0.93 Composite time to complete organ failure resolution (mean days (SD) 9.8 p=0.72	41 (17.45%) Composite time to complete organ failure resolution (mean days (SD) 9.7
ENHANCE (2006) Open-label, non-comparative N=188[58]	Age: < 1 year: 43 (22.9%) 1-8 years: 81 (43.1%) 8-18 years: 64 (34%) Number of organ failures, mean (SD): 2.2 (1.0)	4-day mortality < 1 year: 3 (7%, 95% CI: 1.9 , 18.5) 1-8 years: 8 (9.9%, 95% CI 4.4 , 17.9) 8-18 years: 2 (3.2%, 95% CI: 0.6 , 10.3) 28-day mortality < 1 year: 6 (14%, 95% CI: 6.3 , 27) 1-8 years: 13 (16%, 95% CI: 9.2 , 25.5) 8-18 years: 6 (9.5%, 95% CI: 2.3 , 16.8)	-

* The study was interrupted prematurely

CI: confidence interval / DRT: drotrecogin alfa / SD= standard deviation / RCT: randomized controlled trial

APPENDIX 5 – SAFETY OF DROTRECOGIN ALFA IN ADULT AND PEDIATRIC PATIENTS

Adult patients

Study (year)	SAEs (infusion – postinfusion period)	SAEs (days 0 - 28)
Prowess [7](2001) N=1,690 (DRT: 850 / Pl: 840)	NA	Serious bleeding events DRT: 30 (3.5%) / Pl:17 (2%) p=0.06
Prowess subanalysis[36] >= 75 years N=386 (DRT: 205 / Pl: 181)	NA	Serious bleeding events DRT:8 (3.9%) / Pl.:4 (2.21%) p=0.34 Thrombocitic events 2 (0.98%) / 9 (4.97%) p=0.019 CNS-related event 0 / 5 (2.76) p=0.017
Fry et al.[62] (2004) PROWESS surgical subgroup N=474 (DRT: 228 / Pl.: 246)	Placebo Age (mean, SD): 61.7±1.0) APACHE II: 23.9±0.5	Serious bleeding events DRT: 3.1% / Pl.:0 (p=0.006) Treatment emergent bleeding events DRT: 16.7% / Pl.: 7.7% (p=0.003)
Enhance[18] (2005) N=2,378 (adults)	Serious bleeding events (Infusion and post-infusion) 161(6.8%, 95% CI: 5.4 , 8.4) ICH: 35 (1.4%, 95% CI: 0.9 , 2.3) Fatal ICH: 12 (0.5%, 95% CI: 0.2 , 1.1)	Serious bleeding events (28 days), DRT 155 (6.5%, 95% CI: 5.6 , 7.6) ICH: 35 (1.5%, 95% CI: 1.0 , 2.0) Fatal ICH : 12 (0.5%, 95% CI: 0.3 , 0.9)
Enhance US[89] subanalysis (2004) N=273	Serious bleeding events (infusion + 24 hours) 4.0% (95%CI: 1.7 , 6.4%)	Serious bleeding, DRT 28 days: 5.5% (95% CI: 2.8 , 8.2) ICH 1 (0.35%) (non-fatal)
Address[15] (2005) N=2640 (DRT: 1333 / Pl.: 1307)	Serious bleeding events (days 0-6) 31 (2.4%) / 15 (1.2%) p=0.02 Serious non-bleeding events 46 (3.5% / 66 (5.1%) p=0.04	Serious bleeding events DRT: 51 (3.9%) / Pl: 28 (2.2%) p=0.01 Fatal hemorrhage DRT: 7 (2.9%) / Pl: 2 (0.9%) p=0.12 Any bleeding event leading to transfusion (28 days) DRT: 90 (6.8%) / Pl: 44 (3.4%) p< 0.001 Serious non-bleeding events DRT: 143 (10.9%) / Pl: 168 (13%) p=0.09

DRT: drotrecogin alfa / Pl: placebo / NA= not available / SAE: serious adverse events

Adult patients (cont.)

Study (year)	SAEs (infusion – postinfusion period)	SAEs (days 0 - 28)
All studies combined N=3,667 (DRT:2,786 / PI.: 881) Patients included in clinical trials[61]	Serious bleeding events (during infusion) DRT: 79 (2.8%, 95% CI: 2.3 , 3.5) / Placebo: 6 (0.7%, 95% CI: 0.3 , 1.5)	Serious bleeding events** (28 days) DRT: 5.3% (148/2786) / Placebo: 2.3% (20/881) (p<0.001 2-sided) ICH bleeding (DRT) All events: 32 (1.1%) / Drug-related: 18 (0.6%) Fatal ICH bleeding events (DRT) All events: 17 (0.71%) / Drug-related: 8 (0.3%) Fatal non-ICH bleeding (DRT) All events: 3 (0.1%) Drug-related: 3 (0.1%)
Commercial use spontaneous reports[61] N=3991	NA	Serious bleeding events (timing not clear), DRT 0.9% (34/3991) ICH bleeding 0.2% (8/3991)
Pastores et al. [63] (2005) HSCT N=7 Non-comparative	Serious bleeding events (DRT) 2 (29%) Fatal ICH 1 (14.3%) – already included in serious bleeding events	Serious bleeding events (DRT) 2 (29%) Fatal ICH 1 (14.3%) – already included in serious bleeding events
Kuebler et al.[20] (2006) N= 3,233 DRT (n=302) / no DRT (n=2931)	NA	Severe life threatening hemorrhages (timing of events not specified), DRT 5 (1.7%) NS compared to the other group of patients (actual rate in control group not provided) Local bleeding > 10 (6%) – caused drug discontinuation but associated with life threatening complications
Maurice et al. [64] (2005) N=23 Observational study	Serious bleeding events (within 48 hours), DRT 2 (8.7%)	Serious bleeding events (DRT) 2 (8.7%) Treatment interruption 10 (43.5%)

DRT: drotrecogin alfa / PI: placebo / NA= not available / NS= not statistically significant
HSCT: hematopoietic stem cell transplantation / ICH: intracranial hemorrhage
** Defined as: any intracranial hemorrhage (ICH), any life-threatening bleeding event, requirement of >= 3 units of packed red blood cell transfusion per day for 2 consecutive days, or meeting other criteria for serious adverse events

Pediatric patients

Study (year)	SAEs (infusion – postinfusion period)	SAEs (days 0 - 28)
RESOLVE*[67] (RCT) N=477 (DRT: 240 / Pl.: 237) (abstract)	Serious Bleeding Events (during infusion) DRT: 9 (3.8%) / Pl.: 8 (3.4%) p=0.82 CNS bleeding (during infusion) DRT: 5 (2.1%) / Pl.: 1 (0.4%) p=0.10 (Due to higher non-fatal CNS bleeding in patients < 60 days of age in drotrecogin alfa group compared to placebo, 4 vs. 0 respectively) Serious adverse events DRT: 10.4% / Pl.: 11% p=0.84	Serious bleeding events DRT: 16 (6.7%) / Pl.: 16 (6.8%) p=0.97 Fatal bleeding events DRT: 2 (0.8%) / Pl.: 5 (2.1%) Serious adverse events DRT: 18.3% / Pl.: 19% p=0.85
ENHANCE[58] (2006) Open-label, non-comparative N=188	Serious bleeding events (during infusion), DRT 52 (27.7%) with at least one event 11 (5.9%) with identifiable source < 1 year: 1 (2.3%) 1-8 years: 5 (6.2%) 8-18 years: 5 (7.8%) Bleeding events leading to drug discountinuation (during infusion): 5 (2.7%)	Serious bleeding event with identifiable source of bleeding, DRT 16 (8.5%)

* The study was interrupted prematurely
DRT: drotrecogin alfa / Pl: placebo

APPENDIX 6 – RESULTS OF ECONOMIC ANALYSES IDENTIFIED IN THE LITERATURE

Study / TA report (country , year of publication)	Effectiveness	Cost	Cost-effectiveness
NCCHTA [3] UK (2005) Results for other subgroups provided	All patients Incremental life-years: 1.351 (SD 0.43) Incremental QALYs: 0.810 (SD 0.258)	All patients Incremental cost: $ 7,958	All patients US$ 10,176/LYG US$ 16,964/QALY Multiple organ dysfunction $8,228/QALY $4,931/LYG
Fowler et al.[48] Canada (2003) Costs mainly from US sources Results for other subgroups provided	Life-years DRT: 8.31 Control.: 7.63 Incremental: 0.68 QALYs DRT: 6.63 Control: 6.09 Incremental: 0.54	DRT: $61,751 Control: $51,006 Incremental $10,745	$ 15,801 / LYG $ 20,047 / QALY $ 403,000 / QALY (in less severe sepsis)
Riou França et al. [49] France (2006) Results for other subgroups provided	All patients Incremental life-years: 0.64	All patients Incremental cost: $7,545	$ 11,812 / LYG $ 19,686 / QALY
Hjelmgren et al. [50] Sweden (2005) Results for other subgroups provided	All patients Incremental life-years: 0.544 Incremental QALYs: 0.375	All patients Incremental (hospital) cost: $ 9,701	All patients US$ 22,920/LYG US$ 33,170

DRT: drotrecogin alfa / Pl: placebo / LYG: life-years gained / QALY: quality-adjusted life-years

Appendix 6 cont.

Study / TA report	Effectiveness	Cost	Cost-effectiveness
Davies et al. [51] UK (2005)	Life-years DRT: 10.49 / Plac: 9.38 (PROWESS) QALYs DRT: 7.24 / Plac: 6.47 (PROWESS)	Incremental costs: $ 5,139 (PROWESS)	US$ 8,533/LYG (PROWESS) US$ 8,446/QALY (PROWESS)
Betancourt et al. [52] US (2003) Results for subgroups provided	All patients (>= 1 organ dysfunctions.) 0.06 LYG (incremental) >= 2 organ dysfunctions 0.08 LYG (incremental)	>= 1 organ dysfunction $ 6,246 >= 2 organ dysfunctions $ 6,246	>= 1 organ dysfunction $ 104,100 / LYG >= 2 organ dysfunctions $ 78,078
Neilson et al. [53] Germany (2003)	Life-years 7.81 (3% discounting) Incremental LYG: 0.47	Incremental costs: $8,330	US$ 22,411/LYG (3% discounting)
Angus et al. [55] US (2003)	28 days Lives saved: 0.061±0.22 Long-term incremental LYG: 0.48±0.29 QALYs: 0.33±0.21	28 days Incremental cost: $9,800±2,900 Long-term $16,000±4,200	28 days $ 160,000 / life saved Long-term $ 33,300 / LYG $ 48,800 / QALY
Manns et al. [54] Canada (2002)	Incremental LYG: 0.38	-	$ 27,936 / LYG $ 46,560 / QALY

DRT: drotrecogin alfa / Pl: placebo / LYG: life-years gained / QALY: quality-adjusted life-years

APPENDIX 7 – TECHNOLOGY ASSESSMENT REPORTS – RECOMMENDATIONS

TA Report (publication)	Conclusions / Recommendations
Brazilian National Health Surveillance Agency (November 2006)[26]	The benefits of drotrecogin alfa have been shown in studies with methodological flaws and only for a subset of patients with severe sepsis. A careful selection of patients to be administered the drug should be done as serious adverse events may occur. The estimated budget impact would be approximately CDN$450 million (R$863.7) if all patients with severe sepsis treated through the public healthcare system are administered the drug.
NCCHTA (March 2005) [3]	"Drotrecogin alfa (activated) plus best supportive care appears clinically and cost-effective compared with best supportive care alone, in a UK cohort of severe sepsis patients, and in the subgroup of more severely affected patients with severe sepsis and multiple organ failure" An annual drug acquisition cost of over 80 million pounds to the NHS is expected based on a population of 16,570 patients. £$ 8,228 / QALY
NICE (September 2004) [28]	Guidance: Recommended in adult patients receiving optimum intensive care support who have severe sepsis that has resulted in multiple organ failure (two or more major organs). "The drug should only be initiated and supervised by a specialist consultant with intensive care skills and experience in the care of patients with sepsis"
Catalan Agency for Health Technology Assessment and Research[22] (January 2004)	"The scientific evidence on drotrecogin alfa (activated) is scant and of average or low quality." Use should be limited to patients with APACHE II >= 25 The data may be insufficient to recommend widespread use. Use of the drug should be limited before data from a phase IV study becomes available
Swedish Council on Technology Assessment in Health Care (November 2003)[23] Only summary available in English	Moderate scientific evidence of both survival benefits and cost-effectiveness of drotrecogin alfa compared to placebo. National clinical experience should be systematically monitored
Position Statement for the Critical Care Society of South Africa[29]	Absolute all-cause mortality risk reduction: 6.1% Authors concerned that high cost of the drug poses ethical dilemmas regarding allocation of scarce and expensive resources and that cost-effectiveness analyses from countries with a different socioeconomic status may not be applicable to South Africa. Drotrecogin alfa should only be prescribed by intensivists providing that all other appropriate therapeutic measures have been effectively used.
Institute for Clinical Effectiveness and Health Policy (IECS – Argentina) (July 2003) [27]	The authors concluded that it would be difficult to predict how the results obtained in one RCT would be translated in clinical practice. The authors also pointed out that the long-term benefits with the drug might be marginal and that the drug may represent a substantial cost for the country. The authors concluded that the use of the drug should be carefully considered and that the patients more likely to benefit from the treatment are those with severe sepsis and APACHE II > 25, SOFA score >10, 3 or more organ dysfunctions and no contraindications to drotrecogin alfa.

Appendix 7 cont.

TA Report (publication)	Conclusions / Recommendations
TAU (April 2003)[1]	The results of the only RCT, although encouraging, are not sufficient to support the adoption of the technology at the MUHC.
CADTH (March 2002)[24]	-No evidence of benefit in patients who don't meet the eligibility criteria for the PROWESS trial, therefore, protocols need to be in place in order to ensure appropriate use of the drug. - Additional information on safety and drug interactions is necessary. - "The management of cost by health care institutions may be challenging as the cost of drotrecogin alfa (activated) could be substantial".
National Horizon Scanning Centre (July 2001)[25]	The authors could not assess the financial impact of the introduction of the drug in the health care system at that point, but the authors considered that the costs could be substantial if a large proportion of the estimated 21,000 patients use the drug. Authors believe that the clinical impact may be significant based on the PROWESS trial, however the increased risk of bleeding associated with the use of the drug has to be taken into account.

APPENDIX 8 – VARIABLES USED IN THE PROBABILISTIC SENSITIVITY ANALYSES

Appendix 1 provides the methods used in our cost-effectiveness analyses.

Appendix 3 provides the survival rates and distributions used in our probabilistic sensitivity analyses.

Survival rates beyond what was reported in the RCTs identified were derived from the age-specific general population survival in Quebec (beyond 3 years). For the model in patients with 2 or more organ dysfunctions a 3-year follow-up study in patients who were hospitalized for severe sepsis in Canada [54] was used as the source for survival in years 2 and 3 (table 8.4). The survival rates in the general population were adjusted for a higher severity in severe sepsis patients according to the absolute difference in survival at 3 years between severe sepsis patients obtained [54] and the age-specific survival in the general population.

We pooled the 28-day bleeding rates reported in the two RCTs identified[7 15] using the inverse variance method and we obtained a 3.7% (±1.06) rate of 28-day serious adverse events with drotrecogin alfa and 2.1 (±1.04) with placebo.

The utilities used in our model are given in table 8.1.

The costs used in our model are given in table 8.2.

Table 8.1 – Utilities used in the decision analytic model beyond what was reported in the studies identified.

Utilities	Model with all patients	Model in patients with APACHE II score >=25	Model in patients with >= 2 organ dysfunctions	Source
28 days	0.53	0.53	0.53	Drabinski et al. [88]
3 months	0.68	0.68	0.68	Drabinski et al. [88]
6 months*	0.69	0.69	0.69	Drabinski et al. [88]

With the exception of the model in patients with APACHE II score >= 25, the same survival rates were used for drotrecogin alfa and placebo after year 1 due to lack of evidence of any difference between the two groups (drotrecogin alfa and placebo).

For the same reason the same utility values were used in both groups

* The utility value at 6 months was for the first 3 years after the severe sepsis treatment.

After year 3, a 3.1% absolute increase in the age-specific annual mortality rate of the general population was used in the models with all patients (mortality rate of a 64 year-old in Quebec, males and females: 1.1%[16], 3rd year mortality, all patients, Manns et al.[54]: 4.2%).

In the models in patients with a higher severity, a 5.1% absolute increase in the age-specific annual mortality rate of the general population was used in our model (mortality rate of a 64 year-old in Quebec, males and females: 1.1%[16], 3rd year mortality, patients with APACHE II >=25, Manns et al.[54]: 6.2%).

Table 8.2 – Costs used in the decision analytic models. 3% discounting applied to costs beyond year 1

Costs	**Model with all patients**	**Model in patients with APACHE II score >=25**	**Source**
Drug costs * (drotrecogin alfa)	$11,000	$11,000	MUHC (Pharmacy)
Bleeding episode costs	$13,711	$13,711	Manns et al. [54]
Hospitalization costs (severe sepsis episode)	$54,391	$57,947	Manns et al. [54]
1-year costs (after hospital discharge)**	$23,409	$33,886	Manns et al. [54]
Year 2 costs**	$7,531	$9,167	Manns et al. [54]
Year 3 costs**	$7,133	$6,535	Manns et al. [54]

* Drug costs refer to acquisition costs of drotrecogin alfa, mean treatment costs in patients treated with drotrecogin alfa at the MUHC in 2006. Other costs associated with the severe sepsis hospitalization were assumed to be identical in both groups.

Costs from the article by Manns et al. [54] were converted to Canadian dollars according to the exchange rate used in the article (US$1 = CDN$1.47) and adjusted for inflation according to Bank of Canada rates.

** Costs with 3% discounting

This included direct health care costs for hospitalizations, emergency visits, day surgeries, and physicians' costs[54]

APPENDIX 9 – COST-EFFECTIVENESS ANALYSES RESULTS

Tables 9.1-9.4 show the incremental effectiveness and cost obtained with the different models and time horizons. In all models we have observed that the 95% CI includes values where drotrecogin alfa is less effective than placebo.

Table 9.1 LYG and incremental costs with drotrecogin alfa compared to placebo

Effectiveness measure Life-years gained (LYG)						
	All patients			APACHE II ≥ 25		
Time horizon	**LYG, mean (95% CI)**	**Incremental cost, mean (95% CI)**	**% negative effect.* (drotrecogin alfa)**	**LYG (95% CI)**	**Incremental cost (95% CI)**	**% negative effect.* (drotrecogin alfa)**
30 months**	0.067 (-0.176 , 0.314)	$12,502 ($9,831 , $15,130)	29%	0.311 (-0.11 , 0.632)	$16,561 ($11,595 , $21,613)	3%
5 years	0.11 (-0.27 , 0.49)	$12,502 ($9,831 , $15,130)	28%	0.440 (-0.017 , 0.889)	$15,436 ($11,096 , $19,757)	3%
10 years	0.222 (-0.527 , 0.963)	$12,502 ($9,831 , $15,130)	27%	0.830 (-0.054 , 1.677)	$15,436 ($11,096 , $19,757)	3%
15 years	0.297 (-0.704 , 1.28)	$12,502 ($9,831 , $15,130)	27%	1.062 (-0.073 , 2.155)	$15,436 ($11,096 , $19,757)	3%
20 years	0.344 (-0.807 , 1.476)	$12,502 ($9,831 , $15,130)	27%	1.191 (-0.082 , 2.417)	$15,436 ($11,096 , $19,757)	3%
25 years	0.369 (-0.864 , 1.583)	$12,502 ($9,831 , $15,130)	27%	1.25 (-0.09 , 2.55)	$15,436 ($11,096 , $19,757)	3%
30 years	0.381 (-0.891 , 1.632)	$12,502 ($9,831 , $15,130)	27%	1.28 (-0.09 , 2.6)	$15,436 ($11,096 , $19,757)	3%

* Proportion of the simulations where drotrecogin alfa had a lower effectiveness compared to placebo.

Effect. = effectiveness

** 1 year for >= 2 organ dysfunctionsCI= confidence interval

Table 9.2 – LYG and Incremental costs in patients with 2 or more organ dysfunctions

Difference in survival after 6 months	LYG	Incremental costs, mean (95% CI)
0	0.0114 (-0.0012 , 0.0238)	$13,029 ($11,356 , $14,679)
1%	0.120 (-0.330 , 0.564)	$12,358 ($10,564 , $14,120)
2%	0.228 (-0.218 , 0.669)	$12,432 ($10,619 , $14,213)
3%	0.337 (-0.106 , 0.774)	$12,427 ($10,635 , $14,187)

Table 9.3 Univariate sensitivity analysis using QALYs as the measure of effectiveness (20-year time horizon, 3% discounting)

Incremental Cost and QALY						
	All patients			APACHE II >=25		
Model	**QALY (95% CI)**	**Incremental cost (95% CI)**	**% of negative effect.* (drotrecogin alfa)**	**QALY (95% CI)**	**Incremental cost (95% CI)**	**% of negative effect.* (drotrecogin alfa)**
Incremental Cost and QALYs gained	0.286 (-.0668 , 1.223	$12,502 ($9,831 , $15,130)	27%	1.071 (-0.078 , 2.185)	$15,436 ($11,096 , $19,757)	3%

* Proportion of the simulations where drotrecogin alfa had a lower effectiveness compared to placebo.

Effect. = effectiveness / CI= confidence interval

Table 9.4 – Incremental and LYG with drotrecogin alfa compared to placebo using different discounting rates

Effectiveness measure Life-years gained (LYG)				
	All patients		APACHE II ≥ 25	
Discounting rates	**LYG, mean (95% CI)**	**Incremental cost, mean (95% CI)**	**LYG (95% CI)**	**Incremental cost (95% CI)**
No discounting	0.430 (-1.01 , 1.85)	$12,519 ($9,781 , $15,204)	1.47 (-0.11 , 2.99)	$15,530 ($11,134 , $19,936)
3%	0.344 (-0.807 , 1.476)	$12,502 ($9,831 , $15,130)	1.191 (-0.082 , 2.417)	$15,459 ($11,102 , $19,800)
5%	0.287 (-0.722 , 1.278)	$12,491 ($9,866 , $15,089)	1.052 (-0.072 , 2.135)	$15,414 ($11,093 , $19,720)

Figures 9.1 – 9.3 show the acceptability curves obtained through the 10,000 Monte Carlo simulations probabilistic sensitivity analyses.

The acceptability curves show the probability that a given treatment alternative (drotrecogin alfa or placebo) will be more cost-effective at a given willingness to pay level. The point where the two curves cross refers to a 50% chance that either alternative will be cost-effective.

Figure 9.1 – Acceptability curve (incremental cost/LYG). Lifetime decision model (all patients). 20-year time horizon

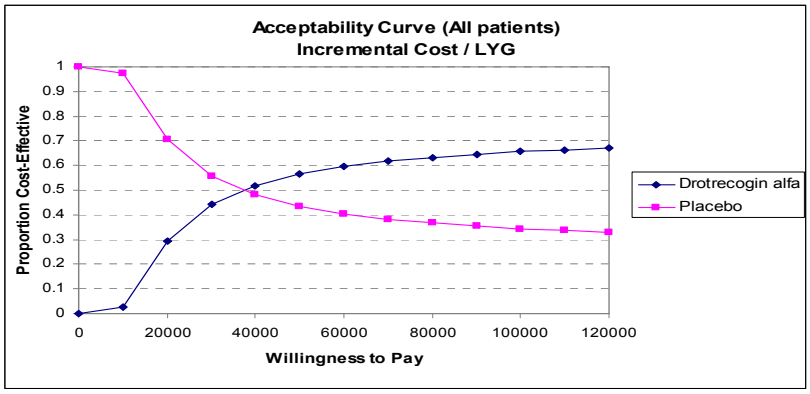


Figure 9.2 – Acceptability curve (incremental cost/LYG). Lifetime decision model (APACHE >=25). 20-year time horizon

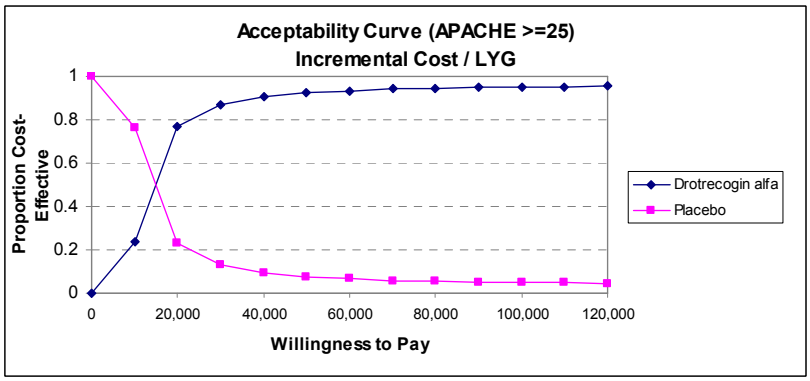


Figure 9.3 – Acceptability curve (incremental cost/LYG). Lifetime decision model (2 or more organ dysfunctions). 20-year time horizon