DEVELOPING A COST-EFFECTIVENESS ANALYSIS OF ANASTROZOLE AND MEGESTROL ACETATE FOR THE PALLIATIVE TREATMENT OF BREAST CANCER

by

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Abstract

This thesis demonstrates the applicability of pharmacoeconomic analysis for two drug therapies used in the palliative treatment of breast cancer. The pharmacoeconomic evaluation explores the techniques that would be used in performing a cost-effectiveness analysis of anastrozole and megestrol acetate therapies. The thesis discusses the methods for collecting, interpreting, and extrapolating clinical and economic data. The analytical techniques include: measuring the effectiveness of breast cancer therapies, applying clinical decision analysis methods to produce a decision tree, reviewing clinical trial data and examining the clinical findings with the numbers needed to treat approach, applying survival data to a pharmacoeconomic evaluation, the valuation of resource items, constructing and using a costs and outcomes table, and calculating the cost-effectiveness ratio and the incremental cost-effectiveness ratio.

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Chapter 1

Introduction

This thesis will illustrate the methodologies that might be used in a pharmacoeconomic evaluation of two drugs for the palliative treatment of breast cancer. The technical aspects of the pharmacoeconomic evaluation will follow the Canadian Coordinating Office of Health Technology Assessment, Guidelines for Economic Evaluation of Pharmaceuticals: Canada (CCOHTA, 1997). The technical areas will include: the perspective of the evaluation, the measurement of costs and outcomes, decision analysis, the analytical time horizon, data sources, uncertainty of data, survival analysis, discounting of costs and outcomes, constructing a cost and outcomes cohort table, and the application of sensitivity analyses (CCOHTA, 1997).

The purpose of this thesis is to develop the analytical techniques needed to perform a cost-effectiveness analysis of anastrozole and megestrol acetate therapies. Hopefully, by developing the analytical techniques, more pharmacoeconomic evaluations on palliative breast cancer therapies will be performed. High quality pharmacoeconomic evaluations will play an important role in encouraging effective, efficient, and equitable drug therapy selection.

Chapter 1 will provide a short discussion on health and economics, pharmacoeconomics, and palliative breast cancer treatments. Chapter 2 will

review the components of the cost-effectiveness ratio, the incremental cost-effectiveness ratio, and the structuring of clinical data into a decision model. Chapter 3 will describe the problems with using randomized clinical trial data in a pharmacoeconomic evaluation. Chapter 4 will review the handling of survival information. Chapter 5 will describe the steps involved in collecting, tabulating, and presenting cost data. A costs and outcomes table for combining clinical and economic data will be provided. Chapter 6 will summarize the analytical techniques and the limitations of these techniques, in performing a cost-effectiveness analysis of anastrozole and megestrol acetate therapies.

Health and economics.

In western societies, much of the consumption of health resources is that which relies on new medical technologies. Economists are advocating the practice of evidence based medicine to ensure that the provision of health care and the use of new medical technologies is equitable, effective, and efficient. It is imperative that effective and economical therapies are promoted in order to ensure the users of our health care system receive the best possible medical care for the resources consumed.

Allocative decision making explores ways in which one can analyze the costs and the benefits of new medical technologies in order to best govern the distribution of scarce resources. Decisions concerning which medical technologies

should be supported by our health care system can be evaluated by using analytical methods taken from the disciplines of epidemiology, social sciences, medicine, economics, and pharmacy.

The method used to evaluate the clinical and economic value of drugs is pharmacoeconomics. Pharmacoeconomics involves the systematic and comprehensive analysis of costs and benefits of drug therapies in order to understand their impact on the health care system (Bootman, Townsend & McGhan, 1996).

Federal and provincial agencies, hospitals, pharmaceutical manufacturers, and universities perform pharmacoeconomic evaluations. A federal agency, the Patented Medicine Prices Review Board (PMPRB), uses clinical and economic information in order to determine whether drugs coming to market offer innovative therapies and whether the cost of those therapies is reasonable. The PMPRB uses pharmacoeconomic information to guide the establishment of Canada wide drug pricing policies. Drug pricing policies are established so that drugs are priced at what is believed to be a fair market value (PMPRB, 1996).

Provincial Ministries of Health use pharmacoeconomics to determine what medications should be available on provincial drug formularies and what medications should be available for government reimbursement. In British Columbia (B.C.), the Therapeutic Initiative and Pharmacoeconomic Initiative

evaluates drugs based on clinical and economic information. The Therapeutic and Pharmacoeconomic Initiatives membership is composed of physicians, economists, health policy experts, and pharmacists. The recommendations from these initiatives are used by the B.C. Ministry of Health to manage the provincial drug formulary and establish a reference based drug pricing program. The reference based pricing program sets a maximum reimbursable drug price for medications that are considered therapeutically equivalent.

While the Therapeutic and Pharmacoeconomic Initiatives evaluate drugs for the B.C. provincial drug formulary, the B.C. Cancer Agency and B.C. hospitals do not utilize such initiatives in their formulary review process. The B.C. Cancer Agency and B.C. hospitals perform few detailed pharmacoeconomic studies as they do not have the resources, or the expertise, that the Therapeutic and Pharmacoeconomic Initiatives have.

Canadian hospitals and cancer agencies also perform pharmacoeconomic evaluations. Hospitals and cancer agencies use pharmacoeconomics to measure the cost-effectiveness of drug therapies. Hospitals and provincial cancer agencies try to support drug therapies which offer clinically significant outcomes at a cost that the institutions can afford. Drug therapies that do not offer clinical outcomes that are not significantly better or where the costs are not less than other equally effective treatments, would not be considered.

Although there are numerous groups performing pharmacoeconomic evaluations, it is only recently that methodological guidelines have been developed. Analysts and users of pharmacoeconomic studies need to have a clear understanding of the methodological principles behind these evaluations. A clear understanding of the methodological principles will ensure that the pharmacoeconomic studies produce reliable and valid information.

In order to facilitate high quality pharmacoeconomic studies the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) has developed pharmacoeconomic guidelines (CCOHTA, 1997). CCOHTA guidelines divide the pharmacoeconomic evaluation process into: a pharmaceutical review of therapy, defining the perspective of the analysis, applying a methodology (e.g. cost-effectiveness analysis), identification and presentation of costs and consequences, measuring costs and consequences, discounting future costs and consequences, performing sensitivity analysis, and presenting the analysis.

Even with high quality data, a pharmacoeconomic evaluation should only be used as an aid in the decision making process. The primary purpose of pharmacoeconomics is to provide the decision maker with clinical and economic evidence that describes the outcomes of a particular intervention and how it will affect the distribution of resources. Pharmacoeconomics should not "replace hard

thinking, careful consideration, good judgment and common sense" (CCOHTA, 1994, p. 1).

Pharmacoeconomics of cancer therapies.

The screening and the treatment of cancer are under scrutiny by health administrators and government bodies because of the large amounts of resources that are being consumed. It is estimated that, in industrialized countries, expenditures on cancer treatments may account for as much as six percent of the gross national product (Jonsson, Clausen & Hansen, 1995). With the increasing numbers of elderly, with the growing exposure of the public to carcinogenic agents, and with improvements in the diagnostic testing of cancerous tumors, the prevalence and the costs of cancer related illnesses will continue to rise (Desch, Hillner, Smith & Retchin, 1993).

Recent attention has focused on how the best possible care can be provided to cancer patients while controlling rising costs. Hospitals, governments and cancer agencies are each trying to find ways to operate as efficiently as possible. Health professionals are being forced to find ways of reducing the consumption of scarce resources while still providing quality care.

While ensuring efficiencies in cancer treatments is paramount, researchers are concerned that there are apparent inequities in funding between different types of cancer treatments. Jonsson et al. (1995) believe that noncurative cancer

treatments are not receiving their fair share of resources. They believe that society has an obligation not to consider incurable cancers as a failure and limit its funding because of prognosis. They go on to state:

> ...we would like to point out that economic allocations and the distribution of resources in the treatment of cancer must be determined by the possible outcome of treatment; however, outcome and cure cannot be equated. We would also like to emphasize the conceptual errors that may be introduced by interpreting cure as 'success' and lack of cure as 'failure', interpretations that are too narrow. Stabilisation of incurable cancer for a period of time, together with the provision of a good quality of life, can itself be considered a satisfactory goal until curative therapy becomes available (p. 280).

Examples of incurable cancers that could receive improved therapies include testicular cancer, some hematological cancers, and metastatic breast cancer (Jonsson et al., 1995). The treatment of these cancers should be evaluated in the same way as curable cancers and the allocation of funds should be based on sound therapeutic and economic analysis. Pharmacoeconomic evaluations of the treatment of incurable cancers that could provide effective cytoreduction therapies need to be promoted.

Given this dilemma of equitable resource allocation and the fact that, when working with finite resources, one must concede some health benefits over others, determining how to choose where funds should be made available is a difficult task. Pharmacoeconomic analysis of cancer therapies should consider measuring outcomes that are meaningful to the specific disease states that are being studied.

For example, event free or disease free survival in curable cancers maybe a more appropriate outcome measure than quality of life. Event free or disease free survival is important when cytotoxic treatments in curable cancers are relatively short in duration compared to the remaining life years and the possibility of success (e.g., cure) outweighs the negative health effects received from the toxic chemotherapy (Jonsson et al., 1995).

For incurable cancers, quality of life and life-years gained are the best outcome measures for most pharmacoeconomic evaluations. Quality of life is important for two reasons. First, research has shown that cancer patients find that severe pain and confinement to a bed is regarded as worse than death (Hall & Tattersall, 1995). Second, when death is inevitable the toxic effects from the treatment may not be worth the gain in survival. Life-years gained would be an appropriate outcome measure for incurable cancer drug therapies where patients feel the extra time attributed to the treatment outweighs the adverse effects (Jonsson et al., 1995).

Although certain outcome measures are more applicable to specific types of cancers, deciding which measurement to use may not be easy. For example, the clinical data needed for the evaluation may not be collected, or the data used in a comparative analysis is not sensitive enough to detect differences between the treatment states being studied (Drummond, Stoddart & Torrance, 1993). In many

pharmacoeconomic evaluations, the outcome measure is quality of life and is considered a cost-utility analysis (CUA). A CUA allows the analyst to apply a utility score according to the quality of life that the patient experiences. In CUA, the outcome measure is expressed as a product of utility and length of survival. In its final form, a CUA is defined by the cost per quality adjusted life years (or QALY) (Bootman et al., 1996).

In the present thesis, the outcome measure of life-years gained will be used to examine which drug therapy, anastrozole or megestrol acetate, is the more cost-effective in treating advanced hormonally responsive breast cancer.

In cost-effective analysis (CEA), the outcome measure could be any clinically significant quantifiable effect that is common to the treatments being studied (Bootman et al., 1996). The costs and the effectiveness components are evaluated separately and then expressed as a cost-to-effectiveness ratio (e.g., cost per life-years gained). A cost-effectiveness ratio is determined for each treatment group and the difference between the two cost-effectiveness ratios is expressed as an incremental ratio. The components of the cost-effectiveness ratio and the specific calculations to arrive at the ratio will be provided later in the paper.

The survival outcome measure for each treatment group can be determined by utilizing clinical data from drug trials and/or from using epidemiological data from cancer registries. The basic strategies underlying the analysis include:

estimating the survival for each treatment group at specific points in time, determining the significance of the survival values, applying the survival rates for a hypothetical cohort of patients in each treatment group, running the cohort for a specified time, and performing a final count of patients for each group (Lee, 1980).

Unfortunately, it is only in the last few years that quality pharmacoeconomic studies of cancer therapies have been performed. Many of the methods used, such as measuring quality of life and the counting of cancer treatment related costs, need further development. Also, while clinical trials of cancer therapies provide valuable information regarding tumor cell response or time to treatment failure, researchers still have difficulty ascertaining the true value of such information (Rubens, 1996). Hopefully, pharmacoeconomic analysis of cancer treatments will promote the use of effective therapies and ensure that funding priorities are equitable.

Breast cancer therapies.

Breast cancer is the most common cancer found in women in Europe and North America. The highest incidence rates in the world are in Hawaii, California, and British Columbia (Veronesi, Goldhirsch & Yarnold, 1995). In British Columbia (B.C.) the estimated age standardized incidence of breast cancer is 121 cases per 100,000 women (National Cancer Institute of Canada, 1996), while in

Japan the estimated age standardized incidence is approximately 12 cases per 100,000 women (Veronsi et al., 1995). Women with breast cancer usually live longer than those with other common types of malignancies, such as lung and colorectal cancers. In Canada one in nine women will be diagnosed with breast cancer and one in twenty-five will die from the disease (National Cancer Institute of Canada, 1996).

Breast cancer is rare in women less than 30 years of age but, as age increases, the incidence rate also increases. Breast cancer usually appears as a slow growing painless mass until detected by physical examination or mammography. The final diagnosis is made by microscopic examination of the breast tissue. Treatment is determined by the extent of the disease and the woman's age. Treatment factors which are to be considered include: "the extent, pattern and aggressiveness of the disease, indices of likely hormone sensitivity, such as steroid receptor status, and menopausal status" (Rubens, 1996, p. 2). When there is no sign of the cancer involving peripheral sites the most common treatment is a lumpectomy, modified radical mastectomy, or a total mastectomy. After surgical resection further cytoreduction, such as radiation and/or chemotherapy, may be performed.

When the cancer has advanced and spread to the lymph nodes and other sites, the disease is said to be metastatic and treatment is considered palliative.

Veronesi et al. (1995) recommend that the treatment objective for metastatic breast cancer "should be to increase the total duration of time with no or few disease related symptoms using the therapy associated with the lowest cost in terms of side-effects" (p. 1274). Figure 1 illustrates a schematic for the treatment of advanced breast cancer in women.

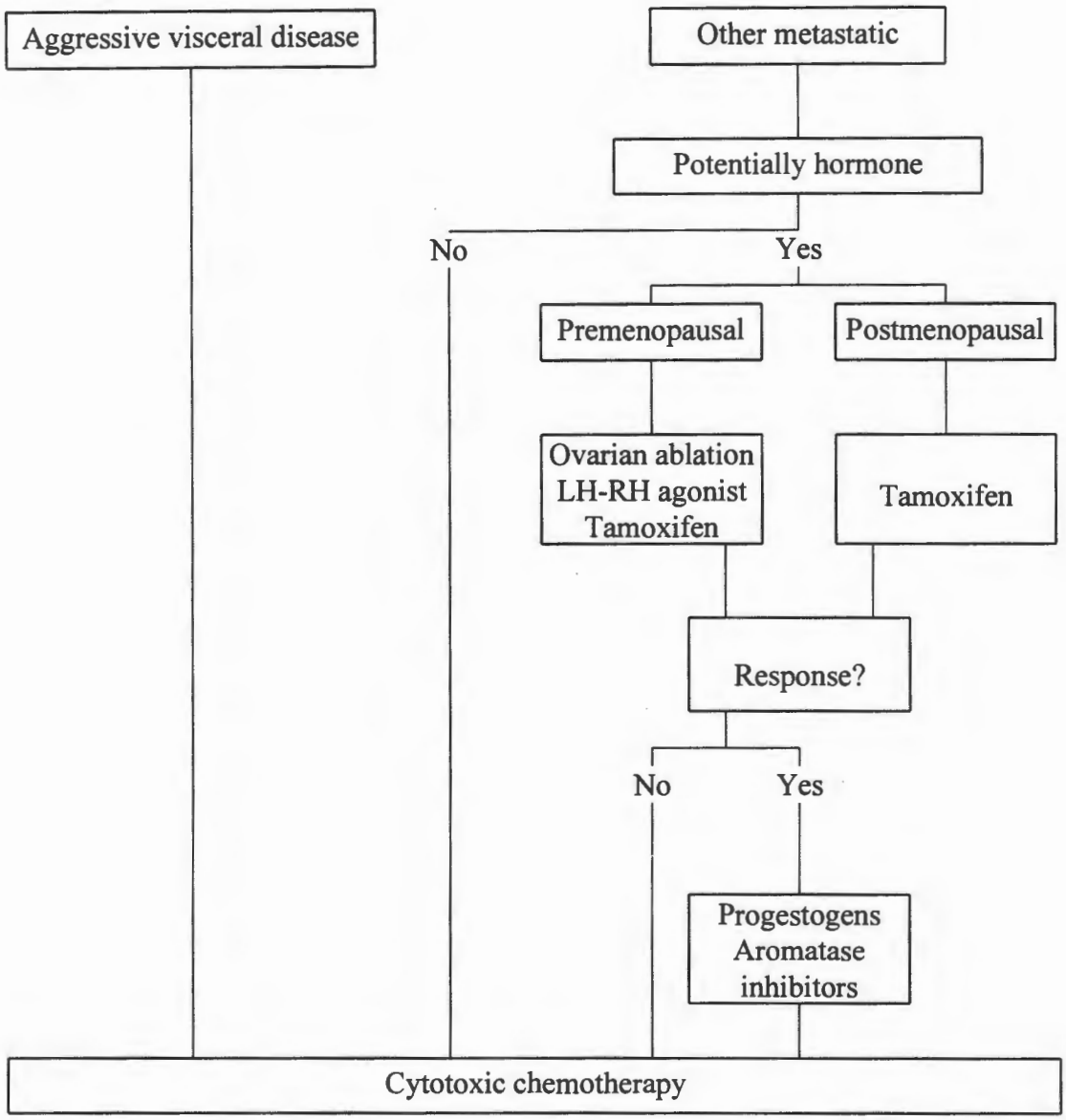

Figure 1 Treatment of advanced breast cancer. From "Key Issues in the Treatment of Advanced Breast Cancer: Expectations and Outcomes" by R. Rubens, 1996, Pharmacoeconomics, 9(Suppl. 2), p. 3.

Women with aggressive metastatic visceral breast cancer require chemotherapy to reduce the rapid progression of the disease. For less aggressive metastatic breast cancers, treatment is dependent upon whether the tumor's mitogenic activity is sensitive to the presence of estrogen. Women whose breast cancer is sensitive to estrogen are considered to have estrogen-positive tumors. These women make up the majority of breast cancer patients and have been shown to have an improved prognosis compared to women with estrogen-negative status (Veronesi et al., 1995).

For women with hormone responsive breast cancer, the primary treatment is altering the hormonal environment of the tumor. The course of therapy depends on menopausal status. Premenopausal women may undergo ovarian ablation or drug treatments with luteinizing hormone-releasing hormone (LH-RH) or tamoxifen. Postmenopausal women who are estrogen-positive will likely benefit from tamoxifen therapy. Tamoxifen competitively forms an estrogen receptor complex which blocks the growth stimulatory mechanisms controlled by endogenous estrogen. However, for some women, receptor mediated blockade will eventually regress and the tumor(s) will grow (Ruben, 1996).

Women who have responded to tamoxifen therapy and then show signs of failure, may experience secondary regressions from additional hormonal manipulation. It is postulated that tumor regression is a result of cellular

adaptation by the development of estrogen receptor mutations (Santen, 1996). The tumor cell may then be able to receive hormonal stimulation by mutating the receptor so that treatment with estrogen receptor antagonists (e.g., tamoxifen) are no longer effective. This may help explain why changing from an estrogen receptor antagonist, when regression develops, to a medication with a different mechanism of action may help delay further disease progression.

Third generation aromatase inhibitors may help to prolong survival in postmenopausal women by inhibiting the biosynthesis of estrogen (Zeneca, 1997a). Although circulating estrogen concentrations are low in postmenopausal women, tumor cells can receive estrogen from the peripheral aromatization from fat and muscle tissue and from local aromatization from the tumor (Brodie, 1996). Therefore, inhibiting estrogen biosynthesis at the peripheral and local level may help to reduce further tumor proliferation. The clinical trials of these third generation aromatase inhibitors suggest that they may be useful in first and second-line therapy (Smith & Henderson, 1996).

Due to the high costs associated with treating breast cancer, and the clinical uncertainty surrounding the benefits of the new pharmaceutical technologies, economic constraints are forcing provincial cancer agencies to limit access to third generation aromatase inhibitors. For example, the British Columbia Cancer Agency (BCCA) has restricted the use of the new aromatase inhibitor

anastrozole to "palliative treatment of hormonally sensitive metastatic breast cancer in patients who have progressed after tamoxifen and megestrol acetate treatment and have unacceptable side effects from aminoglutethimide" (BCCA, 1997, p. 1). Pharmacoeconomic analysis of third generation aromatase inhibitors will help to explore the costs and the effectiveness of this type of new therapy and assist provincial cancer agencies and Ministries of Health to decide how these new drugs fit into their current cancer treatment policies.

Chapter 2

Pharmacoeconomic Analysis

This chapter will describe the technical aspects involved in performing a pharmacoeconomic analysis. The chapter will discuss the cost-effectiveness ratio and the incremental cost-effectiveness ratio. Components that make up these ratios will be highlighted. The chapter will describe three clinical decision modeling methods for the organization of pharmaceutical data.

Developing the cost-effectiveness analysis.

The technical aspects involved in the development of a cost-effectiveness analysis can be divided into three categories. These are: the development and structure of the pharmacoeconomic problem; the assessment of methodological assumptions; and the evaluation of costs (Weinstein, 1981).

In the development of the research problem, the pharmacoeconomist needs to define the population of interest, the treatment options for the specific disease states, the risks and benefits associated with each treatment, and to assess the availability of data. The pharmacoeconomist must identify which intervention will be the comparator and determine what outcomes will be used to measure the drug's effectiveness. During the structuring phase of the evaluation a decision tree model serves as a useful method of structuring and describing the various treatment options and their outcomes.

The second part of a cost-effectiveness analysis is understanding how assumptions made during the early stages of the evaluation can affect the results. Economists recognize that a comprehensive evaluation of costs and health effects often leads to a large number of assumptions being introduced into the study (Weinstein, 1981). These assumptions create uncertainties that impact on the significance of the final results. Testing the significance of the assumptions is carried by sensitivity analysis.

Bootman et al. (1996) state that "sensitivity analysis is a method of determining whether the conclusion of an economic evaluation changes when the value of one variable is varied as all other variables are held constant" (p. 70). Sensitivity analysis is accomplished by first determining which variables contain uncertainty. Those variables with uncertainty are then assessed for the magnitude of the uncertainty and the study is re-run with the revised values (Siegel, Torrance, Russell, Luce & Weinstein, 1997). The results of the re-run study are compared to the original to determine whether the uncertainty had any impact on the findings.

The third part of the cost-effectiveness analysis is the measuring and reporting of all relevant costs and comparing those costs with the effectiveness portion of the analysis. Costs are determined according to the perspective used. The perspective is the point of view from which the analyst conducts the

evaluation. Pharmacoeconomic perspectives include the societal, the institutional, and the patient's. An analysis which uses the societal perspective would consider the consumption of resources for all members of society. Institutional and patient perspectives are more narrow in the evaluation of costs since they encompass only those costs which affect the institution or individual patient.

Costs can be broken down into direct, indirect and intangible categories. Direct costs are those that involve the transfer of money. For example, direct costs include capital costs, drug costs, laboratory costs, labor costs, and patient "out of pocket" expenses (Drummond, Stoddart & Torrance, 1993). Indirect costs are those that do not involve the exchange of money but that affect the use of other resources. For example, indirect costs include lost leisure time and time from work. Intangible costs are costs where no money is exchanged and the effect on the consumption of resources is either difficult to measure or, in dollar terms, is unquantifiable. For example, intangible costs include psychological loss and pain or suffering.

In pharmacoeconomic analysis, a comprehensive list of costs is gathered for each treatment. Final costs are then tallied and compared to the effectiveness of each therapy. The costs and the effectiveness for each treatment are represented as a ratio of costs to effectiveness. The cost-effectiveness ratio for this study is expressed as costs (in Canadian dollars) versus the effectiveness outcome (e.g.,

life years gained). Further economic evaluations may then be performed such as the calculation of an incremental cost-effectiveness ratio.

Components of the cost-effectiveness ratio.

The components of the cost-effectiveness ratio can be expressed as follows (Weinstein, 1977, 1980):

$$\frac{\Delta C}{\Delta E} = \frac{\Delta C_{Rx} + \Delta C_{SE} - \Delta C_{Morb}}{\Delta Y - \Delta Y_{SE} + \Delta Y_{Morb} + \Delta Y_{Symp}} \quad (1)$$

where: in the numerator ΔC_{Rx} is the direct costs of treatment (e.g., drug costs, drug administration costs, costs associated with laboratory tests), ΔC_{SE} is costs associated with the drug's side effects (e.g., nausea, vaginal bleeding), and ΔC_{Morb} is the savings associated with the prevention of morbid events (e.g., brain metastases). In the denominator ΔY is the change in effectiveness (e.g., change in life years), ΔY_{SE} is the adjustment for side effects, ΔY_{Morb} is the adjustment for a reduction in morbidity, and ΔY_{Symp} is the adjustment for the relief of symptoms (Weinstein, 1980).

In Equation 1 the net cost calculated in a cost-effectiveness analysis is represented by the numerator and the net effectiveness is determined by the denominator. Adjustments in the effectiveness component are determined by the

perspective and the methodologies used in the analysis. For example, modifying the effectiveness component of the ratio by applying adjustments for side effects, morbidity and the relief of symptoms is usually considered a cost-utility analysis. Cost-utility analysis allows the researcher to account for less tangible aspects of a person's well being. A person's well being is measured as a utility value. Utility values are applied to the effectiveness portion of Equation 1. Some methods used to determine utility values are the standard gamble, time trade off, healthy years equivalent, and willingness to pay techniques (Bonneterre, Schraub, Lecomte & Mercier, 1996).

CCOHTA (1994) recommends that, once the cost-effectiveness ratio has been calculated, the ratios for each drug therapy should be compared and expressed in incremental terms. The incremental cost-effectiveness ratio is the ratio of the difference between the net costs in the numerator and the difference between the net effectiveness in the denominator (Detsky, 1990). The incremental cost-effectiveness ratio is expressed in Equation 2.

$$\text{Incremental}\frac{\text{C}}{\text{E}} = \frac{C_1 - C_2}{E_1 - E_2} \qquad (2)$$

where: in the numerator C_1 is the net cost for treatment 1 and C_2 is the net cost for treatment 2. In the denominator E_1 is the net effectiveness for treatment 1 and E_2 is the net effectiveness for treatment 2.

The incremental cost-effectiveness ratio provides valuable information as it "reveals the cost per unit of benefit of switching from one treatment strategy (usually already in operation) to a new strategy" (Detsky, 1990, p. 151). For example, the cost-effectiveness ratio for drug A is $1,800 per 2.2 years of life, and for drug B is $1,500 per 1.9 years of life. The incremental ratio is calculated as follows:

$$\text{Incremental}\frac{C}{E} = \frac{\$1{,}800 - \$1{,}500}{2.2\,\text{years} - 1.9\,\text{years}} = \$1{,}000 \text{ per life year gained} \quad (3)$$

Since drug A costs $1,000 for each life-year gained over drug B, Drug B is more cost-effective.

Modeling and decision trees.

The most difficult aspect of carrying out a pharmacoeconomic analysis is first determining what information is required and second deciding how to organize the clinical and economic data. Pharmacoeconomic information will need to be structured into an analytical framework that will break the evaluation

into manageable units. The manageable units will first need to be defined, organized, and then presented in a comprehensive format.

Decision models are useful analytical tools for structuring a pharmacoeconomic evaluation. Decision models organize clinical and economic information into "its component parts so that they can be analyzed individually and then recombined in a systematic way" (Weinstein, Fineberg et al., 1980, p. 4). Decision trees, recursive decision trees, and Markov models are types of decision models used in structuring clinical and economic information. Decision models are used not only for systematically organizing pertinent data into a structured framework, but they can also assist in determining the likelihood of various treatment events occurring.

The decision tree is an analytic tool that tracks the options and the outcomes for each treatment group at a particular point in time. The decision tree contains decision nodes, chance nodes and treatment paths. The tree is structured from left to right starting with a decision node. The timing of the nodes and the paths which connect the nodes, correspond to the clinical course of the event (Weinstein, Fineberg et al., 1980).

Figure 2 illustrates a branch of a decision tree for the treatment of a patient with acute abdominal pain. Decision nodes are points where alternative actions are selected and are represented as squares. The first square in Figure 2 is a point

where a physician must decide to intervene immediately or wait six hours and monitor the patient's abdominal pain. The second square is a point where the physician must decide whether or not to operate. The lines connecting the first two decision nodes are treatment paths.

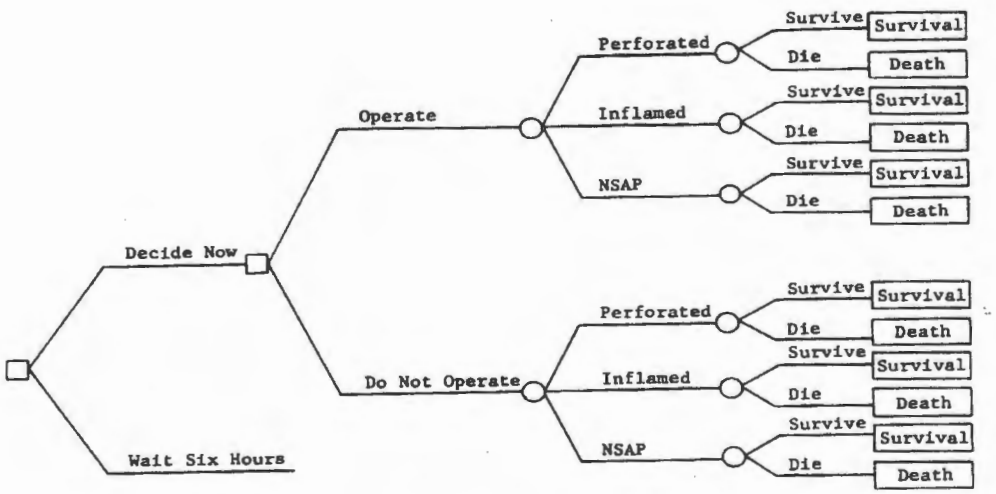

Figure 2. A decision tree branch for the treatment of a patient with acute abdominal pain. NSAP refers to nonspecific abdominal pain. From Clinical Decision Analysis (p. 15) by M. C. Weinstein, Fineberg et al., 1980, Toronto: W. B. Saunders Company.

Chance nodes are points where "one of several possible events beyond the control of the decision maker may take place. It is represented in a decision tree as a small circle" (Weinstein, Fineberg et al, 1980, p. 14). As shown in Figure 2, following the decision of whether or not to operate, the possible events are either

a perforated appendix, an inflamed appendix, or nonspecific abdominal pain (NSAP). Consequences of the three chance nodes branch out to two other chance nodes. Those chance nodes are survival and death.

A recursive decision tree is similar to a standard decision tree in that it outlines the events and outcomes in a systematic diagram. However, a recursive decision tree also provides a means of identifying events that are repeated throughout the clinical course. By including repeated events in the recursive tree the clinical problem can structured according to the time intervals (e.g., a month, or a year) at which these events occur. The cycling of the repeated events in a recursive decision tree helps to track their reoccurrence at various points in time.

Figure 3 shows a recursive decision tree. The chance events from anticoagulant therapy are represented by the first three nodes as bleed, embolus and no event. Bleed and embolus events can be fatal or non-fatal. Since bleed, embolus and no event may occur more than once, the tree structure repeats itself. Period 1 and Period 2 contain the same events in the same order but occur in a different time frame. However, complex analytical problems that are structured into a decision tree can become too large and impractical for modeling purposes. For example, Figure 3 would become too confusing if it extended past period 2.

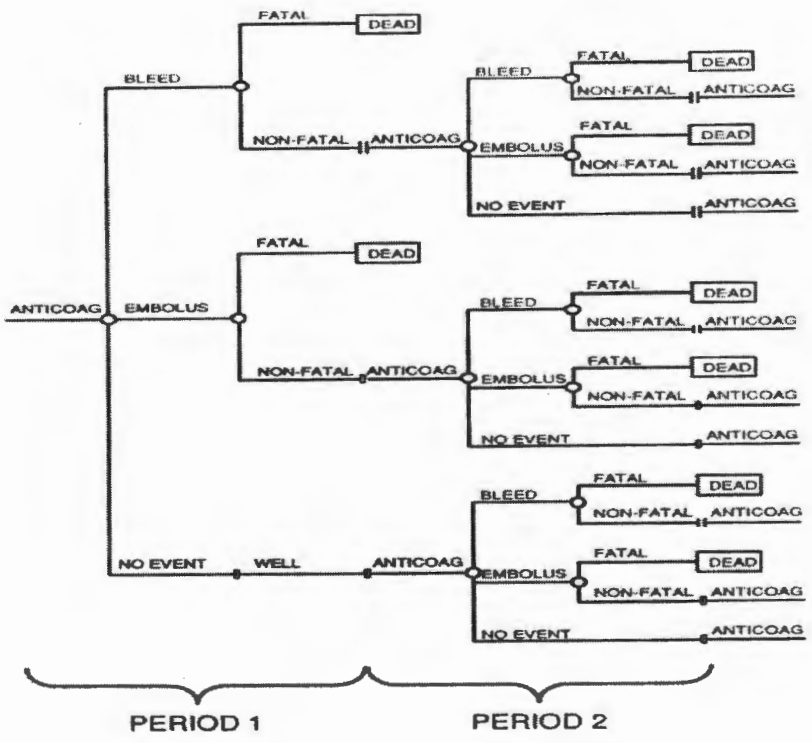

Figure 3. A recursive decision tree of anticoagulant therapy. Period 1 and period 2 is comprised of a main branch starting with bleed, embolus, and no event. From "Markov Models in Medical Decision Making: A Practical Guide," by F. A. Sonnenberg and J. R. Beck, 1994, Medical Decision Making, 13, p. 324.

Another way of structuring repeated health events is by using a Markov model (Briggs & Sculpher, 1997). The Markov model is similar to a recursive decision tree in that it structures events in chronological order and provides a means of documenting the cycling between repetitive events. The Markov model, however, limits the number of health states to only three or four events. More than four events would make the model cluttered and confusing.

Pauker and Kassirer (1987) describe a Markov model as a small set of health states with transitions between the states. The likelihood of changing from one health state to another is called transition probability. Figure 4 illustrates a "three-state Markov Model" where patients reside in any one of the three states and change to other states at different points in time (Beck & Pauker, 1983, p. 421).

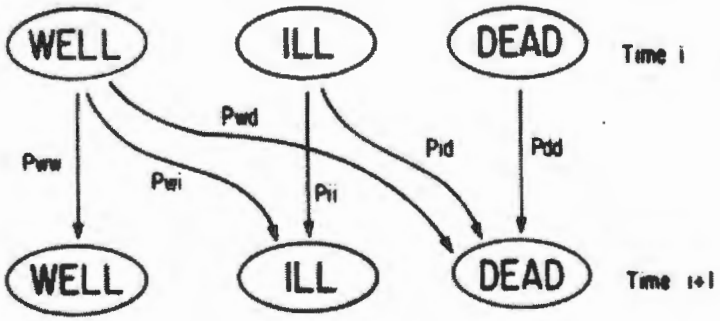

Figure 4. A three state Markov model illustrating transitional probabilities from time i to i+1 for the health states well, ill, and dead. From "The Markov Process in Medical Prognosis" by, J. R. Beck and S. G. Pauker, 1983, Medical Decision Making, 3(4), p. 421.

The three health states are well, ill, and dead. The model allows the patients to be in any one of the three states depending on whether their clinical problem requires them to be in that state (Beck & Pauker, 1983). The patients distribute to other health states according to the transition probabilities after a fixed amount of time. The transition probabilities are shown adjacent to the lines

flowing from one state to another. For example, the transition probability from the well state at time i, to the health state ill at time i+1, is designated as Pwi.

Whatever decision model that is used, the most effective method will incorporate all significant clinical events into a structured tool. Choosing the correct model, and the information to include in the model, should be based on a thorough understanding of the events and outcomes in each treatment group. Knowing how those events and outcomes occur over time, and which events and outcomes are clinically and economically significant, will provide the researcher with an understanding as to which model would be best suited to the pharmacoeconomic evaluation.

Once event or transitional probabilities are determined, a cohort simulation of a defined number of patients can be performed on the decision model. If the model is time dependent, such as with a recursive decision tree or Markov model, the patients would be distributed among the various events or health states after a set period of time (Sonnenberg & Beck, 1993). The simulation would be run until the time horizon is completed. The results of a simulation of a cohort can be tabulated and compared to the cost data.

Chapter 3

Clinical Data

There are many possible sources of clinical data for use in a pharmacoeconomic evaluation. Clinical data comes from randomized clinical trials, retrospective drug information from various databases, epidemiological data from the literature or databases, or from professional organizations or agencies. The primary source of clinical data for the anastrozole/megestrol acetate example used in this thesis could come from randomized clinical trials. This chapter will review the anastrozole/megestrol acetate randomized clinical trial data and how it would be used in a pharmacoeconomic evaluation. Although actual clinical data will be utilized in this chapter, hypothetical values will be used in later chapters for describing pharmacoeconomic calculations and tables.

Pharmacoeconomics and the randomized clinical trial.

A pharmacoeconomic evaluation relies on interpreting and extrapolating results from randomized clinical trials (RCTs). A RCT is required to demonstrate the safety and efficacy of new drugs. A RCT also provides a means of comparing new drug treatments to existing therapies. Drug therapies which have demonstrated at least an incremental advantage over existing therapies "usually require randomized comparison trials to demonstrate convincingly statistically significant improvement[s]" (Kaufman, 1993, p. 2801). The steps involved in

performing a RCT are: assignment of participants into treatment groups, assessment for defined endpoints or outcomes, analysis of the results, and interpretation of the findings (Riegelman & Hirsch, 1989). A RCT that has been carefully designed and has demonstrated a significant improvement in drug therapy is the basis for undertaking a pharmacoeconomic analysis since it is the source of data for the effectiveness data that is required.

Many of the recent advances in the treatment of progressive breast cancer have come from RCT data which have helped to identify safe and effective therapies (Kaufman, 1993). While RCTs have been "capable of identifying effective new therapies and eliminating ineffective, unnecessary, or harmful therapies," pharmacoeconomic evaluations have not kept pace with recent RCT information (Kaufman, 1993, p. 2801).

An overview of anastrozole and megestrol acetate randomized clinical data.

In order to determine whether a pharmacoeconomic analysis is justified, a close evaluation of the clinical findings is necessary. The assessment of the RCT data should consider the strengths and weaknesses of the findings and should consider that clinical trial data may not reflect real-life drug utilization patterns (Clemens et al., 1995). Clemens et al. comment on the problems of applying RCT data to pharmacoeconomic evaluations.

> Clinical trials are the primary source for efficacy data at approval. Clinical trials will generally be powered based on the primary clinical endpoint(s). Such trials may be under-powered for secondary end-points including resource use and cost data (p. 172).

Table 1 shows drug tolerability results from the RCT data for anastrozole and megestrol acetate (Zeneca, 1997b).

Table 1

The Incidence of Adverse Effects for Anastrozole and Megestrol Acetate

Adverse Event Group	Anastrozole 1-mg od (n=262)		Anastrozole 10-mg od (n=246)		Megestrol acetate 40-mg qid (n=253)	
	n	%	n	%	n	%
Gastrointestinal Disturbance (nausea, vomiting, diarrhea)	77	(29.4)	81	(32.9)	54	(21.3)
Hot Flushes	33	(12.6)	29	(11.8)	35	(13.8)
Edema	19	(7.3)	28	(11.4)	35	(13.8)
Thromboembolic Disease	9	(3.4)	4	(1.6)	12	(4.7)
Vaginal Dryness	5	(1.9)	3	(1.2)	2	(0.8)
Weight Gain	4	(1.5)	10	(4.1)	30	(11.9)

Note. From "Arimidex: a Significant Advantage in the Only Reliable Parameter - Survival," by Zeneca, 1997, Product Information Leaflet, Zeneca Pharma, Ontario.

The table shows that, overall, the number and types of adverse effects are similar for both drugs. There are, however, a few significant differences. In the anastrozole 10-mg group, women experienced greater gastrointestinal effects than the megestrol acetate group. However, in the megesterol acetate 40-mg qid group, women experienced greater weight gain than both of the anastrozole groups

(Budzar et al, 1996). Zeneca (1997a) reported that the megestrol acetate group had a greater number of participants who withdrew from the study for intolerable adverse effects than either of the anastrozole groups. The withdrawal rates due to adverse effects for the megestrol acetate 40-mg qid group was 4.0 percent, in the anastrozole 1-mg od group 2.7 percent, and in the anastrozole 10-mg od group 3.3 percent. However, there were no statistically significant differences in withdrawal rates between the three treatments (Budzar et al., 1996).

Critical appraisal and further analysis of the clinical data should be considered before proceeding with a pharmacoeconomic evaluation. It would be disheartening to find that the work of performing a pharmacoeconomic evaluation was wasted because the results reported were based on invalid RCT data or the new treatment offered no additional clinical benefit. For example, in the anastrozole 1-mg and 10-mg daily (od) and megestrol acetate 40-mg four times daily (qid) comparisons the phase III survival data indicates that the anastrozole 10-mg od treatment is less effective than the anastrozole 1-mg od treatment and also exhibits a greater number of adverse effects. A pharmacoeconomic evaluation of anastrozole 10-mg od is therefore not worth pursuing.

The RCT data presented by Zeneca suggested that anastrozole "is well tolerated and as effective as megestrol acetate for the treatment of postmenopausal women with advanced breast cancer" (Budzar et al., 1996, p. 2000). But before

proceeding with the pharmacoeconomic analysis a review of the findings is needed.

Table 2 highlights the survival differences for the anastrozole and megestrol acetate treatments after the median 31 month follow-up period.

Table 2

Summary of Survival Information for Anastrozole and Megestrol Acetate from Clinical Trials 0004 and 0005

Phase III Trial Number	Anastrozole 1-mg od	Anastrozole 10-mg od	Megestrol acetate 40-mg qid
0004			
Number of patients who died (%)	66 of 128 (51.6)	81 of 130 (62.3)	79 of 128 (61.7)
2-year survival rate	62.0%	58.0%	53.1%
Median time to death (months)	29.6	25.7	26.7
0005			
Number of patients who died (%)	85 of 135 (63.0)	70 of 118 (59.3)	92 of 125 (73.6)
2-year survival rate	50.5%	50.8%	39.1%
Median time to death (months)	24.3	24.8	19.8
0004 & 0005 Combined			
Number of patients who died (%)	151 of 263 (57.4)	151 of 248 (60.9)	171 of 253 (67.6)
2-year survival rate	56.1%	54.6%	46.3%
Median time to death (months)	26.7	25.5	22.5

Note. Phase III refers to a stage of clinical research where large numbers of human subjects are given new medications in order to evaluate their safety and efficacy. From "Arimidex: a Significant Advantage in the Only Reliable Parameter - Survival," by Zeneca, 1997, Product Information Leaflet, Zeneca Pharma, Ontario.

A total of 764 women were randomized into the study, 386 women in the North American trial (Canada and USA, trial number 0004), and 378 in the European trial (Europe, Australia and South Africa, trial number 0005) (Zeneca, 1997a). Women were randomized into one of the three treatment groups: anastrozole 1-mg daily, anastrozole 10-mg od, or megestrol acetate 40-mg four times daily. Women were routinely assessed by physical examination, by bone scans, and by radiographic examinations. Women were withdrawn from the trial if they experienced serious adverse effects, unwilling or noncompliant with procedures, or were found to have significant cancer progression (Budzar et al., 1996). Screening, drug tolerability and efficacy assessments were performed on a routine basis. Efficacy assessments included: time to treatment failure, tumor response, response duration and time to death (Zeneca, 1997a, Budzar et al., 1996).

The median time to death for anastrozole 1-mg od, anastrozole 10-mg od and megestrol acetate 40-mg qid was reported to be 26.7, 25.5 and 22.5 months respectively. The two year survival rate for anastrozole 1-mg od, anastrozole 10-mg od and megestrol acetate 40-mg qid was reported to be 56.4, 54.6 and 46.3 percent respectively. The results indicate that the anastrozole 1-mg od group had a median survival advantage of 4.2 months and 3.0 months over the anastrozole 10-mg od and megestrol acetate 40-mg qid groups respectively. The anastrozole 1-

mg od group was found to have a two year survival advantage of 9.8 and 1.5 percent over the anastrozole 10-mg od and the megestrol acetate 40-mg qid groups respectively.

Since RCT findings are reported in numerous ways, researchers are recommending that clinical trial information should be presented in a less confusing and a more standardized format (Laupacis, Naylor & Sackett, 1992, Therapeutics Initiative, 1996). Laupacis et al. (1992) suggest that "for clinical trials, a complementary and simple way to represent the difference between 2 groups emphasizes the clinical effect of the treatment being studied" (p. 12). They state that "the number needed to treat is a useful method of expressing the efficacy of a therapy because it incorporates the baseline risk in untreated patients, is easily calculated (the inverse of the absolute risk reduction), and allows an estimate of the effort and cost associated with the therapy" (pp. 13-14). Clinicians who use RCT findings that have been reported in terms of relative risk reductions have been described as being less critical about the results than if they were reported as absolute risk reductions or number needed to treat (Therapeutics Initiative, 1996).

In the anastrozole versus megestrol acetate case, the absolute risk reduction is calculated by taking the percent mortality rate for the megestrol acetate 40-mg qid group minus the percent mortality rate for the anastrozole 1-mg od group. The absolute risk reduction for women taking anastrozole 1-mg od for a median time

the 31 months was found to be 10.2 percent. This means that 10.2 percent fewer deaths were found to occur with the anastrozole 1-mg od group over the 31 month treatment period than with the megestrol acetate 40-mg qid group. The number needed to treat was found to be 10, which indicates that if 10 women were treated with anastrozole 1-mg od for a median duration of 31 months, instead of with megestrol acetate 40-mg qid, one death would be prevented. Table 3 outlines these findings.

Table 3

Analysis of Clinical Trials 0004 and 0005 Mortality Data for Anastrozole and Megestrol Acetate

Megestrol acetate 40-mg qid # of patients		Anastrozole 1-mg od # of patients		Absolute Risk Reduction	Number Needed to Treat
Total	Death	Total	Death		
253	171 (67.6%)	263	151 (57.4%)	67.6% - 57.4% = 10.2%	100/10.2 = 10

The phase III efficacy data, and the numbers needed to treat results, indicate that a 31 month median treatment with anastrozole 1-mg od demonstrates a survival advantage over that of the megestrol therapy. Although the RCT efficacy data "refers to the performance of a drug under highly controlled circumstances," a cost-effectiveness analysis of these two drug therapies is worth considering (CCOHTA,

1997, p. 20). However, it is important to recognize that the findings cannot be reliably extrapolated beyond the 31 month median follow-up period.

Chapter 4

Developing the Pharmacoeconomic Analysis

This chapter will discuss the study population and the time horizon for the pharmacoeconomic evaluation. Since CCOHTA recommends that a societal perspective should be used whenever an economic analysis is performed, the anastrozole/megesterol acetate example will be based on that perspective. Using the societal perspective ensures that all clinical and economic outcomes that have an impact on the study will be accounted for. Methods for determining the costs to the individual patient, the family, the hospital or agency caring for the patient, and to the government will be reviewed. A hypothetical list of direct and indirect costs, for developing the anastrozole/megestrol acetate evaluation, will also be discussed. Actual costs will not be gathered and so hypothetical values will be used for calculation purposes.

Study population.

In this example, the study population will be defined as comprising women with postmenopausal estrogen receptor positive breast cancer, whose disease has progressed while on tamoxifen and have switched therapy to either anastrozole 1-mg od or megestrol acetate 40-mg qid.

Method of evaluation.

The method of evaluation will be a cost-effective analysis. The effectiveness portion of the evaluation will consider the differences in survival between the two treatment groups. A cost-effectiveness ratio will be calculated from hypothetical cost and survival data and will be expressed as costs versus life years (time from start of therapy to death). An incremental cost-effectiveness ratio will also be described by using the cost-effectiveness information from each cohort. The incremental cost-effectiveness ratio will describe the cost per life-year gained for one cohort relative to another.

The multicentered, randomized anastrozole and megestrol acetate phase III trials, and the follow-up period information, will be used as the primary data source (Budzar et al., 1996, Zeneca, 1997a). Although Zeneca's clinical trial data contains time to disease progression, best tumor response, duration of response and duration of stable disease, only survival (i.e., time to death) will be included in the model. Extracting the retrospective data into the evaluation can be problematic and so limitations in the anastrozole and megestrol acetate data will be highlighted. Since phase III RCT data measures the efficacy of the treatments and not effectiveness, all assumptions made should "be explicitly and thoroughly tested with sensitivity analysis" (CCOHTA, 1997, p. 20).

Other sources of data could include: drug prescribing rates, clinic and drug costs, and epidemiological information from the British Columbia Cancer Agency; cost information from the Ministry of Health; drug prescribing and cost information from British Columbia Pharmacare; clinical and drug cost information from local hospitals; epidemiological information from Vital Statistics; and information from literature sources. The specific requirements for the types of data will become more apparent as the analysis progresses.

Time horizon.

When analyzing survival data, the most appropriate time horizon is to run the study until all the participants have died (Lee, 1980). In the 31 month median period approximately sixty-two percent of the women participants died. Most pharmaceutical company sponsored RCTs are run for the shortest possible duration while still being able to demonstrate statistically significant outcomes. In order to meet CCOHTA recommendations the time horizon should be extended "far enough into the future to capture the major clinical and economic outcomes related to the treatment under study" (CCOHTA, 1997, p. 18).

Since the ideal time horizon should be greater, modeling techniques are required to make up the missing data. It is important that modeled data be considered since the survival benefit for either anastrozole and megestrol acetate at greater than 31 months is unknown. If the clinical trial cannot be run until all

patients are absorbed then there should be good clinical evidence to support a shorter period.

In order to determine the time horizon for the modeled data, a review of other clinical data for hormonal therapy of progressive breast cancer is needed. The long term data from the National Surgical Adjuvant Breast and Bowel Project have shown that pre and post-menopausal women, with or without estrogen receptor positive breast cancer, receive significant benefit from taking tamoxifen for up to five years (Frankel, 1995). Treatment with tamoxifen greater than five years has be shown to provide no additional efficacy (Frankel, 1995). Applying a similar five year time horizon for this economic evaluation seems appropriate since treatment with the first line therapy has been demonstrated to be effective for a maximum of five years.

Chapter 5

Quality of Life and Survival

Most clinicians consider quality of life, or survival, as the most important criteria for evaluating cancer treatments. Although many cost-effectiveness analyses study both quality of life and survival together, in this evaluation only survival will be reviewed. Determining whether to include quality of life in a cost-effectiveness analysis of cancer therapies should be based on how much impact the treatment affects the patient's quality of life and whether the data is available.

Quality of life was not considered in this evaluation for two reasons. First, since treatment with hormonal therapy for progressive breast cancer results in fewer side effects than with cytotoxic chemotherapy, the effect on quality of life would be significantly less than other more toxic therapies. Most evaluations that have included quality of life have been for surgical or cytotoxic therapies where the intervention have a significant impact on a person's well being. Second, although quality of life data was gathered during the phase III trials, the information was not published by Zeneca due to inconsistencies in data collection.

In order to develop a better understanding of how anastrozole 1-mg od and megestrol acetate 40-mg qid impacts on survival, this chapter will examine concepts and methods used in survival analysis. This chapter will also review how participants of clinical trials are followed, what the identifiable starting point of

treatment is, how losses to follow-up affect the findings, and what methods are used to organize and interpret the survival results.

Survival analysis.

In Zeneca's phase III trials, women were entered into the study based on specific criteria: menopausal status, current medical status (e.g., other illnesses), type of breast cancer, and their current medical treatments. Once women met the selection criteria, they were then randomized into one of the three groups (i.e. anastrozole 1-mg od, anastrozole 10-mg od, and megestrol acetate 40-mg qid).

The date of randomization was used as the start date for treatment and was the point from which the duration of therapy was measured. The participants were followed until the end of the study or until loss to follow-up. The participants of the study may die before the end of the study, some may withdraw early, and some may be alive at the end of the trial (Lee, 1980).

The timing of the various events is central to the analysis of survival. Figure 5 illustrates how timing of crucial events and the censoring of data can occur in trials where survival is evaluated. Twelve fictitious subjects, identified as A through L, in a 36 month study are shown on the y-axis of Figure 5. Subjects who relapsed or died, are labeled with a R at the time of relapse. Subjects labeled with a L were lost to follow-up during the study. Subjects labeled with C were

censored. Censored subjects are those who where still alive at the time the study ended.

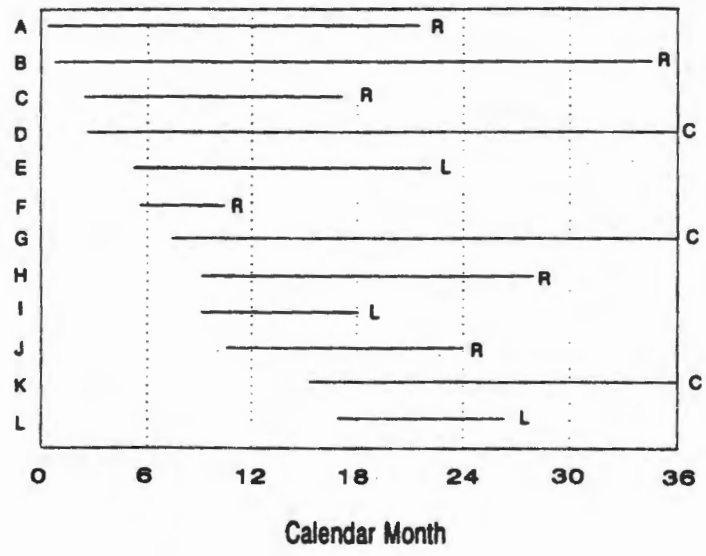

Figure 5. Time lines for twelve fictitious study participants. Participant's time lines ending with R died at that point in their treatment. Participant's time lines ending with L where lost during the study and those ending with C where alive at the end of the 36 months. From "'Stayin Alive': An Introduction to Survival Analysis" by, D. L. Streiner, 1995, Can. J. Psychiatry. 40, p. 439-444.

Figure 5 illustrates the problems with presenting the data as median survival time or relapse rate. Based on the figure, median survival time is determined from the study population of only those individuals who died during the trial period. For example, only the patients A, B, C, F, H and J would be used in calculating the median survival time (Streiner, 1995). Censored patients would

not be included. By excluding censored data the analyst would miss important information of who did not die and who dropped out of the trial.

Without examining the reason for assigning a patient to the censored category, the pharmacoeconomist may not be aware that the loss to follow-up could be related to the treatment the participants received. If the loss of follow-up was related to the treatment then the study would be underestimating the risk of therapy (Streiner, 1995). By not including censored participants, the median survival time calculation underestimates the benefit accruing to those who are most successful in their treatment (Luke, 1993).

Unfortunately, Zeneca's clinical trial data does not comment on patients who were lost to follow-up or who lived beyond the follow-up period (Budzar et al., 1996; Zeneca, 1997a). This is a concern since forty percent of the population were still alive at the end of the study. Since the number of participants lost to follow-up is also unknown the exact survival time cannot be determined. Unless there is more information regarding the censoring of data the pharmacoeconomist cannot be certain about the reliability of the results. Analysts need to ensure that survival probabilities are an accurate representation of all of the clinical data.

Using relapse rate as a measure of the efficacy can also be problematic. As with using median survival times, relapse rates do not take into account participants who were lost to follow-up or who were still alive at the end of the

study period. In order to accurately evaluate the survival data the pharmacoeconomist needs access to the "raw" RCT data. Raw data should contain basic information for each participant. The information should include the date of randomization, the participants' randomized treatment group, the date of death, and the date of loss to follow-up if it occurred. Information as to the reasons for loss to follow-up should also be obtained. Once this information has been gathered the analyst can then interpret the data by running it through one of the many computer programs that analyze survival information, or the analyst may organize the data into a statistical table and plot a survival curve. Unfortunately, the raw survival data was not available from Zeneca and therefore a thorough analysis of survival could not be performed.

Constructing survival curves.

There are two methods for constructing survival curves. The first method is called the product-limit method and is also known as the Kaplan Meier method. The product limit method is useful when the study population is less than 100 and the exact date of the event (e.g., death) being monitored is known (Lee, 1980). The analyst plots the exact point in time each participant died (Kaplan & Meier, 1958). The resulting curve "is simply the proportion surviving at various points in time" (Coldman & Elwood, 1979; p. 1065).

Figure 6 shows the Kaplan Meier survival curves for the anastrozole 1-mg od and megestrol acetate 40-mg qid therapies (Pritchard, 1997). The curves represent the overall survival data from the two clinical trials number 0004 and 0005. Time zero represents the point at which the women where randomized. As time increases along the x-axis the percentage of women surviving decreases. The curves provide a graphical representation of the survival data and help to depict the differences in survival between the two types of treatments.

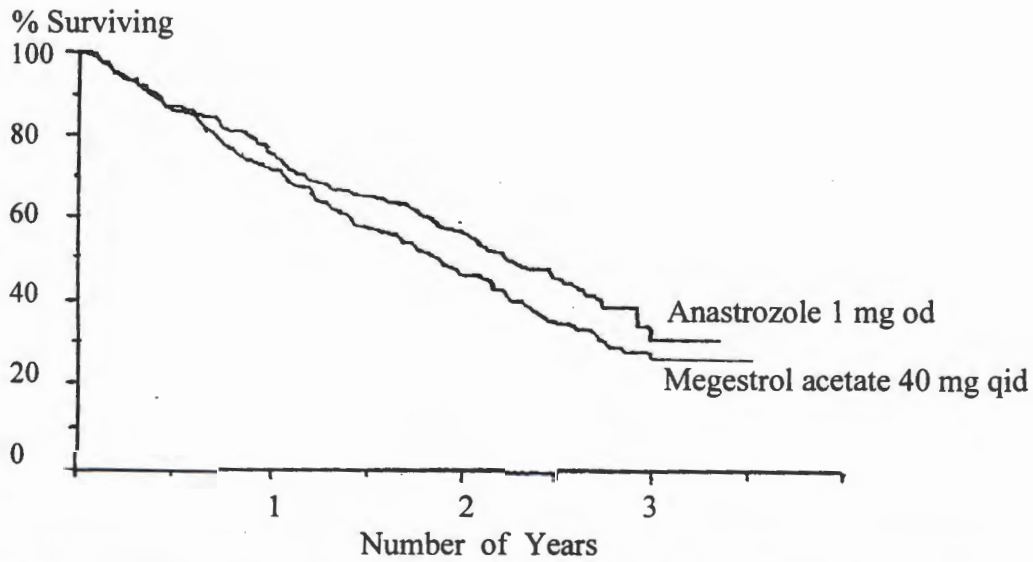

Figure 6. Survival curves from combined trials 0004 and 0005. From "Arimidex: A Significant Advantage in the Only Reliable Parameter - Survival" by, Zeneca, 1997, Product Information Leaflet, Zeneca Pharma, Ontario.

Another method of evaluating raw survival data is by using a life table. The life table method is useful when the time of an event (e.g., death) cannot be

accurately determined. The life table method is also useful when the study population is large (e.g., greater than 100) or when modeled data is required. Since the time horizon for Zeneca's randomized clinical trial should be extended, a life table method would be useful in producing the modeled data (Lee, 1980).

A sample of a life table is shown in Table 4.

Table 4

Life Table of 12 Fictitious Participants

Interval (months in the study)	Number at risk	Number died	Number lost to follow-up	Hazard	Proportion surviving	Cumulative proportion surviving	Probability density function
0-6	12	1	0	0.0833	0.9167	0.9167	0.0764
6-12	11	0	2	0.0000	1.0000	0.9167	0.0000
12-18	9	2	1	0.2353	0.7647	0.7010	0.1649
18-24	6	2	1	0.3636	0.6364	0.4461	0.1622
24-30	3	0	1	0.0000	1.0000	0.4461	0.0000
30-36	2	1	1	0.6667	0.3333	0.1487	0.0991

Note. From "'Stayin Alive': An Introduction to Survival Analysis" by, D. L. Streiner, 1995, Can. J. Psychiatry. 40, p. 441.

Table 4 represents the data from the fictitious study of 12 people previously shown in Figure 5 (Streiner, 1995). The life table contains the number of participants at risk, the number who died, the number lost to follow-up, the hazard (the proportion of participants at risk of dying during a specific interval), the proportion of participants surviving, the cumulative proportion of participants

surviving, and the probability density function (probability of a participant dying in a specific time interval).

The hazard ratio, shown in the fifth column of the table, is a useful statistic for comparing the survival experiences of two or more treatment groups. Unlike survival rate or median survival time, the hazard ratio incorporates all of the participant data whether censored or not (Mathews & Farewell, 1985). A hazard ratio is calculated from data over time and, unlike other descriptive survival statistics, reflects the whole treatment period. A hazard ratio of 0.5 indicates that the risk of death is one-half the hazard ratio of 1.0. A hazard ratio of 1.0 indicates there is neither an increased nor decreased risk of death. A hazard ratio of 1.5 suggests a 50 percent increase in risk (Pritchard, 1997).The hazard ratio is calculated according to equation (4) as follows:

$$\text{Hazard} = \frac{\#\text{ of people who died during the interval}}{\#\text{ at risk} - \frac{\#\text{ lost during follow-up}}{2}} \tag{4}$$

For example, the hazard ratio for the 18 to 24 month interval would be calculated as:

$$\text{Hazard} = \frac{2}{6 - \frac{1}{2}} = 0.3636 \tag{5}$$

The proportion of participants at risk of dying for the 18 to 24 month interval is 0.3636, or 36 percent. The only interval with a greater hazard ratio is the 30 to 36 month interval (i.e., hazard ratio is 0.6667).

The hazard ratio accounts for participants who were lost during the follow-up by assuming that the participants lost were at risk for one-half the interval. This is why in equations 4 and 5 the number lost to follow-up is divided by two (Streiner, 1995; Lee, 1980). The proportion of participants surviving is equal to one minus the hazard ratio. The cumulative proportion of participants surviving in the first interval is the proportion of participants surviving in the first interval multiplied by one. The cumulative proportion of participants surviving in the second interval is the proportion of participants surviving in the second interval multiplied by the cumulative proportion of participants surviving in the first interval, and so on for the remainder of the table (Streiner, 1995). The probability density function is the hazard ratio multiplied by the cumulative proportion of participants surviving for each interval.

The cumulative proportion of participants surviving is also known as the survival function and when plotted against time is known as the survival curve (see Figure 7 for the survival curve of the data represented in Table 4). Plots of the hazard ratios and the probability density functions can also be graphed against time. These two types of graphs help the analyst understand how the study

population's risk of dying during a particular treatment varies over time. For most treatments, where survival is the outcome being measured, the risk of death will increase and decrease over the treatment period (Lee, 1980). Understanding how the risk of death changes over time provides the analyst with additional information as to the treatment's effectiveness.

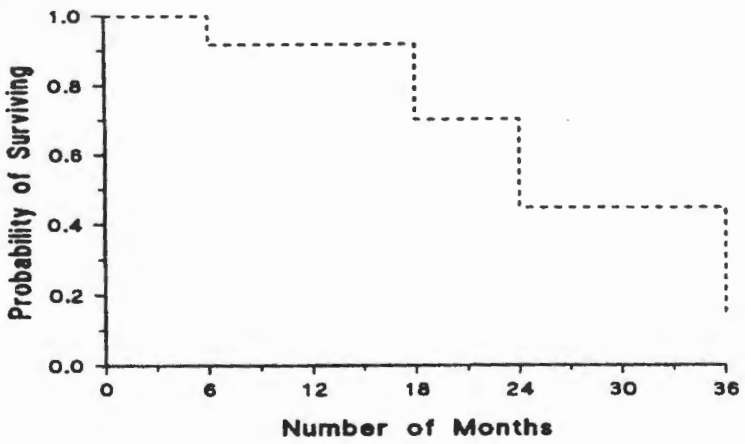

Figure 7. Survival curve for 12 fictitious participants. From "'Stayin Alive': An Introduction to Survival Analysis" by, D. L. Streiner, 1995, Can. J. Psychiatry. 40, p. 442.

Modeled data.

Extending the survival curve past the available data can be accomplished by using analytical modeling procedures (CCOHTA, 1997). Estimating future data points on the survival curve can be carried out by using the survivorship, probability density, and hazard function information. This information provides the pharmacoeconomist with an understanding of which analytical model would

best estimate the survival distribution. The analyst would choose the model according to a detailed understanding of the data or by fitting the model to the survival, hazard or density curves (Gehan, 1975). The validity of the model is checked by testing the goodness of fit between the model and the curves. Choosing and testing an analytical model is beyond the scope of this paper. The reader will find Lee (1980), Gehan (1975), and Buyse et al (1984) are key references for creating and handling modeled data.

Evaluating survival curves.

The analyst should also be aware of the shapes of survival curves and the information they provide. Figure 8 shows three different curves.

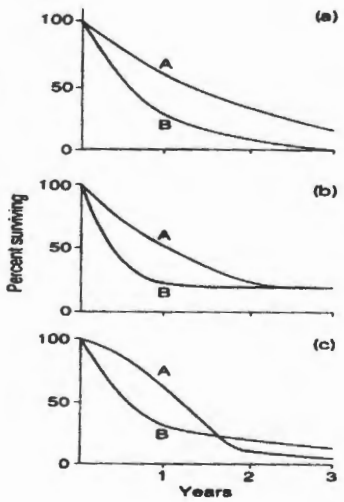

Figure 8. Comparing three sets of survival curves for treatment A and B. From "Cancer clinical trials: methods and practice," by M. E. Buyse, M. J. Staquet, and R. J. Sylvester, 1984, Toronto, Oxford University Press, p. 383.

The survival curves of anastrozole 1-mg od and megestrol acetate 40-mg qid therapies shown in Figure 6 are similar in appearance to curve (a) as the anastrozole 1-mg od curve lies above the megesterol acetate curve and separates as time increases. The anastrozole and the megestrol acetate curves are different to curve (a) as they have less separation and that the percentage of participants surviving does not reach zero. Curve (a) indicates that treatment A is uniformly superior to treatment B over the entire life of the participant. In curve (b) death occurs more quickly than with treatment B, but the long term use of either treatment results in the same proportion of people dying. Since the proportion of participants surviving greater than three years is unknown in the anastrozole/megestrol acetate case, the pharmacoeconomist cannot be certain whether the anastrozole curve will not follow the same shape as curve (b) or curve (c). Curve (c) indicates that treatment A is initially superior to treatment B, but treatment B is more superior over the long term than treatment A. Being aware of the potential long term consequences of these types of drug therapies is important to consider when evaluating their effectiveness.

Not only do survival curves provide a useful graphical representation of the data but they can also be used to estimate the proportion of participants surviving. Knowing the proportion of people surviving is valuable information.

Survival probabilities at various points in time can be estimated and used in the decision model. The probability information would be used to describe specific survival outcomes for the treatments under investigation.

Estimating the proportion of participants surviving can be extrapolated directly from the survival curve. Determining survival probabilities from extrapolating the data from a curve brings with it considerable error or uncertainty. Buyse et al. estimate that, when using survival curves to determine the proportion of participants surviving, the "range in error of the curve at a given time is roughly $\pm 1/\sqrt{(N')}$, where N' is the number of participants who have either already died or are followed up to that time" (Buyse et al., 1984, p. 368). A two year survival rate for megestrol acetate extrapolated from the survival curve would be approximately 46%. Using the above equation: $\pm 1/\sqrt{253} = \pm 0.06$, the true survival rate would be somewhere between 40 and 52%.

A z-test allows the analyst to compare the probability of survival for two treatments at a single point in time. The analyst would be able to use the survival data already gathered in the life table to determine whether there is a significant difference in survival between the two therapies. The z-test equation is as follows (Streiner, 1995, p. 442):

$$z = \frac{P_1 + P_2}{\sqrt{[SE(P_1)]^2 + [SE(P_2)]^2}} \quad (6)$$

The cumulative proportion surviving at a specific point in time for the two treatments are P_1 and P_2 (this data is already collected in the life table). The standard error (*SE*) for treatment number one is (Streiner, 1995, p. 442):

$$SE(P_1) = P_1 \sqrt{\frac{1 - P_1}{R_1}} \quad (7)$$

The value of R_1 is the number of the study population who are at risk at a specific point in time for treatment number one. The standard error for the second treatment group would be calculated the same way as the first treatment. If the value for z is found to be 1.96 or greater, then there is strong evidence (at the 0.05 significance level) that the probability of surviving between these two types of therapies are different (Streiner, 1995). If the value for z is less than 1.96 then the probability of survival for the two treatments at the point in time does not differ at the 0.05 level of significance.

Chapter 6

Organizing and Presenting Clinical and Economic Data

This chapter will discuss the three final steps in the pharmacoeconomic evaluation of anastrozole and megestrol acetate. It will first describe the construction of an anastrozole/megestrol acetate decision model, following which it will review the collection, tabulation, and presentation of cost data. A costs and outcomes table will be used to organize the clinical and economic information and provide the basis for the calculation of cost-effectiveness ratios.

Decision model.

The anastrozole and megestrol acetate randomized clinical trial information will be used to construct a decision model. The decision model will quantify the life years gained for a hypothetical cohort of patients receiving anastrozole or megestrol acetate therapies. The model will include clinical events that track and quantify the amount of life patients receive over the five year time horizon. The clinical events will include the loss of patients to death and the loss of patients to drop-out. Patient drop-out may result from disease progression and/or drug induced adverse effects.

A recursive decision tree will be used to track the probability of fatal and non-fatal events occurring throughout the five year time horizon using one year periods. The probability of fatal events (i.e., death) for each drug therapy, will be

estimated from survival data. The probability of non-fatal events (e.g., patient drop-out) will be estimated from drug utilization data obtained from provincial cancer agencies, by using epidemiologic information, or by informed guesswork (Weinstein, Fineberg et al., 1980).

Figure 9 illustrates the main branch of the recursive decision tree.

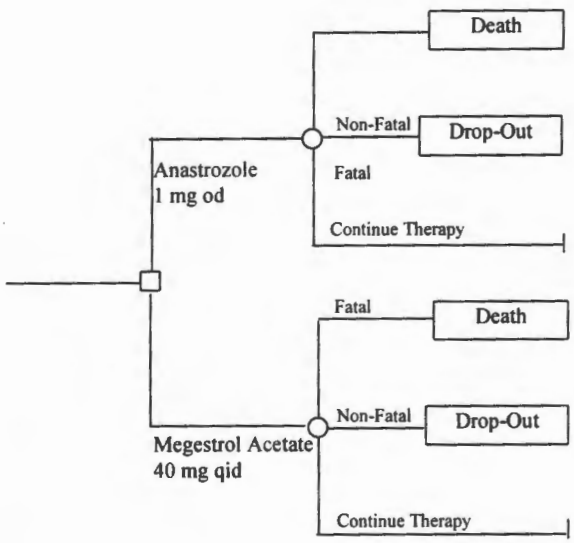

Figure 9. Main branch of the recursive decision tree for anastrozole 1-mg od and megestrol acetate 40-mg qid therapies.

The main branch starts with a decision node that is represented as a square and is the point at which the anastrozole 1-mg od or megestrol acetate 40-mg qid therapy is selected. Down the treatment path from the decision node is a chance node. The chance node is depicted as a circle and branches out to a fatal event, a non-fatal event, and a "continue therapy" path. The fatal event ends with the outcome

"death". The non-fatal event ends with the outcome "drop-out". The "continue therapy" path represents all patients who would move on to another period of drug therapy. The outcome of the non-fatal treatment path is labeled drop-out as patients who are considered as using other therapies are still alive and are no longer tracked in the model. Patients who drop-out include those who have experienced ineffective or intolerable drug therapy.

Figure 10 shows a five year recursive decision tree for anastrozole and megestrol acetate.

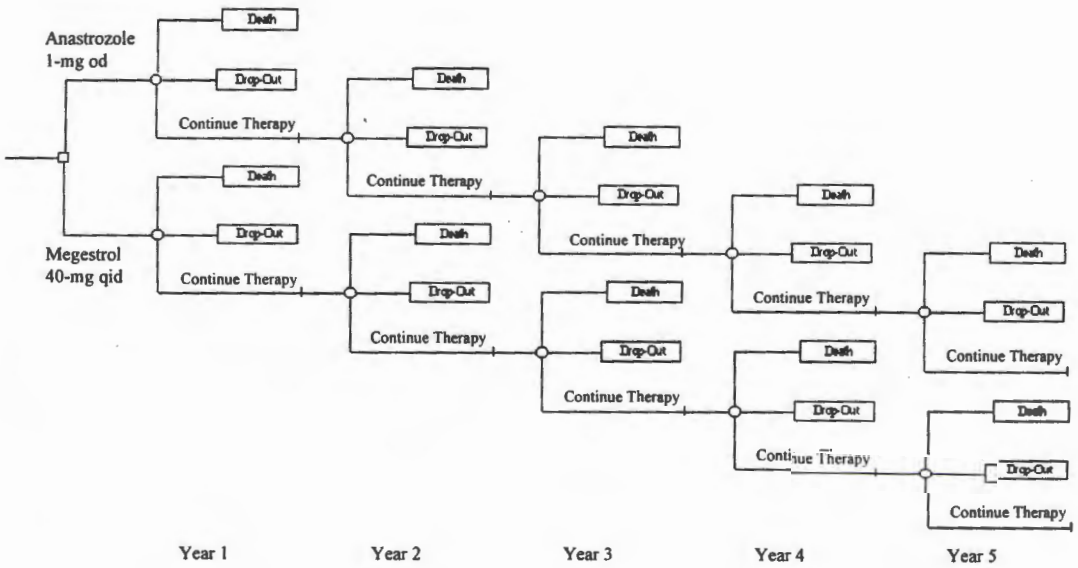

Figure 10. Five year recursive decision tree for anastrozole and megestrol acetate.

In the five year tree the main branch represents a one year period and is repeated five times. Patients who continue therapy from the first year enter the second year and distribute between the fatal and non-fatal events and the "continue therapy" path. The remaining patients continue to distribute between the two events and the one path until the end of the fifth year.

Determining the cost of therapy.

Determining costs in a pharmacoeconomic evaluation involves three main steps: (1) identifying the types of resources consumed, (2) measuring resource consumption, and (3) placing a dollar value on resource consumption.

Identifying the types of resources consumed can be determined from a detailed examination of the events found on the decision tree. The costs attached to fatal events, nonfatal events, and the continue therapy path can be separated into medical, non-medical and indirect expenses. Medical costs would be divided into costs for therapy and costs for treating adverse effects. Non-medical costs would include travel expenses, accommodations, food, and telephone. Indirect costs would include the loss of earned income by the patient or their families.

Measuring the costs associated with caring for the patient's additional years of life that result from the treatment would not be included. CCOHTA believes that "costs associated with persons living longer and consuming health care resources are subject to debate" and should not be included (CCOHTA, 1996, p. 12).

A detailed review of consumable resource items affecting medical, non-medical and indirect expense groups will need to be performed. A list of consumable resource items and the sources of cost information are provided in Table 5.

Table 5

Resource Item List and Sources of Cost Information

Resource Item	Sources of Cost Information	Comments
Physician fees or salaries	-Provincial fee schedules. -Canadian Institute for Health Information (CIHI) National Physician Database.	-In some instances, physicians are paid on salary. -Cost per service.
Nursing services	-Victoria Order of Nurses (VON) offices.	- Use cost per intervention.
Clinic services or Home care services	-VON and fee schedules from provinces. -National health expenditure survey. -Could allocate costs for heating, lighting, housekeeping, etc. based on size of clinic.	-No classification system for fee schedules in place. -Could use hourly rate.
Laboratory and diagnostic tests	-Fee schedules are available from the provinces.	-Cost/test should be used. -Private and public costs differ.
Medical imaging	-Provincial fee schedules available.	-Use cost/exam.
Drugs (hospital, cancer agencies)	-Hospital or cancer clinic pharmacies. -Hospital drug contracts.	-Cost should be at invoice price plus overhead charges.
Drugs (Pharmacy services)	-Patented Medications Prices Review Board and provincial price information. -Individual pharmacies.	-Co-payment must be accounted for according to the perspective of the analysis.
Medical supplies	-Retail or manufacturer pricing.	-Use cost/item.
Lost wages	-Employer salary costs including benefits.	-Use hourly rates.
Out-of-pocket expenses	-Collected by questionnaire Encompass items paid out by patients and/or family.	-These costs may include non-medical costs.

Note. From "A Guidance Document for the Costing Process" by, CCOHTA, 1996, Ottawa: National Library of Canada. pp. 6-11.

Once resource items have been identified, the next step in the evaluation is to determine the dollar values. There are different methods that can be used to

determine the value of resource items. Whatever the method chosen, each technique "entails a certain amount of complexity, time and effort and yields a certain precision" (CCOHTA, 1996, p. 5). CCOHTA (1996) describes the challenge of valuing resource items as "strik[ing] the appropriate balance between the need for precision and the avoidance of bias and the effort needed to provide the increased precision" (p. 5).

When performing the cost analysis the pharmacoeconomist should consider pricing some resource items according to their opportunity cost. The opportunity cost is "the value of the foregone benefits because the resource is not available for its best alternative use" (Drummond et al., 1993, p. 41). For example, the opportunity cost for a family member to provide home care to an ill patient would be the family member's lost wages, plus any other costs or loss of revenue that the family member might incur while providing care.

The cost per unit of output is useful for evaluating the consumption of resources for many items since it assigns a monetary value to the consumption of specific resource units. Examples of cost per unit of resource output include cost per laboratory test, cost per chest x-ray, cost per 1-mg dose of anastrozole, and cost per physician service/intervention.

Other resource items, like home care or clinic services, can be determined from per diem rates. Per diem rates represent a daily average cost per patient for

providing the service. These can be multiplied by the average length of stay to estimate the total costs (CCOHTA, 1996).

When collecting resource item expenses the pharmacoeconomist should provide a range of costs that can be used in the sensitivity analysis. A range of costs can be based on the accuracy of the resource item estimates.

Table 6 shows the range of resource unit costs for each year of drug therapy for a hypothetical case of participants receiving anastrozole 1-mg therapy (CCOHTA, 1996). Dollar values are for illustrative purposes only and do not represent actual costs (Walker, 1997; Prince George Regional Hospital, 1998).

Table 6

Cost Valuation of Continuous Therapy Resource Items

Resource Unit	Year 1	Year 2	Year 3	Year 4	Year 5
Physician fees	$285-$305	$190-$220	$190-$220	$190-$220	$190-$220
Nursing services	$135-$150	$90-$100	$90-$100	$90-$100	$90-$100
Clinic services	$360-$440	$240-$305	$240-$305	$240-$305	$240-$305
Laboratory	$30-$35	$20-$25	$20-$25	$20-$25	$20-$25
Medical imaging	$170-$190	$0	$0	$0	$0
Anastrozole 1-mg od	$1740-$1790	$1740-$1790	$1740-$1790	$1740-$1790	$1740-$1790
Medical supplies	$0	$0	$0	$0	$0
Lost wages	$75-$150	$50-$100	$50-$100	$50-$100	$50-$100
Out-of-pocket	$20-$60	$10-$30	$10-$30	$10-$30	$10-$30
Total	$2815-$3120	$2340-$2570	$2340-$2570	$2340-$2570	$2340-$2570

Note: Dollar values are for illustrative purposes only and do not represent actual values. From "A Guidance Document for the Costing Process" by, CCOHTA, 1996, Ottawa: National Library of Canada. p.14.

In the case of anastrozole/megestrol acetate, there would be a cost valuation table for fatal and non-fatal events and the continuous therapy path, for both anastrozole and megestrol acetate therapies. Resource item costs would depend on the treatments and the events that are being studied. For example, out-of-pocket costs would be greater for patients and their families, in fatal and non-fatal events than in the continuous therapy path. The costs of fatal and non-fatal events would be greater because these events would most likely result in more lost time from work, greater travel, greater accommodation requirements, higher phone costs, and more lost wages. Non-fatal medical costs associated with disease progression would be larger than continuous therapy medical costs as these patients would require more medical interventions (e.g. laboratory work, physician monitoring, nursing support).

Costs and outcomes table.

Once resource item costs have been determined, the next step in the analysis is to calculate the total costs and the total effectiveness for anastrozole and megestrol acetate therapies. Total costs and total effectiveness are calculated on the costs and outcomes table by performing a cohort simulation of patients to which survival and cost information can be applied (Walker, 1997). The costs and outcomes table uses mortality, drop-out, and continuing therapy rates to predict the number of patients surviving, the number of patients who died, the number of

patients who dropped out, and the number of patients who continued with therapy. Once these numbers of patients have been determined, the total survival time and the total cost of therapy, for each year of treatment, is then calculated. Survival time can be calculated by summing the years that patients are alive. Patients receive one-half of a year of survival time for fatal and non-fatal events and a full year for each year in the continuous therapy path.

Table 7 shows the hypothetical costs and outcomes for anastrozole 1-mg od therapy while Table 8 shows the hypothetical costs and outcomes for megestrol acetate therapy. While the values used in the costs and outcomes table do not represent actual values, the table illustrates how total costs and total effectiveness, how the cost-effectiveness ratio, and how the incremental cost-effectiveness ratio can be calculated.

Table 7

Hypothetical Costs and Outcomes Table for Anastrozole 1-mg od

Costs and Outcomes	year 1	year 2	year 3	year 4	year 5
mortality rate	0.23	0.26	0.39	0.31	0.25
drop-out rate	0.06	0.06	0.09	0.1	0.1
continuing therapy rate	0.71	0.68	0.52	0.59	0.65
costs for death ($/pt)	$2,523	$2,285	$2,285	$2,285	$2,285
costs for drop-out ($/pt)	$2,055	$1,817	$1,817	$1,817	$1,817
costs for continuing therapy ($/pt)	$2,815	$2,340	$2,340	$2,340	$2,340
# pts surviving	770	570	348	240	180
# of pts died	230	200	222	108	60
# of pts dropped out	60	46	51	35	24
# pts continuing therapy	710	524	297	205	156
total survival time in cohort (life years)	855	647	434	276	198
total cost in cohort (Canadian $)	$2,702,095	$1,766,626	$1,295,937	$789,228	$545,359
discount factor (at a 5% discount rate)	0.9524	0.907	0.8638	0.8227	0.7835
discounted survival time in cohort	814	587	375	227	155
discounted costs in cohort	$2,573,475	$1,602,330	$1,119,430	$649,298	$427,289

total survival time for five year treatment (after discounting)	2158 life years
total cost for five year treatment (after discounting)	$6,371,822
Cost-Effectiveness Ratio	$2,953/life year

Note: A hypothetical cohort of 1000 patients at day 1. Distribution of patients into death and drop-out events, and continue therapy path determined at the end of each year of treatment according to mortality, drop-out, and continue therapy rates.

Table 8

Hypothetical Costs and Outcomes Table of Megestrol Acetate 40-mg qid

Costs and Outcomes	year 1	year 2	year 3	year 4	year 5
mortality rate	0.28	0.36	0.39	0.21	0.18
drop-out rate	0.05	0.06	0.09	0.09	0.1
continuing therapy rate	0.67	0.58	0.52	0.7	0.72
costs for death ($/pt)	$2,427	$2,285	$2,285	$2,285	$2,285
costs for drop-out ($/pt)	$1,959	$1,817	$1,817	$1,817	$1,817
costs for continuing therapy ($/pt)	$2,624	$2,149	$2,100	$2,050	$2,000
# pts surviving	720	461	281	222	182
# of pts died	280	259	180	59	40
# of pts dropped out	50	43	41	25	22
# pts continuing therapy	670	418	297	197	160
total survival time in cohort (life years)	835	569	408	239	191
total cost in cohort (Canadian $)	$2,535,590	$1,568,189	$1,109,697	$584,208	$451,447
discount factor (at a 5% discount rate)	0.9524	0.907	0.8638	0.8227	0.7835
discounted survival time in cohort	795	516	352	197	150
discounted costs in cohort	$2,414,896	$1,422,347	$958,556	$480,628	$353,709

total survival time for five year treatment (after discounting)	2009 life years
total cost for five year treatment (after discounting)	$5,630,135
Cost-Effectiveness Ratio	$2,802/life year
Incremental Cost Effectiveness Ratio (ICER = C_1-C_2/E_1-E_2)	$4978/life year gained

Note: Hypothetical cohort of 1000 patients at day 1. Distribution of patients into death and drop-out events, and continue therapy path determined at the end of each year of treatment according to mortality, drop-out, and continue therapy rates.

Once total survival time and total cost for the cohort is determined, a discount factor is applied to survival and cost data (CCOHTA, 1997). The discount factor is multiplied by the cost and survival time for each year of treatment (Drummond et al., 1993). The total survival time and the total cost for the five year treatment of the hypothetical cohort of patients are then calculated.

The cost-effectiveness ratio is determined by dividing the total cost by the total survival time for the five year treatment after discounting. The incremental cost-effectiveness ratio can be calculated after the cost-effectiveness ratios for both drug treatments have been determined.

The costs and outcomes table also provides a simple way of adjusting variables for performing sensitivity analysis. Walker (1997) recommends generating the costs and outcomes table on a computer spreadsheet (e.g. Microsoft Excel®) and programming the simple mathematical formulas so that, when performing sensitivity analysis, the variables can be easily adjusted and the calculations can be performed automatically.

Chapter 7

Summary

This thesis has outlined the methodological techniques for performing a cost-effectiveness analysis of anastrozole and megestrol acetate in the treatment of progressive breast cancer. The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) document "Guidelines for Economic Evaluation of Pharmaceuticals" has been used to provide a comprehensive and structured approach to the methodological techniques needed in a pharmacoeconomic analysis (CCOHTA, 1997). Hopefully, researchers carrying out similar pharmacoeconomic studies will find this review useful and will encourage effective, efficient, and equitable use of pharmaceutical therapies.

The principal pharmacoeconomic methodology used to evaluate anastrozole versus megestrol acetate was a cost-effectiveness analysis (CEA). The CEA of anastrozole/megestrol acetate was selected for two reasons. First, researchers have suggested that inequitable resource allocation has occurred in the area of palliative cancer therapies and that close evaluation of these therapies needs to be performed (Jonsson et al., 1995). Second, the anastrozole/megestrol acetate case has provided an opportunity to describe methodological techniques

that would be useful in measuring the effectiveness of palliative breast cancer drug therapies.

While investigators in the anastrozole/megestrol acetate phase III trials reported the findings as two year survival rates and median time to death, the data was reevaluated by methods considered by some researchers as being less biased. The anastrozole and megestrol acetate survival information was expressed as absolute risk reduction and numbers needed to treat.

The absolute risk reduction for women taking anastrozole 1-mg od for a median time of 31 months was found to be 10.2 percent. This indicated that women being treated with anastrozole 1-mg od for 31 months had 10.2 percent fewer deaths than women treated with megestrol acetate 40-mg four times daily (qid) for the same duration.

The number needed to treat was calculated to be 10, indicating that if 10 women were treated with anastrozole 1-mg od for 31 months, instead of megestrol acetate 40-mg qid, one death would be prevented. This demonstrated that anastrozole 1-mg od offered a survival advantage over megestrol acetate 40-mg qid and that a pharmacoeconomic evaluation of these therapies would be worthwhile. However, because the randomized clinical trial data may not reflect real-life drug utilization patterns and because the phase III drug trial findings

cannot be reliably extrapolated beyond the 31 month median follow-up period, these results may not be generalizable.

Before methodological techniques were reviewed the pharmacoeconomic study population was defined, the perspective of the analysis was stated, and the time horizon for the analysis was determined. The pharmacoeconomic population was defined as women with postmenopausal estrogen receptor positive breast cancer whose disease has progressed while on tamoxifen and who have switched therapy to either anastrozole 1-mg od or megestrol acetate 40-mg qid. The analysis followed the societal perspective as recommended by CCOHTA. The time horizon for the analysis was determined to be five years based on efficacy data from other hormonal breast cancer therapies.

In chapter 2 decision modeling methods were discussed. Decision modeling was used to systematically organize clinical and economic information into a structured framework of events. A standard decision tree, a recursive decision tree, and a Markov model were described. A recursive decision tree was selected for the analysis of the anastrozole/megestrol acetate case. The recursive decision tree comprised a main branch of two events and one treatment path. The events selected were "death" and "drop-out", and the path was "continue therapy". These events were selected to provide a means of quantifying the survival time obtained from each therapy.

The main branch of the recursive decision tree represented a one year period of therapy. The main branch was repeated five times and formed the five year recursive tree. Structuring the tree in this way provided a method of tracking the distribution of patients through the five year therapy. At the end of the five year horizon the amount of survival time was estimated by summing up the amount of life-years for a hypothetical cohort of patients.

In reviewing the phase III trial data it was found that the anastrozole/megestrol acetate 31 month median treatment period was too short by CCOHTA's standards. According to CCOHTA, the ideal time horizon for a pharmacoeconomic analysis of survival times should be until all participants in the study have died. If this information is not available, then modeled data would need to be used. It was determined that modeled data would need to extend the phase III trial data from 31 months to at least 60 months according to efficacy data from other hormonal therapies.

In order to determine the likelihood of patients surviving after each year of drug therapy, the probability of death had to be determined. In order to calculate the probability of death, raw survival data from the phase III trials was needed. Raw survival data would provide the analyst with the opportunity to calculate the mortality rate, the hazard ratio, the probability density function, and predict survivorship beyond the 31 month median time frame. Since raw survival data

was not available another method of estimating mortality/survival rates was discussed. Survival rates could be estimated by extrapolating the values from the survival curves but, while extrapolating survival rates is easy to perform mathematically, the validity and the reliability of the findings in the present case is too imprecise to justify using this method.

Once the recursive decision tree was developed, the next step in the evaluation was to determine the costs for anastrozole and megestrol acetate therapies. The evaluation of costs for therapy encompasses three main steps: identifying the types of resources, measuring resource consumption, and determining the dollar value of resource consumption. Resource items were identified from the events found on the recursive decision tree and were based on the societal perspective. A list of resource items, the sources of cost information, and specific points to consider when measuring those resource items were also discussed. Even though costing of resource items was not performed, one method for calculating the value of resource items could be determined from cost per unit of resource output and per diem rates. When valuing resource items a range of costs would be gathered and used in a sensitivity analysis.

The final stage of the pharmacoeconomic evaluation involved combining clinical and economic data into a single table. A sample table of costs and outcomes for anastrozole and for megestrol acetate therapies were provided (see

Tables 7 and 8). The tables were used to demonstrate how survival time, discounting, and cost-effectiveness ratios could be calculated from a hypothetical cohort of patients. The data used in the tables did not represent actual values but were provided for illustrative purposes only.

The costs and outcomes table combined mortality, drop-out, and continuing therapy rates so as to determine the number of patients in each of the three events in years one through five. Costs per patient, determined from the consumption of resource items, were then applied to the number of patients in each event. Survival times were determined from the number of patients in the death and drop-out events, and the continue therapy path. Patients who dropped out, or died, were given one-half of a year of survival time. Patients who continued with therapy received one full year of survival time. Costs and survival times were totaled and a discount rate of five percent would be applied to both costs and survival times. The cost-effectiveness ratios, after discounting, was then determined. The incremental cost-effectiveness ratio for anastrozole 1-mg od and megestrol acetate 40-mg qid was determined from the cost-effectiveness ratios.

Limitations.

Performing a retrospective cost-effectiveness analysis from clinical trial data poses several problems. The randomized clinical trial efficacy data for anastrozole and megestrol acetate was designed to demonstrate a particular

primary endpoint and was not intended for secondary pharmacoeconomic analysis.

The anastrozole and megestrol acetate clinical phase III data were found to use a dosing regimen for megestrol acetate that is not normally being prescribed in Canada. The clinical trials used a four times daily dosing regimen for megestrol acetate instead of the more popular daily regimen. Noncompliance with the qid dosing regimen is more likely to occur than with the od regimen. If a significant portion of patients in the phase III trials was noncompliant then the survival results could be compromised. For example, the improved survival times for anastrozole may have been a result of better patient compliance than of superior pharmacotherapeutic properties of this drug..

Further limitations include extending the time horizon of the analysis. Extending the time horizon to five years requires modeling procedures that can lead to unreliable data. Modeled data for determining the mortality rates for years three, four, and five, would have to be thoroughly tested by sensitivity analysis. Sensitivity analysis would also need to be applied to drop-out and continue therapy rates. Sensitivity analysis would need to be applied to cost valuation of resource items and discount rates. The sensitivity analysis would be performed by adjusting variables in the costs and outcomes table.

While the recursive decision tree provided a method for tracking the survival of patients during anastrozole and megestrol acetate therapies, the model may be too simplistic for actual use. A more detailed recursive decision tree with a greater number clinical events and paths may help to improve the predictability of survival for hormonal therapy in palliative breast cancer.

Future research.

Although the practice of pharmacoeconomics is considered in its infancy, guidelines for performing and evaluating pharmacoeconomic studies are becoming commonplace. Guidelines, such as those developed by CCOHTA, are helping to ensure that the methods of economic and clinical evaluation of health care programs are based on accepted analytical techniques. Future research will be required to illustrate how these guidelines can be used in everyday health care practice. For example, health care managers, responsible for the allocation of resources, will need to understand how pharmacoeconomics can be used to assist in drug policy decision making.

Since the accuracy and validity of pharmacoeconomic studies is reliant on quality data, future pharmacoeconomic research should promote methods of obtaining accurate and reliable information. Randomized clinical trials are important sources of information but can be of limited value. Randomized clinical trials are designed to study drug safety and efficacy under controlled situations,

but in pharmacoeconomic evaluations, it is how the drug works in the real world that is of importance. Future research should find ways to overcome the pitfalls of using randomized clinical trial data in pharmacoeconomic evaluations.

It would be hoped that the B.C. Cancer Agency and other institutions in British Columbia will, in the future, use criteria similar to those of the Therapeutic Initiative and the Pharmacoeconomics Iniative in the selection of drugs for patients under their care.

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