

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Manns BJ, Lee H, Doig CJ, et al. An Economic Evaluation of Activated Protein C Treatment for Severe Sepsis. *N Engl J Med* 2002;347:993-1000.

SUPPLEMENTARY APPENDIX 1

Monte Carlo Simulation and Cost-Effectiveness Acceptability Curves

The standard way of expressing uncertainty in classic statistics is through the use of measures of variance, such as the 95 percent confidence interval around a mean for normally distributed variables. As highlighted below, this approach is problematic in economic evaluations, which has led to the use of other methods designed to deal with and express analytic uncertainty.^{1,2} For instance, uncertainty in estimates of probability, clinical effectiveness, or cost are usually considered in the sensitivity analysis.

Classic univariate sensitivity analysis has been criticized because it considers only the uncertainty present in one (or two) variables at a time, and it may underestimate the uncertainty inherent in the cost-effectiveness ratio.^{1,2} As a result, some analysts have attempted to construct 95 percent confidence intervals around cost-effectiveness ratios.¹ This approach presents a statistical challenge, since incremental costs (the numerator) and incremental life-years gained (the denominator) may not be normally distributed and usually do not meet the assumption of independence.¹ In addition, it may be difficult for decision makers to interpret the results of an economic analysis in the context of 95 percent confidence intervals.¹ For instance, suppose we had reported a 95 percent confidence interval for the cost per quality-adjusted life-year gained (reported for the overall model as \$46,560) and noted that it overlapped \$50,000. Should decision makers reject funding of this therapy if they have set their maximal cost per quality-adjusted life-year gained at \$50,000 (even though analysis according to techniques to be discussed below suggest that the probability that this therapy is cost effective at a cost of \$50,000 per quality-adjusted life-year is 86 percent)? Others have argued against the use of confidence intervals for cost-effectiveness ratios and have recommended the use of Monte Carlo simulation.^{3,4}

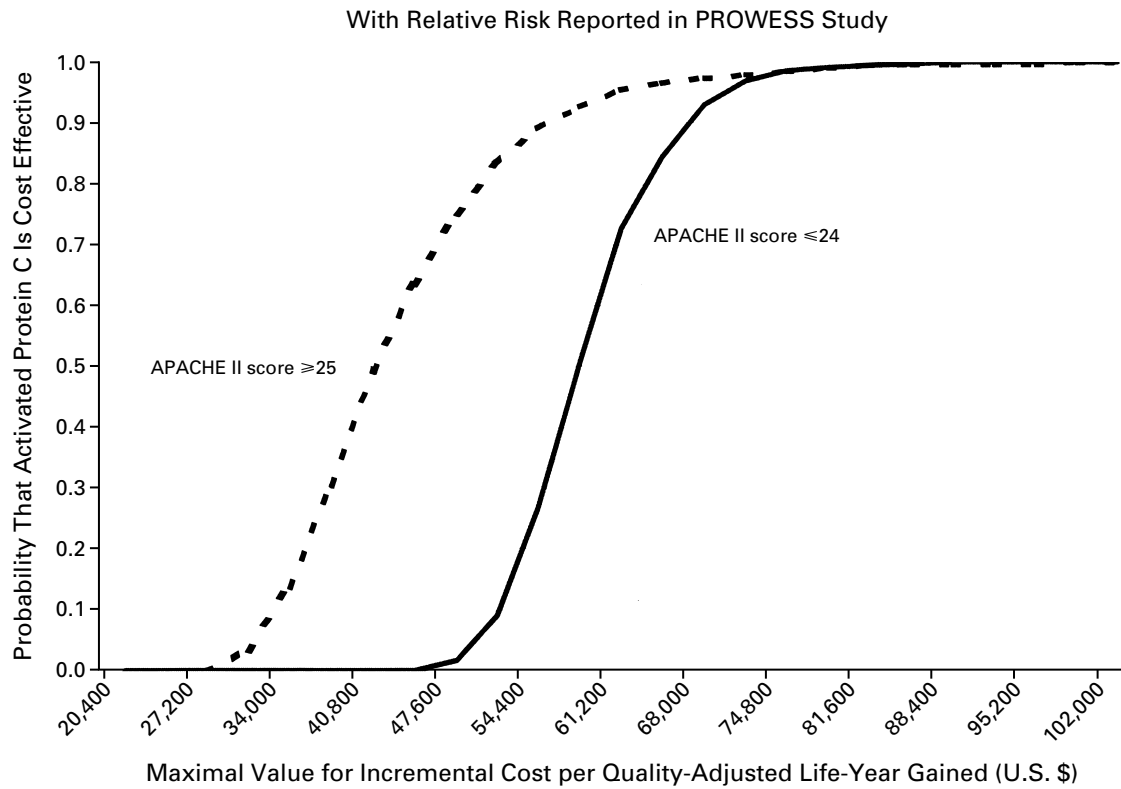
Monte Carlo simulation allows for the simultaneous sensitivity analysis of all variables for which there was substantial uncertainty of measurement. It does so by replacing estimates of probabilities, utilities, and costs with specific probability distributions, which are based on the reported means and variances for each variable.^{3,5,6} The analysis is then repeated 1000 times, with different values sampled from the appropriate distributions for each of the variables. In this way, a statistical distribution is built up around the incremental cost-effectiveness ratio, giving a better reflection of the uncertainty inherent in the analysis.

With Monte Carlo simulation, one can also con-

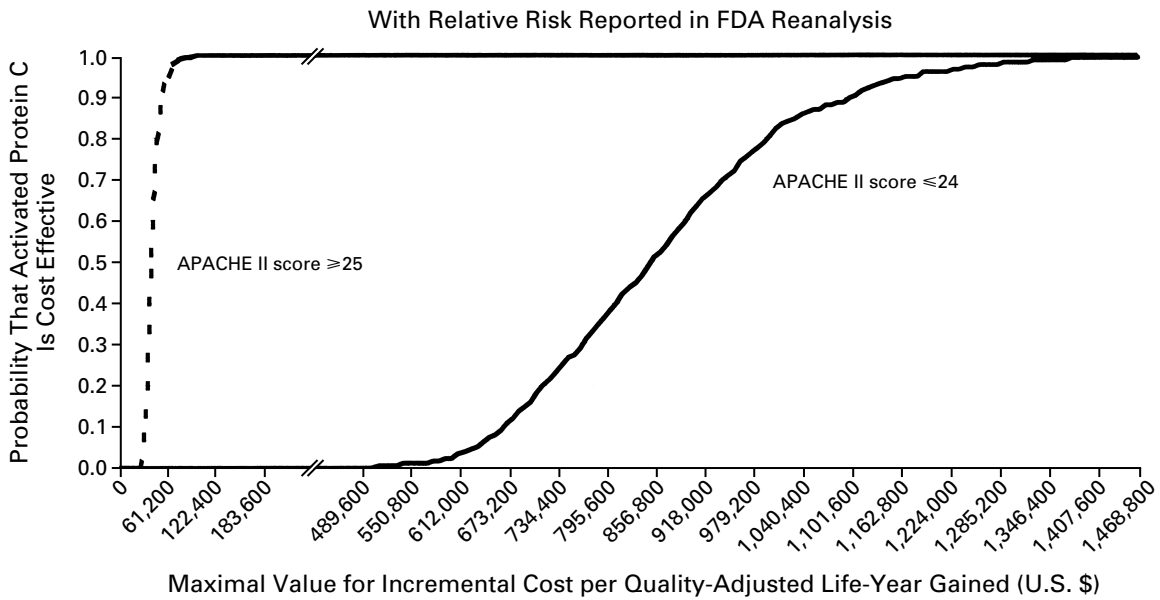
sider the uncertainty with respect to the maximal cost per quality-adjusted life-year that decision makers would consider acceptable (i.e., some decision makers will choose only to fund therapies associated with a cost per quality-adjusted life-year of less than \$20,000⁷; others, with larger budgets, may choose to fund therapies with a cost per quality-adjusted life-year of up to \$50,000 to \$100,000). This variation is shown graphically in the form of a cost-effectiveness acceptability curve indicating the probability that the use of activated protein C is associated with a cost per quality-adjusted life-year gained that is lower than a range of displayed maximal cost-effectiveness ratios.

We performed Monte Carlo simulation for our overall model (Fig. 1 of the article) and for subgroups defined according to the severity of illness and the estimate of clinical effect (with the use of the relative risk of death with activated protein C reported in the PROWESS study and that reported in the FDA's reanalysis^{8,9}). The results of the latter two simulations are presented here. Statistical distributions were created around all of the variables for which there was substantial uncertainty of measurement and for which distributions could be estimated. The following distributions were considered: a beta distribution (range, 0 to 1; shape defined by two variables — the number of deaths and the number of survivors during the given period) was used to describe the risk of death for hospital survivors after discharge and the absolute age-related increment in the risk of death; a normal distribution (shape defined by mean \pm SD) was used to describe the ICU and hospital costs during the initial hospitalization, since these variables were normally distributed (range, 0 to infinity), the utility associated with sepsis survivors (range, 0 to 100), and the relative risk of death associated with activated protein C (range, 0 to 1); a log-normal distribution (values bounded by 0 and infinity; shape defined by mean \pm SD of the distribution of the natural log of the variable) was used to describe the health care costs per year after hospital discharge for survivors, since these costs were positively skewed.

In general, if there were no uncertainty in any of the input variables, then a cost-effectiveness acceptability curve would appear as a straight vertical line passing through the mean cost per quality-adjusted life-year gained (in the case of the overall model, \$46,560). At this point (\$46,560) on the curve shown in Figure 1 of the article, there is a 50 percent probability that activated protein C will be cost effective, which is the case when the estimates for all the variables are equal to their mean values (i.e., the center of their statistical distributions). However, there is uncertainty in the variables of our model, re-



Cost-Effectiveness Acceptability Curves for Activated Protein C Treatment in Patients Stratified According to the Severity of Illness, Given the Relative Risk of Death Calculated in the PROWESS Study. The relative risks are as determined by Bernard et al.⁸



Cost-Effectiveness Acceptability Curves for Activated Protein C Treatment in Patients Stratified According to the Severity of Illness, Given the Relative Risk of Death Calculated in the FDA's Reanalysis. The relative risks are as determined by the FDA.⁹

flected in the slope of the cost-effectiveness acceptability curve, which tends to flatten out near the bottom and the top as uncertainty in all input variables reaches a maximum.

Here, we show two sets of cost-effectiveness acceptability curves for patients stratified according to APACHE II score (≤ 24 or ≥ 25). In the first graph, we used the relative risk of death reported in the PROWESS study.⁸ The probability that the use of activated protein C would be cost effective if one were willing to pay only \$50,000 per quality-adjusted life-year gained is 7 percent for patients with an APACHE II score of 24 or less and 82 percent for those with a score of 25 or more.

The second graph highlights the effect of the FDA's reanalysis on the cost effectiveness of activated protein C for patients with severe sepsis.⁹ The probability that the use of activated protein C would be cost effective for patients with an APACHE II score of 25 or more is 25 percent if one is willing to pay \$25,000 per quality-adjusted life-year gained and 93 percent if one is willing to pay \$50,000 per quality-adjusted life-year gained. Because of the very small incremental gain in quality-adjusted life-years predicted by the use of activated protein C in patients with an APACHE II score of 24 or less, the curve for this subgroup is very wide. Despite this

uncertainty, the probability that the use of activated protein C would be cost effective at a level below \$500,000 per quality-adjusted life-year gained for patients with an APACHE II score of 24 or less is very low (<1 percent).

REFERENCES

1. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Econ* 1998;7:723-40.
2. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994;3:95-104.
3. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779-87.
4. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999; 18:341-64.
5. Critchfield GC, Willard KE. Probabilistic analysis of decision trees using Monte Carlo simulation. *Med Decis Making* 1986;6:85-92.
6. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation: a practical approach. *Med Decis Making* 1985;5:157-77.
7. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146:473-81.
8. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
9. Xigris: drotrecogin alfa (activated): PV 3420 AMP. Rockville, Md.: Food and Drug Administration, 2001.

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