

Design of the economic evaluation for the Interventional Management of Stroke (IMS) trial

Patrick D. Mauldin^{1*}, Kit N. Simpson², Yuko Y. Palesch³, Judy S. Spilker⁴, Michael D. Hill⁵, Pooja Khatri⁶, and Joseph P. Broderick⁷, for the IMS III Investigators

Rationale Stroke is a common and costly condition where an effective early treatment may be expected to affect patients' future quality of life, the cost of acute medical treatment, and the cost of rehabilitation and any supportive care needed for their remaining lifetime. To assist in informing discussions on early adoption of potential treatments, economic analyses should accompany investigations that seek to improve outcomes for stroke patients.

Aims The primary aim is to assess whether i.v./i.a. rt-PA therapy is cost-effective at 3 months compared with i.v. rt-PA, and provides cost-savings or is cost-neutral by 12 months.

Design Cost-effectiveness of the two treatment arms will be measured at months 3, 6, 9, and 12. Cost-effectiveness will be calculated using

1. standard cost-effectiveness methodology (incremental cost-effectiveness ratios), and
2. an econometric model to assess multiple outcome measures while controlling for multiple subject and treatment-related factors that are known to affect both outcomes and costs.

Study outcomes Total cost for the initial hospitalization of treating stroke subjects randomized to either i.v./i.a. or i.v. rt-PA treatment arms will be measured, as will differences in types of resource utilization over 12 months between the two arms of the trial. Quality-of-life data (EuroQol EQ-5D) will be collected over a 12-month period and quality-adjusted life years will be used as a morbidity-adjusted measure of effectiveness. Subgroup analyses will include dichotomized NIH Stroke Scale (<20, ≥20), country, time between onset and randomization, and i.a. devices.

Key words: cost-effectiveness, economic evaluation, quality of life, resource utilization

Introduction

Stroke is a common and costly condition where an effective early treatment may be expected to affect patients' future quality of life, the cost of acute medical treatment, and the cost of rehabilitation and any supportive care needed for their remaining lifetime. The mean lifetime direct cost of ischemic stroke in the United States was estimated at \$140 048 in 1996 (1), with inpatient hospital costs for an acute stroke event accounting for 70% of the first year poststroke costs, and the first 30 days poststroke costing nearly \$20 346 for severe ischemic strokes (2). Room charges (50%), medical management (21%) and diagnostic costs (19%) were the major cost drivers (3). The estimated total direct and indirect cost of stroke in the United States in 2004 was projected to be over \$50 billion. To assist in informing discussions on early adoption of potential treatments, economic analyses should accompany investigations that seek to improve outcomes for stroke patients. Because the cost of stroke care may accrue to a number of different organizations and payers, we must examine more than one economic parameter over multiple time periods to identify the relevant economic benefits and/or burdens.

Fagan and colleagues evaluated the economic implications of rt-PA when given to patients with ischemic stroke (4). Their

Correspondence: Patrick D. Mauldin*, Department of Pharmacy and Clinical Sciences, MUSC College of Pharmacy, PO Box 250144, QF213B, Charleston, SC 29425 USA. e-mail: mauldinp@musc.edu

¹Department of Pharmacy and Clinical Sciences, Medical University of South Carolina, and the Ralph H. Johnson VA Medical Center, Charleston, SC, USA

²Department of Health Administration and Policy, Medical University of South Carolina, Charleston, SC, USA

³Department of Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina, Charleston, SC, USA

⁴Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

⁵Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

⁶Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

⁷Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

results revealed that rt-PA treated patients had significantly shorter length of hospital stays than placebo-treated patients (10.9 vs. 12.4 days, $P = 0.02$) and more rt-PA patients were discharged to home than to inpatient rehabilitation or nursing home (48% vs. 36%; $P = 0.002$). Their Markov model estimated an increase in hospitalization costs of \$1.7 million and a decrease in rehabilitation costs of \$1.4 million and nursing home costs of \$4.8 million per 1000 eligible treated patients. Thus, treating acute ischemic stroke patients with rt-PA within 3 h of symptom onset may be expected to promote both clinical benefits to the patient, and potential net cost savings to the health care system. A pooled analysis from the ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators (2004) further reveals that giving patients rt-PA in a timely manner significantly increases the benefit to the patient, especially if started within 90 min (5) [for additional reviews of cost-effectiveness analyses related to stroke, see (6–8)].

The general aim of economic evaluations is to provide information on the incremental cost effectiveness of a new treatment as compared to current practice. This single measure, the incremental cost effectiveness ratio (ICER), or 'value for money' for a new therapy is generally considered to be 'good value' for the US health system if it is below \$50 000 per quality-adjusted year of life gained. In addition to an ICER, the economic study proposed here will be able to project what changes in the level and allocation of expenditures to expect should the i.v./i.a. approach to recanalization be adopted. It is important for third party payers to understand if part or all of a potential increase in their initial expenditures will be partially or fully offset by a decrease in future expenditures (i.e., repeat hospitalizations, long-term care services).

Primary economic hypothesis

i.v./i.a. rt-PA therapy is cost-effective at 3 months compared with i.v. rt-PA, and provides cost-savings or is cost-neutral by 12 months.

Economic outcome measures

- (1) Total cost for the initial hospitalization of treating stroke subjects randomized to either i.v./i.a. or i.v. rt-PA treatment arms;
- (2) differences in types of resource utilization over 12 months between the two arms of the trial, including hospitalizations, procedures, length of stay, time to first hospitalization/procedure, diagnostic procedures, medications, rehabilitation, and outpatient visits, personal patient costs;
- (3) cost-effectiveness of the two treatment arms over 12 months using (1) standard cost-effectiveness methodology, and (2) an econometric model to assess multiple outcome measures while controlling for multiple subject and treatment-related factors that are known to affect both outcomes and costs; and

- (4) key economic performance measures (cost and cost-effectiveness), broken-out by health care system (United States and Canada), over 12 months of the treatment arms.

Methods

Economic analysis

The IMS III economic analysis will determine the cost-effectiveness of the i.v./i.a. approach to recanalization compared with subjects treated with standard i.v. rt-PA in the setting of optimal medical therapy. Comprehensive information will be gathered on resource utilization and subjects' valuation of their quality of life over 12 months for all subjects in IMS III. This will allow us to estimate expected differences in-hospital costs, cumulative health care costs over the first year, and differences in subjects' value of their quality of life over 12 months for all subjects. From these measures we will calculate ICERs and cost increases/cost offsets due to the differences in therapy.

Cost will be evaluated over 12 months from a societal viewpoint as best as possible. While it will be attempted to include all health care costs; costs of the initial stroke can be expected to dominate over a 12-month period. The reason for including all costs is that it is sometimes difficult to distinguish stroke related from nonstroke events. However, given the randomized nature of this study, once past the initial hospitalization, the long-term impacts of the types of nonstroke episodes of care should occur evenly between the groups. In addition the effectiveness of each recanalization strategy through clinical endpoints and quality of life measures will be examined. Quality-adjusted life years (QALYs) will be used as a morbidity-adjusted measure of effectiveness. A cost-effectiveness analysis will be used to compare the two recanalization strategies at 3, 6, 9 and 12 months in dollars per QALY gained. Standard cost-effectiveness methodology will be used as recommended by the task force of experts organized by the US Public Health Service (PHS) (9). For the 3-month cost-effectiveness analysis (primary economic hypothesis), the mean costs for each arm over the initial 3 months of the study will be used in the numerator and the mean QALYs of each treatment arm will be used in the denominator. The median costs and QALYs will also be used as an alternative estimate of the cost-effectiveness ratio. These analyses will provide the best estimates of the cost-effectiveness of i.v./i.a. approach relative to i.v. rt-PA over a 3-month period. Cost-effectiveness will also be measured at months 6, 9, and 12. The results of the economic analyses may be used by health care decision makers to compare the cost-effectiveness of i.v./i.a. and standard i.v. rt-PA therapy to other health care interventions.

As a secondary analysis, an econometric model (10,11) to assess the cost-effectiveness within IMS III at months 3, 6, 9, and 12 will be developed. This model will permit assessment of the cost-effectiveness using multiple outcome measures and

for subgroups in a multivariate manner not possible with standard cost-effectiveness analysis. The econometric model assumes multiple causes affect multiple indicators through an unobservable health effect. Because the true health improvement is not directly observed, multiple outcome indicators are used as proxies for health improvement. Interaction terms will be included in the analysis. They will capture the separate effect of, for example, i.v. rt-PA alone on subgroups of subjects identified by specific exogenous variables. Subgroup analyses will include dichotomized NIH Stroke Scale (<20 , ≥ 20), country, time between onset and randomization, and i.a. devices. If it turns out that the average results suggest that i.v./i.a. is more effective, the interaction terms could identify certain types of patients who benefit more than average from i.v. rt-PA alone. If, for example, the interaction term of age is sufficiently positive, it would imply that older patients receive more health improvement with i.v. rt-PA alone than with i.v./i.a., other things being equal. The intent of this approach is to systematically define and analyze how the clinical and subject variables interrelate to obtain a better understanding of which factors are most powerful or the best predictors in explaining treatment costs and outcomes. By systematically analyzing the major factors which contribute to the cost and outcomes of alternative therapies and comparing these results on the dimensions of time, sample subsets, and variable subsets, not only will the overall understanding of the relationship between the cost and outcomes of these therapies be illuminated, but it will also systematically evaluate which combinations of variables are most appropriate and useful. Comparison of the overall effectiveness and the individual outcome group effectiveness will provide a richer understanding on how the different factors contribute to the overall outcome of the therapy.

Thus, the cost, cost/effectiveness, econometric analyses should be seen as complementary forms of analysis, with the econometric model looking internally within IMS III, and the cost-effectiveness and cost analyses providing our most generalizable measures.

IMS III participant resource utilization

Initial hospitalization

Hospital – United States

One problem common to all empirical studies evaluating the cost effectiveness of any medical procedure that involves hospital services is that the actual cost of the services is not available. The typical solution to this problem in the literature is to approximate the cost of a patient's hospitalization using charge information obtained from hospital billing datasets. Estimates of the total cost of a hospital episode are determined by adjusting charge information using hospital wide cost-to-charge ratios (9,12,13). In this approach, the total cost of each hospitalization is calculated as the product between total billed charges during the patient's hospital episode found in the

hospital billing database and the hospital's overall cost-to-charge ratio available from the Medicare cost report.

For this study, the cost of the initial hospitalization from US sites will be estimated by collecting UB-04 hospital billing forms for each initial subject's hospitalization. This is a uniform billing statement used by all third party carriers. All available codes will be used in this study. Costs will be derived from charges using the appropriate hospital based Medicare cost-to-charge ratio.

Hospital – Canada

For subjects treated in Canada, initial hospitalization costs will be estimated using multivariate regression analysis. The strategy is to use data from US hospitals and subjects to create a cost regression model that captures the financial effect of various patient characteristics and events on initial hospitalization costs. Because no province in Canada has an itemized billing system, for the purpose of uniform costing of resources for patients in the two countries, the estimated cost weights calculated for US subjects will be assigned to Canadian subjects with similar clinical characteristics and events. In other words, we will attempt to estimate the initial hospitalization cost for Canadian subjects as if they were treated in the United States. Because teaching hospitals have historically had higher costs, a categorical variable will be included to capture this effect. The effects of this costing method will be assessed in a sensitivity analysis that uses published cost weights from the province of Ontario for all resources used by trial participants.

Physician

Estimating physician utilization during the initial hospitalization for therapeutic and diagnostic procedures will be straightforward. For example, if a subject receives a CT scan during the trial, the standard fee specified for this procedure will be applied. Physician utilization for subject consultations however will require some additional considerations. In addition to diagnostic and interventional procedures, physicians can claim for consultations and assessments given to subjects while they are in hospital. To assess the total number of physician consultations or assessments provided to subjects, a committee of study neurologists will be consulted to produce a protocol of the type and number of consultations/assessments normally claimed for ischemic stroke hospitalizations in the United States and Canada. This protocol will be applied to each hospitalization and will vary according to select patient characteristics and events. Length of stay will be considered by country to account for the historically different management of stroke rehabilitation between the United States and Canada (US patients are traditionally transferred from acute care to rehabilitation or nursing facility; Canadian patients typically receive rehabilitation in the initial hospital).

Follow-up

There is good support in the literature for patient recall for up to 4 months for health resource use (office visits, diagnostic examinations, treatments, hospital admissions, etc) for studies

of complex chronic conditions (14–16). However there is general agreement in the field of health economics that 12-month recall data are biased against recall of outpatient visits and treatments. Normally one would collect data only 4 months back at an annual visit and then annualize the results. However, for complex chronic conditions with episodic use of health resources (e.g. stroke) this is unlikely to be a valid approach. Therefore, actual event data will be collected on IMS III participants based on 3-month recall.

Resource utilization data in the form of answers to survey questions will be collected on separate CRFs by the study coordinator or nurse who interviews subjects accrued within this study. The Baseline Visit CRF and the Standard Follow-up CRF (3 month recall) are one and two pages, respectively, and capture information on hospitalizations, physician/professional visits, employment information, and personal subject costs at baseline, 3, 6, 9, and 12 months. All subjects/proxies will fill out each form. Select questions were constructed from forms used in the Agency for Healthcare Research and Quality and RAND co-sponsored HIV Cost and Services Utilization Study, and an NIH sponsored study comparing nelfinavir and zidovudine for HIV patients (17,18). Minor modifications in wording have been made to allow for a condensed questionnaire.

IMS III participant valuation of quality of life

The EuroQol Group's EQ-5D is a brief, preference-based health status measure designed for use in evaluative studies and policy research, and has been recommended for use by the United States PHS's Panel on Cost-Effectiveness in Health and Medicine (9,19–21). For the IMS III Economic study, the EuroQol EQ-5D will be collected over a 12-month period, at baseline and each 3-month follow-up visit to assess participant's valuation of their health state. For the baseline visit, the Resource Utilization Survey and the EuroQol EQ-5D will be collected from both the participant and proxy at Day 5 or discharge. This will allow for the participant to have maximum cognitive capability for filling out the forms. If the patient cannot complete the survey due to aphasia, cognitive change, or death, a proxy will be utilized. At all time periods, the EuroQol EQ-5D will be collected immediately following the administration of the Resource Utilization Surveys.

Telephone administration of surveys

Resource Utilization Surveys (including Concomitant Medications) and the EuroQol EQ-5D will be administered face-to-face at baseline and 3-month follow-up, and by telephone to the subject and a proxy at months 6, 9, and 12. The EuroQol EQ-5D has not been validated for phone administration. Thus, for a sample of IMS III subjects, the EuroQol EQ-5D will be validated for phone administration. Agreement of responses on the 'face-to-face' and telephone interviews will be made by Cohen's simple and weighted κ statistic for each of the items on

the EuroQol EQ-5D. Logistic regression will be applied to identify factors (e.g., age, race, sex, order of administration of face-to-face vs. telephone interview) affecting the concordance of the two responses.

Proxy

A proxy will be asked to complete:

- (1) the Resource Utilization Surveys,
- (2) concomitant Medication Form, and
- (3) the EuroQol EQ-5D assessments, and attempts will be made for the same person to serve as the subject's proxy at baseline and every follow-up visit as much as possible.

The proxy should be someone well acquainted with the subject's health and healthcare utilization. The proxy will be asked to keep in mind to respond from the participant's perspective. In the event that a subject is incapable or unable to self-administer the Resource Utilization Surveys, Concomitant Medication Form, or the EuroQol EQ-5D during the study, the proxy's response will serve as an appropriate measure of the subject's utilization of resources and valuation of their health state. There will be a proxy identification form at each administration of the EuroQol EQ-5D even if the same proxy has responded previously.

Valuation of participant survey response events

Primary method for resource utilization – archival billing databases

Patient-oriented resource utilization data will be linked to IMS III clinical data and a set of standard cost weights developed from archival billing data sources from patients with strokes. The resources reported by the study participants (including Medications) will be converted to dollar values (a proxy for opportunity cost) using standard cost weights as follows:

- (1) medications will be valued according to the Red Book Average Wholesale Price value,
- (2) as a common unit of measure, health care services cost weights will be constructed using charges from the South Carolina (SC) Medicaid program, and hospital admissions records from both the national Hospital Cost and Utilization Project (HCUP) database and the SC Medicare database, and
- (3) the opportunity cost of missed days from work will be estimated based on subjects' self-report of income range and missed days.

The SC Medicaid database includes billing data for all Medicaid patients. This dataset includes all billing data elements for provider visits, outpatient surgeries, hospital admissions, nursing home stays, and prescription drug coverage. The SC Medicare dataset includes claims from inpatient hospitals, physician/suppliers, outpatient-care facilities, skilled nursing facilities, home health agencies, and hospice care. HCUP includes the largest collection of longitudinal hospital care data in the United States, with all-payer, discharge-level

information beginning in 1988. HCUP databases include inpatient data from a national sample of over 1000 hospitals, and data from ambulatory care encounters.

For IMS III, events and Episodes-of-Care will be constructed from the SC Medicaid, Medicare and national HCUP databases by ICD-9 or 10 codes and appropriate cost weights applied to the clinical and follow-up data for IMS III participants. These data will be used to provide regional comparisons of costs, as well as provide ranges appropriate for preliminary sensitivity analysis. All cost estimates will be made in constant dollars, with the adjustment factor being the medical component of the consumer price index. No discounting of costs are necessary as the follow-up period is for 1 year only. Table 1 suggests a hypothetical patient and the sources of data for their economic assessment.

Secondary method for resource utilization-literature for sensitivity analysis

To gain further insight into the variation in the resource utilization and costs of IMS III, several sensitivity analyses will be performed. Sensitivity analysis involves systematically altering our assumptions about the cost and effectiveness of the

i.v./i.a. approach to recanalization compared with standard i.v. rt-PA. Two types of sensitivity analyses will be performed. The first set of calculations will be one-way sensitivity analyses. In one-way sensitivity analysis, the assumption about each parameter is varied over a reasonable range of values with all other parameters fixed. Specifically, we will vary one-by-one our estimates of the different cost components of IMS III over the initial hospitalization, and then over the 12 months of follow-up. Robust estimates from the literature will be used to provide ranges (7,4,22–25). Specifically, Fagan *et al.* provide a comprehensive estimate of costs (from the literature) for most of the components of acute ischemic stroke (4). Perhaps most valuable to our analysis is the fact that the estimates are broken down by Rankin Score. These estimates, and others mentioned above, will provide credible values to test the sensitivity of our estimates.

Determining utility weights – valuation of the EuroQol EQ-5D

Valuation of the health states as determine by the EuroQol EQ-5D will be based on the scientifically accepted indexed values determined by Dolan (20,21). Dolan’s model predicted the mean values for 42 EuroQol EQ-5D health states in terms of level of severity associated with each dimension of the survey. Once IMS III participants complete the EQ-5D survey at baseline and each 3-month follow-up visit, responses will be entered into the database and the mean values will be applied to their responses for an appropriate valuation of their health state.

Economic power

The number of subjects who will be enrolled in IMS III has been chosen based on the power required to detect a clinically significant difference between the treatment arms at 3 months. Given the importance of rt-PA for the treatment of stroke patients it would not be ethical to enlarge the study sample size in order to enhance the ability to detect economic differences. Furthermore, several economic parameters will be measured that together will be used to describe the expected economic differences between the two therapies. However, it is believed that most decision makers will agree that cost savings, or at least cost neutrality at 12 months is a very desirable economic outcome, given the study population. Thus, the study’s power to identify 10% savings in cost at 12 months for the i.a./i.v. rt-PA treatment group, compared to the i.v. rt-PA treatment group will be examined. Data from a prior study on a sample of 21 S.C. Medicaid patients hospitalized with a primary diagnosis of ischemic stroke (ICD-9 code of 434) indicate that the average annual cost for patients with stroke was \$60 157 in 2000. The study’s power to detect differences in annual costs with 600 subjects in the combined i.v./i.a. arm and 300 in the i.v. arm ($\alpha = 0.05$ and a two-sided test) is estimated in Table 2.

Table 1 Economic data sources for hypothetical IMS III patient

Timeline	Utilization	Valuation
Initial hospitalization	Hospital costs (US)	UB-04 hospital bill (cost-to-charge ratio)
	Physician costs (i.e., Neurologist; Interventional; Neuroradiologist for CT × 2, MR, echo; Rehab consult; Critical Care Physician × 2 days)	Reimbursement rates Average number of consultations determined by study committee of neurologists [valued using HCUP, and South Carolina (SC) Medicaid and Medicare Databases]
Follow-up (Resource Utilization Survey)	Skilled nursing home stay × 4 months	SC Medicaid and Medicare Databases
	Re-hospitalization for CHF at 5 months	HCUP, and SC Medicaid and Medicare Databases
	Outpatient physician visits × 2 at month 4	HCUP, and SC Medicaid and Medicare Databases
	Physical therapist visits for 4 months	HCUP, and SC Medicaid and Medicare Databases
	150 missed days from work	Patient-reported salary
	Equipment purchase walker	Patient-reported expense
	Home modification ramp	Patient-reported expense
	Concomitant medications	Redbook Average Wholesale Price

HCUP, Hospital Cost and Utilization Project; IMS, Interventional Management of Stroke.

Table 2 Power for economic analyses

Mean annual cost	\$60 157
Standard deviation*	\$30 078
Reduction in cost (10%)	\$6016
Per cent power	80%

*Assuming that control variables explain 50% of the variance in total cost.

Previous cost regressions of clinical trial data from patients with complex chronic conditions have shown that baseline control variables can explain at least 50% of the variance in the annual cost for these types of patients. Given that the clinical study has 600 subjects in the combined i.v./i.a. arm and 300 in the i.v. arm, at least 80% power to identify a 10% cost difference is expected. Most economists agree that an annual cost reduction of 10% is a meaningful amount of saving for this type of patient.

The bootstrap technique (26,27) will be used to assess the variation in the cost effectiveness ratios estimated from the study data to obtain a 90% confidence interval around the estimated costs. This technique is appropriate when costs are estimated from the recorded resource use data combined with the standard costs weights.

While there is sufficient power to determine a difference in costs, there are other factors which may affect the power of our econometric model (covariates, unknown regression coefficients, covariance structures). Power associated with the econometric model will be determined based on the statistical associations derived from the model.

In anticipation of missing resource utilization data, it will be assumed all missing data to be missing at random (28). Thus, missing resource utilization data will be imputed using the multiple imputation method. Sensitivity analysis will be performed for additional clarity.

Summary

This prospective economic study is designed to 'piggy-back' the IMS III clinical trial of i.v./i.a. rt-PA vs. i.v. rt-PA while minimizing the burden of additional data collection on clinical investigators and enrolled subjects. In addition, the study will continue quarterly resource utilization and quality of life data collection for 9 months after the end of the 3-month clinical trial. Subjects will be asked by the study nurses to recall their use of major cost drivers for stroke (hospital admission, ER use, procedures, medications, etc.). They will also be asked to value their current health using the EuroQol EQ-5D instrument. These data will be combined with hospital billing data, and cost weights derived from several large medical billing data bases and utility weights from the literature to construct the measures required to assess cost effectiveness and compare expected economic impacts for the therapies over time.

Acknowledgements

Funding: The economic substudy is funded by the National Institute of Neurological Diseases and Stroke (NINDS # U01 NS054630). The primary clinical study is funded by NINDS (NINDS # U01 NS052220). The trial receives rt-PA from Genentech, and devices from Concentric, EKOS, and Johnson & Johnson.

References

- Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF: Lifetime cost of stroke in the United States. *Stroke* 1996; **27**:1459–66.
- Leibson CL, Hu T, Brown RD, Hass SL, O'Fallon WM, Whisnant JP: Utilization of acute care services in the year before and after first stroke: a population-based study. *Neurology* 1996; **46**:861–9.
- Diringer MN, Edwards DF, Mattson DT et al. Predictors of acute hospital costs for treatment of ischemic stroke in an academic center. *Stroke* 1999; **30**:724–8.
- Fagan S, Morgenstern L, Petitta A et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. *Neurology* 1998; **50**:883–90.
- Hacke W, Donnan G, Fieschi C et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; **363**:768–74.
- Holloway RG, Witter DM Jr, Lawton KB, Lipscomb J, Samsa G: Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology* 1996; **46**:854–60.
- Evers SM, Ament AJ, Blaauw G: Economic evaluation in stroke research: a systematic review. *Stroke* 2000; **31**:1046–53.
- Demaerschalk BM, Yip TR: Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. *Stroke* 2005; **36**:2500–2503.
- Gold MR, Siegel JE, Russell LB, Weinstein MC: Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
- Lee JS, Bailey MJ, Jeong J, Mauldin PD, Weintraub WS: A study on the cost-effectiveness of coronary revascularization: introducing the simultaneous mimic health status model. *Health Econ* 1997; **6**:613–23.
- Mauldin PD, Jeong J, Weintraub WS, Becker ER: A multiple outcome model to assess cost-effectiveness: results from the Emory Angioplasty vs. Surgery Trial (EAST). *Biometrical J* 1999; **41**:3–23.
- Mauldin PD, Weintraub WS, Becker ER: Predicting hospital costs for first-time coronary artery bypass grafting from pre-operative and post-operative variables. *Am J Card* 1994; **74**:772–5.
- Ashby J: The accuracy of cost measure derived from Medicare cost report data. *Hosp Cost Manage Acc* 1992; **3**:1–8.
- Epstein AM et al. Costs of medical care and out-of-pocket expenditures for persons with AIDS in the Boston Health Study. *Inquiry* 1995; **32**:211–21.
- Tourangeau R, Rasinski KA: Evaluation of Data Collection Frequency and the Use of a Summary in the National Medical Utilization and Expenditure Survey. Medical Care Utilization and Expenditure Survey, Series A. Washington, DC: US Government Printing Office, 1987.
- Killeen TK, Brady KT, Gold PB, Tyson C, Simpson KN: Comparison of self-report versus agency records of service utilization in a community sample of individuals with alcohol use disorders. *Drug Alcohol Depend* 2004; **73**:141–7.
- Shapiro ME, Morton SC, McCaffrey DF et al. Variations in the care of HIV-infected adults in the United States results from the HIV cost and services utilization study. *JAMA* 1999; **281**:2305–15.
- Perez G, MacArthur RD, Walmsley S et al. A randomized clinical trial comparing nelfinavir and zidovudine in patients with advanced HIV disease (CPCRA 042/CTN102). *HIV Clin Trials* 2004; **5**:7–18.

- 19 The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**:199–208.
- 20 Dolan P *et al.* A social tariff for EuroQoL: results from a UK general population survey. Discussion paper 138. In: Center for Health Economics. York, UK: The University of York, 1995.
- 21 Dolan P: Modeling valuations for EuroQol health states. *Med Care* 1997; **35**:1095–108.
- 22 Sandercock P, Berge E, Dennis M *et al.* Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke* 2004; **35**:1490–7.
- 23 Porsdal V, Boysen G: Costs of health care and social services during the first year after ischemic stroke. *Int J Tech Assess Health Care* 1999; **15**:573–84.
- 24 Lipscomb J, Ancukiewicz M, Parmigiani G, Hasselblad V, Samsa G, Matchar DB: Predicting the cost of illness: a comparison of alternative models applied to stroke. *Med Decision Making* 1998; **18**:S39–56.
- 25 Holloway RG, Witter DM, Lawton KB, Lipscomb J, Samsa G: Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology* 1996; **46**:854–60.
- 26 Efron B, Tibshirani RJ: *An Introduction to Bootstrap*. New York: Chapman and Hall, 1993.
- 27 Chaudhary MA, Stearns SC: Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. *Stat Med* 1996; **15**:1447–58.
- 28 Little RA, Rubin DB: *Statistical Analysis with Missing Data*. New York: Wiley and Sons, 1987.