Synthesis of "Statistical Innovations for Cost-Effectiveness Analysis"

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Synthesis of "Statistical Innovations for Cost Effectiveness Analysis"
Translating Research into Policy and Practice (TRIPP)

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ABSTRACT

Cost-effectiveness analysis (CEA) has been promoted as a useful tool in the effort to prioritize expenditures on health care programs. By quantifying the trade-offs between resources that need to be deployed and health benefits that accrue from use of alternative interventions, CEA offers guidance in decision-making by structuring comparisons between these interventions. The core of Dr. Gardiner's research was the recognition that both costs and benefits were stochastic in nature and thus summary measures such as the cost-effectiveness ratio would have inherent variability that should be quantified. His research was also designed to produce new and more advanced statistical models that improve the assessment of costs and patient outcomes.

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EXECUTIVE SUMMARY

The Agency for Healthcare Research and Quality (AHRQ) continues to be a leader in advancing the use and science of cost-effectiveness analysis (CEA) in health care. AHRQ supports extramural research in CEA and advances the science of clinical economic evaluation. AHRQ has also acted as a facilitator for other agencies within the Federal Government to develop and use CEA for the enhancement of their goals and objectives. During the period of 1997-2003, Dr. Joseph Gardiner, Ph.D., of Michigan State University, College of Human Medicine, was awarded an original grant and continuation to study "Statistical Innovations for Cost-Effectiveness Analysis" (AHRQ Grant Number HS09514). The major goals of this research were to develop new statistical models and methods that fill methodological gaps, and resolve inconsistencies in current cost-effectiveness analysis.

The purpose of this manuscript was to synthesize Dr. Gardiner's research developments related to Translating Research into Policy and Practice (TRIPP). As a result of developing and testing new methods and models for cost-effectiveness studies, and demonstrating their application in several ongoing clinical studies, this research not only offers an array of promising techniques, but also bridges the gap between methodological development and implementation. All statistical derivations such as equations and formulae were omitted in an effort to synthesize and highlight significant and relevant research findings, and applications related to TRIPP.

Cost-effectiveness analysis (CEA) has been promoted as a useful tool in the effort to prioritize expenditures on health care programs. By quantifying the trade-offs between resources

that need to be deployed and health benefits that accrue from use of alternative interventions, CEA offers guidance in decision-making by structuring comparisons between these interventions. The core of Dr. Gardiner's research was the recognition that both costs and benefits were stochastic in nature and thus summary measures such as the cost-effectiveness ratio would have inherent variability that should be quantified. His research was also designed to produce new and more advanced statistical models that improve the assessment of costs and patient outcomes.

The specific aims of their research were:

1. **To specify stochastic models for costs and health outcome measures;**
2. **To assess the development of new models and procedures;**
3. **To test and validate statistical procedures; and**
4. **To apply and test procedures on existing data sets.**

Markov models provide a natural setting to describe the evolution of event histories of patients through different health states. They are used in clinical decision analyses and cost-effectiveness analyses. Using this longitudinal framework, Gardiner *et al* describe stochastic models that reflect the experience of patients in sustained and changing states of health. Costs are engendered at random amounts at random points in time during the course of a health care intervention. By compiling these expenditure streams at the individual level into costs per unit time of sojourn in a health state, and in transition between health states, Gardiner *et al* were able to estimate the distribution of present value of all expenditures, and summary statistics such as mean and median costs. They then estimated health outcome measures such as life expectancy, median survival and survival rates, all discounted where appropriate at a constant rate and adjusted for quality of life.

With AHRQ's support, the research team led by Dr. Gardiner identified major problematic areas in CEA and has taken several steps in addressing these issues.

- Despite the rapid development of techniques for conducting economic evaluation studies in medicine and health, the statistical methodology to support these studies is in the developmental stages. Gardiner's research formulates statistical models that inform identification of patient characteristics and resource-use elements that influence both costs and outcomes.
- Recognizing the natural setting in which cost and health outcomes would manifest over time, his current research addresses development of longitudinal models that incorporate covariate information and permit estimation of their impact on summary measures such as the cost-effectiveness ratio (CER) and net health cost (NHC).
- Gardiner's interdisciplinary team of statisticians, health economists, health services researchers and clinical investigators has built a repertoire of publications addressing both applied and methodological issues in CEA.
- Many methodological developments are theoretically sound and can be tested on simulated data. In practice, these sophisticated methods have limited use unless they address the inherent problems in data sets commonly available to researchers from clinical and epidemiologic studies. Gardiner's research team recognizes the natural setting in which health outcomes and costs arise in practice, accounting for issues of censoring, truncation, and sample selection.
- The longitudinal framework that underlies their analytic techniques can be used to provide a complete specification of alternative models for estimating health care costs and outcomes.

Gardiner's research methods and models offer practitioners of CEA a powerful set of tools for the improvement of statistical analysis of cost, health care utilization and cost-effectiveness data.

Summary and Significance of Gardiner's Research Findings Related to Translating Research into Policy and Practice (TRIPP)

- A comprehensive review[38] was published in 2004 addressing statistical issues in assessing statistical power and sample size for cost-effectiveness studies. This was at the request of the editors of *Expert Review of Pharmacoeconomics & Outcomes Research* following their earlier work in *Health Economics*.[37] Their work in this area has led to collaboration with an international team of researchers in designing a study for evaluating the effectiveness and cost-effectiveness of treatment strategies for decreasing the burden of depression in developing nations.
- The issue of testing of hypotheses on cost-effectiveness ratios (CER) and assessing statistical power and sample size is addressed in an article in *Health Economics*. Following the pioneering work of O'Brien *et al*[32] this was the first attempt to place hypothesis testing on CERs on a formal statistically sound framework.
- Gardiner's method incorporates the correlation between cost and effectiveness measures, and leads to substantially lower sample size requirements than methods that ignore the correlation. It extends work by several other researchers.[39-41,73]
- An important element in reporting the results of CEA is to gauge the precision of estimates such as the CER. Gardiner's work compares three of the popular parametric techniques for constructing confidence intervals for the CER.[17] This work demonstrates

relationships between the three approaches and shows how the interpretation of the CER can be compromised when the incremental effectiveness is not statistically significant.

- In recognition of the work of their on statistical inference for CEA and its potential use in public health policy, the editors of the critically acclaimed *Handbook of Statistics* invited their contribution to a volume addressing *Bioenvironmental and Public Health Statistics*.[11] A summary is presented of how uncertainty in estimated parameters can be assessed by their sampling error and conventional statistical inferential techniques. These techniques can then be applied to problems of estimation, tests of hypotheses, sample size, and power determinations in planning economic evaluation studies of health care programs.
- Gardiner's statistical method for assessing the cost-effectiveness of the ICD was the first to address construction of statistical confidence intervals for the CER from survival data.[25-27] His articles in the *American Heart Journal* and *Medical Decision Making* have received over 55 citations in professional literature.
- Gardiner's team continues their research in CEA to address the formulation of regression models that could inform identification of patient characteristics and resource-use elements that influence both costs and outcomes, and the cost-effectiveness of competing interventions. Applications are contemplated in cardiovascular studies and in cancer treatments studies. The methods could ultimately improve standardization in reporting the results of economic evaluation studies, and provide objective means for assessing subgroups in which an intervention could be cost-effective.
- Through experience with analyses of length of stay and cost in hospitalizations for heart failure, Gardiner *et al* have developed methods[20,23,24] to estimate the cumulative cost of

health interventions over a specified duration while controlling for a mix of patient-specific variables. This method blends statistical and econometric techniques to address issues in the analysis of health care costs and allows for a greater use of total cost data, typically found in hospitalization records and claims files, that has not been previously attempted.

- Gardiner's research proposes a unified framework to estimate summary measures commonly used in cost analyses and CEA. These include life-expectancy, quality-adjusted life years, net present values, cost effectiveness ratios, net health cost and net health benefit. Since patient demographics, clinical variables and intervention characteristics can affect these summary measures, regression models have been developed that incorporate covariate information into structural equations for cost and outcome measures.
- These regression models are uniquely designed to account for costs engendered at transition times between health states (e.g., changes in health state that trigger resource use), and costs of sojourn in health states (e.g., resource use while in remission, relapse, or different treatment phases). For health outcomes such as quality of life assessments, their longitudinal models incorporate patient heterogeneity and address the issue of censoring commonly found in these types of studies.

In summary, several aspects and complexities in the analyses of health care costs and outcomes are incorporated into these models, and collectively these new methods promise useful application in CEA. Demonstration of their methods in practice with clinical and epidemiologic data is an equally important goal of their endeavors.

Introduction

Rapid increases in health care costs continue to concern the public, federal and state agencies, and private industry. Publicly funded insurance programs such as Medicare and Medicaid are continually faced with difficult decisions in allocating health care dollars. Private industries are similarly challenged in providing health care benefits to their employees. Expenditures on health care now account for 16 percent of the U.S. gross national product.[1]

Given the high and growing cost of health care in the U.S, the need to contain health care costs forces us to consider which interventions produce the greatest value. CEA offers a structured approach for making economic evaluations of health care programs. It can be used for optimizing health benefits from a specified health care budget, or in finding the lowest cost strategy for a specified health effect.[2]

Faced with pressures to contain costs while optimizing value, policymakers world-wide have turned to evidence of cost-effectiveness in addition to evidence of health benefit in allocating resources for health care services. In Australia, the Pharmaceutical Benefits Advisory Committee makes recommendations, based on effectiveness and cost-effectiveness evidence, on drug products that should be subsidized and placed in the Pharmaceutical Benefits Scheme.[3] In the United Kingdom, the National Institute of Clinical Excellence makes similar requirements for use of new healthcare technologies in the National Health Service, and in Ontario, Canada, the Drug Benefits Plan uses economic data when supporting new additions to its formulary.[4,5] Additionally, the U.S. Preventive Services Task Force and the Panel of Cost-Effectiveness in Health and Medicine have urged consideration of cost-effectiveness in addition to clinical effectiveness to help inform investment of health care dollars.[6,7]

Improvement of health is an important objective of social policy. In welfare economics, output is judged according to the extent to which it contributes to overall welfare, as determined by individual preferences over health, relative to other considerations in utility functions.[2,8,9] The perspective of the welfarist calls for judging output of health care according to its contribution to health itself, and therefore requires careful assessment of health outcome as it affects an individual's well-being. By defining health as a state of "complete mental, physical, and social well-being and not merely the absence of disease," the World Health Organization in 1948 endorsed the broader perception of health as it is viewed today.[10]

Components of Cost-Effectiveness Analysis

Measuring Costs

An important step in CEA is the identification of all relevant cost items followed by their measurement and estimation. The Panel on Cost-Effectiveness in Health and Medicine recommended that costs in economic evaluation studies consist of both direct and indirect costs.[7] The direct medical costs of an intervention are those incurred in providing care, such as payments for drugs, medical/surgical supplies and professional services from nurses, physicians or other health care providers associated with intervention. These include the costs of treating side effects and complications resulting from the intervention. Direct non-medical costs include costs incurred because of the illness or the need to seek care such as caregiver costs, transportation and child-care expenses incurred by patients and their families. Indirect costs, also called productivity costs, represent costs not associated with the transactions for goods or services, such as morbidity that results in time lost from work, or the inability to participate in leisure activities.

Measuring Benefit

The next component of the CEA is the measurement of health benefit resulting from adoption of a specific treatment or intervention. Depending on the context one could use any clinically meaningful measure such as improvement in life expectancy, deaths averted, or number of toxic side effects prevented. Since the goal of any health care intervention is much broader than simply treating the disease condition or preventing death, the use of quality-adjusted life years (QALYs) in CEA has been advocated. A precursor to CEA was *cost-benefit analysis* which attempted to quantify in monetary terms the effect of the disease.[7] Health care programs designed to prevent disease could be compared relative to their costs and benefits on the same scale. However, the difficulty of placing a monetary value on health outcomes has prevented its widespread adoption.

A cost-identification analysis is often conducted for treatments and procedures that are believed to be equivalent in their clinical efficacy. For example, if two competing programs do not differ on average in their health benefits, then the one with the lower average cost will be preferred. This is the argument cited for the promotion of generic drugs because they offer the same therapeutic benefits as more expensive brand-name versions of the same drugs. On the other hand, if the costs of two programs are judged equivalent, the intervention with the greater health benefit will be preferred. A decision has to be made when one program has both higher cost and greater benefit than does its competitor. Is there a critical value below which society would consider the more costly intervention still “cost-effective”?

Quality-Adjusted Life Years

A quality-adjusted life year (QALY) represents a patient's perception of the reduction in value of one year in perfect health due to pain, disability, and suffering caused by illness. It can be viewed as the proportional decrement in quality of life in the state of ill health, multiplied by years of expected life. Formally, for each unit of time spent in some health state, a quality weight is the relative value placed on that health state against the state of perfect health. Perfect health has a quality weight of 1, while death (or states judged equivalent to death), get a quality weight of 0. All other health states receive a quality weight between 0 and 1. Quality of life studies seek to measure the impact of health conditions on patients' functional status, including their physical, mental and social functioning, as well as their emotional well-being.[14,15]

In CEA, use of the QALY to quantify health outcomes provides a common metric across different diseases. For example, the decision maker facing resource allocation can compare cost-effectiveness of coronary artery bypass surgery versus percutaneous coronary intervention, the cost-effectiveness of lipid lowering therapies for the prevention of cardiovascular disease, and the cost–effectiveness of different regimens of screening women for their susceptibility to breast cancer.

Cost-Effectiveness Ratio

The cost–effectiveness ratio (CER) is an important summary statistic for comparing the costs and effectiveness of competing interventions. The CER is the additional cost at which the new or alternative intervention delivers one unit of additional health benefit, relative to the standard intervention to which the new intervention is being compared. In cost-effectiveness

studies, the CER is a useful statistical aid in decision-making processes and in the allocation of health care resources.

The CER is computed as the ratio of the net difference in costs of two interventions relative to the net difference in their effectiveness.[11] Since the CER is assessed from inputs on cost and effectiveness that are subject to variation, sensitivity analyses are used to assess the extent of uncertainty in the CER. However, with patient-level data collected on costs and benefits in clinical trials, the CER may be viewed as a function of the parameters of the distribution of cost and effectiveness. Thus, given a probability model for sampling costs and health benefits, the CER can be estimated from available data and formal statistical inference can be applied to assess the variability in the estimated CER.

As a ratio the CER presents some difficulties in its statistical analysis. In addition, problems of interpretation arise with negative values of the ratio, and using the ratio alone can lead to very different conclusions.[16] Several investigators have also cautioned using the CER when the incremental effectiveness is not statistically significant.[17,18] In order to overcome these difficulties another summary measure, the net health cost (NHC) or net health benefit (NHB) has been proposed.[18] The NHC, denominated in monetary units, is the incremental cost minus the incremental benefit. The incremental benefit is converted into monetary units using the maximum value of the CER—the upper limit of what society is willing-to-pay to gain one unit of effectiveness The NHB is analogously defined in terms of effectiveness units.[19]

Stochastic Variation

A common aspect of cost and benefit measures is their stochastic nature. When measured at the level of the individual patient, cost and health outcome measures will vary across the

population of patients. These outcomes will depend on demographic factors such as age, gender, ethnicity, socioeconomic variables such as income and education, lifestyle factors such as smoking, alcohol consumption, physical activity, and health conditions as well as comorbidities. Incorporating stochastic variation in outcomes and covariables involves notions of probabilities. This allows the analyst to express and quantify the degree of uncertainty in estimates of cost and benefit.[11,16]

Another important feature of cost and benefit comes is that they accrue longitudinally. When an intervention is deployed costs are incurred through resource use over time. The basic framework that Gardiner *et al* have adopted recognizes that over the course of an intervention, a patient's event history unfolds as transitions between different health states and that sojourns in these states, as well as transitions between health states, are associated with costs. The ending state is usually death or some other terminal state which ends the evolution of the patient's event history. Because costs that might be incurred in the future are valued less at the present time, all future costs are discounted at a fixed rate. The discounted total cost of the intervention over a finite time horizon is then the *net present value* (NPV) of all expenditures incurred in transitions between health states, and during sojourn in health states.[11] As recommended by the Panel on Cost-Effectiveness in Health and Medicine, this time horizon must be sufficiently long to capture all costs of the intervention and the health benefits that accrue over time.[7]

Specific Research Design: Goals, Aims and Objectives

Description: Motivated by the need for new techniques for analyses of health care costs from clinical and epidemiological studies, the goal of this research was to develop new statistical techniques that fill methodological gaps in current CEA models. When a health care

intervention is deployed, cost is engendered through the use of resources. These occur in random amounts at random times that may differ by patient attributes, as well as clinical and intervention characteristics. Study design and sampling may lead to incomplete observation of key outcomes in some patients. By incorporating these components into statistical models that accurately reflect the experience of the patients as their health histories manifest over time permits consideration of health outcomes and costs jointly. This research was designed to produce newer and more advanced statistical models that improve the assessment of costs and patient outcomes. Gardiner *et al* use a Markovian regime to model the dynamics of movement of patients through different health states, accounting for costs incurred at transitions between states and sojourns between states. Applying a constant discount rate where appropriate, they estimated summary health outcome measures (i.e. life expectancy, quality-adjusted life years, net present value, net health care cost and benefit, and cost-effectiveness ratios). In addition, they assessed the impact of various factors on these statistical parameters and provided a uniform framework for statistical inference. They tested the performance and sensitivity of the procedures with real and simulated data.

The specific aims of the research were:

1. **To specify stochastic models for costs and health outcome measures.**

   Longitudinal stochastic models were utilized that reflect the experience of patients in changing states of health. Costs are engendered in random amounts at random times during the course of a health intervention. By compiling these expenditures at the individual level into costs per unit time of sojourn in a health state, and in transition between health states, the researchers estimated the distribution of present value of all expenditures, and summary statistics such as mean and median costs. Using Markov

models to describe the evolution of patient histories over time, they were able estimate health outcome measures such as life expectancy, median survival and survival rates, all discounted at a constant rate and adjusted for quality of life.

2. **To assess the development of new models and procedures.** The researchers exploited the capability of the proposed models and new procedures for assessment of health care costs and outcomes. For CEA, the proposed methods yielded estimates of intervention effects adjusted for variables that might have impact on measures of cost and effectiveness. The research team then formulated procedures for statistical inference on summary statistics used in CEA such as cost-effectiveness ratios, net benefit and net cost measures.

3. **To test and validate statistical procedures.** A useful tool in evaluating the performance of the estimators of effectiveness, cost and cost-effectiveness is to perform a simulation study. Since a patient event history is manifested over time by the occurrence of discrete events (i.e., transition between health states, cost at transition times) the principle of discrete event simulation (DES) may be used to track the flow of patients through health states and gather the relevant observations for estimating the summary measures of interest. Simulation studies were used to assess the performance of their models with regard to sensitivity to assumptions made in their specification. Scenarios for these studies were taken from published cost-effectiveness studies that are often framed under a decision-theoretic model with numerous assumptions on the inputs of utilization and effectiveness. The performance

of the competing procedures was studied for estimating cost-effectiveness ratios, net benefit and net cost measures in CEA.

4. **To apply and test procedures on existing data sets.** The investigators utilized the Michigan Inter-Institutional Collaborative heart (MICH) study, which is a prospective investigation of health care utilization and patient outcomes in admissions for acute myocardial infarction (AMI) to 5 mid-Michigan hospitals during the period January 1, 1994, through April 30, 1995. A second phase of the study was conducted in 1997 which examined similar outcomes after changes in medical management and treatment options for AMI were instituted in these hospitals. The primary objective of this study was to assess sources of variability by race and gender in the use of invasive cardiac procedures-cardiac catheterization (CATH), percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG), in the treatment of AMI. Analyses have been conducted to detect changes in long term-survival between patients in each phase.[22] The same study was also used to analyze hospital charges and length of stay by cardiac procedures, accounting for variations in patient characteristics such as age, gender, race, comorbidities and ejection fraction.[23,24]

Using data from previous published studies, the researchers also evaluated the effectiveness and cost-effectiveness of the implantable cardiac defibrillator (ICD). Estimates of life-expectancy of ICD patients have been compared with patients treated under electro-physiology guided therapy.[25-27]

Methodology for Analysis of Health Care Costs and Outcomes

With increasing attention being given to gathering and compiling economic data alongside clinical investigations, there is a need to develop rigorous statistical models and techniques to jointly analyze both costs and patient outcomes. Current methods generally focus on a single measure of cost or health outcome and do not fully exploit the longitudinal dynamic mechanisms that engender cost and outcome data. It is critical to understand how individual characteristics might impact summary measures, such as the cost-effectiveness ratio, as well as median cost and survival. This is paramount in predicting resource utilization and informing policy on allocation of health care dollars.

Gardiner *et al* apply a stochastic framework for estimation of summary measures in cost-effectiveness analyses. Stochastic modeling of patient health and cost outcomes is a useful tool in identifying and assessing the important individual characteristics that influence these outcomes. It is a critical step in cost-effectiveness analysis which aims to structure comparisons between competing health care interventions on both health outcomes and costs. Gardiner *et al* use a Markov process to describe the occurrence of patient events that unfold over time. States of the process represent health conditions or health states (i.e. well, ill, or dead). Commonly used measures in cost-effectiveness analyses, such as net health benefit, net health cost, cost-effectiveness ratio, life expectancy and quality-adjusted survival, are defined in terms of expected values of functions of the process. Costs are incurred through medical resource while sojourning in health state, and in transitions between health states. By combining these expenditures, Gardiner *et al* define net present value for expected total cost over a specified period of time. In this longitudinal framework, they describe statistical models for estimation of these summary statistics and quantifying the impact of important variables in the process.

Although more general processes can be utilized, Markov processes have been the main choice in decision analyses and CEA.[20,28-31] Markov models have become the paradigm for studying the progression of patients through various states following an intervention of treatment. The Markov property restricts the dependence of the future evolution of the process given the past, only to the most recent past. It is sufficiently flexible to permit modeling of both observable and unobservable patient-specific characteristics through the transition intensities, and assessing their impact on costs and outcomes.

In order to be useful in practice, data arising from cost measures and health outcomes must incorporate the dynamics of health care utilization as it manifests over time. There are several advantages of using a longitudinal model. Apart from its accurate description of an evolving patient history, it incorporates many of the critical elements that are needed to carry out cost-effectiveness analyses of interventions. A Markov process used to describe a patient's evolving history provides a rigorous basis for quantifying variation in costs and health outcomes.

Another advantage of the approach of Gardiner *et al* is that it separates the time dynamics of transition between health states and costs as they become known over time. From a statistical point of view, this allows for modeling costs using modifications of regression methodology applied to longitudinal correlated data. This also permits analyses of differential covariate effects on costs and transitions between health states.

Research Accomplishments & Impact on Translating Research into Policy and Practice (TRIPP)

Gardiner's research team has produced 25 peer-reviewed publications in health services research and clinical journals, invited presentations at professional meetings, and opportunities to

collaborate in new research ventures. Dr. Gardiner has demonstrated the application of his methods in practice with clinical and epidemiologic data. His methodological advances in CEA continue to be cited by other researchers with collectively over 250 citations. In the year 2006, the American Statistical Association honored Dr. Joseph Gardiner by inducting him as Fellow with the citation:

"*For development of statistical methodologies for cost-effectiveness analyses and health services research; for significant collaborations in public health, epidemiology, and health services research.*"

Dr. Gardiner is an Elected Member of the International Statistical Institute.

Cost-Effectiveness of the implantable cardioverter defibrillator

In a series of articles Gardiner *et al* developed the fundamentals for statistical inference on the cost-effectiveness ratio. The initial investigation was motivated by their study of the cost-effectiveness of the implantable cardioverter defibrillator (ICD). The ICD is an effective medical device in treating patients with severe ventricular arrhythmias and therefore at the risk of sudden death. These devices can detect ventricular tachycardia or ventricular fibrillation and restore normal heart rhythm, either through rapid pacing or by delivery of appropriate electrical shock. Improvements in ICD technology have increased the reliability and life of the ICD generator, reduced its size through micro-circuitry, and added features such as the capability of reprogramming of the device to individualize treatment, and memory to store information on time and level of electrical discharges. Delivery of the ICD technology is relatively expensive.

The researchers' study of the cost-effectiveness of the ICD was led by the prominent cardiologist Joel Kupersmith, MD. It followed their comprehensive study of cost-effectiveness

of treatments in heart disease. Four articles have to date been cited in over 165 publications.

1. Kupersmith J, Hogan A, Guerrero P, Gardiner J, Mellits ED, Baumgardner R, et al. Evaluating and Improving the Cost-Effectiveness of the Implantable Cardioverter-Defibrillator. *American Heart Journal* 1995;130(3):507-515.
2. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost-Effectiveness Analysis in Heart-Disease. 1. General- Principles. *Progress in Cardiovascular Diseases* 1994;37(3):161-184.
3. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost-Effectiveness Analysis in Heart-Disease. 2. Preventive Therapies. *Progress in Cardiovascular Diseases* 1995;37(4):243-271.
4. Kupersmith J, Holmes-Rovner M, Hogan A, Rovner D, Gardiner J. Cost-Effectiveness Analysis in Heart-Disease. 3. Ischemia, Congestive-Heart-Failure, and Arrhythmias. *Progress in Cardiovascular Diseases* 1995;37(5):307-346.

The research team continues to be actively engaged in studies related to newer technological improvements to the ICD and their impact on patient survival. Two recent publications in the area are

5. Evonich RF, Maheshwari A, Gardiner JC, Khasnis A, Kantipudi S, Ip JH, et al. Implantable cardioverter defibrillator therapy in patients with ischemic or non-ischemic cardiomyopathy and nonsustained ventricular tachycardia. *Journal of Interventional Cardiac Electrophysiology* 2004;11(1):59-65.
6. Soundarraj D, Thakur RK, Gardiner JC, Khasnis A, Jongnarangsin K. Inappropriate ICD therapy: Does device configuration make a difference? *Pace-Pacing and Clinical Electrophysiology* 2006;29(8):810-815.

Methodological studies in estimation of the cost-effectiveness ratio

When the CER is estimated from patient-level data it is important to gauge the precision of the estimate. Statistically this can be achieved by estimating the standard error of the estimated CER or providing a confidence interval for the CER. An enormous literature has been built to address this problem. The CER of a test treatment compared to its next best alternative (called the referent treatment or standard), is the ratio of its incremental cost relative to its incremental benefit. When comparing two treatments on their costs and health benefits, the significance of

the incremental benefit is often of primary importance followed by the significance of the incremental cost. Gardiner *et al* compare three popular parametric techniques for constructing confidence intervals for the CER. They demonstrate relationships between the three approaches and show how interpretation of the CER could be compromised when the incremental effectiveness of treatment is not statistically significant. Indeed, some researchers have argued that cost-effectiveness considerations should be postponed until the significance of effectiveness of a treatment compare to its competitor has first been established.

Their six publications in this area continue to draw the attention of researchers and have been cited in over 50 articles and research reports.

7. Gardiner J, Hogan A, Holmes-Rovner M, Rovner D, Griffith L, Kupersmith J. Confidence-Intervals for Cost-Effectiveness Ratios. *Medical Decision Making* 1995;15(3):254-263.
8. Gardiner J, Holmes-Rovner M, Goddeeris J, Rovner D, Kupersmith J. Covariate-adjusted cost-effectiveness ratios. *Journal of Statistical Planning and Inference* 1999;75(2):291-304.
9. Gardiner JC, Huebner M, Jetton J, Bradley CJ. Power and sample size assessments for tests of hypotheses on cost-effectiveness ratios. *Health Economics* 2000;9(3):227-234.
10. Gardiner JC, Huebner M, Jetton J, Bradley CJ. On parametric confidence intervals for the cost-effectiveness ratio. *Biometrical Journal* 2001;43(3):283-296.
11. Indurkhya A, Gardiner JC, Luo ZH. The effect of outliers on confidence interval procedures for cost-effectiveness ratios. *Statistics in Medicine* 2001;20(9-10):1469-1477.
12. Gardiner JC, Indurkhya A, Luo Z. The performance of estimation procedures for cost-effectiveness ratios. In: Balakrishnan N, editor. *Advances on Methodological and Applied Aspects of Probability and Statistics*. New York: Taylor & Francis, 2002:547-559.

Design of cost-effectiveness studies

The recent growth in conducting economic evaluation studies alongside traditional investigation of efficacy of treatments has led inevitably to considerations of appropriate sample size for demonstrating cost-effectiveness. For example, several recent randomized clinical trials on the ICD have collected the requisite patient-level data that would allow for subsequent economic analyses. Several researchers have proposed techniques for assessing sample size and

power for cost-effectiveness studies. Gardiner *et al's* formal statistically rigorous approach to this problem provides a framework for deriving statistical power and sample size expressions for testing different hypotheses on the CER.

Gardiner *et al's* manuscript # 9 was the groundwork for this approach. Tests of hypotheses on the CER were constructed from the net cost and incremental effectiveness measures. Their methods account for the correlation between cost and effectiveness and lead to smaller sample size requirements than comparative methods that ignore the correlation. Their arguments indicate that in commonly encountered circumstances, a study powered to demonstrate cost-effectiveness would require a substantially larger number of patients than that needed to show effectiveness alone. In the context of treatment trials this raises the ethical dilemma of continuing a study to gather data to test economic hypotheses after there is evidence of a statistically significant and clinically meaningful difference in treatment efficacy. Because the researchers' methods permit hypothesis testing on the CER in a trial powered for effectiveness, they can be used to compute the power for tests on the CER. The practical implication of these findings is that large scale clinical trials should collect whenever feasible pertinent data for economic information to conduct modest cost-effectiveness studies. Post-marketing surveillance studies used by most pharmaceutical companies and administrative databases on utilization maintained by insurance companies could be valuable resources for carrying out cost-effectiveness studies. However, the challenge is what methodological principles and practices should be applied so that the ensuing inference would be reliable and valid.

Gardiner *et al* recently updated and critically appraised the currently available techniques for assessing sample size and power for cost-effectiveness studies. Their review #13 below was

deemed one of the most read papers with over 95 full-text downloads from the website future-drugs.com maintained by the publishers Future Drugs Ltd of the *Expert Review.*{accessed 10/27/2006 http://www.future-drugs.com/action/showMostReadArticles}

13. Gardiner JC, Sirbu CM, Rahbar MH. Update on statistical power and sample size assessments for cost-effectiveness studies. *Expert Review of Pharmacoeconomics & Outcomes Research* 2004;4(1):89-98.

Methodological studies for costs and health outcomes in longitudinal studies

Longitudinal epidemiologic and clinical studies record events occurring in individuals over time. As a typical individual's history unfolds, one observes the time of occurrence of events and their type. Multi-state models are commonly used in this context to describe the evolution of longitudinal data. States defined as "well", "ill" or "dead" are the simplest description of a person's health history and forms the basis of illness-death models. In studies of survival one recognizes just two states, a starting state "well" and the final destination state, "death".

Multi-state models are well suited to study the dynamics of change in patient health over a period of time. They have also been advocated in analyses of quality of life data where multiple assessments of an individual's functioning are made (eg, physical and mental health functioning using the SF-36). The statistical framework for multi-state modeling is a stochastic process that describes the health states that a patient may visit. Typically, there are several transient states and one or more absorbing states. A transient state is one if visited would be exited after a finite sojourn, whereas an absorbing state is never exited once entered. To describe the dynamics of movement between transient states and sojourns, Markov models have been gainfully applied in several biomedical studies. The biostatistics and epidemiology literature is replete with

applications of these flexible models especially in evaluating treatment effects while adjusting for the influence of confounding explanatory variables.

Gardiner *et al* have used this same framework to incorporate costs. Costs may emanate from two streams. First, costs that are incurred at transition times. This would occur when there is a change in health condition that requires an additional use of resources. This change is often represented in the model by a transition from one transient state to another. An example from cancer follow up studies is a patient who previously was in remission but has now relapsed and requires additional surgery. A second type of cost is incurred while sojourning in a health state. The typical example here is a hospital stay. A patient may sojourn through several care units in the hospital (eg, ED, ICU, CCU, Recovery unit) before being discharged. The cost incurred is each unit would be different as different resources would be used.

In a series of articles Gardiner *et al* have discussed different aspects of this unified framework to carry out inference for cost-effectiveness studies. First, they built upon expanding the definitions of the commonly used measures in cost-effectiveness analysis to this new framework. These include life-expectancy, net present value, quality adjusted life years, net health cost, net health benefit and the cost-effectiveness ratio. The research team is hopeful that their recent publication (#23) would be useful to theorists and well as to practitioners of the craft of cost-effectiveness analysis.

14. Gardiner JC, Bradley CJ, Huebner M. The cost-effectiveness ratio in the analysis of health care programs. In: Rao CR, Sen PK, editors. *Handbook of Statistics, Bioenvironmental and Public Health Statistics*. New York: North-Holland, 2000:841-869.
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27. Luo Z, Goddeeris J, Gardiner JC, Lyles JS, Smith RC. Cost of a primary care intervention for patients with medically unexplained symptoms – a randomized controlled trial. *Psychiatric Services* 2007;58:1079-1086.

In (#24) Gardiner *et al* demonstrate the application of a dynamic model for estimation costs following treatments given to cancer patients. During the 2 year follow-up period, patients experienced episodes of normal physical function interspersed with periods of impaired physical function, before succumbing to death. The underlying process is modeled as a 3-state Markov process with states: normal function, impaired function, and dead. The researchers found that sojourns in the transient states were associated with different costs that also depend on the type of cancer (breast, colon, lung, or prostate) and the initial stage of their cancer diagnosis. In their

article (#25) the investigators provide mathematical details on how multi-state models can subsume many of the previously published analytic models for assessing cost and effectiveness. In (#26) they provide details on how standard statistical software can be used in estimation of multi-state models, and in (#27) they report on the relative cost of an intervention delivered in a primary care setting to patients with medically unexplained symptoms. The efficacy of this intervention had been previously published.[74]

Identification of Major Problematic Areas in CEA and How Gardiner's Research Is Addressing These Issues

As a result of my review of the literature, I have identified what I consider to be the major problematic areas in CEA. These are:

- The central problem seems to be a lack of standardization in CEA.
- CEAs can be complex and difficult to conduct due to inadequate representation of cost and effectiveness data. Many cost-effectiveness studies use complex models that rely on numerous assumptions where evidence is lacking or inconsistent.
- Current methods generally focus on a single measure of cost or health outcome and do not fully exploit the longitudinal character of data needed for CEAs and its impact on summary measures such as the CER as well as median cost and survival rates. These measures are paramount to predicting resource utilization and informing policy on the allocation of health care dollars.
- CEAs are often reported in a way that makes it difficult for users to understand how results are obtained.

- There are many difficulties in statistical analysis for CEA. Rigorous statistical techniques must be developed to analyze jointly both costs and patient outcomes.
- When differences in approach, assumptions, methods, and quality lead to conflicting conclusions, potential users may be confused and credibility of the CEA undermined.
- Inadequate attention to the design of cost-effectiveness studies can lead to inconsistencies.

With AHRQ's support, the research team led by Gardiner has taken several steps in addressing these issues:

- Despite the rapid development of techniques for conducting economic evaluation studies in medicine and health, the statistical methodology to support these studies is in the developmental stages. Gardiner's research formulates statistical models that inform identification of patient characteristics and resource-use elements that influence both costs and outcomes.
- Recognizing the natural setting in which cost and health outcomes would manifest over time, his current research addresses development of longitudinal models that incorporate covariate information and permit estimation of their impact on summary measures such as the CER and NHC.
- The Australian Pharmaceutical Benefits Advisory Committee guidelines on conduct of CEA[3] advise adoption of methods that are "responsive in differences in health states between individuals and to changes in health states over time experienced by any one individual." In addition, they also advise consideration of the impact of patient heterogeneity and sensitivity on results of a CEA. Gardiner's interdisciplinary team of statisticians, health economists, health services researchers and clinical investigators has

built a repertoire of publications addressing both applied and methodological issues in CEA.

- Many methodological developments are theoretically sound and can be tested on simulated data. In practice, these sophisticated methods have limited use unless they address the inherent problems in data sets commonly available to researchers from clinical and epidemiologic studies. These include problems with patient heterogeneity, skewness in cost distributions, incomplete follow up, truncation, censoring and sample selection. Gardiner's research team uses multi-state models for the dynamics of movement of patients through health states. They recognize the natural setting in which health outcomes and costs arise in practice, accounting for issues of censoring, truncation, and sample selection.
- The longitudinal framework that underlies their analytic techniques can be used to provide a complete specification of alternative models for estimating health care costs and outcomes.
- Gardiner's research methods and models offer practitioners of CEA a powerful set of tools for the improvement of statistical analysis of cost, health care utilization and cost-effectiveness data.

The flexible framework for stochastic CEA being developed by Gardiner and colleagues draw upon the following features:

- Recognizes that costs are stochastic and incurred at random times in random amounts as patients' transition between health states and sojourn in health states.
- Exhibits the role of discounting costs as they manifest over time.

- Defines all the summary measures used in CEA as functions of statistical parameters arising from the underlying probability model. These include, net present value, quality-adjusted life years, cost-effectiveness ratio, net health benefit and net health cost.
- Incorporates patient-specific explanatory variables (covariates) into the analysis, allowing for the assessment of their influence of summary measures used in CEA.
- Addresses the impact of sampling plans under which the data on costs and outcomes ensue in the longitudinal model, including the role of censoring and outcomes.
- Formalizes statistical inference on net present value, quality-adjusted life years, cost-effectiveness ratio, and net health cost by providing a rigorous basis for their estimation, as well as derivation of their statistical distributions. This allows for quantifying uncertainty in estimates through standard errors and confidence intervals.
- Permits testing of hypotheses on net present value, quality-adjusted life years, cost-effectiveness ratio, and net health cost. Given the data gathering mechanisms for costs and outcomes, this provides a comprehensive scheme for statistical inference based on these entities.
- Addresses design issues in CEA such as assessment of statistical power and sample size for planning of cost-effectiveness studies.

Summary and Significance of Gardiner's Research Findings Related to Translating Research into Policy and Practice (TRIPP)

- A comprehensive review[38] was published in 2004 addressing statistical issues in assessing statistical power and sample size for cost-effectiveness studies. This was at the request of the editors of *Expert Review of Pharmacoeconomics & Outcomes Research*

following their earlier work in *Health Economics*.[37] Their work in this area has led to collaboration with an international team of researchers in designing a study for evaluating the effectiveness and cost-effectiveness or treatment strategies for decreasing the burden of depression in developing nations.

- The issue of testing of hypotheses on cost-effectiveness ratios and assessing statistical power and sample size is addressed in an article in *Health Economics*. Following the pioneering work of O'Brien *et al*,[32] this was the first attempt to place hypothesis testing on CERs on a formal statistically sound framework.
- Gardiner's method incorporates the correlation between cost and effectiveness measures, and leads to substantially lower sample size requirements than methods that ignore the correlation. It complements the work by several other researchers.[39-41,73]
- An important element in reporting the results of CEA is to gauge the precision of estimates such as the CER. Gardiner's work compares three of the popular parametric techniques for constructing confidence intervals for the CER.[17] His work demonstrates relationships between the three approaches and show how the interpretation of the CER can be compromised when the incremental effectiveness is not statistically significant.
- In recognition of the work of Gardiner *et al* on statistical inference for CEA and its potential use in public health policy, the editors of the critically acclaimed *Handbook of Statistics* invited their contribution to a volume addressing *Bioenvironmental and Public Health Statistics*.[11] A summary is presented of how uncertainty in estimated parameters can be assessed by their sampling error and conventional statistical inferential techniques. These techniques can then be applied to problems of estimation, tests of

hypotheses, sample size, and power determinations in planning economic evaluation studies of health care programs.

- Gardiner's statistical method for assessing the cost-effectiveness of the ICD was the first to address construction of statistical confidence intervals for the CER from survival data.[25-27] His articles in the *American Heart Journal* and *Medical Decision Making* have received over 55 citations in professional literature.
- Gardiner's team continues their research in CEA to address the formulation of regression models that could inform identification of patient characteristics and resource-use elements that influence both costs and outcomes, and the cost-effectiveness of competing interventions. Applications are contemplated in cardiovascular studies and in cancer treatments studies. The methods could ultimately improve standardization in reporting the results of economic evaluation studies, and provide objective means for assessing subgroups in which an intervention could be cost-effective.
- Through experience with analyses of length of stay and cost in hospitalizations for heart failure, Gardiner *et al* have developed methods[20,23,24] to estimate the cumulative cost of health interventions over a specified duration while controlling for a mix of patient-specific variables. This method blends statistical and econometric techniques to address issues in the analysis of health care costs and allows for a greater use of total cost data, typically found in hospitalization records and claims files, that has not been previously attempted.
- Gardiner's research proposes a unified framework to estimate summary measures commonly used in cost analyses and CEA. These include life-expectancy, quality-adjusted life years, net present values, cost effectiveness ratios, net health cost and net

health benefit. Since patient demographics, clinical variables and intervention characteristics can affect these summary measures, regression models have been developed that incorporate covariate information into structural equations for cost and outcome measures.

- These regression models are uniquely designed to account for costs engendered at transition times between health states (e.g., changes in health state that trigger resource use), and costs of sojourn in health states (e.g., resource use while in remission, relapse, or different treatment phases). For health outcomes such as quality of life assessments, their longitudinal models incorporate patient heterogeneity and address the issue of censoring commonly found in these types of studies.
- In summary, several aspects and complexities in the analyses of health care costs and outcomes are incorporated into these models, and collectively these new methods promise useful application in CEA. Demonstration of these methods in practice with clinical and epidemiologic data is an equally important goal of their endeavors.

Future Plans related to Translating Research into Policy and Practice (TRIPP)

The methods that Gardiner *et al* described can be of considerable benefit in assessing patient health and cost outcomes stemming from new health initiatives such as economic evaluations of the implementation of Medicare Part D. The Medicare Prescription Drug Improvement and Modernization Act (MMA) was signed into law by President Bush in 2003. The MMA offers prescription drug benefits to Medicare beneficiaries and is the first substantial expansion of Medicare benefits in nearly 4 decades. With this expansion comes considerable cost—it is estimated that people aged 65 years and older spend approximately $2300 each year on prescription drugs. The net federal cost of the benefit is projected to be about $37 billion in 2006

and $724 billion from 2006 to 2015. Currently, prescription drugs account for about 17% of overall healthcare expenditures.

As new prescription drugs are approved by the Federal Drug Administration, cost-effectiveness considerations would be important. The Centers for Medicare and Medicaid Services (CMS) will continue to monitor the need to include specific drugs to in its Part D coverage. Plans now cover at least two drugs in each therapeutic class or category and provide access to a "broad range of medically appropriate drugs," including a majority of drugs within the following classes: antidepressants, anti-psychotics, anti-convulsants, anti-retrovirals, immuno-suppressants, and anti-neoplastics. Other countries that provide similar benefits to its citizens have adopted formal guidelines for the conduct of cost-effectiveness analysis. It is likely that prescription drug plans in the United States will also find it necessary to engage in methods of cost-effectiveness analysis in order to select drugs for its formularies.

Recently CMS has provided researchers informed access to the Medicare Part D Prescription Drug Event (PDE) database. The PDE is similar to an administrative pharmacy record database. It contains recipient-specific claim records submitted by Part D plans for each filled prescription. In addition to the standard information on insurance, coverage status and beneficiary copays, service and payment dates, the PDE identifies the drugs dispensed (from National Drug Codes), its quantity, and chemical compound codes. With some recipient identifiers, the PDE can be linked to demographic factors (eg, patient date of birth and gender), other Medicare service utilization and diagnoses. However, due to the sensitive nature of PDE the CMS requires researchers to have a formal data use agreement for specific analyses.

The methods that Gardiner *et al* have advanced can be of considerable benefit in assessing patient health and cost outcomes stemming from new health initiatives such as the MMA. The non-homogeneous Markov process can be used to develop a credible model of patients' longitudinal costs and health outcomes. This model is well-suited to inputs from administrative data such as Medicare claim files, which contain claims for health care services from inpatient and outpatient facilities, skilled nursing facilities, home health care, health care providers, and hospice providers. Claims data—particularly if combined with disease registries such as the Surveillance, Epidemiology, and End Results (SEER) cancer registry—can be neatly subdivided into disease states and health outcomes. An advantage of using the methods Gardiner *et al* describe along with claims data is it allows for the evaluation of costs and benefits in a dynamic framework where costs incurred in one area (eg., prescription drugs) may be offset by benefits in another area (eg., inpatient utilization).

In a limited capacity, the formal evaluation of pharmaceutical benefits is currently underway in many private health care plans. Policy initiatives such as the MMA will dramatically increase the demand for evaluation of health costs and outcomes data along with methods appropriate for the formal assessment of new health care interventions. We anticipate that benefit managers and policy analysts will become skilled experts at evaluating the methodological quality of cost-effectiveness studies. These experts will require methodological rigor along with model sophistication, which recognizes that health care costs and outcomes rarely occur in a deterministic environment. Sophistication in methodological development to meet these challenges via a copulation of statistical and econometric techniques seems inevitable. Markov models can serve as a basis of a longitudinal model for patient costs and health outcomes that

meets both methodological rigor and sophistication required to make decisions regarding the relative value of health care interventions.

The usefulness and versatility of cost-effectiveness analyses is not restricted to health care and medicine. In the regulatory environment policy makers have used cost-benefit analyses to assess the likely impacts of alternative regulatory strategies on human health and safety. Since 2003, the US Office of Management and Budget (OMB) has required agencies to supplement cost-benefit analyses with cost-effectiveness analyses when recommending changes to health and safety regulations. A recent report from the Institute of Medicine highly recommends the use of cost-effectiveness analyses for regulatory analyses in environmental, health, and safety regulation. One may conclude with some degree of conviction that the development of new methodologies for cost-effectiveness analyses will continue unabated. The challenge that lies ahead is their implementation and translation into practice that could ultimately benefit our society by optimally deploying our resources in the most efficient manner.

Research Products

Dr. Gardiner has produced several publications in peer-reviewed journals, abstracts and invited presentations at professional meetings. Listed below are the research products.

Publications

1. Gardiner J, Hogan A, Holmes-Rovner M, Rovner D, Griffith L, Kupersmith J. Confidence-Intervals for Cost-Effectiveness Ratios. *Medical Decision Making* 1995;15 (3):254-63.
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1. Guererro P, Hogan A, Gardiner J, Mellits D, Baumgardner R, Levine J, Rovner D, Holmes-Rovner M, Griffith L, Kupersmith J. Strategies to improve cost effectiveness of the implantable cardioverter defibrillator. *Clinical Research* 1993; 41(2):122a, presented.
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