DEVELOPING CONDITION-SPECIFIC HOSPICE FORMULARIES

FOR CONGESTIVE HEART FAILURE AND DEPRESSION

CONDITIONS AND THE EVALUATION OF

THEIR ECONOMIC IMPACT

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DEVELOPING CONDITION-SPECIFIC HOSPICE FORMULARIES FOR CONGESTIVE HEART FAILURE AND DEPRESSION CONDITIONS AND THE EVALUATION OF THEIR ECONOMIC IMPACT

Nikhil Khandelwal

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DISSERTATION ABSTRACT

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With the increasing costs of providing pharmaceutical care, hospices in the U.S are burdened with the high costs of providing optimum healthcare. There is a need to implement cost-containment strategies such as drug formulary at hospices that will aid in curbing pharmacy-related costs. While most hospices do not have a formulary, there are some that have a preferred drug list of most commonly used drugs, however, they lack appropriate methodology for the purpose of including or excluding particular drug(s) on the list. The main objective of this study was to develop rational hospice drug formulary

based on scientific methodology. The study also investigated the economic impact of the drug agents that were selected for the formulary. This study was conducted at a hospice center located in the rural township of Alabama State. Multi-Attribute Utility Theory (MAUT) methodology was employed to develop a rational hospice drug formulary. MAUT is a systematic drug selection method that assists the P&T committee in selecting appropriate drugs on the basis of assessing important drug attributes such as efficacy, safety, cost, and dosage-form related parameters. For each therapeutic drug class, members of the drug selection committee at the center ranked and weighted their preferences for different drug attributes that were considered most important for final drug selection process. The preference values were combined in mathematical formulas with the literature-based values that were obtained through systematic literature review process to yield total utility score values for individual drugs. Within each therapeutic class, final decisions to include particular drug on the formulary were made on the basis of total utility scores i.e. those drugs with highest total utility scores were selected for the formulary. The drug selection committee at the hospice successfully developed condition-specific drug formularies using MAUT methodology. For each condition, three categories of drug costs (i.e. total drug costs related to the condition; specific-drug costs; and other drug costs related to the condition) were computed and compared across pre and post-formulary groups. For each condition, all types of drug costs were found to be lower in the post-formulary group as compared to the pre-formulary groups, however, these were not found to be statistically significant at an alpha of 0.05 (except depression-specific drug costs). Due to the contract price differentials in the pre and post-formulary periods, adjustments to the drug prices were made to the post-formulary drug prices. After adjusting for the price differentials, post hoc analysis for the formulary agents were conducted and drug costs incurred before and after the implementation of the formulary were compared. The analysis showed that on a per patient day level, about 8 cents was saved as a result of implementing depression formulary; and about 44 cents was saved as a result of implementing CHF formulary. Thus the study showed that, annually the hospice of EAMC could achieve an estimated cost savings of about $456.00 and about $1813.00 as a result of implementing depression and CHF formularies respectively.

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1. INTRODUCTION

The term “hospice” is derived from the Latin word *hospitium*, meaning entertainment, hospitality, lodging, or inn. Hospice, in the medieval times, was broadly referred to as a concept of providing shelter and rest for the fatigued or ill travelers who were on a long journey. Since the Middle Ages, hospices have proliferated not only in numbers but have also expanded their role from providing shelter and care to tired travelers to providing care to sick and dying people. The modern hospice movement in the United States started in 1974, when the first hospice, the Connecticut Hospice, was established at Yale Medical Center. By the late 1970s, there were a few more grassroots programs that were being started in the U.S. The positive outcomes demonstrated by these programs led the U.S. Department of Health, Education and Welfare in 1978, to publish a report, affirming that hospice was really a viable concept of providing care to terminally-ill people and their families at a reduced cost. Over the years, hospices have gained tremendous recognition and were a significant provider of end-of-life care to Americans. There has been a rapid growth not only in the number of hospices that are operationally functioning, but also there has been a expansion of end-of-life care services provided by them. Hospice providers in the mid-1970s primarily served cancer patients, but today’s hospices address a broad range of terminal illness, serving patients with end

stage heart, kidney, and liver diseases, along with dementia, lung disease, and other chronic diseases. Hospices flourished largely because of the result of a legislation passed by Congress that created a Medicare Hospice Benefit (MHB). According to the National Hospice and Palliative Care Organization (NHPCO), in 1985 there were about 1,500 hospice programs that were operating throughout the country. By the end of 2003, more than 3,300 hospice programs were reported to be scattered across the nation, are caring for about 700,000 patients per year (approximately 30% of Americans who die).

1.1. An Overview of Hospice

Hospice is a specialized, compassionate form of care that is provided to patients with life-limiting illnesses. Hospices offer multidisciplinary, holistic care in a variety of settings (such as the home, hospices, hospitals, or skilled nursing facilities) that include the provision of physical, emotional, social and spiritual support to patients at the end-of-life. Because patients at the end-of-life are considered to be very vulnerable to a variety of symptoms, the major goal of hospice is to control pain and other symptoms so that patients can remain as alert and comfortable as possible. Thus, hospice care is not intended to extend life per se, but is focused on improving the quality of remaining life. A majority of the hospices (67%) in the U.S. are non-profit organizations, while some organizations are for-profit (27%) and few others (3%) are government organizations (NHPCO, 2004). Almost half of the hospices (50%) operate as small; independent (free standing); community-based organizations. About 31% of the organizations are affiliated with hospitals, while 18% of them are associated with home health agencies.

A specially trained interdisciplinary team consisting of clinical and non-clinical staff helps patients live each day to the fullest, thereby providing comfort and enhancing their quality of life. Additionally, support services are also provided to loved ones caring for the patient during illness and into bereavement. Only those patients or clients who have been diagnosed with a terminal illness and who have a projected survival time of six months or less based on disease progression are eligible for such services. Thus, hospices provide their services not only to the elderly population, but also cater to anyone who has been diagnosed with life-limiting diseases, regardless of race, age, creed, or ethnicity. The interdisciplinary team is typically composed of a doctor, registered nurse, social worker, pharmacist, and a pastoral or other counselor. Other professionals such as surgeons, anesthesiologists, psychiatrists, and volunteers may also serve on such teams. The team conducts a thorough evaluation of each new patient's medical and personal situation and then tailors a plan of care to meet individual and family needs. Often times, physician services, nursing services, medications, and other treatment needs are made available on a 24-hour basis. In order to meet the specific needs of the patients who are enrolled, hospices may provide the following services such as occupational therapy, physical therapy, speech therapy, dietary consultation, homemakers, and home health aides. Some hospices even offer music or recreation therapy, art therapy, and massage therapy (Bennahun D, 2003).

Each of the hospice professionals may provide services either by visiting the patient and family at their home or working from the hospice's office. Hospices generally provide four different levels of care to the patients such as routine home care, continuous home care, inpatient respite care, and general inpatient care. The actual level of care that

the patient receives depends upon his or her condition. As the condition changes, the level of care could change if needed to meet the patients and the family's needs. At the time of admission, the nurse case manager takes note of the patient's symptoms, evaluates and assesses the needs of the patient for various services and reports to the attending physician about the patient's current status and the orders that may be needed to start hospice care services to the patient's needs. The social worker and other professionals may also contact the physician for orders to provide the care related to their specialty. Members of the interdisciplinary team then meet together to discuss the patient’s care needs and prepare the care plan for that individual. In other words, the team decides the appropriate services to be included in the care plan in order to help improve the comfort of the patient, manage symptoms, deal with other difficulties such as emotional distress, problems with coping, grieving, nutrition, and help with problems the patient may face with regards to performing routine tasks and assist with other problems related to their terminal illness.

1.2. Funding For Hospices

Medicare is the main financing mechanism for medical and other support services provided by hospices to the terminally-ill patients. Many hospices also get some charitable contributions to cover the cost of care for terminally-ill patients who cannot manage to pay for their care. In 1982, Congress enacted legislation creating a Medicare hospice benefit program that covered terminally-ill Medicare beneficiaries with a life expectancy of six months or less. Since then, Medicare hospice participation has grown at a dramatic rate. From 1984 to January 2002, the total number of hospices participating in

Medicare rose from 31 to 2,265, which was more than a 73-fold increase (MedPAC, 2004). Currently, Medicare under Part A covers about 83 percent of all those who die in U.S. hospices (NHPCO, 2004). Medicare reimburses the hospices on a capitated per diem rate basis (i.e. based on fixed daily rates). Medicare Part A covers hospices on four different levels of care that includes routine home care, continuous home care, inpatient respite care, and general inpatient care. Of the different levels of care, routine home care is the default care that is provided to a majority of the hospice enrollees. The daily reimbursement rate is intended to provide coverage for all supportive services including medical, nursing, home health aide, social, and bereavement. The Center for Medicare and Medicaid Services (CMS) sets up the reimbursement rates for the different levels of care, which are adjusted every year to the inflation rate and varies across geographical region as well as according to rural or urban setting. Apart from Medicare, Medicaid and other private insurers offers similar type of hospice coverage. Even though Medicare is the single largest payer for hospice services, the funding provided by Medicare is very limited. Because of the limited funding hospices throughout this country are currently facing certain challenges with respect to provision of quality services needed by the patients (MedPAC, 2002).

1.3. Issues and Challenges Faced By Hospices

In the last three decades, hospice providers in the United States have expanded the care for dying people and their families by providing options and choices that enable patients to be in control of their care at the end-of-life. Although there has been a tremendous proliferation of the end-of-life care concept, hospices today still face a

number of challenges. The rising cost of hospice care has been the most important challenge not only to the health care providers in this field, but also to the federal Medicare program, as well as state Medicaid programs. Recently, a report published by the American Health Consultant, described some of the crucial issues faced by the U.S. hospice programs. One of the important issues described relates to the limited funds available through the flat per diem reimbursement rate offered by Medicare, while the second most important issue related to the skyrocketing prices of medications that are consuming a larger proportion of the total hospice budget (American Health Consultant, 2000). Mentioned below are a few of the consequences that have resulted because of the financial constraint situation.

1.3.1. Funding issues: Medicare provides a limited daily reimbursement rate for end-of-life care services provided by hospices (current national reimbursement rate is $118 per day). The per diem rate covers physician services, medical social services, medical appliances and supplies, medications related to the terminal illness and other end-of-life services that may be needed by the patient. Because Medicare is the primary funding source, and provides only limited funds, hospices throughout this country are currently facing certain challenges with respect to the provision of quality services needed by patients and their families (MedPAC, 2004). The restricted funding available to hospices often limits their ability to deliver optimum patient care. As most of the hospice programs operate as small, independent, community-based organizations with restricted funding opportunities, they have very limited support for their staff to deliver optimum intensive medical treatments to meet the patients care needs (Huskamp, 2001). If hospices admit patients who require extensive care, they may end up with a lower or negative profit

margin on these patients (Huskamp, 2001). With the limited funds available, it's very difficult for hospices to provide comprehensive care to the patients. Moreover, the current national per diem rate fixed by Medicare to cover for routine home level of care, which is the most predominant care provided by hospices is around $118 per day (CMS, 2003). This reimbursement amount of $118 remains fairly constant, irrespective of the patient case-mix (the rate however varies according to the geographical region). A survey conducted by Huskamp et al. on the health care providers who are compensated by Medicare on a fee-for service basis showed that a majority of providers expressed their concerns that that the per diem rate set by Medicare were too low. The respondents also stated that because of the limited funds it was difficult for the hospices to provide expensive medications, procedures, certain type of durable medical equipments, and blood transfusion and products (Huskamp, 2001). Another study, sponsored by the National Hospice and Palliative Care Organization, demonstrated that on average there was a 10-20 % shortfall between the costs incurred by the hospices for delivering end-of-life care and Medicare's reimbursement rate. It was reported that the primary reason for such a significant difference in the hospices cost and the Medicare's reimbursement rate was due to the inadequacy of the reimbursement to cover for the costs of prescription drugs and outpatient therapies (Cheung, 2001).

1.3.2. Pharmaceutical cost issues: In the past several years, the rising cost of pharmaceuticals has caused a lot of concerns in the hospice industry. A study published in 2004 reported that there was a steep increase in the prices of drugs in the year 2003, especially on those that were used in the elderly population. The study showed that the percentage increase in drug prices was more than the inflation rate reported for that year,

indicating that medications were becoming more costly as compared to the previous year. The study focused only on those drugs that were specially used among elderly population, and found that the prices on the 30 of the most widely used brand-name drugs rose to about 6.5 percent from January 2003 to January 2004. Moreover, the study also reported that out of the 30, prices on 26 drugs agents increased about 22 percent over a span of three years (Families USA, 2004). According to another report released by the American Health Consultant group, hospice drug costs were rising at an average rate of 18.3% per year, and total pharmacy costs constituted a large portion of the hospice's direct costs (American Health Consultants, 2000). The study also provided recommendations that in order to provide a comprehensive end-of-life care with provision of optimum pharmacotherapy to the terminally-ill patients, hospices implement appropriate cost containment strategies such as drug formulary, which will be able to curb the escalating costs of pharmaceuticals.

1.4. Cost Containment Strategies

Implementing an evidence-based drug formulary has been suggested by experts in the field as an alternative strategy for containing costs (American Health Consultants, 2000). A drug formulary is a restricted listing of drugs that are considered most useful in providing optimal therapeutic care, and reflects the current clinical judgment of the medical staff at a given practice setting. In 2004, the Medicare Payment Advisory Commission (MedPAC), a committee that advises Congress on Medicare issues, reported that there were no data or information available indicating whether or not the hospices were using drug formularies to help manage their drug costs (MedPAC, 2004). The report

also stated that most of the hospices do not have a systematic procedure for developing a drug formulary or do not carry a drug formulary, as they adhere to a philosophy of providing quality patient care, at whatever cost that they may have to bear. Instead of managing a drug formulary, most hospices have a list of drugs that they use at their centers, which primarily consists of the most commonly used agents for treating symptoms or conditions. Although the list contains the names of most widely agents, there is no rationale or justification for the inclusion of any drugs in the list, and the list lacks information on subsequent clinical and economic outcomes (Babington, 1997). Thus, there is a need to explore these issues so that appropriate measures can be taken by hospices to contain the costs, and at the same time provide optimal pharmacotherapy.

1.5. Need for Research

In order to contain the overall costs, hospices need to implement cost containment strategies. Developing an efficient drug formulary system has been suggested as one of the most effective way to contain the skyrocketing costs of drugs, as well as aid in providing optimum pharmacotherapy (American Health Consultants, 2000). Since most hospices do not have a formal drug formulary; there is a need to develop a structured, rational, and systematic hospice drug formulary. In order to determine if a drug formulary aids in containing pharmaceutical costs, it is also necessary to conduct analyses of the economic impact of drug therapies selected in the formulary.

It is reported that many Pharmacy and Therapeutics (P&T) committees who are responsible for developing drug formularies, generally start their drug selection process based on the needs of the community i.e. they focus on specific conditions that have been

identified locally. Some P&T Committees develop formularies in stages, starting with specific medical conditions or drug classes first and then going on to other conditions or drug classes (Rational Pharmaceutical Management Plus Program, n.d.). This study will follow a similar approach, which is used by most P&T Committees in hospitals and other healthcare institutions. In order to focus on specific conditions, this study will necessitate prioritization of medical conditions and symptoms. For this project, hospice formularies will be developed for those medical conditions or symptoms which are costly in terms of drug therapy management. Therefore, there is a need to explore and identify what medical conditions or symptoms consume the maximum pharmacy funds. The study will then focus on developing drug formularies for those conditions where the pharmacy resource utilization is highest.

1.6. Study Purpose

The present study was conducted at Hospice of East Alabama Medical Center (EAMC), a rural hospices located in Auburn, Alabama. The purpose of this proposed study was two-fold. (i) The primary aim of this study was to develop a hospice drug formulary for selected medical conditions, using the Multi-Attribute Utility Theory (MAUT) technique. (ii) Additionally, the economic impact of the selected drug agents in the formulary was evaluated. The total drug costs, condition-specific drug costs, and other drug costs related to selected medical conditions will be computed and compared before and after implementation of the formulary.

1.7. Study Objectives

The first objective of the study is to assist the drug selection committee at a local rural hospice to develop rational hospice drug formularies for the medications used to treat Congestive Heart Failure (CHF) and depression. These conditions were selected because they consume the largest portion of the total pharmacy funds, in other words, they were the most expensive to manage (outside of pain medications). For each of these conditions, the specific study objectives include:

1. To develop a rational depression-specific hospice formulary based on a scientific method such as the Multi-Attribute Utility Theory method that can provide optimum therapeutic care to terminally-ill patients with depression while reducing the pharmacotherapy costs currently incurred for managing the condition.
2. To compare total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary.
3. To compare other drug costs associated with depression before and after implementation of the depression formulary.
4. To compare the depression-specific drug costs per patient enrollment day before and after implementation of the depression formulary.
5. To develop a rational CHF-specific hospice formulary based on a scientific method such as the Multi-Attribute Utility Theory method that can provide optimum therapeutic care to terminally-ill patients with CHF while reducing the pharmacotherapy costs currently incurred for managing the condition.
6. To compare total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

7. To compare other drug costs associated with CHF condition per patient enrollment day before and after implementation of the CHF formulary.
8. To compare the CHF-specific drug costs per patient enrollment day before and after implementation of the CHF formulary.

1.8. Research Questions and Hypotheses

The present study will answer and test the following research questions and hypotheses:

Research Question 1: Is there any difference in total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary?

Null Hypothesis:

H_{01}: There is no difference in total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary

Alternate Hypothesis:

H_{A1}: There is a difference in total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary

Research Question 2: Is there any difference in other drug costs associated with depression before and after implementation of the depression formulary?

Null Hypothesis:

H_{02}: There is no difference in other drug costs associated with depression before and after implementation of the depression formulary

Alternate Hypothesis:

H_{A2}: There is a difference in other drug costs associated with depression before and after implementation of the depression formulary

Research Question 3: Is there any difference in the depression-specific drug cost per patient enrollment day before and after implementation of the depression formulary?

Null Hypothesis:

H_{03}: There is no difference in the depression-specific drug cost per patient enrollment day before and after implementation of the depression formulary

Alternate Hypothesis:

H_{A3}: There is a difference in the depression-specific drug cost per patient enrollment day before and after implementation of the depression formulary

Research Question 4: Is there any difference in the total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary?

Null Hypothesis:

H_{04}: There is no difference in the total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary

Alternate Hypothesis:

H_A: There is a difference in the total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary

Research Question 5: Is there any difference in other drug costs associated with CHF condition per patient enrollment day before and after implementation of the CHF formulary?

Null Hypothesis:

H_{05}: There is no difference in other drug costs associated with CHF condition per patient enrollment day before and after implementation of the CHF formulary

Alternate Hypothesis:

H_{A5}: There is a difference in other drug costs associated with CHF condition per patient enrollment day before and after implementation of the CHF formulary

Research Question 6: Is there any difference in the CHF-specific drug costs per patient enrollment day before and after implementation of the CHF formulary?

Null Hypothesis:

H_{06}: There is no difference in the CHF-specific drug costs per patient enrollment day before and after implementation of the CHF formulary

Null Hypothesis:

H_{A6}: There is a difference in the CHF-specific drug costs per patient enrollment day before and after implementation of the CHF formulary

1.9. Significance of the Study

Although, very few studies have used the multi-attribute utility theory (MAUT) as a technique for developing a rational drug formulary, none have evaluated the economic impact of the drugs selected by this technique. The results obtained through this study will give further insights as to whether the proposed procedure is effective in producing desired economic outcomes. If the method is effective, then this will help the drug selection committee at the hospice of EAMC to utilize similar methodology, for selecting other drugs and developing drug formularies for other medical conditions, not covered in the scope of this study. The study will further guide the drug selection team at other hospices to follow the methodology used for this study in developing specific evidence-based treatment models for each of these conditions at their respective centers.

1.10. OPERATIONAL DEFINITIONS:

CHF-total drug cost: It is the sum of costs of all drugs filled for the patient during the study period divided by the total length of treatment days for which the patient received care during the study period. This is expressed as $$ per patient day.

$$\text{CHF-total drug cost for each patient} = \frac{\text{(Sum of cost of all drugs filled during the study period)}}{\text{(Total length of treatment in days during the study period)}}$$

CHF-specific drug cost per patient day: It is the sum of costs of all CHF drugs filled for the patient during the study period divided by the total length of treatment days for which the patient received care during the study period. This is expressed as $$ per patient day.

$$\text{CHF-specific drug cost for each patient} = \frac{\text{(Sum of cost of CHF-specific drugs filled during the study period)}}{\text{(Total length of treatment in days during the study period)}}$$

Other drug costs associated with CHF: It is the sum of cost of all ancillary drugs filled for the patient for managing symptoms and conditions associated with CHF condition during the study period, divided by the total length of treatment days for which the patient received care during the study period. This is expressed as $$ per patient day.

$$\text{Other drug costs for CHF} = \frac{\text{(Sum of cost of all ancillary drugs filled during the study period)}}{\text{(Total length of treatment in days during the study period)}}$$

Depression-total drug cost: It is the sum of costs of all drugs filled for the patient during the study period divided by the total length of treatment days for which the patient received care during the study period. This is expressed as $$ per patient day.

$$\text{Depression-total drug cost for each patient} = \frac{\text{(Sum of cost of all drugs filled during the study period)}}{\text{(Total length of treatment in days during the study period)}}$$

Depression-specific drug cost per patient day: It is the sum of costs of all CHF drugs filled for during the study period divided by the total length of treatment days for which the patient received care during the study period. This is expressed as $$ per patient day.

$$\text{Depression-specific drug cost} = \frac{\text{(Sum of cost of all depression-specific drugs filled for each patient during study period)}}{\text{(Total length of treatment in days during the study period)}}$$

Other drug costs associated with depression: It is the sum of cost of all ancillary drugs filled for the patient for managing symptoms and conditions associated with depression condition during the study period, divided by the total length of treatment days for which the patient received care during that study period. This is expressed as $$ per patient day.

$$\text{Other drug costs for depression} = \frac{\text{(Sum of cost of all ancillary drugs filled during the study period)}}{\text{(Total length of treatment in days during the study period)}}$$

Total drug costs for depression-specific drugs: It is the sum of costs of all depression-specific drugs filled for the patient during the study period

Total drug costs for CHF-specific drugs: It is the sum of costs of all CHF-specific drugs filled for the patient during the study period

Average drug costs per patient for depression-specific drugs: It is the sum of costs of all depression-specific drugs filled for the patient during the study period divided by the total number of patients who filled those prescriptions during the study period

Average drug costs per patient for CHF-specific drugs: It is the sum of costs of all CHF-specific drugs filled for the patient during the study period divided by the total number of patients who filled those prescriptions during the study period

Average drug costs per patient day for depression-specific drugs: It is the average drug costs per patient for depression-specific drugs calculated during the study period divided by the mean length of treatment for patients during the study period

Average drug costs per patient day for CHF-specific drugs: It is the average drug costs per patient for CHF-specific drugs calculated during the study period divided by the mean length of treatment for patients during the study period.

2. LITERATURE REVIEW

This chapter gives deeper insight into the major components of the study. The purpose of this chapter is to provide background information related to this study by reviewing the literature in the area of hospice and the hospice movement, particularly focusing on the approaches for developing and managing the hospice drug formulary and also providing background information about the two medical conditions selected for this study. This study is aimed at developing drug formularies for specific medical conditions, such as Congestive Heart Failure (CHF) and depression. In order to reduce the voluminous literature to a manageable size, literature review for this study has been restricted to the following topics:

- Hospice and end-of-life care
- Historical background of the hospice movement
- Eligibility and reimbursement for hospice services
- Hospice care payment system and related issues
- Drug formularies and their historical background
- Formulary development approaches
- Drug selection criteria for formulary development
- Drug selection methods for developing drug formulary
    - Multi-Attribute Utility Theory (MAUT)
    - Clinical Decision Analysis (CDA)

- System of Objectified Judgmental Analysis (SOJA)

- Background information on selected medical conditions

  - Congestive Heart Failure (CHF)

    - Epidemiology and symptoms of CHF
    - Treatment of CHF
    - Management of CHF at the end-of-life

  - Depression

    - Epidemiology of depression
    - Treatment of depression

2.1. Overview of Hospice and End-of-life Care

"Hospice" is a concept that is usually associated with terminally-ill patients. The National Hospice and Palliative Care Organization, describes hospice as an approach that is designed to provide comprehensive, coordinated and compassionate care to people with limited life expectancy. This type of care is provided either at home or in institutional settings such as hospitals, nursing homes and long-term care facilities. As opposed to providing curative care, hospices aim at providing biopsychosocial care to their terminally-ill patients. That is they provide supportive, medical, social, emotional and spiritual care; with special emphasis on providing as high a quality of life as possible. Hospice is thus referred to as a specialized form of care that focuses on providing quality and not quantity of care. It focuses on relieving suffering and providing comfort, peace and dignity to patients who are nearing death (Mittal, & Flaherty, n.d.). Hospice services are available to all terminally-ill patients, irrespective of their age, religion, race, or

illness. Hospice care also supports the well being of those (usually the family members) who take care of patients by providing bereavement care for survivors, both during the dying process and after the death occurs (Fine, n.d.). There are no limitations for people to enroll into such programs, except that the individuals should have a life expectancy of less than six months, if the disease runs its expected course (Dahlin, 2003).

Hospice care involves a team-oriented approach tailored to meet the medical, social, emotional and spiritual needs of the terminally-ill patients and is typically provided by an interdisciplinary health care team. The team usually works with patients and their primary caregivers, generally their family members. The care team consists of a physician, nurse, nurse assistant, pharmacist, one or more home health aides, a nutritionist, physical therapist, a speech therapist, non-professional volunteers who provide supportive care, a social worker and the chaplain who provides spiritual care. Members of this interdisciplinary team make regular visits to assess the patient and are also involved in developing a care plan that meets each patient's individual needs for managing the disease and its related symptoms prevalent during the final stages of life. Additionally, they are responsible for reviewing and updating the plan of care and establishing the policies governing hospice care and services (Eustler, 2003).

2.2. Historical Background on Hospices

The term "hospice" comes from the Latin word *hospitium*, meaning entertainment, hospitality, lodging or inn. Back in medieval times, hospices typically served as places of shelter and respite for fatigued travelers or ill travelers who were on a long journey. But over the years, their roles have expanded from merely providing shelter to travelers to taking care of the sick and dying people. In the 19th century, hospices

operating in countries like Ireland and France started providing terminal care at the end-of-life stage (Bennahum, 2003). However, it was only in 1967 that the term hospice was first applied to this specialized care that was being provided to the dying patients. The name was proposed by a physician named Dame Cicely Saunders, who founded the first modern hospice – St. Christopher's hospice in Sydenham, one of the residential suburbs of London (Meghani, 2004; Gage, 2000). The work done by this hospice was soon recognized and appreciated by health care providers throughout the world.

The very first hospice in the United States was started in New Haven, Connecticut in 1974 by Florence Wald, dean of the graduate school of nursing at Yale University along with Ed Dobihal who was the Chaplin at the Yale University hospital. At that time, cancer was the most prevalent medical condition of patients enrolled in this hospice and therefore it served as the primary disease model during the development of hospice and palliative care services. In 1975, another hospice was established at St. Luke's Hospital in New York. This was the first model in the U.S. that incorporated hospice care into an existing medical center and included services such as inpatient care, home care, clinic care and bereavement services (Bennahum, 2003; Meghani, 2004). In 1977, the National Hospice Organization (NHO), was established in the U.S., which included all those institutions that offered such services. Later in 1978, the United States Department of Health, Education and Welfare endorsed a proposal that the hospice movement should receive federal support. However, at that time many questions were raised about the effectiveness of such programs. Therefore in 1979, the Health Care Finance Administration (now the Center for Medicare and Medicaid Services), conducted a two-year demonstration study to assess the costs, benefits and feasibility of having Medicare

pay for hospice care (Gage, 2000). The study included 26 hospices across the nation and was aimed at evaluating the patterns of care, patient outcomes, family outcomes and the cost and utilization impact of the hospice model. The demonstration project showed that: (1) hospices provide better pain relief and improve patients' quality of life more than conventional care; (2) hospice prepares patients and their families emotionally and spiritually for death; and (3) hospices could result in potential savings over traditional care in proving end-of-life care (Greer, 1986; Greer & Mor, 1986; Aiken, 1986). The findings from the study convinced the U.S. Congress to consider hospice benefits for Medicare beneficiaries. Therefore, in 1986 the Medicare Hospice Benefit (MHB) was made permanent by the Congress under the Tax Equity and Fiscal Responsibility Act and each state was given the option of including hospices in their Medicaid option. Hospice care was expanded beyond the civilian market in 1991, when it was authorized for military hospitals and for patients that were insured by the military though the CHAMPUS program. In the same year, hospices were also recommended for the Veteran's Administration and in 1992 it was recommended for the Indian Health Services (Gage, 2000).

Since the last decade, there has been a tremendous increase in the number of organizations or foundations that have funded a variety of end-of-life care projects. Some of these organizations include the National Institute of Health, the Robert Wood Johnson Foundation and the Archstone & Andrus Foundation. Due to this widespread recognition, there has also been a rapid expansion in the type of hospice services that are available and are being provided to terminally-ill patients. Hospices have broadened their scope of care, from not only providing services that were exclusive to cancer patients, but also to

patients with other life-limiting illnesses such as end-stage cardiac or pulmonary disease, advanced dementia and other chronic diseases. The concept of hospice is not only followed by the organizations who believe in the principles of providing compassionate care, but has also stimulated the interests of many national and international health organizations worldwide. For example in recent past, the National Institute of Health has funded a wide range of research projects related to cancer, Alzheimer's disease and HIV AIDS. The Department of Veterans Affairs (VA) has also initiated several important studies examining the best ways to improve care for terminally-ill veterans (Gage, 2000).

2.2.1. Hospice Facts and Figures

In the last three decades there has been a tremendous increase in the number of hospice organizations across the nation. The growth of the hospice industry in this country is represented in Figure 1. The proliferation of the use of hospice services among patients and their family members is shown in Figure 2, indicating that there is strong growth in public demand for these types of services. The facts and figures compiled by the National Hospice and Palliative Care Organization (NHPCO, 2004),

Figure 1: Growth in US Hospice Programs (National Hospice and Palliative Care Organization, 2004)

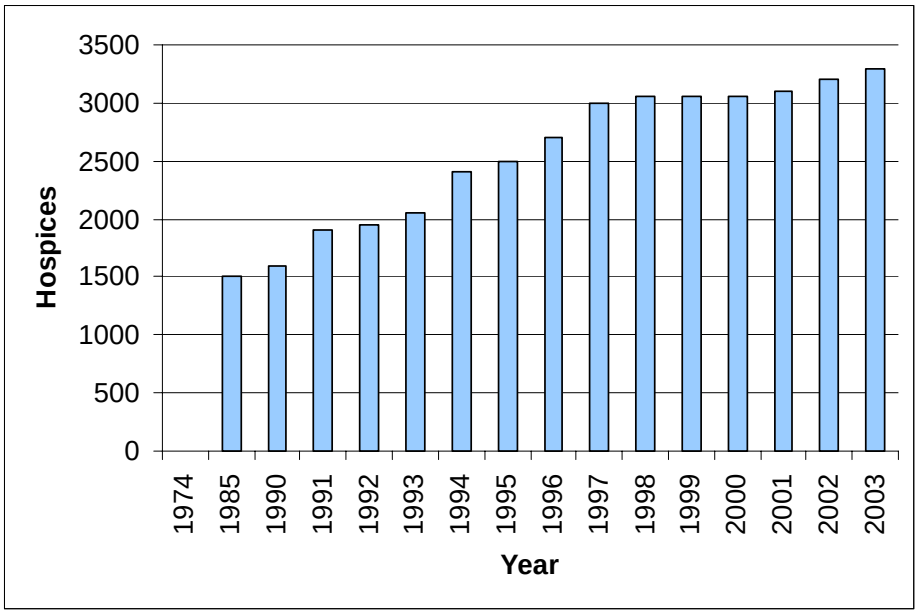
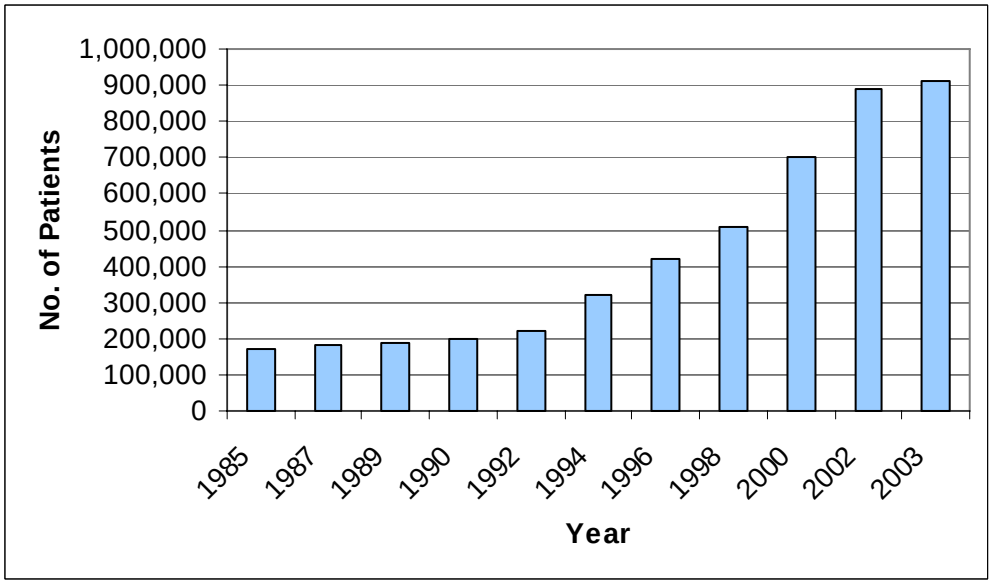


Figure 2: Use of hospice among patients between 1985 and 2003 (National Hospice and Palliative Care Organization, 2004)



showed that in 1992 there were about 1,900 hospices that were operationally functioning in the country, which by the end of 2003 this has jumped to 3200. Additionally, the number of beneficiaries using hospice services has increased four-fold between 1992 and 2002 (from 210,000 to 885,000). There was an almost eight percent increase in the number of Medicare-certified hospices between 2001 and 2003, where not-for-profit organizations (56%) represented the largest group. Additionally, during this same time period there was a significant increase in the for-profit organizations, which grew by almost 25% (NHPCO, 2003). The most recent report released by the NHPCO showed that by the end of 2003, there were more than 3300 hospice programs in the United States that included both primary and multiple locations for individual hospices. Of these 67% were non-profit, 29% were for-profit and 4% of the hospices were government organizations and approximately 95% of the hospice programs were Medicare certified and about 64% were accredited organizations (NHPCO, 2004).

Over the years, more and more people belonging to all age groups used hospice services. However, the fastest growth was reported in the oldest group, those whose age was 75 years and above (MedPAC, 2004). Between 1992 and 2002, the percentage of Medicare beneficiaries who died while in hospice care rose from 12 percent to 23 percent. Hospice use has increased for beneficiaries of each race, but it has been reported that white Caucasian beneficiaries tend to use the hospice benefit more than beneficiaries of other races. In 1992, most individuals who used hospice services had cancer as their primary diagnosis. By 2002, the profile of the typical user had changed and a growing number of beneficiaries with non-cancerous diseases seeking hospice care were reported.

Beneficiaries with non-cancerous diagnosis such as heart disease, dementia, lung disease etc. were among the fastest-growing groups of hospice patients (MedPAC, 2004).

One of the recent surveys conducted by Gallop organization, asked people about their preference for a setting where they would like to seek hospice care. The survey results showed that a majority of them (about 90%) reported their own home or a family member's home as the preferred care setting for receiving hospice care, if they were terminally-ill (Schumacher, 2004). Moreover, the 2004 NHPCO facts and figures report also showed that in the year 2003 almost about half of the patients (50%) enrolled in hospice died at home. Apart from home, about 23% died in a nursing home facility, 9% died in a hospital and about 7% died in a free-standing inpatient facility operated by the hospice. Data collected on patients who were enrolled in hospices in the year 2003 showed that a majority of the patients were male (54%), over the age of 75 years (63%) and were White or Caucasian (81%). About 9 % of the patients were African-American, 4% were Hispanic and 1 % of the patients were Asian/Hawaiian/Pacific Islander. Cancer diagnosis accounted for almost about 49% of the hospice admissions in 2003. The top five non-cancerous diagnoses in hospices included end-stage heart disease (11%), dementia (9.6%), lung disease (6.8%), end-stage renal disease (2.8%) and end-stage kidney disease (1.6%). About 37% of the patients served by hospices died in seven days or less and about 7 % died in 180 days or more. The average length of stay was reported to be about 55 days, while the median length of stay was 22 days (NHPCO, 2004).

2.3. Eligibility and Reimbursement for Hospice Patients

Medicare is the major source of funding that covers hospice services. Other groups that cover hospice care include Medicaid, Veteran's Affairs (VA) benefits and

various types of commercial insurance, such as those provided by health maintenance organizations (HMO), preferred provider organizations (PPO) and indemnity plans. However, since Medicare is the major payer for hospice services, the reimbursement structure, is defined by the Medicare guidelines.

Eligibility Criteria for Hospice Admission: In order to receive hospice care and services, patients must comply with the following conditions-

(i) Individuals should be certified as being terminal. They should have a life expectancy of six months or less, if the illness runs its normal course. This type of certification may be issued by either the individual's attending physician or the hospice medical director.

(ii) Individuals should desire hospice care. In other words, the individual must forego other Medicare services related to curative treatment of their terminal illness.

(iii) Individuals must have a physician who is willing to provide medical care and consultation.

Hospice Reimbursement: The Medicare Hospice Benefit (MHB) was established in 1986 for terminally-ill patients and is covered under Medicare Part A (hospital insurance). Medicare beneficiaries who choose hospice care receive a full range of medical and supportive services for their terminal illness. The reimbursement plan covers a wide range of services, including physician services, medical social services, medical appliances and supplies and medications related to the terminal illness and palliation of symptoms. Additionally, it also covers speech therapy, short-term inpatient and respite care, physical and occupational therapy, dietary counseling, homemaker and home health aide services, continuous care, counseling and social work service, spiritual care and

bereavement services. As long as individuals meet the eligibility criteria, they will be covered for all the hospice service they receive. The initial benefit period as defined by Medicare is 90 days, which may be followed by another 90-day benefit period. Subsequently, a beneficiary may qualify for an unlimited number of 60-day extensions. The only condition that is required to qualify for such type of enrollments is that, at the beginning of each benefit period, the medical director of the hospice must recertify the patient as being terminally-ill (MedPAC, 2004).

2.4. Medicare Hospice Payment Structure:

Medicare reimburses hospices on a per-diem basis. For each day a beneficiary is enrolled in the hospice program. The payment structure is based on four different levels of care, namely routine home care, continuous home care, general inpatient care and inpatient respite care. The daily payments on all four levels of care are fixed, regardless of patient case-mix or the services provided, which are outlined below (Gage, 2000; MedPAC, 2004).

Routine home care: Under routine home care, patients receive services only at home or in a nursing facility. This is the most common level of care and remains the only level of care that is provided to all hospice patients. This is clearly reflected in the 2004 NHPCO report, where routine home care accounted for about 95 % of patient days.

Continuous home care: This is an expanded level of care that is provided at home, where the individual may receive home health aide or homemaker services in addition to routine home care. This type of care allows the use of skilled nursing for up to 24 hours a day, in order to ease patients during periods of crisis so that further hospitalizations (that may occur if symptoms are not appropriately managed) may be prevented. This level of care is

paid on an hourly basis. According to the NHPCO 2004 report, this level of care accounted for around 1 % of patient days in hospice care in 2003.

General inpatient care: This level of care is usually provided for a short period of time in a Medicare-certified facility to patients with certain medical problems that require special types of nursing and medical management, which otherwise could not be managed in other settings. In other words, any individual whose care is complex and demands that the family can no longer continue to provide care at home is eligible for getting this type of care. According to the NHPCO report, this level of care accounted for four percent of patient days in 2003.

Inpatient respite care: At this level of care, patients receive short-term care at a different facility, which is aimed at providing a short period of relief to the family caregivers. Respite care is provided in a Medicare-certified facility. According to the NHPCO report, this level of care accounted for less than one percent of patient days in 2003.

2.4.1. Hospice Care Payment Issues

Hospices offer multidisciplinary and holistic care in a variety of settings. A majority of hospice organizations rely on Medicare for reimbursement for the services they provide to their Medicare beneficiaries. However, there are several reimbursement issues currently faced by U.S. hospice organizations pertaining to the payment structure established by Medicare (Weiner et al, 2003). Medicare reimburses hospices at a flat rate for each day a beneficiary is enrolled in the services, irrespective of the extent and intensity of services received by beneficiaries on any given day.

Table 1: FY2004 hospice payment rates for care and services furnished on or after October 1, 2003, through September 30, 2004 (CMS)

Description of Hospice Care	**Medicare Reimbursement Rate**
Routine Home Care	$118.08
Continuous Home Care	
Full Rate=24 hours of care ($29.66 hourly rate)	$689.18
General Inpatient Care	$122.15
Inpatient Respite Care	$525.28

The per diem rates are different for different levels of care that the patients may receive. The most common level of care or the default care that the patient receives is routine home care. Table 1 summarizes the rates for each level of care for the fiscal year 2004, as set by the Center for Medicare and Medicaid Services (CMS, 2003).

The method that Medicare employs for calculating the reimbursement payments for hospice services is very basic and has not been changed since the implementation of the hospice benefit program. In order to calculate the reimbursement rate, CMS considered the cost estimates for the main service components of routine home care. These cost estimates were analyzed from the data collected during the 1980-1982 Medicare Demonstration Project. Since then, CMS has made no major adjustments to the reimbursement rates, which thus fails to take into account any recent technological, pharmaceutical and medical delivery advancements. Compared to the care provided 20 years ago, today's hospices practice more intense levels of care, as they include more advanced and thus more expensive interventions, pharmaceuticals and treatments in their

care plan. Additionally the rates do not take into consideration certain factors such as patient case-mix or the extent to which services are provided. These payment rates are updated annually in two ways. Firstly, the rates increase or decrease regionally based on a wage index intended to account for local labor costs. The rates are adjusted annually on the basis of the wage index. In the second method, hospice caps are increased by the medical expenditure category of the Consumer Price Index (CPI) every year for all urban consumers. The reimbursement rates are adjusted annually to allow for the inflation rate. There are also different cost structures for hospices in rural and urban areas and the rates are adjusted according to the geographic location (MedPAC, 2004).

Although the daily payment rates for individual hospice are updated for inflation over time and are adjusted with respect to geographical location, the Medicare Payment Advisory Committee has submitted reports (MedPAC, 2002, 2004) to Congress suggesting the Secretary of the Department of Health and Human Services re-examine the cost of the services currently incurred by hospices. There were several reasons cited by MedPAC for recommending re-examination of the reimbursement rates. First, the current 2004 national Medicare per diem payment rate for the default service, which is the routine home care, was set to an amount of about $118. Within this limited payment system, hospices have to provide a wide array of services related to terminal illness, including physician services, medical social services, patient counseling (dietary, spiritual etc.), medical appliances and supplies, medications for pain control and symptom management, home health aide services and any other service that may be necessary to manage the terminal illness. Secondly, a majority of the hospices in U.S. function as small, free-standing, community-based organizations and may not have sufficient

resources to deliver optimal symptom management to their terminally-ill patients, because of which they may not be able to directly or contractually meet all the needs of the patient. Additionally, because of the limited daily reimbursement amount, hospices may not be able to cover some of the more expensive treatments such as diagnostic tests, drugs and other therapies.

The limited funding could actually lead some hospices to face economic incentives to select only certain type of patients (Lorenz, 2004). For example, some terminally-ill patients may require expensive treatments. They may require extensive care and thus may utilize more resources than others. Because some patients may be more costly than others, hospices tend to admit only those patients who are less expensive to treat. If they admit patients who are likely to be expensive, they may end up with a lower, or even a negative, profit margin on these patients. This will definitely affect for-profit organizations and therefore, some hospices may avoid patients who may need more complex care or who need more expensive care than the average patient (Lorenz, 2004; Huskamp, 2001). Huskamp et al. conducted a study where structured in-person interviews were taken of the health care providers who provide end-of-life care. They investigated issues pertaining to Medicare methods and rules and how the Medicare benefit design has influenced the provision of end-of-life care services among providers. Although most of the respondents in the study appreciated the comprehensive nature of the Medicare coverage, a majority of them reported that the reimbursement rates were very low, because of which it was difficult for them to provide expensive medications, procedures such as chemotherapy, certain types of DMEs, etc. The study concluded that

the reimbursement rate paid by Medicare in the hospice benefit program was inadequate and that the rates did not reflect hospice treatment patterns.

In order to explore some of the financial challenges faced by hospices, the NHPCO sponsored a study (Cheung, 2001) that compared hospice costs with hospice revenue. Based on an analysis of 1998-1999 hospice cost and service data collected from nearly 10,000 patients, the study identified two important contributors that were responsible for the imbalance between hospice costs and revenues. The study demonstrated that an increase in the intensity of hospice services has led to a considerable increase in the hospice cost per day. The rapid growth in prescription drug and outpatient costs has especially contributed to this increase. In addition, the study also showed that Medicare does not reimburse hospices for essential services and activities such as grief and bereavement support and volunteer coordination that add to the total hospice care costs.

Moreover, the June 2004 report published by MedPAC, reported that there was a growing concern amongst hospices about the prices of the drugs that are typically used by terminally-ill patients. The skyrocketing prices of such drugs were causing the total pharmacy costs to rise, because of which the pharmacy costs constituted a major proportion of the total expenses incurred by hospices. However, very little is known about the type, mix, intensity, or acquisition costs of the drugs that hospice patients use. Nowels et al. conducted a study, where they analyzed the pharmaceutical cost data collected from a cross-sectional survey of 34 hospices and studied their trends. Most of the survey respondents reported that they had incurred higher pharmaceutical-related costs between 1998 and 2002; but very few reported that their costs had actually

decreased. The study also showed that the pharmaceutical costs varied by patient setting (Nowels, 2004). A recent report released by Families USA, a nationally based watchdog group, showed that there has been a steep increase in the price of drugs, especially for those that are used in the elderly population. The percentage increase on the drug prices in the year 2003 did not match the inflation rate, but surpassed it, thereby indicating that the medications had become relatively more expensive than the previous year. The group studied the drugs specially used among elders and concluded that the prices on the 30 of the most widely used brand-name drugs rose by about 6.5 % between January 2003 and January 2004. Out of those drugs, the prices on 26 of them had increased by about 22 % over a span of just three years (Families USA, 2004).

It has been reported that the prices of drugs are increasing at a rate of about 15% to 20% each year and those that are specifically used in hospices are rising at a rate of 18.3% per year (American Health Consultants, 2000). It is also reported that in hospices, a sharp increase in the drug price has led to an increase in the total pharmacy costs, which now accounts for the biggest portion of the hospice's direct costs (American Health Consultants, 2000). The drug costs and therefore the total healthcare costs, could be rising, because of higher drug utilization, inappropriate drug utilization and an increasing elderly population (American Academy of Actuaries, 2001). However, if no appropriate measures are taken, it is estimated that these drug costs may double in a three to five years period. In order to address the ongoing challenges and issues, experts in the field have suggested some of the strategies such as –

- Hospices should manage their predictable costs

- Hospices should try to influence the payers (CMS) to increase the reimbursement rates
- Hospices should try to measure costs and outcomes to determine the effectiveness of the drug agents and carefully select those agents for the formulary which are more cost effective (American Health Consultants, 2000).

In order to combat some of the financial challenges that hospices are facing today, individual hospices would be required to step up and adopt appropriate measures such as containing the rising drug costs, which will allow them to optimize therapeutic care and therefore the end-of-life care they provide. In order to control their overall costs, especially those related to the use of drugs, hospices would have to implement some cost-containment strategies at their local centers. Implementing a rational drug formulary is one of the cost-containment strategies recommended by experts in the field, which will allow only selected drugs with established safety and efficacy profile to be used at the hospices (American Health Consultants, 2000).

2.5. Drug Formulary and Formulary System

There is no single definition for 'formulary,' but instead various concepts and definitions have been coined to describe the concept of formulary and formulary system. According to the American Society of Hospital-Pharmacists (ASHP) and the American Hospital Association (AHA), a hospital formulary is defined as a "continually revised compilation of pharmaceuticals (plus important ancillary information), that reflects the current clinical judgment of the medical staff" (Lipman, 1992). The concept of a drug formulary is not limited to hospitals, but has also been adapted in a variety of health care settings such as a PBM or an HMO. While a formulary is a simple listing of drugs to be

used in a given practice setting, a formulary system is a method through which the medical staff of that institution, works through the Pharmacy and Therapeutics (P&T) Committee and evaluates, appraises and selects drug products from among several available drug entities and drug products considered to be the most useful in providing optimal therapeutic care (AMCP, 1997).

2.5.1. Historical Perspective of Drug Formularies

Although the very first formulary in the United States was published for the Continental forces during the American Revolution, it was only in 1816 that the first formulary for a private civilian hospital was compiled (AJHP, 1986). Later, in 1933, the first ever guidelines for operating a formulary system were formulated by Dr. W.J. Stainsby, a physician and Dr. Robert A. Hatcher, a pharmacologist. The recommendations provided by Stainsby and Hatcher about the development of drug formularies had a tremendous influence on the growth of formularies in American hospitals. The principles of developing a formulary they proposed served as a useful guide to the operation of formulary system in American hospitals. In 1936, it was proposed that a special committee be established in hospitals, consisting of representatives from medicine and pharmacy areas that should primarily function as a liaison between the two specialized fields. In 1965, the Joint Commission on Accreditation of Hospitals encouraged all hospitals to establish a Pharmacy and Therapeutics Committee and recommended that they develop a drug formulary to be used at their institutions, (AJHP, 1986). Over the years, national organizations such as the American Society of Hospital Pharmacists (now known as the American Society of Health-System Pharmacists or ASHP) have taken the initiatives to clearly define the

requirements and responsibilities of the P&T Committee. ASHP has drafted several documents such as the *ASHP Guidelines on Formulary System management*, *ASHP Technical Assistance Bulletin on Drug Formularies* and *Principles of a Sound Drug Formulary System*, each of which were specifically designed to educate P&T committees in hospitals and other health care institutions about the principles and the process of developing a drug formulary.

2.5.2. Types of Drug Formulary

Open, closed and incentive-based are the three basic types of formulary that have been adopted and are currently being employed in health care institutions such as hospitals or HMOs or PBMs.

Open Formulary: This is the simplest type of formulary and consists of all the drugs used by the medical staff. It is often referred as an open or unrestricted formulary because it contains a comprehensive list of drugs and has very few, if any, restrictions on the providers. In this system, the payer (the health plan, the employer, or a pharmacy benefit management company [PBM] or an employer) primarily provides coverage for all drugs, regardless of whether they were listed on the formulary. Patients may not incur additional out of pocket expenses for using non-formulary drugs. Since there are no restrictions if the preferred product is not dispensed, this type of formulary often has little impact on physicians' prescribing habits. As a result, it is not effective in controlling utilization and expenses (AMCP, 1997; Goldberg, n.d.).

Closed/ Restricted Formulary: A closed or restricted formulary contains a narrower list of drugs and it restricts medical staff to prescribe only those drugs that are listed in the formulary. In this type, only the formulary agents are reimbursed, while the non

formulary drugs are not reimbursed by the payer. This list usually consists of brand-name drugs along with the generics for these brand-names which are also covered. Such formularies generally offer several choices in each therapeutic category. In this type of formulary, the P&T Committee develops specific protocols for obtaining authorization to use a non-formulary drug. Such authorization may require a letter from the prescribing physician stating that the particular medicine or drug is of a medical necessity. Compared to open formularies, closed formularies provide more rational choices of drugs or therapeutic agents (AMCP, 1997; Goldberg, n.d.).

Incentive-based Formulary: An incentive-based formulary is one that promotes the use of preferred drug products through some kind of incentive system. The incentive can be offered either to the physician, the pharmacist, or the patient. For physicians, the incentive is usually in the form of a risk-sharing agreement between the physician and the payer. In other words, physicians can be at partial or full risk if they sometimes or never follow the drug formulary list. If the physicians do not prescribe formulary drugs, part of their capitation allowance is withheld and prescription costs are deducted from this withhold. At the end of the contract period, the physicians receive the money remaining in the withhold account. The most common type of patient incentives is the price differential offered to patient for preferred and non-preferred drugs (say for example the patient pays $5 co-payments for generic drugs, $10 for preferred branded drugs and $35 for non-preferred drugs). In these instances, patients will have a financial incentive to request preferred medications over non-preferred drug (AMCP, 1997).

2.5.3. Usefulness of Drug Formularies

Drug formularies typically serve two main purposes. They primarily serve to control and contain the total drugs costs and secondly, they also aid in improving patient care. There are several reasons as to why formularies could result in reduced total costs. First, since only a limited number of drugs would be present in the formulary, it is not necessary for the pharmacy to purchase a vast variety of medications in small amounts. Second, if the pharmacy carries only formulary products, they can benefit from a variety of discounts for purchasing specific medications in large quantities (Olmstead, 1999). Lastly, as the formulary includes a list of the best drugs (with respect to efficacy and safety aspects) from among several drug products that are available, they tend to reduce some of the additional costs (for treating side effects or adverse effects) that may occur if inferior or less superior products were prescribed. For all these reasons, prescriptions of formulary drugs will tend to control the overall costs.

Drug formularies may also aid in improving patient care, in the sense that a well-designed and rational drug formulary will limit the number of prescriptions to include only those drugs that have been found to be the most effective for a given condition and patient population. Thus, physicians who strictly follow the formulary will prescribe the best possible drug available for patients, which should produce better results. As physicians are also involved during the drug reviewing process of the formulary development, the system helps to reeducate them about the alternative therapies with respect to drug efficacy and safety. During this process, they tend to become more aware and experienced about the chosen drugs with established superiority, which may actually result in reducing certain kinds of risks such as medication errors and adverse drug

reactions that might otherwise occur, if other unsafe and less efficacious drugs were prescribed (International Foundation, n.d.).

There is plenty of evidence in the literature that suggests that drug formularies, when carefully implemented, may significantly reduce the overall drug costs. Studies have shown that various components of the formulary system, such as therapeutic interchange, generic substitutions and use of drug protocols or guidelines, reduce the overall drug cost (Roberts, 1986). However, discrepancies in the benefits of drug formularies as a cost containment tool have also been reported in the literature (Kader, n.d.; Jewesson, 2000). Although, there is evidence suggesting that the development of drug formularies may provide quality care to patients and consequently aid in containing the additional costs that could have incurred by the health care institution, few studies have shown that formularies may actually increase costs. A study conducted by Horn et al. (1996) examined the relationship between various HMO cost-containment strategies and the utilization of ambulatory care visits, hospital admissions and prescription drugs. The study showed that for most disease conditions, formulary limitations on drug availability were significantly and positively related to higher rates of emergency department visits and hospital admissions and positively related to drug cost, drug count and office visits. Other researchers (Skaar, Oki, & Elenbaas, 1992; Dunne & Soberman, 1993) have argued that formularies could not be an effective cost-containment tool if inadequate decision criteria were used to support formulary decisions. Although, there is ambiguity reported for the effectiveness of the formularies, most experts in the field still favor the concept of drug formularies. The literature has continuously stressed that more

work needs to be done in this area before any strong conclusions could be made as to whether or not formularies can actually serve as an effective cost-containment tool.

2.6. Formulary Development

Formulary development is a systematic and rational process by which a formulary, a preferred list of drug products, is constructed and continuously revised to reflect improvements in available therapies to be used in current clinical practice (AMCP, 1997). Such a process is based on a combination of the clinical experiences of the medical staff and an evaluation of scientific data. In a typical formulary system, the P&T committee, or sometimes a group of medical staff, of a health care organization evaluates, appraises and selects appropriate drugs they consider would be most useful for patient care and includes them in the organization's formulary. Normally, the staff reviews and updates the formulary on a regular basis (such as quarterly or half-yearly) depending upon the organization's review policy. The organization generally appoints a P&T committee to review the drugs being considered for formulary additions or deletions. The typical functions of the P&T Committee include determining which drugs are available, who can prescribe specific drugs, implementing policies and procedures regarding drug use, conducting quality assurance activities such as drug utilization reviews and drug use evaluations, reporting adverse drug reactions and educating the clinical staff and patients about appropriate drug use (AMCP, 1997).

It is a common practice for the pharmacy department to do much of the preparatory work for the P&T Committee. Pharmacists play a key role in the formulary development process and are also responsible for the success of formulary management. Pharmacists have the knowledge and skills needed to coordinate the activities of the P&T

Committee and lead formulary management initiatives. Pharmacists usually have the vital expertise required to guide the P&T Committee through the steps of deciding whether or not particular drug(s) should be selected for inclusion in the drug formulary. Additionally, they are also responsible for analyzing and circulating scientific, clinical and economic information to the P&T Committee members and communicating the decisions taken by the committee to the prescribers and other health care professionals and patients, as appropriate (AMCP, 1997).

2.6.1. Approaches to the Formulary Selection Process

The P&T Committee plays a very important role in drug therapy problem solving. They collaborate with physicians and educate them about criteria-based prescribing and also help them to understand the process of developing disease-specific treatment protocols with individually tailored drug therapy. Generally, the P&T Committee operates under certain time constraints and therefore, it would not be feasible for them, time-wise, to perform a detailed review of every single drug entity proposed for formulary addition or deletion. Therefore they usually follow a scientific protocol or guideline that allows them to provide optimal drug therapy while maintaining or improving outcomes and simultaneously controlling costs (Olmstead, 1999). Some of the approaches for drug selection mentioned in the literature (Crane, 1993) include inventory management, cost accounting and criteria-based approaches, which are summarized in Table 2.

Inventory Management Approach: This is a simple method of formulary selection but is not always the ideal approach. In this approach, drugs are compared only on the basis of their acquisition cost while clinical implications of the drugs being compared, such as

efficacy and safety, are considered to be equivalent. In other words, the drug agents being compared are considered to be bioequivalent. The biggest advantage of using this method is that it is not time-consuming. However, the most critical disadvantage is that it assumes all agents in a therapeutic class have equal safety, efficacy and bioequivalence profiles, which is a limiting factor when selecting the most appropriate drug agent within a particular therapeutic class.

Table 2: Types of Approaches to the Formulary Selection Process:

	Inventory Management Approach	**Cost Accounting Approach**	**Criteria-based Approach**
Assumptions	All agents in therapeutic class have equivalent safety, efficacy and bioequivalence	Relative equivalence for agents in a therapeutic class regarding safety, efficacy and bioequivalence and associated costs	Quantifies agents with regards to safety, efficacy and bioequivalence
	Focuses on acquisition cost	Accounts for drug-driven costs; focuses on total identifiable costs	Focus is on overall therapeutic outcomes of the decision
Objectives	Compare and select drugs	Compare and select drugs	Optimize therapeutic outcomes cost-effectively
	Decrease acquisition cost/unit	Minimize acquisition cost and drug-driven costs	Decrease overall costs of therapy
	Decrease inventory carrying costs	Decrease inventory carrying costs	Decrease overall costs of therapy
			Develop objective patient outcome measurement tools

Cost-Accounting Approach: This method is slightly different from the inventory management approach in that it assumes equivalent relative safety, efficacy and bioequivalence of drugs within a therapeutic category, but takes into account the acquisition and other associated direct costs as well. Although this method takes into

consideration all direct costs associated with a drug's use, it also fails to quantify uncertain events such as adverse drug effects or treatment failures.

Criteria-based Approach: This is the most appropriate approach to the formulary process and allows decision-makers to be aware of all the available options and possible consequences (both clinical and economic) of the decision. The primary goal of this approach is to develop a therapeutic formulary which emphasizes the clinical and economic outcomes associated with the formulary decision (Crane, 1993).

It is, however, very important for the P&T Committee to note that the application of a carefully designed formulary, theoretically, provides the foundation for guiding clinicians in choosing the safest, most effective drug agents for treating particular medical conditions. Selection of the best medication for inclusion in the formulary can be achieved by rationally evaluating all drug alternatives in all relevant aspects or criteria, such as drug safety, effectiveness and efficacy, particularly in relation to all similar agents belonging to the same therapeutic class.

2.7. Criteria for Drug Selection: Selecting the drugs to be included in the formulary is the most important function of the formulary system. The evaluation of drugs and drug classes requires a rigorous approach that looks at some of the documented parameters or criteria on the basis of which appropriate drugs would be selected. The most common approach followed for the drug selection process is based on a multiple-criteria decision making process. As the drugs are selected by comparisons made on multiple parameters related to drug characteristics, a multifactorial selection process should be considered (Rational Pharmaceutical Management Plus Program, n.d.). Some of the important factors or criteria that are commonly used for the purpose of drug selection are drug

efficacy, drug safety, drug availability and drug costs, each of which is described below (Chambliss, 1996).

Drug Efficacy: Efficacy is generally the most vital characteristic of a drug agent. Questions such as how well the drug treats the disease or symptom for which it is prescribed are used to quantify or assess its efficacy. The best information on the efficacy should be gathered from large, randomized, double-blind studies in populations of patients that are similar or representative to one's own patients.

Drug Safety: The safety parameter is the second most important characteristic of the drug agents that should be taken into consideration. The safety profile of a drug is measured by reviewing three criteria: the frequency of major adverse effects, the frequency and severity of drug interactions and the frequency of side effects associated with the medication.

Drug Availability: There are several factors that can be used to assess the availability of a particular drug. These include factors such as the frequency of administration, dosage form availability and availability in different strengths.

Drug Costs: The final criterion that is utilized for drug selection purposes is the cost of the drugs. If all the above parameters are roughly equal, then drug costs are used to compare different drug agents. Generally, when comparing drug agents, acquisition costs of the drugs are taken into consideration.

2.8. Methods for Developing a Drug Formulary

In order to develop a drug formulary which is both clinically sound and efficient, it is very important for the P&T Committee or any other drug selection committee to incorporate certain rationality into their decisions. Sometimes formulary-related decisions

are intuitive. For example, a particular drug could be easily selected or included in the formulary because it is less expensive than similar drug agents that are equally effective and safe. Other times, decisions regarding drug agents are complicated and require members of the P&T Committee to weigh numerous criteria, such as efficacy, safety, economics and other outcome issues in their decisions. In such situations a more practical approach is needed to judge multiple considerations for the drug selection process. Some of the methods that have been used successfully in the past for drug formulary development include Multi-Attribute Utility Theory (MAUT), Clinical Decision Analysis (CDA) and System of Objectified Judgmental Analysis (SOJA). Regardless of the methods used for developing the formulary decisions made by or taken by the P&T Committee or drug selection team involve working on some of the basic principles of decision making theory that are outlined below.

2.8.1. The Decision Making Perspective

Decision-making is a process by which a person, group, or an organization identifies a choice to be made. They gather and evaluate information about alternatives and select the best one from among the available alternatives. The way people can and do make decisions varies considerably. Some of the early research in decision-making has focused on how one makes decisions or how one should theoretically make decisions. A variety of theories (also known as decision analysis theories) have been proposed in this field, from which a wide range of decision making models have emerged. Depending upon the methodological foundation, basic types of decision making models are classified as descriptive, prescriptive or normative (Chase, Crow, & Lamond, 1996; Thompson, & Dowding, n.d.)

Descriptive decision model: A descriptive decision model typically deals with how people make their judgments or decisions. The goal of this model is to understand and predict choices. The approach used in this model involves human cognitive functioning and therefore such models are generally used during the initial structuring of the decision.

Prescriptive decision model: In contrast to descriptive models, the prescriptive model helps individuals improve their judgments by examining how they actually make their judgments or decisions. This method tries to clarify certain perceptions of the attributes associated with the alternatives so that there are no inconsistencies, confusions, or biases on part of the decision makers and then alter the decision rule.

Normative decision model: This model assumes that an individual or a group is rational and logic and focuses on how decisions should be made in an ideal world. A normative approach is a very formal and mathematical approach and is often concerned with how good a judgment or a decision within the group is, while not really considering how those judgments or decisions were made in real life. (Chase, Crow, & Lamond, 1996)

These basic models are not helpful when decisions are to be made in a more complex situation such as selecting appropriate drugs for a formulary, where decision makers have to make their decisions regarding including or excluding specific drugs based on multiple evaluating criteria. In order to make decisions based on multiple criteria, additional decision-making models have been proposed and developed. Models such as prescriptive models with an attribute focus have been proposed and are being used in health care as well as in business research.

Prescriptive Model with Attribute Focus: In this model, the decision rules are based on economic theories such as Subjective Expected Utility Theory (von Neumann &

Morgenstern, 1944) and mathematical principles such as Bayes Theorem (Edwards, 1961). In this method, the decision maker responds to a series of questions about the attributes that compose real or hypothetical alternatives and their priorities or weights are noted. Based on an *a priori* decision rule drawn from normative theory, the decision analyst constructs a representation of the decision makers' preference, which is then used to assist the decision maker in making better decisions (Carroll, & Johnson E.J, 1990).

Requisite Decision Model: If a group is involved in the decision-making process, then principles outlined in the basic decision analysis models are no longer applicable; as the basic models take into account individual persons' perceptions rather than a group's perception. A few researchers (Philips, 1982) have argued that the traditional decision analysis models are not appropriate in a group setting for the simple reason that every person in the group who has a stake in the decision has a different view of the problem and a different opinion. Moreover, these methods are either not capable of using or have not used sensitivity analysis as a method of dealing with differences in opinion. Thus, basic decision-making models are applicable only when there is a single decision maker, as the preferences of a single individual are only taken into consideration. Therefore, whenever a group is involved, it is necessary to include the perceptions and views of all those who are responsible into the model. A model in which decisions are made based on such group considerations is referred to as "Requisite Decision Modeling" (Philips, 1982).

In this type of modeling, it is expected that individuals may change their view or differ in their view of the problem during the development of the model. Sensitivity analysis thus plays a key role in incorporating such changes, which helps resolve

disagreements and also allows one to check whether views from one or several decision makers affect the conclusions drawn from the model. The Multi-Attribute Utility Theory (MAUT) is one such example of a requisite decision model which has been widely used in the engineering, business and health care arenas.

2.9. Drug Selection Methods for Formulary Development: There are several drug selection methods or techniques that have previously been employed by P&T or drug selection committees at hospitals, or health care institutions. These methods include:

- Multi-Attribute Utility Theory (MAUT)
- Clinical Decision Analysis (CDA)
- System of Objectified Judgment Analysis (SOJA)

They are discussed next.

2.9.1. Multi-Attribute Utility Theory (MAUT)

The Multi-Attribute Utility Theory (MAUT) is one of the decision models that is based on principles of a 'prescriptive model with an attribute focus' and 'requisite decision-making model'. This method was developed as a decision aid by Keeney & Raiffa in 1976 (Cooksey, 1996). It was an extension of modern utility theory that is also known as the Expected Utility Theory, which was developed by von Neumann and Morgenstern in 1944 (Eils, & John, 1980). The MAUT method can be applied in situations where

(i) programs have multiple members and the interests or decisions of those members are to be taken into consideration

(ii) a decision based on a comparative evaluation is to be undertaken

(iii) a decision about a particular action is to be taken, which can be explained by multiple attributes and the evaluations have to assess how important these attributes are for the decision maker in making their final decision

(iv) judgments are a part of any evaluation and the magnitude of those judgments have to be explained numerically.

The MAUT method provides a theoretical basis for representing the experts' judgment and views related to a real event and translating them into a mathematical function. (Keeney & Raiffa, 1976; von Winterfeldt & Edwards, 1986). The key steps in this method involve

- defining a set of attributes
- designing a scale to measure each attribute and
- assigning a weight that denotes the relative contribution of the individual attribute to the total evaluation.

In MAUT, specific instances of an event are referred to as '*entities'*, which are objects that individuals within a group can assess and then assign numerical scores to provide a value. A key principle of this theory is that the subjective valuation or preferences of entities given by individuals in the group can be expressed mathematically. For example, in this study a drug formulary will be developed using a drug selection process. Therefore, each drug that will be considered for initial formulary inclusion will be referred to as an entity of the drug selection process and the score assigned by individuals is an individual's own subjective value, or in other words it's a personal preference for that entity. The next sub-component in this method is called an '*attribute'*. Attributes are characteristics or simple features of an entity, which when

taken together describe the overall phenomenon of interest. For example, in this study, the different attributes that will be considered for the drug selection process include drug characteristics or attributes such as drug safety, drug efficacy, drug availability and drug costs.

The next important aspect in this method is to understand that entities may vary from one another with respect to the degree or amount of an attribute. For example drugs under formulary consideration may vary from each other in the degrees of efficacy, safety and cost parameters. Therefore, comparing alternatives (drugs) that are assessed on different attributes, which are measured on different scales, may present a problem to the decision makers who need to choose and decide upon the best option. To tackle this problem, the theory has suggested the use of either quantitative scales (0-100 scale) or phrase anchored strategies (Likert-type scale such as; Not at all – At all times), which will allow one to translate the subjective assessment of entities on all attributes on one common scale. The values obtained on these scales are referred as the '*single-attribute utilities'*, which represent the subjective valuing of a specific entity on a specific scale.

Within MAUT, each attribute contributes individually to the final composite of a given entity. Entities may vary in the amount or level of each attribute they have. Translating these amounts or levels into numbers reflects decision makers' desirability which helps capture the subjective value or preference. Sometimes this translation is straightforward in the sense that higher levels correspond to greater desirability (e.g. drug safety; higher the safety profile, greater will be the individual preference). However, sometimes inverse translations may also exist, so that the decision makers' evaluation for that attribute may indicate that the lower value is always better than the higher value.

(e.g. drug cost; higher the cost of the drug, lower will be the individual preference) Additionally, attributes may also vary in their contribution to the final score and overall assessment. In order to identify the contribution of individual attributes to the final score, a weight is assigned to each attribute, where the weight reflects the importance of that attribute to the overall evaluation. Individual attribute scores across all attributes are combined into a composite score with the help of aggregation function, such as additive or multiplicative function. Finally, the score resulting from this mathematical function serves as a global evaluation of subjective valuation. Higher scores imply greater subjective valuation; lower scores imply lower subjective valuation. The scoring scheme for each attribute and for the total model, is developed through an iterative process. Scoring of a particular entity results from a weighted sum of the evaluation of entity on each of the single attribute scales, this is multiplied by the weight for that specific attribute.

Applications of the MAUT methodology typically involve the following steps:

(i) List a set of all alternatives or options that needs to be evaluated

(ii) Specify a set of attributes with respect to which each alternative that is to be evaluated

(iii) Numerically assess the value of each alternative with respect to each attribute

(iv) Rank order and assign weights to each attribute in terms of importance

(v) Employ appropriate mathematic evaluation rule to determine the overall value of each alternative

Some of the earlier evaluation studies (Bronner & De Hoog, 1983; Humphreys & McFadden, 1980) have shown that users' acceptance and evaluation of MAUT decision

aids are favorable. While Humphreys and McFadden found that with the help of the MAUT method individuals became more capable of making decision, others (Aldag & Power, 1986) found no differences between aided (with MAUT) and unaided decision making methods. The MAUT method has also been applied in the field of nursing as well as in health care. It has been specifically used for treatment decision-making models and in the formulary decision making process (Brennan & Anthony, 2000; Schumacher, 1991; McCoy, 1998; Schapira, 2004). There are several studies which have used the MAUT methodology for making formulary decisions regarding particular drug classes. Schumacher has used the MAUT to make a formulary decision involving calcium-channel blockers (Schumacher, 1991), while McCoy et al used this method for evaluating and including Histamine H_2-receptor antagonists in the formulary.

2.9.2. Decision Analytical Technique /Clinical Decision Analysis

The process of decision-making generally involves choosing the best option after weighing the risks and benefits of all the available alternatives. A clinical decision very rarely involves choosing only one possible option with absolute certainty of its outcomes. Rather, clinicians are often challenged with situations involving a range of options all with an uncertain outcome either associated with diagnostics or treatment. While all clinical decisions are made under conditions of uncertainty, the degree of uncertainty decreases when the literature addresses or publishes relevant evidence. However, where there is less evidence or very few published studies found in the literature, the uncertainty increases. One of the approaches for making decisions under uncertain conditions is “Clinical Decision Analysis” (CDA). It is a quantitative method used for making decisions and incorporates both probabilistic data and value judgments, along with

clinical and economic factors. It provides a method to link choices, actions and outcomes. The method requires decision makers to outline the decision they are faced with and to identify the consequences of all possible outcomes of that decision. Clinical decision analysis is *explicit*, that is it forces one to structure the decision as well as identify the consequences of the possible outcomes. It is *quantitative*, in that it forces one to assign numbers to probability estimates and outcome valuations. It is *prescriptive*, in that the analysis identifies the decision route to take to maximize the expected value of the decision (Schumacher & Barr, 1995). Thus CDA is a systematic approach that has been employed to

- assist the decision maker to identify the available options
- predict the consequences and outcomes of each option
- assess the likelihood or probability of each result occurring
- determine the value of each outcome and finally
- select the decision option that will provide the best returns

Applications of the CDA method: The clinical decision analysis method has been used for a wide variety of decisions-making processes. It has been applied to select drugs for addition to a formulary; to conduct a cost-effective analysis; to determine a treatment strategy; to interpret therapeutic drug monitoring; and has also been used to set targets for national health policy outcomes. The method is quantitative in that it requires one to assign values (monetary or non-monetary) to the possible outcomes. Therefore, it has been used as a tool to measure or predict the estimated costs and/ or outcomes, if prior knowledge about all possible options, as well as probability or uncertainty of the consequences of those options is available (Barr & Schumacher, 1994). This method has

also been used as a tool to aid P &T committee in the selection of drugs for formulary addition (Kresel, 1987; Cano, 1988; Barriere, 1991). Kresel et al. (1987) conducted a study where they employed CDA as a decision analysis tool in the selection of a third-generation cephalosporin for formulary addition. The study used a combination of information in the medical literature and a panel of experts to assess probabilities, with hospital-specific costs included as an outcome measure. Based on this information, a decision tree was developed and a final decision regarding the drug selection was made.

Steps in the decision analytic process: The different steps involved in the clinical decision analysis (Schumacher & Barr, 1995) approach include:

(i) Identify and bound the decision: In the first step, general rules are set with respect to the decision maker and decisions that will be taken. The following questions are answered at this stage: (a) Who will be the decision maker? (b) What is the decision and what alternatives will be considered in the decision? (c) Over what time period will the analysis apply? That is how long into the future does the decision maker want to extend the analysis? Answers to the following questions will assist in properly structuring the decision and also in collecting appropriate data.

(ii) Develop a decision tree: In this step, a decision tree is constructed to provide a framework for the elements of the decision, which helps to explicitly identify the possible consequences related to all available options. For each option, the decision maker sequentially identifies the consequences of that alternative by asking a series of “what if” questions.

(iii) Assess the probabilities: For each alternative, the decision maker estimates the probability of occurrence for each consequence related to that option, which are

quantitative estimates of the decision maker's sense of how likely the various consequences are to occur. In clinical situations, probability values can be obtained from the literature or derived from an expert panel.

(iv) Value outcomes: The purpose of this step is to quantitatively value the worth of different outcomes associated with each option so that they can be compared to all possible alternatives. For each possible outcome, the unit of quantification should be the same within a decision analysis. For example, if costs were measured in terms of their dollar amount, then the same metric should be used across all decision paths.

(v) Choose the preferred course of action: In order to choose the best option, the value of each outcome measure for that alternative is combined with its probability of consequences of actions that could occur. This is called averaging out and folding back. It is performed for all outcomes measures associated with each alternative. All outcome measures associated with a particular alternative are multiplied by their corresponding probability values and such values are then added across that particular option. The obtained additive value is referred as the "*expected utility measure*", which is nothing but the weighted average of the value of all possible outcomes, where the weights are the probabilities of the events occurring. The alternative that has the highest expected utility score is finally selected.

(vi) Perform sensitivity analysis: Sensitivity analysis is conducted to demonstrate the validity or strength of the data collected. The probabilities of the key events are varied and their influences on the related outcomes are observed. Confidence in the

study results is raised if variations in the values of the study variables do not change the conclusion.

2.9.3. System of Objectified Judgment Analysis (SOJA)

System of Objectified Judgment Analysis (SOJA) is another model that has been employed for the drug selection process, specifically for formulary purposes. This method, initially called the System of Objective Judgement Analysis, was devised by Robert Janknegt and was specifically established for the purpose of developing a drug formulary. In this method, health outcomes data are utilized for the purpose of selecting pharmaceutical products for a formulary. The system is based on a 'vendor rating' principle and uses methods such as linear averaging or weighted factor score methods for the computation of the total SOJA scores. As only drug-related selection criteria (not patient-related factors such as age, co-morbidity, sex, etc.) are taken into account, the SOJA scores that are computed are used only as a formulary decision making model and not for drug decision making in treating individual patients (Janknegt, 1997).

Steps in the System of Objectified Judgment Analysis (SOJA): The SOJA method is a three-stage process which is outlined below (Janknegt, & Steenhoek, 1997).

(i) Select criteria for decision making: In this method, selection criteria for a given group of drugs are prospectively defined and the extent to which each individual drug fulfils the requirements for each criterion is studied. Generally, a panel of experts (either a P&T Committee or drug selection committee) is responsible for determining the selection criteria for the class of drugs under consideration. The selection criteria include clinical efficacy, incidence and severity of adverse effects, dosage frequency, drug interactions, drug cost, number of formulations and

indications and supporting documentation. This is a standard set of criteria, which is used in all SOJA methods. Apart from these criteria, there are some group-specific criteria (e.g. effect of beta blockers and ACE inhibitors on mortality when used for hypertension) that may be added. Information on all the selected criteria is collected either from the pharmaceutical manufacturers or through a comprehensive literature search.

(ii) Evaluate evidence for selection criteria: The expert panel weighs each of the selection criteria according to its perceived importance and determines the relative score for each therapeutic agent in the class, resulting in a single composite score that can be used for ranking purposes. The drugs are ranked according to the final composite scores and the drug with the highest overall score is considered most suitable for formulary inclusion.

(iii) Perform sensitivity analysis: In the final step, every individual on the expert panel uses their own relative scores with changed weightings (weights are changed as deemed appropriate) and the effect on their selection process is observed**.**

2.10. Selection of Specific Medical Conditions for the Study

Typically, any P&T Committee or the drug selection teams who are primarily responsible for developing and maintaining drug formulary, perform a variety of functions and contribute significantly to the goal of providing rational drugs to be used for their patients. Some of their crucial roles include optimizing rational drug use by evaluating the clinical use of drugs, developing policies for managing drug use and managing the formulary system. For the purpose of maintaining a drug formulary, the

committee undertakes routine drug class review activities, where comprehensive review of a complete section of drugs under each drug class is performed. As there are numerous drug products available under each drug class that are employed for managing a variety of medical conditions, the review process is usually cumbersome and time consuming. Thus, the review process for all current as well as new drugs are generally evaluated in a systematic manner, starting with certain selected medical conditions or drug classes, which is then followed by others so that the entire formulary is reviewed over a two-to three-year period. A majority of those who are responsible for developing drug formularies report that it is a common practice to they start the drug selection process based on the needs of the community or they could focus primarily on those conditions that have been identified locally as being an expensive or even difficult to manage (Rational Pharmaceutical Management Plus Program, n.d.).

For this study, congestive heart failure and depression were chosen as the conditions for which hospice formularies will be developed. The next section of this chapter will deal with describing these conditions in details.

2.10.1 Congestive Heart Failure (CHF):

Congestive heart failure (CHF) is the clinical syndrome caused by insufficient cardiac output, leading to either pulmonary or systemic congestion. Nearly 5 million people in the United States are affected by this syndrome, with more than 400,000 new patients being diagnosed annually. It has been reported that every year the U.S. healthcare system spends about $20 to $40 billion for managing the condition, which includes $500 million spent on drugs alone (Benatar, 2003). Moreover, it has been

reported that as the US population ages, the incidence and prevalence of CHF is expected to increase. CHF is the most common admitting diagnosis for people older than 65 years of age. It is reported that CHF is the most common indication for hospitalizations and is also the most frequent diagnosis submitted for Medicare reimbursement (Taylor, 2003; Benatar, 2003). A greater fraction of Medicare dollars are spent for the diagnosis and treatment of CHF than for any other diagnosis. CHF is the primary non-cancerous disease condition for which patients seek hospice admission (Taylor, 2003). The 2004 facts and figures updates published by the NHPCO reported that about 11 % of patients admitted by hospice programs in 2003 were diagnosed with end-stage heart disease, making it the topmost non-cancerous condition in patients that seek hospice services.

2.10.1.1. Epidemiology of CHF:

The majority of the patients with end-stage CHF have been reported to suffer from left ventricular (LV) dysfunction. However, some patients with CHF have extracardiac or valvular heart disease that limits cardiac output, even if the ventricular function is reported to be normal. Various disorders of the pericardium, myocardium and endocardium can lead to heart disease. Coronary Artery Disease (CAD) is the leading cause of heart failure, occurring in almost two-thirds of the patients with CHF. Conditions such as hypertension, arrhythmias and dilated cardiomyopathy may also lead to development of CHF (Quaglietti, 2000; Addington-Hall, 2003).

2.10.1.2. Symptoms and Severity of Heart Failure Condition:

The most common symptoms associated with heart failure that may require appropriate management include problems such as breathlessness, activity limitations, fluid retention, nausea, constipation, anxiety and depression. The clinical course of CHF is characterized by a progressive worsening of symptoms and frequent acute episodes of deterioration that may require further hospitalization. Fluid retention is the most predominant symptom in CHF patients. If deterioration subsequently occurs, it is associated with breathlessness, coughs, nocturia, swollen limbs/sacrum, anorexia, nausea and abdominal bloating (ACC/AHA[b], 2003).

Once a diagnosis of heart failure has been established, symptoms may be used to classify the severity of the heart failure and can also be used to monitor the effects of therapy (National Guidelines Clearinghouse, n.d.). The approach most commonly used to classify heart failure patients based on the presence of symptoms was first developed by the New York Heart Association (NYHA). This system assigns patients to one of four functional classes (Table 3), depending on the degree of their existing symptoms. Patients who show symptoms of heart failure at rest are categorized as Class IV. Those who demonstrate less-than-ordinary exertion are classified as Class III. Those who show symptoms on ordinary exertion as Class II, while those who have symptoms only at levels of exertion that would limit normal individuals as Class I. (National Guidelines Clearinghouse, n.d.).

Table 3: New York Heart Association Classification of Heart Failure

NYHA Class	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

2.10.1.3 .Treatment of CHF:

The therapeutic approach to managing heart failure has undergone considerable changes in the past several years. Currently therapeutic management strategies not only concern symptomatic improvement, but also focus on preventing the transition of asymptomatic cardiac dysfunction to symptomatic heart failure; altering the progression of heart failure; and reducing mortality. Because heart failure is a complex disease, the therapeutic approach may require multiple strategies, including general measures, pharmacological therapy, mechanical devices and surgical interventions, some of which may not be applicable to all patients (National Guidelines Clearinghouse, 2001).

Recommended therapies typically used for managing the condition are published in clinical or practice guidelines that are developed and circulated by certain national

organizations. Treatment or practice guidelines are systematically developed statements that assist health care providers, as well as patients in making decision about appropriate health care for specific medical conditions. In 1995 the American Heart Association and the American College of Cardiology published guidelines describing the pharmacological treatment of heart failure, subsequent revisions to which were made in 2001. Similarly, the European Society of Cardiology has also developed guidelines for managing heart failure which was published in the year 2002 (Ahmed, 2003). Both these guidelines recommend therapies that are based on systematic reviews of the literature and also represent the consensus of leaders and experts in the field. According to the American Heart Association and the American College of Cardiology guidelines, there are four different stages of heart failure which correspond of the four classes of heart failure described by the NYHA. Figure 3 summarizes the different stages of heart failure and the recommended therapy by stage (ACC/AHA[a]; ACC/AHA[b], 2003). Table 4 summarizes the different treatment options that are recommended by the European Society of Cardiology.

2.10.1.4. Managing CHF condition at the end-of-life:

For managing terminal illnesses, some national organizations have developed guidelines that more or less focus on end-of-life care, futile care, or the choice to forgo life support. Such guidelines are crucial first step to educate health care providers about palliative and hospice care. However, so far, treatment guidelines outlining the different therapeutic options specific to certain patient populations (e.g. hospice patients) or certain medical conditions (e.g. CHF) are not available or have not been published. Most of the patients who receive end-of-life care at hospices or nursing homes or long term care

facilities fall into either Class III or Class IV of the NYHA categories. For example, when physicians look for current standards on treating a patient with class IV heart failure, they usually refer to the two recent guidelines outlined by the American College of Cardiology or the European Society of Cardiology guidelines on CHF. Both of these heart failure guidelines were published in 2001 and include a few recommendations which are outlined in Figure 3, for older adults, or hospice patients (ACC/AHA[b], 2003).

Figure 3: Different stages of heart failure and the recommended therapy by stage adapted from* ACC/AHA *guidelines.

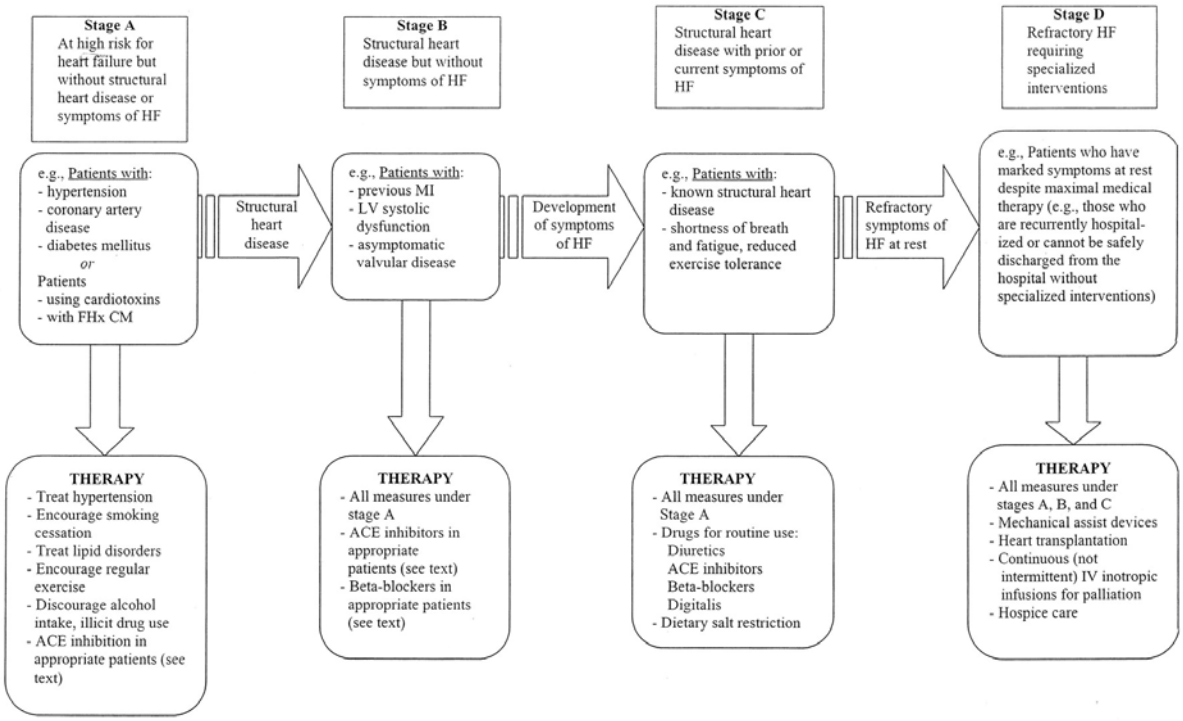


Table 4: CHF treatment options–general advice and measures, pharmacological therapy, devices and surgery as recommended by the European Society of Cardiology

Non-pharmacological Management	General advice and measures including weight control; dietary measures such as salt restriction; fluid and alcohol intake reduction; weight control; smoking cessation; advice on traveling, sexual activity and immunizations; and drug counseling Exercise and exercise training
Pharmacological Therapy	**Angiotensin-converting enzyme (ACE) inhibitors:** Examples- enalapril, lisinopril, captopril, ramipril, randolapril, benazepril, etc **Diuretics:** Examples- loop diuretics (furosemide, bumetanide, torasemide); thiazides (hydrochlorothiazide, metolazone, indapamide); and potassium-sparing diuretics (amiloride, triamterene, spironolactone) **Beta-adrenoceptor antagonists:** Examples- bisoprolol, metoprolol, carvedilol **Aldosterone receptor antagonists:** Examples- spironolactone and eplerenone **Angiotensin receptor antagonists:** Examples- losartan, valsartan, irbesartan, candesartan cilexetil, telmisartan, eprosartan **Cardiac glycosides:** Examples- digoxin, digitoxin **Vasodilator agents:** Examples- nitrates/hydralazine **Positive inotropic therapy:** Examples- dobutamine and phosphodiesterase inhibitors (milrinone, amrinone, enoximone) **Antithrombotic and anticoagulant therapy:** Examples- aspirin and heparin **Antiarrhythmic agents:** Examples- amiodarone **Calcium antagonists:** Note: Considered but not recommended for heart failure due to systolic dysfunction
Oxygen Therapy	Considered but not Recommended for Chronic Heart Failure
Devices and Surgery	Revascularization (catheter interventions and surgery), other forms of surgery Pacemakers Implantable cardioverter defibrillators Heart transplantation, ventricular assist devices, artificial heart Ultrafiltration, haemodialysis

2.10.2 Depression:

Depression is one of the most common symptoms present in patients with advanced irreversible disease conditions. Major depression is a disabling mental disorder that is marked by a low mood or loss of pleasure or interest in usually preferred activities. Depression is usually accompanied by changes in appetite; sleep disruption; restlessness and/or lack of energy; impaired concentration; amplified feelings of guilt or worthlessness and may even have suicidal feelings (Goy, 2003).

2.10.2.1. Epidemiology of depression

The exact etiology of depression in cancer and other terminal illness is unknown, but several theories have been put forward. Several precipitating factors have been suggested in the literature and they include emotional impact, side effects of certain treatments, progression of cancer with associated disability, and symptoms of cerebral dysfunction (Goy, 2003). Many of the other symptoms which are common in depressive patients, such as sleep and appetite disturbances, are often present and are usually attributable to their physical illness or to their primary medical condition. One of the major difficulties in establishing an appropriate diagnosis for depression is that there are no biological markers, physical signs, or diagnostic tests that can be used to decide what can be termed "appropriate sadness" as patients approach the end of life (Goy, 2003).

2.10.2.2. Depression at End-of-life:

Depression in terminally-ill patients is usually thought to result from the underlying medical condition. It has been reported that depression is usually accepted as being a normal feeling and therefore the critical evaluation of the management of

depression in terminally-ill patients is not adequate (Goy, 2003). Diagnosis therefore depends on the assessment of the patient, focusing on feelings of helplessness, worthlessness and inappropriate guilt (Goy, 2003; Lloyd-Williams, 1999). Estimates of the prevalence of depression in terminally-ill patients vary considerably, but it has been reported that a quarter of terminally-ill patients have a treatable depressive illness. About 25-75% of all terminally-ill patients have depression as one of their many symptoms. Prevalence rates of depression range from 1 % to 15 % in elderly community patients to 10 % to 20 % in Alzheimer's patients, 9 % to 25 % in cancer patients, 33% in patients with dementia and up to 45% in patients with cardiovascular disease (Goy, 2003).

There are several factors related to medical illness or functional impairment that have been identified as risk factors for developing depression in individuals who are approaching death. It has been reported that older patients with functional limitations and those who are acutely ill and in pain are more likely to suffer from depression. The presence of physical symptoms that is related to the disease, such as pain, tends to increase the likelihood that a patient might develop depression. A variety of medical conditions have also been associated with the development of depression, such as cancer, chronic obstructive pulmonary disease, neurological disorders, cardiac disorders and endocrine disorders. Some pharmaceutical agents (such as steroids, benzodiazepines, beta-blockers, etc) have been identified as possible causes of depression and therefore patient should be evaluated before and after the initiation of the therapy. (Lipman, 2000).

2.10.2.3 .Treatment of Depression:

In order to improve appropriate diagnosis and treatment of depression, several evidence-based treatment guidelines have been published. The Agency for Health

Research and Quality (AHRQ); the American Psychiatric Association (APA) and the Texas Implementation of Medication algorithms (TIMA) are some of the major practice guidelines that have been used for managing depression. Each of these guidelines outlines diagnostic, as well as treatment considerations for managing depression. Although these guidelines are not specifically tailored to terminally-ill patients, they outline the diagnostic and treatment considerations unique to older patients (American Psychiatric Association, 2000; TIMA 2000). Outlined next are the non-pharmacological and pharmacological treatment options as recommended by these clinical guidelines.

Non-Pharmacological Treatment Management for Depression:

There are several ways in which health care providers can control depressive symptoms non-pharmacologically. Providing psychological support to patient's suffering from depression can significantly enhance their well being and promote rapid recovery. Providing counseling to terminally-ill patients is another way by which their depression can be controlled. Counseling is widely available, but to date there is very little evidence to suggest that counseling alone is beneficial for patients who are depressed. Psychotherapy has also been widely used in patients with cancer. It has four basic components: providing social support, improving emotional expression, restructuring cognitive functioning and providing coping skills training (Goy, 2003).

Pharmacological treatment management for depression: Table 5 summarizes the different therapeutic agents that are recommended for managing depression (American Psychiatric Association, 2000).

Table 5: Commonly used antidepressant medications for managing major depressive disorders (American Psychiatric Association, 2000).

Drug Class	**Drug included (Generic name)**		
Tricyclics & Tetracyclines	Amitriptiline Imipramine Nortriptiline	Clomipramine Trimipramine Amoxapine	Doxepin Desimipramine Maprotiline
SSRIs	Citalopram Fluovoxamine	Fluoxetine Sertraline	Paroxetine
Dopamine-norepinephrine reuptake inhibitors	Bupropion	Bupropion, sustained release	
Serotonin- norepinephrine reuptake inhibitors	Velafaxine	Velafaxine, extended release	
Serotonin modulators	Nefazodone	Trazadone	
Norepinephrine-serotonin modulator	Mirtazapine		
MAOIs	Phenelzine	Tranylcypromine	Moclobemide
Selective noradrenaline reuptake inhibitor	Reboxetine		

Thus with a background information on the hospice, the need for formulary development and the methods that are generally used for creating formulary that was covered in this chapter, the next chapter will specifically deal with the methodology that was applied in this study for the purpose of developing hospice formularies for two specific medical conditions: CHF and depression.

3. METHODOLOGY

This chapter describes the study methodology. This study was an exploratory study that focused on developing drug formularies for a local hospice for specific medical conditions based on Multi-Attribute Utility Theory (MAUT) methodology. The study assisted the clinical care team at the center in providing a rationale or justification for including appropriate medications on the formulary for congestive heart failure (CHF) and depression. Additionally the study evaluated the economic impact of the drug agents selected in the drug formularies that were used for managing CHF and depression, respectively. The methodology for this study will be discussed under the following sections: Study Design, Setting, Selection of Medical Conditions, Procedures, Sample Selection and Data analyses.

3.1. Study Design

Prior to conducting this project, a preliminary study was conducted to identify and select specific medical conditions for which hospice formularies were to be developed. Broadly, this study was conducted in two distinct phases. In the first phase, drugs used for managing CHF and depression were selected for the formulary whereas in the second phase, the economic impact of the selected drug agents for each condition were

evaluated. A criteria-based decision-making method was employed to achieve the first goal of the study. The MAUT method was used for selecting drugs for the formularies. The economic impact of the selected drug agents included in the formulary was evaluated using a separate-samples pretest-posttest study design.

3.2. Setting

The present study was conducted at the Hospice of East Alabama Medical Center (EAMC), located in Auburn, Alabama. The facility serves patients in eight surrounding rural counties of Eastern Alabama. The center is a non-profit organization and admits nearly 25 patients per month from a wide range of socioeconomic and educational backgrounds, irrespective of their payment ability or funding agency source.

3.3. Study Approval

Approval was obtained from the Auburn University Institutional Review Board (IRB) to conduct this study [Appendix A]. The IRB required that the data collected from the medical and pharmacy records at the center be kept confidential. To comply with the IRB, data on all subjects involved in the study were coded. The data were entered in electronic database files and therefore no links could be made between the assigned codes and individual subjects. Additional approval was also obtained from the Institutional Review Board at the East Alabama Medical Center for conducting this study at its hospice. Permission was obtained to gain access to the medical records and pharmacy database to obtain relevant patient information required for this study [Appendix B].

3.4. Selection of Medical Conditions (Pre-Study phase)

Since this is an exploratory study that is primarily focused on developing and evaluating hospice formularies based on the MAUT methodology, it was imperative for

this study to select specific medical conditions for which formularies needed to be developed. Those medical conditions with high drug therapy costs were considered for formulary development Therefore, one of the goals of the pre-study phase was to determine which medical conditions have the highest treatment costs at the center.

An ABC analysis was performed, since this technique is particularly useful in determining and comparing drug costs for managing different medical condition(s). ABC analysis is a method by which drugs are divided into three tiers according to their annual costs and usage. Three tiers are called Class A, Class B, and Class C for analysis.

CLASS A: These are the drugs that account for highest cost/highest volume items. (i.e. these are 10-20 % of items that account for 75-80% of the funds spent).

CLASS B: These are drugs that are classified as moderate cost items (i.e. these are 10-20 % of items that account for 15-20 % of funds).

CLASS C: These are drugs that are the lowest cost items (i.e. these are 60-80 % of items that account for 5-10 % of funds).

Drug items that are included in Class A represent the highest cost medications used. When such drugs are arranged by medical conditions/symptoms, those with the highest management costs can be identified. Thus, an ABC analysis was performed using one year hospice pharmacy data, collected from October 2003 through September 2004. The annual pharmacy usage data were extracted from the pharmacy database system maintained by the pharmacy manager at the hospice of EAMC. The preliminary analysis showed that the hospice incurred the highest drug management costs for managing conditions such as congestive heart failure (CHF) and depression (outside of pain management), because of which these were selected for formulary development process.

Decisions were jointly taken by the researcher along with the pharmacy manager to select CHF and depression as the prototype conditions and symptoms respectively, for which formularies were developed in this study. The present research project therefore focused on developing formularies for these selected medical conditions utilizing scientific methods.

3.5. Procedures

The procedures that were followed in this study are described under the following subheadings:

Study Phase-I: Develop condition-specific hospice formularies for CHF and depression

Study Phase-II: Evaluate economic impact of drug agents selected for the two condition-specific hospice formularies

3.5.1. Study Phase-I: Develop condition-specific hospice formularies:

In any healthcare setting, a rational or an evidence-based drug selection process is considered to be very important for formulary development. It is expected that the selection process be transparent and incorporate the viewpoints of all the members of the P&T Committee or the drug selection committee that is responsible for developing drug formularies. Moreover, there are several decision theories and methods suggested in the literature that emphasize or aid in formulary decision-making process. Some of the decision making methods or principles are aimed at making individual decisions, while some specifically focus on attaining group decisions. Typically, the drug selection process involves a decision made by a group (either by P&T committee or by specific drug selection committee). Thus for this study, the Mutli-Attribute Utility Theory

(MAUT), a method that specifically considers multiple-criteria evaluation process and involves group interaction was selected for making rational drug selections.

3.5.1.1. Multi-Attribute Utility Theory (MAUT) Procedures:

The MAUT is a systematic identification and analysis method that incorporates the viewpoints of all members of the drug selection committee and provides a common basis for assessing and comparing different drug selection variables involved in the decision making. This approach is particularly valuable for the formulary decision making process, which not only involves individual members' inputs on multiple criteria, but also takes the entire group's input on those criteria into consideration for making final decisions. This method therefore encourages decision makers to identify and agree on alternatives on the basis of various drug attributes that best compares each treatment option. The following steps prescribed by the MAUT method were followed for the purpose of selecting appropriate drug agents for CHF and depression formularies.

Step1: Identify different therapeutic drug classes for managing CHF and depression:

For the purpose of developing formularies for CHF and depression, it was necessary to identify important pharmacological or therapeutic drug classes and the individual drugs that are included within each class. Two different approaches were used to broadly identify drugs and drug classes for formulary consideration. These approaches are outlined next:

- Approach 1: Identify important drug classes as recommended by standard treatment guidelines published by professional organizations

- Approach 2: Identify drugs used by the hospice of EAMC for managing CHF or depression conditions

Approach 1: A computerized literature search was conducted to identify different treatment guidelines or clinical guidelines for managing CHF and depression, specifically relevant for hospice and palliative care practice. The main purpose of this approach was to review the clinical guidelines for the treatment and management of CHF or depression, specifically among terminally-ill patients.

Approach 2: In the second approach, the researcher gathered information about the different drugs that were used by the hospice of EAMC for managing CHF or depression. This approach was followed to identify different drugs used by this particular hospice for managing the two conditions respectively. Drug lists for CHF and depression were compiled by the researcher in an excel spreadsheet, using the annual pharmacy data (October 2003 - September 2004) collected for the preliminary study. The list served as a secondary source for identifying which specific drugs or drug classes should be taken into account for formulary inclusion.

Based on the information collected from both approaches mentioned above, lists comprised of all important drug and their classes used for treating CHF or depression were compiled.

Step2: Conduct literature review on drug agents represented in different therapeutic classes.

Since the aim of this study was to develop a formulary list for managing specific medical conditions, one of the goals was to select only the best drug agents in each drug class. The main purpose of conducting a comprehensive literature review was to identify

certain criteria and gather their literature-based values, which would enable one to compare different drugs present within a particular drug class. Certain classes only had a single drug as its representative therapeutic agent and did not have other comparators or competitors. Due to the absence of any comparator agents, a literature review step was excluded for drug classes that had single representative agent and the process was limited to only those drug classes that had more than one drug agent listed under them. A comprehensive and systematic literature search was conducted to identify all scientific studies related to the drugs in each therapeutic drug class that were considered for formulary development. Separate searches were performed for CHF and depression to:

1. find some of the common criteria upon which different drugs within the same therapeutic drug class could be compared, and
2. collect information or obtain literature-based values on those criteria for each drug agent in the respective drug class.

For example, antidepressants class of drugs such as selective serotonin receptor blockers (SSRIs) contained four drugs (i.e. citalopram, paroxetine, sertraline and fluoxetine) that are typically used for managing depression. The literature review process primarily assisted in identifying certain criteria which were commonly assessed for these agents and which were also found to be useful in comparing all SSRIs. For example response rate is one of the criteria that is generally used for assessing the efficacy of these drug agents, and is defined as the proportion of individuals that demonstrated a mean reduction of 50 percent of the depressive symptoms from the baseline scores after initiating the antidepressant treatment. The next step in literature review process involved gathering all

those studies that have assessed the response rate for these agents and report the response rate values (i.e. literature-based values) from these studies.

A detailed literature review procedure that was followed for this study is outlined below:

A Boolean search of Ovid MEDLINE, International Pharmaceutical Abstracts, CINAHL, and PsycINFO databases was conducted. The search strategy for CHF included keywords such as congestive heart failure or cardiac failure or cardiac insufficiency or heart failure either crosslinked with the name of the therapeutic class (ACE-inhibitors, loop diuretics, beta blockers, nitrates, angiotensin receptor blockers) or with the name of the individual drugs (fosinopril, ramipril, quinapril, enalapril, benazepril, lisinopril, torsemide, furosemide, bumetanide, carvedilol, metoprolol, nitroglycerine, isosorbide dinitrate, isosorbide mononitrate, valsartan, irbesartan, losartan). Similarly for depression, the search strategy included the following key words such as (depression, antidepressants) crosslinked with individual drugs (citalopram, fluoxetine, paroxetine, sertraline). The literature search was focused on articles published in English between 1980 and April 2005. A separate set of potentially useful articles (title of the study along with the abstract, if available) related to individual drugs in each therapeutic class was identified and imported into an EndNote database (version 7.0). In addition to the computerized generated article search, the researcher performed additional review articles search utilizing the Cochrane database. Certain inclusion and exclusion criteria were devised for a systematic literature search and review process. These included-

- Systematic review articles, randomized clinical trials, meta-analysis type of studies were included
- Only those studies that have assessed the most common drug evaluative factors were taken into consideration
- All relevant clinical trials were included, regardless of the sample size
- If there were more than one publication from a given trial, only data from the overall trial were included
- Cohort studies, case reports, case-control studies, and pharmacokinetic trials were excluded
- Studies that have assessed the drug evaluative factors for combination therapy (principal drug agent + some other agent) were excluded.

Three levels of searches were performed on the combined database. In the first level, key word searches of the EndNote database were conducted using terms such as randomized controlled trials or RCT or placebo controlled trials or controlled clinical trial or meta analysis to identify articles with specific study design. Based on the inclusion and exclusion criteria, the abstracts of these articles were classified as "related" or "unrelated" respectively. Unrelated abstracts were removed from the databases and only the usable abstracts were included for this study. If the information regarding different drug selection criteria or factors was not found after reviewing the abstracts, then the full papers were ordered for review. In the second level, all relevant studies addressed in review articles or meta-analysis types of articles were reviewed. If the review articles or meta-analysis articles did not provide adequate information about the literature-based values, then the full paper on those studies was ordered and reviewed. In the third level,

abstracts of some of the selected citations listed in the bibliographies or the reference section of the articles were reviewed. If they were found to be useful, full papers for those articles were ordered. Similar procedures were followed for all the six therapeutic drug classes.

Step3: Identify drug selection criteria (drug attributes and factors):

Before making decisions regarding which specific drugs would be selected for the hospice formulary for managing CHF or depression, it was important to define or address the different criteria on which these decisions would be based. A thorough literature search for the drugs or drug classes used for the management of CHF and depression was performed to identify some common criteria or characteristics upon which the drugs within the same therapeutic class could be compared. These criteria are referred to as "drug attributes" and "drug factors".

All the major drug characteristics that were evaluated in previously published studies were identified and referred to as *drug attributes*. The three principal types of attributes or drug characteristics that are typically considered and assessed for making drug selection for a formulary include drug efficacy, drug safety and drug cost. Apart from these criteria, there are few other criteria such as availability of a drug in different dosage form, dosage strength and dosing frequency are also considered useful for formulary decision making process. Thus, all of the aforementioned criteria that are used for making rational selection of drugs for the formulary would be considered for this study. For the purpose of this study, variables such as dosage form availability, dosage strength availability, and frequency of administration were combined into a "drug

availability" category. Drug selections in this study were therefore based on four major attributes described as drug efficacy, drug safety, drug availability and drug cost. Each of these attributes may have one or more variables or quantitative measures that describe the attribute. Such measures are referred to as "drug factors" and describe the contribution of that attribute to the decision making process.

Drug assessment or evaluation studies report different factors or measurements for evaluating different drug attributes. Since studies may not evaluate all of the aforementioned drug attributes, it is important to identify which drug attributes and factors are most commonly addressed in the literature. Additionally, since drug factors could vary from one drug class to another, one major task in this step is to determine common drug factors reported in the literature for drugs in each therapeutic class. After careful review of the relevant literature, the common drug factors that best quantified the attributes were identified and selected for the study. For example, the commonly assessed drug factors found in the literature that measured or quantified the attribute "drug efficacy" for various SSRIs agents were '*response rate*' (defined as the proportion of individuals that demonstrate a mean reduction of 50 percent of the depressive symptoms from the baseline scores after initiating the antidepressant treatment); and '*total drop-out rate*' (defined as the proportion of individuals who have discontinued drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or due to incidences of serious adverse drug events) were..

Step 4: Compile literature–based factor values for all study drugs and drug classes:

In this step, information regarding different drug factors that were consistently addressed in the literature was collected. Data regarding drug attributes and their related

factors were gathered from different resources. Table 6 lists the different sources of information that were used in the study.

Table 6: Sources used for collecting information on drug agents

Factors	**Factor values obtained from**
Drug efficacy factors	Systematic literature review
Drug safety factors (except drug interaction)	Systematic literature review
Drug interaction	Facts & Comparisons, by Hansen and Horns
Drug availability factors (dosage forms, doses, and dosing frequency)	American Hospital Formulary Service (AHFS)- Online Drug Information System
Drug cost	EAMC Hospice Pharmacy database

Drug efficacy and drug safety factors were obtained from a systematic search of the abstracts from the EndNote database, which was conducted using the inclusion and exclusion criteria mentioned above. Information on drug interactions was obtained from the Facts & Comparisons reference book. According to Facts & Comparisons, interactions are reported as one of the five categories listed in Table 7. For this study, all drug interactions reported as category 1, 2, or 3 were taken into account since these are significant and/or necessitate some action. Moreover, data on drug availability (such as number of dosage forms, doses, and dosing frequency) were obtained from the online

drug information system by the American Hospital Formulary Service, and information on drug cost was directly extracted from the EAMC hospice pharmacy database.

Table7: Categories of drug interactions reported in Facts & Comparisons

Drug interaction category	Evidence	Action
1	Potentially severe or life-threatening interaction; occurrence has been suspected, established or probable in well controlled studies	Avoid combination
2	Interaction may cause deterioration in a patient's clinical status; occurrence suspected, established or probable in well controlled studies	Usually avoid combination
3	Interaction causes minor effects; occurrence suspected, established or probable in well controlled studies	May avoid combination
4	Interaction may cause moderate-to-major effects; data are very limited	No immediate action needed
5	Interaction may cause minor-to-major effects; occurrence is unlikely or there is not good evidence of an altered clinical effect	No immediate action needed

Compilation of the factor (literature-based) values: Once all the relevant articles were identified and reviewed, factor values reported in those articles were recorded. The compilation of the factor values was done in the following steps:

- For each of the therapeutic drug classes, excel spreadsheets were created which included information about the literature-based factor values for the different factors on all the individual drugs in that class.
- For each factor, the minimum; the maximum along with the range was recorded, across all drug agents present in that class.
- For each factor value, a weighted average was calculated.

For example, consider total drop-out rate to be one of the drug factors that is considered for measuring efficacy for SSRIs such as citalopram. Total drop-out rates for citalopram were found to be 7.1%, 33.3% and 12.0% reported across three studies involving 14, 30 and 58 subjects respectively. Thus, 7.1%, 33.3% and 12.0% are the literature-based factor values for total drop-out rates reported for citalopram, with the minimum and maximum values reported as 7.1 and 33.3 respectively. Additionally, a weighted average of drop-out rate for citalopram was computed in the following steps:

- Multiply individual drop-out rate value (factor value) by the total number of subjects included in that study (or in the study arm if the study under consideration was a randomized control study)
- Sum up all the values obtained in the previous step. For the weighted average calculation, this number is the numerator [In the above example, X=1795.3]
- Sum up all the N's (sample size) across all studies or the study arms and during weighted average calculation, this number is the denominator [In the above example, Y=102]
- The weighted average of total drop-out rate for citalopram was computed as f = [X]/[Y] = 1795.3/102=17.6

For individual drug classes, the factor values, range for factor values and weighted average values for all drug factors were derived from the above mentioned steps.

Step 5: Conduct first focus group meeting to evaluate and determine individual members' preferences for different drug selection criteria

A drug selection committee at the hospice served as the focus group for this project. This group consisted of the medical director, pharmacy manager, admission nurse, manager of the center, director of hospice and oncology services at EAMC, clinical coordinator, and the pharmacist. The medical director is the only person in this group who is one of the many physicians that prescribes medications for the patients at this hospice. The meeting was facilitated by the researcher and his academic advisor. There were several purposes for conducting the first focus group meeting. These included-

- To explain the detailed drug selection procedures
- To review different pharmacologic classes used for managing CHF and depression
- To present the summary tables of the range of the factor values for drugs within each therapeutic class
- To acquire consensus on the drug attributes and factors chosen for drug selection process
- To obtain individual member's preferences in regards to his or her rankings and weightings for different drug attributes and factors included in the study.

Before the first focus group meeting, the facilitators met, and discussed the agenda for the first and second focus group meetings. The facilitators discussed the ranking and weighting protocol prepared by the researcher that described the different drug attributes and factors for each drug class [Appendix D]. Additionally, the facilitators prepared the summary slides describing the different recommendations suggested by the practice guidelines; and also reviewed the detailed explanation of the drug selection procedures that were also included into the presentation slides. The handouts for the presentation were included in a folder (binder) that was provided to each participating member. For each drug class, information regarding drug attributes and the various factors describing drug attributes were also included in the folder. The folders provided to the committee members were coded differently, but they all contained the following materials:

(1) A copy of the presentation slides (PowerPoint slides) given by the facilitators, which included (a) summary of the practice guidelines and (b) important procedural points on ranking and weighting method [Appendix C].

(2) Summary tables containing the literature-based values for drugs within each therapeutic class that were prepared by the researcher [Table nos. 23-28, included in Chapter 4].

(3) Ranking and weighting protocol sheets for each drug class [Appendix D].

(4) Definitions for all of the drug attributes and factors that were considered for this study [Included at the end of this chapter, Page nos. 104-111].

The following steps were used during the first focus group meeting:

1. The facilitators presented the different pharmacological or therapeutic drug classes along with the recommendations that were described by the published guidelines.
2. Discussions were carried out with the group to identify important drug classes that were typically used to manage CHF or depression.
3. For CHF, those drug classes that contained a single drug agent were identified. For such drug classes, the committee discussed the importance of these single agents for CHF management and a consensus was obtained to include important single agents directly for the formulary. For example, digoxin an important cardiac glycoside is the only agent included in that class and is typically used as a standard therapy for CHF management. A consensus was therefore obtained from the group to directly include digoxin for the CHF formulary. Likewise, consensus on other drug classes that contained single agents was also obtained.
4. For other drug classes (i.e. classes with multiple drug agents), facilitators explained to the group the detailed procedures about how drugs in those classes would be considered for the formularies. The facilitators explained the entire drug selection procedure with the help of an example. SSRIs, which is an antidepressant class of drugs was used as an example, during which the facilitators placed special emphasis on how the individuals would assign their ranking and weightings for different drug attributes and factors based on their preferences.
5. The rankings and weightings procedures were conducted for one drug class at a time. For each drug class, definitions for the different drug attributes and factors

that were associated with that class were explained to the group. In this study, a total of five therapeutic drug classes were considered for CHF formulary, while a single drug class was considered for depression formulary for which ranking and weighting procedures were followed. Procedures for deriving individual members' ranks and weights for the drug attributes were followed first. This was followed by similar (ranking and weighting) procedures for drug factors considered under each attribute. The steps for assigning ranks and weights to different drug attributes as well as factors considered under each drug attribute included:

- The individuals were asked to give their consensus for the different drug attributes and factors that were included in the study. They were also asked to include any other attribute or factor, not listed in the protocol that they thought would be essential to include in this study. Individual were asked to rank and weight their preferences, based not only on their clinical experience, but also keeping in mind the definitions for different attributes and factors that were explained to them. For example, for SSRIs class of drugs, the different drug attributes considered included efficacy, safety, drug availability and drug cost. Response rate and total drop-out rate were factors included under efficacy; while drop-out rate due to adverse effects, total number of treatment-limiting severe adverse effects and total number of drug interactions were some of the factors included under safety. Similarly, number of dosage forms, number of doses and dosing frequency were some of the factors included under drug availability attribute.

- Each member of the group was then asked to rank the four drug attributes (drug efficacy, safety, availability, and cost) according to their importance, if they were to select a drug regimen for their patients. They were asked to rank those criteria from 1 - 4 (1=most important to 4 = least important). For example, if an individual thought efficacy to be the most important attribute for selecting the SSRI, followed by safety, availability and cost, then he/she was asked to assign a rank of 1, 2, 3 and 4 to those attributes in that order respectively.
- Each member was then asked to determine the weights for each selection criterion, by setting the weight of the least important criteria as 1. For example, if "cost" was the least important criterion, then a weight of 1 was assigned to "cost." The weight of the next least important criteria in the list was determined with respect to the weight of the least important criteria. In the example above "availability" is the next least important criterion relative to "cost", so the weight for "availability" was determined by considering how much more important it is than cost. If availability was thought to be twice as important as cost, then the weight for availability was assigned a value of 2.
- The weights for the remaining criteria were determined in the same manner by order of increasing importance ending with the most important criteria. To set weights, it was emphasized to the group to always compare the criteria that were currently being evaluated against the least important criteria.
- After obtaining rankings and weightings for drug attributes, similar procedures were followed for drug factors listed under each drug attribute in

that particular drug class, which was then followed by drug attributes for another class. Likewise, rankings and weightings were obtained from each member for all the drug classes.

- All members of the drug selection committee gave their responses on the ranking and weighting protocol sheets that were included in their individual folders [See Appendix D].

Step 6: Compute factor utility scores for each factor:

One of the challenges often faced by decision makers reported in the literature is choosing the best option from various available alternatives that are measured on different scales. It becomes very difficult for decision makers to quantify and compare alternatives on disparate measures. This is equally true during the drug selection process or formulary development process where comparisons are typically made across different drug attributes such as drug efficacy, drug safety, drug availability and drug cost, which are assessed on different scales or units. One way to resolve this issue (as reported in the literature) is to transform different measures onto a common scale measure which will then allow us to compare different alternatives. A common utility scale was created for each factor ranging from '0', which is the worst plausible value for a factor (V_{min}) to '100', which is the best plausible value for a factor (V_{max}). The following steps were followed for computing the factor utility score:

- For individual factor in each drug class, all literature-based values were obtained from the literature, and the minimum and maximum values for those factors were reported in Excel spreadsheets.

- For individual drug class, a common utility scale was developed for which a plausible range of +/- 20% of the minimum and maximum factor values obtained for each factor was calculated. For example, let's say, citalopram and paroxetine are the two SSRI agents that are being compared, and total drop-out rate is one of the factor that is being considered for evaluating the drug efficacy. Assume that 7.1%, 33.3% and 12.0% are the literature-based factor values for "total drop-out rate" for citalopram, while 12.8%, 4.5% and 10.8% are total drop-out rate values for paroxetine reported from different studies. Thus, the minimum and maximum factor (total drop-out rate) values for the agents included in SSRIs drug class would be 4.5 and 12.0 respectively. The common utility scale for drop-out rate for both these agents was designed in such a way that it incorporated the +/- 20% of the minimum and maximum factor values for those agents. In other words, the common utility scale had 80% of the minimum value at the lower end and 120% of the maximum value at the higher end. Thus, the scale for total drop-out rate for SSRIs had 3.6 at the lower end and 14.4 at the higher end.
- The values for the common utility scale were then transformed on a 0-100 scale. Thus, the '0' on the scale was represented by a number equivalent to 80% of the minimum factor value (V_{min}), and the '100' on the scale was represented by a number equivalent to 120% of the maximum factor value reported for that factor (V_{max}). Thus, 3.6 and 14.4 are the V_{min} and V_{max} values in the above example. They represent the '0' and '100' scale values reflecting the worst and best plausible value for that factor respectively. The same procedures were followed for all factors in all six therapeutic classes.

- Utilities (or worth) of some factors tend to have a direct relationship with regards to factor measures, meaning that the utility of such measures increases with the measurement (e.g. consider response rate as a drug factor- greater is the response rate; greater will be its utility or preference). On the other hand, utilities (or worth) of some other factors are inversely related to their factor measures, meaning that the utility of such measures decreases with the measurement (e.g. consider drug interactions as a drug factor- higher the number of drug interactions, lower will be its utility or preference). Thus, based on the nature of the factors, different formulas were used to compute the factor utility score. Thus, for all those factors where a direct relationship exists between the factor measures and their utilities, Equation (1) was employed to compute the factor utility score.

$$U_f = \frac{100\,(f - V_{min})}{(V_{max} - V_{min})} \quad \text{……Equation (1)}$$

where f is the weighted average value of the factor, and V_{max} and V_{min} are the maximum and minimum plausible values obtained for each factor respectively.

For example, consider the weighted average factor value for response rate (f) for citalopram to be 15, and the V_{min} and V_{max} values to be 3.5 and 20.5 respectively. Response rate is a factor for which a direct relationship exists between the factor measures and its utility. Using equation (1), the factor utility score (U_f) for citalopram was calculated, which was found to be at 67.64

On the other hand, for all those factors where an inverse relationship exists between the factor measures and their utilities, Equation (2) was used to calculate the factor utility scores:

$$U_f = \frac{100\,(V_{max} - f)}{(V_{max} - V_{min})} \quad \text{……Equation (2)}$$

For example, consider the weighted average factor value for drug interactions (f) for citalopram to be 4, and the V_{min} and V_{max} values to be 1 and 7 respectively. Drug interaction is a factor for which an inverse relationship exists between the factor measures and its utility. Using equation (2) the factor utility scores (U_f) for citalopram was calculated, which was found to be at 50.

Thus in short, appropriate mathematical formulas were used for directly and inversely related factors, and the values obtained after mathematical computation were referred as the "factor utility score" for that factor.

Step 7: Calculate total utility scores for individual study drug:

Using the drug attribute's weight and drug factor's weight obtained from Step 5 and the factor utility scores computed in Step 6, composite scores for each drug were computed in the next step. The composite scores are referred to as "total utility score," and were calculated for each drug agent within a therapeutic class. The following steps were followed for calculating the total utility score for each drug in each drug class:

- Ratio weights were calculated from the ranks and weights obtained for drug attributes and factors. Responses obtained from all members of the drug selection committee were entered in Microsoft Excel spreadsheets, along with the code number that was assigned to individual members' folder.
- For each member of the group, ratio weights for individual drug attributes were calculated. Similarly, ratio weights for individual drug factors explaining the drug attribute were also calculated. The ratio weights for drug attribute were referred as

"attribute ratio weight" and is denoted as (W_a), while the ratio weights for factors were referred as "factor ratio weight" and is denoted as (W_f). Weights assigned by each individual to all attributes or all factors explaining a particular attribute were summed, and then a ratio weight was computed as a percentage of the summed weight. For example, consider that an individual has ranked efficacy, safety, availability, and cost in the order or 1, 2, 3 and 4, and has assigned weights of 8, 6, 3 and 1 respectively for those attributes. In order to compute each attribute ratio weight, the weights that the person has assigned are summed across all attributes, which would give a value of 18 (8+6+3+1). The ratio for each attribute is then calculated as a percentage of the summed weight. That means if efficacy has a weight of 8 out of a total of 18, then its ratio weight would be 0.44. Likewise, the ratio weights for safety, availability and cost would be 0.33, 0.17 and 0.06 respectively. Thus, similar procedures were used to compute the ratio weights for all drug factors described under each drug attribute.

- The total utility score for each drug alternative was calculated in the following steps:

  Step 1: In the first step, for each individual member, the factor utility score (U_f) obtained for each factor [which was calculated using Equation (1)] was multiplied by the corresponding factor ratio weight (W_f) computed for that individual and for that particular factor. In other words, for every individual member, his/hers' factor ratio weights (for factors included in an attribute) are multiplied by the corresponding factor utility score. The products (W_f*U_f) obtained for all factors

described under a particular attribute were then summed together in Equation (3) to give an "individual attribute utility score" (U_a).

$$U_a = \sum_{f=1}^{n} W_f * U_f \quad \text{.....Equation (3)}$$

For example, for SSRI class, consider the ratio factor weights for response rate (W_f1) and total drop-out rates (W_f2) computed for an individual member to be 0.6 and 0.4 respectively. Additionally, consider that the factor utility scores for the two factors for a single SSRI agent (citalopram) were U_f1= 30 and U_f2=67.64 respectively. The ratio factor weights are first multiplied by their corresponding factor utility scores for that agent, which is then summed up to give the attribute utility score for efficacy for that particular agent. Thus, using Equation (3), the attribute utility scores for "efficacy", for citalopram, computed for that individual is $U_a = \sum(W_f1 * U_f1) + (W_f2 * U_f2) = 45.05$. The same procedures were followed for all factors included across all individual drug attributes, and the respective individual attribute utility scores were calculated.

Step 2: Each individual member's total utility score value (U_T) for each drug was calculated using Equation (4), where the attribute utility scores (U_a) obtained for different attributes were multiplied by their corresponding attribute ratio weight (W_a) calculated for that individual. Thus, for each drug product, a single total utility score was obtained from every individual member of the drug selection committee.

$$U_T = \sum_{n=1}^{n} W_a * U_a \quad \text{.....Equation (4)}$$

Say for example, the attribute utility scores for the attributes efficacy, safety, availability, and cost for citalopram were found to be $U_a1=50$, $U_a2=35$, $U_a3=60$ and $U_a4=40$ respectively, and the attribute ratio weights for a particular individual for these attributes were $W_a1= 0.5$, $W_a2= 0.25$, $W_a3= 0.2$ and $W_a4= 0.05$ respectively. Thus using equation (4), the total utility score for citalopram computed for that individual would be $U_T = \sum (W_a1*U_a1) + (W_a2*U_a2) + (W_a3*U_a3) + (W_a4*U_a4) = 47.75$. Likewise, for each member of the group, similar procedures were used to compute the total utility scores for all agents in that particular drug class.

- In addition to calculating the total utility scores for each member, the total utility score for the entire group was also calculated for each drug, taking into account the average ratio weights for drug attributes and related factors across the group.
- Drugs within each therapeutic class were ranked based on the total utility score values. The drug with highest value was ranked number 1, followed by the drug which had the next highest score. Such rankings were obtained for each member as well as for the group. As an example assume that the total utility scores for citalopram, paroxetine, sertraline and fluoxetine were found to 47.75, 55.90, 30.40 and 38.40 respectively. Based on the total utility scores values, the different agents in SSRIs drug class are ranked in the descending order as paroxetine ranked first, followed by citalopram which is ranked 2nd, fluoxetine ranked 3rd and then sertraline ranked 4th.

- In order to determine the strength of the analysis, a sensitivity analysis was performed by varying the utility scales values related to all drug attributes and factors, to see if any of the relative rankings for drugs in each class changes. In this study, the common utility scales for all drug attributes and factor were redesigned by taking into account a plausible range of +/- 10% of the minimum and maximum factor values. After incorporating the new utility scales, the factor utility scores, and thus the total utility scores were recomputed and the relative rankings of the drugs were determined and rechecked to verify the robustness of the results that were obtained in the study.
- Summaries of drug rankings and the different combination of rankings that were observed across the group were organized in tabular formats.

Step 8: Conduct second focus group meeting and make final drug selection for the two condition-specific hospice formularies

The second focus group meeting involving all members of the drug selection committee at the hospice was held. The main reasons for conducting the second focus group meeting were to

1. Summarize the results of the individual members as well as the groups' ranking on individual drugs in each drug class and
2. Obtain consensus for the final drug(s) to be selected in the individual CHF and depression drug class

The following action steps were followed during the second focus group meeting.

- The facilitators presented the summary of rankings for different drug agents in each drug class that were based on the total utility score values computed for those agents.
- The facilitators explained the detailed procedures for selecting drugs for the final formulary
- In each therapeutic class, drugs that were ranked first or second were automatically considered to be included in the final inclusion list. Other drugs were included, only if the group felt the need to include other agents into the final inclusion list.
- After including drugs in the final inclusion list, a consensus was obtained from all members of the committee regarding specific drug agents to be selected for the final formulary. Consensus was also taken on the total number of drug agents in each therapeutic class to be included for the formulary.
- A protocol, based on the nominal group technique, was utilized for obtaining consensus for the final drugs that were to be included in the respective formularies. In order to reach consensus about the final drug selections, the nominal group technique was followed in addition to the MAUT method, which assisted the drug selection committee to identify and rank drugs within each therapeutic drug class. Each member was asked to write positive (pros) and negative (cons) comments about individual drugs to be selected. Each participant then provided one item from his/her list that were not been given by other group members until the list was exhausted. Based on the pros and cons discussed by the

group members, the final decisions about selecting the drugs for hospice CHF and depression formularies were made.

3.5.2. Study Phase-II: Evaluate economic impact of drug agents selected for the two condition-specific hospice formularies

The second phase of the study dealt with evaluating the economic impact of the selected formulary drug agents for each condition. Separate patient samples representing CHF and depression were selected, six months prior to and six months after the washout period following implementation of the formulary. Thus, two pre-formulary patient samples were identified and selected (one representing pre-formulary CHF patients and the other representing pre-formulary depression patients). Two other post-formulary patient samples were identified and selected (one representing post-formulary CHF patients and the other representing post-formulary depression patients. In this phase, drug costs were computed and compared across pre-formulary and post-formulary patient samples with CHF or depression. The operational definitions for the different types of drug costs that were computed for this study are included in Chapter 1 page nos. 16-17.

3.5.2.1 Sample Selection

The populations considered for this study were the clients of hospice of EAMC. Since the aim of this study was to develop condition-specific drug formularies for terminally-ill patients with CHF or depression, the medical and pharmacy records were sampled during both pre-formulary and post-formulary periods for the CHF and

depression groups. The inclusion and exclusion criteria for sample selection are mentioned below:

3.5.2.2. Inclusion and Exclusion Criteria for Sample Selection

Inclusion Criteria for pre-formulary CHF-patients:

All medical records from hospice of EAMC patients were evaluated who had:

(i) a documented diagnosis of CHF as the primary diagnosis, for which the clients were enrolled into the program and were receiving care at the center

(ii) at least 30 days of documented care data between January 1, 2005 to June 30, 2005

Exclusion Criteria for pre-formulary CHF-patients:

(i) Medical records that had a documented diagnosis of CHF as the secondary diagnosis

(ii) Medical records for those patients who had less than 30 days of documented care between January 1, 2005 and June 30, 2005

Inclusion Criteria for pre-formulary depression-patients:

All medical records from hospice of EAMC patients were evaluated who had:

(i) a documented diagnosis of depression, irrespective of the primary diagnostic condition for which the clients were enrolled into the program and were receiving care at the center

(ii) at least 30 days of documented care data between January 1, 2005 to June 30, 2005

Exclusion Criteria for pre-formulary depression-patients:

Medical records for those patients who had less than 30 days of documented care between January 1, 2005 and June 30, 2005

Inclusion Criteria for post-formulary CHF-patients:

All medical records from hospice of EAMC patients were evaluated who had:

(i) a documented diagnosis of CHF as the primary diagnosis, for which the clients were enrolled into the program and were receiving care at the center

(ii) at least 30 days of documented care data between September 1, 2005 and February 28, 2006

Exclusion Criteria for post-formulary CHF-patients:

(i) Medical records that had a documented diagnosis of CHF as the secondary diagnosis

(ii) Medical records for those patients who have less than 30 days of documented care between September 1, 2005 and February 28, 2006

(iii) Medical records for those patients who were receiving care at the center during the periods of January 1, 2005 – June 30, 2005 as well as during September 1, 2005 and February 28, 2006

Inclusion Criteria for post-formulary depression-patients:

All medical records from hospice of EAMC patients will be evaluated who had:

(i) a documented diagnosis of depression, irrespective of the primary diagnostic condition for which the clients were enrolled into the program and were receiving care

(ii) at least 30 days of documented care data between September 1, 2005 and February 28, 2006

Exclusion Criteria for post-formulary depression-patients:

(i) Medical records for those patients who have less than 30 days of documented care between September 1, 2005 and February 28, 2006

(ii) Medical records for those patients who were receiving care at the center during the periods of January 1, 2005 – June 30, 2005 as well as during September 1, 2005 and February 28, 2006

3.5.2.3. Economic Impact Evaluation Procedure:

The economic impact evaluation procedure involved the following steps:

1. Collected pre-formulary utilization and cost data for hospice patients diagnosed with CHF or depression six-months prior to implementing the formulary
2. Collected post-formulary utilization and cost data for hospice patients diagnosed with CHF or depression six-months after the washout period following the implementation of the formulary
3. Analyzed and compared pre-formulary and post-formulary drug costs for both sets of patient samples

<u>Collect pre-formulary data for hospice patients diagnosed with CHF or depression:</u>

Before selecting the drug agents for condition-specific hospice formulary, relevant medical and pharmacy data were reviewed for selected patients with CHF or

depression (between January 1, 2005 and June 30, 2005). A retrospective review of patients' pharmacy data was conducted to examine the drug use patterns among patients with CHF or depression. Identification of drug use patterns was useful in getting information about the total number of drugs along with their costs. For the purpose of this study, total drug costs for managing the condition were categorized into condition-specific drug costs (i.e. pre-formulary CHF-specific drug costs and pre-formulary depression-specific drug costs) and other drug costs (i.e. pre-formulary CHF-related drug costs). All types of drug costs were expressed in terms of per patient enrollment day. Additional information regarding the patients' demographic information (age, gender, and ethnicity), presence of other co-morbid condition(s), were obtained by reviewing medical records for the respective patients. All data were collected in the following steps:

Step 1: All CHF or depression patients that were enrolled in the hospice and were seeking hospice care were identified. Irrespective of the primary diagnosis, all those patients who filled prescriptions for antidepressant medications during that time period were identified from the pharmacy database system maintained by the pharmacy manager. On the other hand, using appropriate diagnosis code, all patients who had a primary diagnosis of CHF were identified from the resource utilization report that was extracted by the hospice manager. Those patients that met the inclusion criteria were identified and selected for this study.

Step 2: All relevant information regarding the patients' demographics and clinical information from the medical records was collected from the medical record. Data

regarding resource utilization was collected from the resource utilization report generated by the hospice managers' computer system. Whereas, all the pharmacy-related data for those selected patients were gathered from the drug utilization report generated by the pharmacy database system maintained by the pharmacy manager.

Step 3: Information including Patient ID, age, gender, ethnicity, Medicare insurance status, start of care date, care end date, length of treatment (LOT), primary diagnosis, total number of co-morbid conditions, were collected from medical records. Information regarding the different resources used by the patient during their stay in that period was collected from the resource utilization report. The drug profile for the patient during that time period was collected from the drug utilization report, which included information about the total number of drugs prescribed along with their doses, dosage regimen, and the respective drug costs. All relevant information was reported on a data collection form. A unique patient ID was assigned to each patient, whose information was collected for this study.

Step 4: After collecting all relevant patient information researcher then transferred the data into excel spreadsheets.

Step 5: For both groups (pre-formulary CHF patients and the pre-formulary depression patients), the researcher computed different types of drug costs in terms of drug cost per patient enrollment day.

Post-formulary data for hospice patients diagnosed with CHF or depression:

Procedures and steps similar to those used during the pre-formulary stage were repeated for the purpose of collecting post-formulary data. The CHF and depression formularies were implemented from September 1, 2005. Therefore, the medical and pharmacy records of the selected patients who met the inclusion criteria for post-formulary considerations were followed during the six-month post-formulary period. Thus, depression-total drug cost; depression-specific drug cost; and depression-other drug costs were computed for post-formulary depression patients. Similarly CHF-total drug costs; CHF-specific drug costs; and CHF-other drug costs were computed for post-formulary CHF patients. All types of drug costs were computed in terms of per patient enrollment day.

3.6. Data analyses

All data input and analyses were performed using the Microsoft Office Excel 2003, the Statistical Package for Social Sciences (SPSS version 12.0) and Statistical Analysis Software (SAS version 9.1.3) packages. Descriptive statistics were conducted to examine the patient characteristics for both medical conditions in pre-formulary and post-formulary periods. For all continuous variables, two-tailed independent samples t-tests; and for all categorical variables chi-square analysis were employed to examine and compare patient characteristics for both medical conditions in pre-formulary and post-formulary periods. Parametric and non-parametric statistical tests (such as two-sample independent two-tailed t-tests and Wilcoxon 2-sample tests) were conducted to tests the different research hypotheses or determine the statistical significant differences (at an alpha=0.05) in the drug costs in the pre and post-formulary periods.

3.7. Definitions of Different Drug Attributes and Drug Factors Included in the Study:

Drug efficacy: It is a drug attribute, which is described by factors such as clinical evidence or documentation on how well that agent is used to treat particular condition or symptom.

Drug safety: It is a drug attribute, which is described by different safety factors in terms of frequency of mild to moderate adverse events, rare adverse events, potential side effects, and drug interactions resulting in medical consultation or hospital admission.

Drug availability: It is a drug attribute, which relates to the availability of the agent (in terms dosing frequency, availability of drug in different dosage forms, and strengths) for the purpose of use in the patients.

Drug cost: It is the cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Drug availability in different dosage forms: It is the number of different preparations in which the drug is available in the market such as tablet, capsule, injection, etc

Drug availability in different doses: It is the number of different doses or strengths in which the drug is available in the market.

Dosing Frequency: It is the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

DRUG EFFICACY FACTORS FOR ANTIDEPRESSANTS CLASS OF DRUGS

Response Rate: Defined as the proportion of individuals that demonstrate a mean reduction of atleast 50 percent of the depressive symptoms from the baseline scores after initiating the antidepressant treatment (for atleast 4 weeks) as measured by various depression assessment tools such as Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS)

Total Drop-out Rate: Defined as the proportion of individuals who had discontinued the drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or due to incidences of serious adverse drug events.

DRUG SAFETY FACTORS FOR ANTIDEPRESSANTS CLASS OF DRUGS

Drop-out Rate due to ADRs: Defined as the proportion of individuals who had discontinued the drug therapy during the study period because of experiencing one or several adverse drug reactions (ADRs).

Treatment-limiting ADRs: Defined as the total number of serious adverse drug reactions (ADRs) occurring in individuals during the study period, as a result of taking the medication, that may have led them to either discontinue the drug or seek special medical attention (including hospital admission or an ER visit).

Other ADRs: Defined as the average number of most commonly occurring mild to moderate Adverse Drug Reactions (ADRs) experienced by individuals during the study period, as a result of taking the medication.

Drug Interactions: Defined as the number of possible drug interactions associated with the drug molecule as reported in literature or drug monographs that requires caution while prescribing.

DRUG EFFICACY FACTORS FOR ACE-INHIBITORS CLASS OF DRUGS

All Cause Mortality Rate: Defined as the proportion of individuals that have died either due to cardiovascular causes (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular causes, pulmonary embolism, and nonvascular causes) at the end of the study period.

Functional Capacity: Defined as the percent improvement in the baseline exercise scores as measured by different exercise tests such as treadmill exercise tests or bicycle at the end of the study period.

DRUG SAFETY FACTORS FOR ACE-INHIBITORS CLASS OF DRUGS

Drop-out Rate due to (ADRs): Defined as the proportion of individuals who had discontinued the drug therapy during the study period because of experiencing one or several adverse drug reactions (ADRs).

Adverse Drug Reactions: Defined as the average number of most commonly occurring mild to moderate adverse drug effects experienced by individuals as a result of taking the medication.

Drug Interactions: Defined as the number of possible drug interactions associated with the drug molecule as reported in literature or drug monographs that requires caution while prescribing.

DRUG EFFICACY FACTORS FOR BETA BLOCKERS CLASS OF DRUGS

All Cause Mortality Rate: Defined as the proportion of individuals that have died either due to cardiovascular causes (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular causes, pulmonary embolism, and nonvascular causes) at the end of the study period.

Percent Mortality & Hospitalization Rate: Defined as the proportion of individuals those have died or have been hospitalized for heart failure.

Functional Capacity: Defined as the percent improvement in the baseline exercise scores as measured by a 6-minute walk test at the end of the study period.

DRUG SAFETY FACTORS FOR BETA BLOCKERS CLASS OF DRUGS

Drop-out Rate due to (ADRs): Defined as the proportion of individuals who had discontinued the drug therapy during the study period because of experiencing one or several adverse drug reactions (ADRs).

Treatment Limiting ADRs: Defined as the total number of serious adverse drug reactions (ADRs) occurring in individuals during the study period, as a result of taking the medication, that may have led them to either discontinue the drug or seek special medical attention (including hospital admission or an ER visit).

Other Adverse Defined as the average number of most commonly occurring mild to

Drug Reactions: moderate adverse drug effects experienced by individuals as a result of taking the medication.

Drug Interactions: Defined as the number of possible drug interactions associated with the drug molecule as reported in literature or drug monographs that requires caution while prescribing.

DRUG EFFICACY FACTORS FOR LOOP DIURETICS CLASS OF DRUGS

NYHA Functional Status: Defined as the proportion of individuals that have shown **i**mprovement in atleast one NYHA functional class during the study period, as defined by the New York Heart Association.

Mean Body Weight: Defined as the mean reduction in the body weight values obtained at the end of the study period.

Edema Improvement: Defined as the percentage of individuals that have shown improvement in the edema conditions at the end of the study.

DRUG SAFETY FACTORS FOR LOOP DIURETICS CLASS OF DRUGS

Treatment Limiting Adverse Drug Reactions (ADRs): Defined as the proportion of individuals that experienced serious adverse events as a result of taking the medication during the study period that may have led them to either discontinue the drug or seek special medical attention (including hospital admission or an ER visit).

Other Adverse Drug Reactions: Defined as number of most commonly occurring mild to moderate adverse events that did not lead to any special medical attention or hospital admission or an ER visit.

Drug Interactions: Defined as the number of possible drug interactions associated with the drug molecule as reported in literature or drug monographs that requires caution while prescribing.

DRUG EFFICACY FACTORS FOR ARBs CLASS OF DRUGS

All Cause Mortality Rate: Defined as the proportion of individuals that have died either due to cardiovascular causes (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular causes, pulmonary embolism, and nonvascular causes) at the end of the study period.

Hospitalization Rate: Defined as the proportion of individuals that were re-hospitalized during the study period as a result of increased morbidity or worsening heart failure conditions.

Left Ventricular Ejection Fraction: Defined as the percent improvement in the left ventricular ejection fraction (LVEF) values, from the baseline values as a result of taking the medication.

Total Drop-out Rate: Defined as the proportion of individuals who had discontinued the drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or due to incidences of serious adverse drug events.

DRUG SAFETY FACTORS FOR ARBs CLASS OF DRUGS

Drop-out Rate due to (ADRs): Defined as the proportion of individuals who had discontinued the drug therapy during the study period because of experiencing one or several adverse drug reactions (ADRs).

Treatment Limiting ADRs: Defined as the total number of serious adverse drug reactions (ADRs) occurring in individuals during the study period, as a result of taking the medication, that may have led them to either

discontinue the drug or seek special medical attention (including hospital admission or an ER visit).

Other Adverse Drug Reactions: Defined as the average number of most commonly occurring mild to moderate Adverse Drug Reactions (ADRs) experienced by individuals during the study period, as a result of taking the medication.

DRUG EFFICACY FACTORS FOR NITRATES CLASS OF DRUGS

Pulmonary Capillary Wedge Pressure: Defined as the percent reduction in the pulmonary capillary wedge pressure (PWP) values, from the baseline values as a result of taking the medication.

Cardiac Index: Defined as the percent improvement in the Cardiac Index (CI) values, from the baseline values as a result of taking the medication.

Pulmonary Arterial Pressure: Defined as the percent reduction in the Pulmonary Arterial Pressure (PAP) values, from the baseline values as a result of taking the medication.

Systemic Vascular Resistance: Defined as the percent reduction in the Systemic Vascular Resistance (SVR) values, from the baseline values as a result of taking the medication.

DRUG SAFETY FACTORS FOR NITRATES CLASS OF DRUGS

Drop-out Rate due to (ADRs): Defined as the proportion of individuals who had discontinued the drug therapy during the study period because of experiencing one or several adverse drug reactions (ADRs).

Treatment Limiting ADRs: Defined as the total number of serious adverse drug reactions (ADRs) occurring in individuals during the study period, as a result of taking the medication, that may have led them to either discontinue the drug or seek special medical attention (including hospital admission or an ER visit).

Drug Interactions: Defined as the number of possible drug interactions associated with the drug molecule as reported in literature or drug monographs that requires caution while prescribing.

4. RESULTS

This chapter will describe the results of this research project. Broadly, this study consisted of two study-phases: Phase-I which involved the development of condition-specific hospice formularies for CHF and depression, and Phase-II which involved the economic evaluation of the formulary agents that were selected for the two conditions mentioned above.

4.1. PHASE-I: Developing condition-specific hospice formularies for CHF and depression:

This phase of the study was sub-divided into the following sections:

Step1: Identifying different therapeutic drug classes for managing CHF and depression.

Step2: Conducting a literature review on drug agents represented in different therapeutic classes.

Step3: Identifying drug selection criteria (drug attributes and factors).

Step4: Compiling literature-based (factor) values for all study drugs and drug classes.

Step5: Conducting first focus group meeting for evaluating and determining rankings and weightings of different drug selection criteria.

Step6: Calculating total utility scores for individual study drugs and ranking them in descending order.

Step7: Conducting second focus group meeting for making final drug selection for the two condition-specific hospice formularies. Elaboration of each of the step follows:

4.1.1. Step1: Identifying different therapeutic drug classes for managing CHF and depression conditions

The first step involved in formulary development process was to identify important pharmacological or therapeutic drug classes and the individual drugs that are included within each class. Two approaches were used to identify drugs and drug classes for formulary consideration.

Approach 1: The guidelines published by the American College of Cardiology and the American Heart Association were utilized for CHF (ACA/AHA), while the Texas Implementation of Medication Algorithms (TIMA) and the American Psychiatry Association (APA) guidelines were used for depression.

Table 8 lists different drugs that are included in the respective drug classes that are typically used for CHF management. While some of the drug classes listed in the table include more than one drug agent in the class, there are many drug classes for which the ACC/AHA guidelines suggests the use of a single drug agent for managing the CHF condition.

Table 8: Drug therapy management as recommended by ACC/AHA guidelines for managing CHF

Drug class	**Therapeutic agents/drugs included**
Drug classes with multiple drug agents	
Angiotensin-Converting Enzymes Inhibitors (ACE-Inhibitors)	Lisinopril, Ramipril, Fosinopril, Quinapril, Benazepril, Enalapril
Loop diuretics	Furosemide, Torsemide, Bumetanide
Beta blockers	Carvedilol, Metoprolol
Nitrates	Isosorbide mononitrate, Nitroglycerin, Isosorbide dinitrate
Angiotensin Receptor Blockers (ARBs)	Valsartan, Irbesartan
Drug classes with single drug agent	
Calcium channel blockers	Amlodipine
Cardiac glycosides	Digoxin
Vasodilators	Hydralazine
Aldosterone receptor antagonists	Spironolactone
Anticoagulants	Warfarin
Thiazide diuretic	Hydrochlorthiazide
Thiazide-like diuretics	Metolazone

For the purpose of achieving an improvement in different CHF-related symptoms, the ACC/AHA guidelines have suggested the use of drug agents in specific therapeutic classes such as diuretics, cardiac glycosides and ACE-Inhibitors. In order to improve

survival rates of the patients, the guidelines have suggested the use of ACE-Inhibitors, beta blockers, aldosterone receptor antagonist such as spironolactone and also have recommended the use of a combination therapy consisting of oral nitrates and hydralazine. The guidelines have provided additional recommendations regarding certain drug agents belonging to specific therapeutic classes to be used specifically for managing patients in New York Heart Association (NYHA) class III or class IV patients, (i.e. to those who have severe condition) and who may seek hospice care. These recommendations are summarized in Figures 4 and 5.

Figure 4 illustrates the standard therapeutic management of CHF in NYHA Class III or Class IV patients. This consists of combination therapy using an ACE-Inhibitor, digoxin, beta-blockers and diuretics. These therapies are primarily responsible for either reducing mortality and morbidity (ACE-Inhibitors and beta-blockers) or they aid in reducing symptoms or in improving functional capacity, clinical status, and overall-well-being of the patients (diuretics, digoxin, and beta-blockers). For patients who cannot tolerate ACE-Inhibitors, alternative therapies such as Angiotensin receptor blockers (ARBs); or a combination therapy comprising of hydralazine and nitrate therapy are recommended. Along with the standard therapy, the guidelines also recommend the use of Aldosterone antagonist (spironolactone) to reduce mortality; anticoagulant (warfarin) to reduce the risk for developing thromboembolic events, and anti-platelet agents (low-dose aspirin) to reduce the risk of future ischemic events (Refer to Figure 5).

For patients who have CHF along with other medical conditions (such as hypertension, hyperlipidemia, diabetes, coronary artery disease, myocardial infarction, atrial fibrillation, or ventricular arrhythmia), the guidelines have provided additional

recommendations regarding the indications and contraindications related to certain drug agents which are outlined in Table 9. CHF is a medical condition which is more dominant in older patients and therefore may co-exist with other medical conditions. This may also be true in terminally-ill patients where they could have more than one medical condition existing with their primary condition. In such situations, recommendations provided by the guidelines regarding appropriate pharmacotherapy may be very useful in effectively managing the primary as well as other co-existing conditions.

Figure 4: Standard CHF treatment as recommended by ACC/AHA guidelines.

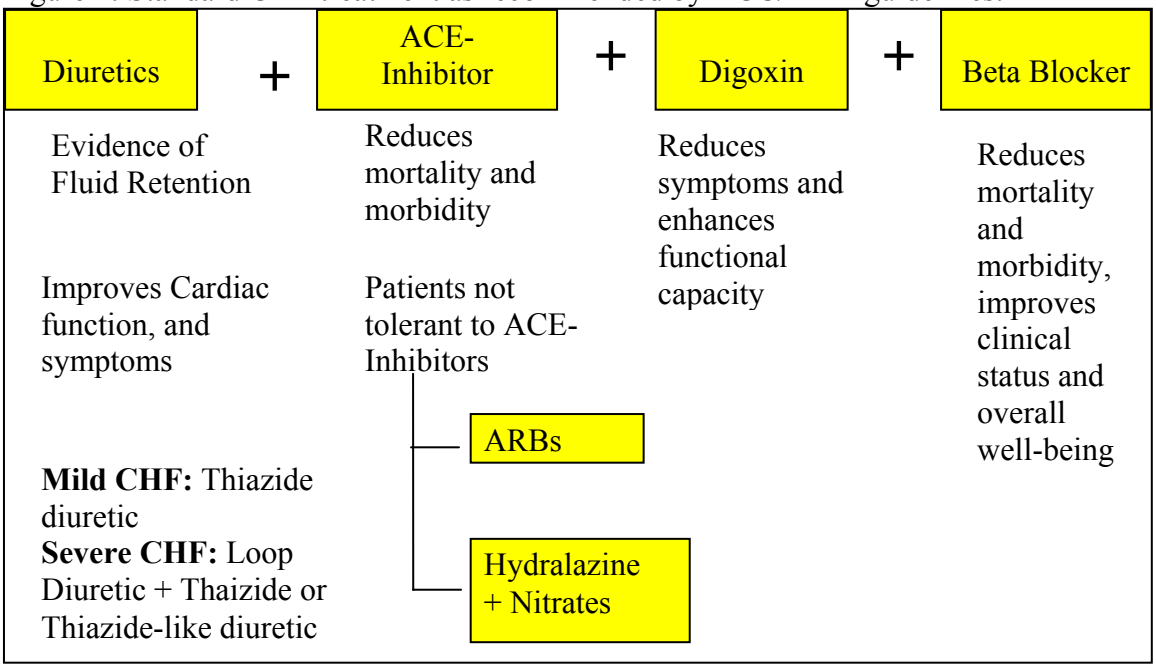


Figure 5: Supplementary treatment along with standard CHF treatment as recommended by ACC/AHA guidelines.

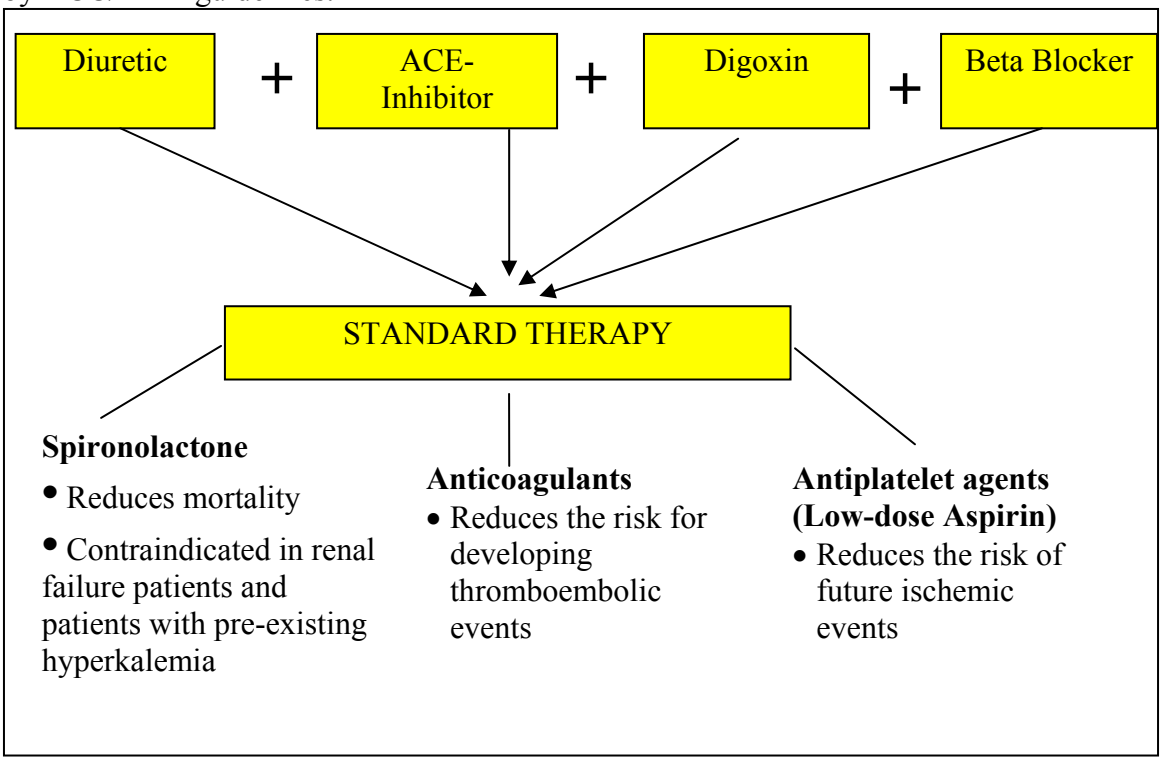


Table 9: Recommendations provided by ACC/AHA guidelines for CHF treatment in specific co-morbid conditions

Co-morbid conditions	**ACC/AHA guideline recommendations**
Hypertension/Hyperlipidemia or Diabetes	➢ Treatment should be followed for concomitant conditions, as if the patients did not have CHF ➢ Drugs that both control blood pressure and treat CHF should be preferred (diuretics, ACE-Inhibitors, and beta-blockers) ➢ Avoid calcium channel blockers
Coronary Artery Disease	➢ Drugs that both relieve angina and treat CHF should be preferred ➢ Nitrates and beta-blockers ➢ Avoid calcium channel blockers (except amlodipine)
Myocardial Infarction: (Without Heart Failure/Angina)	➢ ACE-Inhibitors + beta-blockers ➢ Aspirin or clopidogrel (Antiplatelet agents)
Atrial Fibrillation (Supraventricular Arrhythmia)	➢ Digoxin is the most commonly used agent ➢ Beta-blockers (carvedilol, bisoprolol, or metoprolol) are more effective than Digoxin ➢ Avoid calcium channel blockers (such as verapamil or diltiazem) ➢ If beta-blockers are ineffective, or contraindicated, then amiodarone is recommended
Ventricular Arrhythmia	➢ Beta-blockers (timolol or propranolol) are recommended ➢ Amiodarone is recommended, increases Ejection Fraction, and decreases worsening heart failure conditions

Treatment Guidelines for Depression:

Although the guidelines published by the Texas Implementation of Medication Algorithms (TIMA) and the American Psychiatry Association (APA) for managing depression are not specifically targeted towards terminally-ill patients, they recommend

the use of following classes of drugs such as Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), Dopamine reuptake inhibitors, Serotonin reuptake inhibitors, Serotonin modulators, Norepinephrine modulators, and Monoamino oxidase inhibitors (MAOI) for managing the condition. (Refer to Table 5).

Approach 2: An Excel spreadsheet of all the drugs used by the hospice of EAMC for managing CHF or depression conditions was compiled. For CHF, the center used all of the drug agents that were included in all major therapeutic classes recommended by ACC/AHA guidelines. For managing depressive symptoms, the center used drug agents that were only included in the SSRI drug class.

Since the hospice was using drugs from all major therapeutic drug classes mentioned in the CHF guidelines, all of the classes of drugs were reviewed in the next step. However, for depression, only the SSRI class of drugs was reviewed in the next step, as they were used exclusively by the center to manage depression. Furthermore, there wasn't any convincing evidence regarding the preferential use of agents in other drug classes for hospice patients.

4.1.2. Step2: Conducting literature review on drug agents represented in different therapeutic classes

After broadly identifying drugs in each therapeutic drug class, a comprehensive and systematic literature search was conducted to identify all relevant scientific studies related to the drugs in each therapeutic drug class. Table 10 lists all the drug classes for which comprehensive literature search and review process was conducted.

Table 10: Literature search and review process conducted on the following drug classes

Medical condition/ symptom	**Drug class**	**Therapeutic agents / drugs included**
Congestive Heart Failure (CHF)	ACE-Inhibitors	Lisinopril, Ramipril, Fosinopril, Quinapril, Benazepril, Enalapril
	Loop Diuretics	Furosemide, Torsemide, Bumetanide
	Beta Blockers	Carvedilol, Metoprolol
	Nitrates	Isosorbide mononitrate, Nitroglycerin, Isosorbide dinitrate
	ARBs	Valsartan, Irbesartan, Losartan
Depression	SSRIs	Citalopram, Fluoxetine, Paroxetine, Sertraline

A total of 3,230 articles in all the six therapeutic drug classes listed in Table 10 were stored in six separate EndNote database files. In addition to the article search generated by the computer databases, additional review articles for drugs or therapeutic classes listed in Table 10 were obtained from the Cochrane database. A total of 12 review articles were obtained from the Cochrane database. After performing the basic literature search, the next crucial step was to identify and select specific criteria or factors which will allow different drugs within the same therapeutic class to be compared. These criteria will be referred to as "*drug selection criteria*" in the later part of this chapter and other following chapters.

4.1.3. Step3: Identifying drug selection criteria (drug attributes and factors)

As a result of the assessment of the published studies and review articles some common criteria upon which the drugs within the same therapeutic class could be

evaluated and compared were identified. These criteria are categorized as drug attributes and drug factors. The most common drug attributes reported in the literature include drug efficacy, drug safety, drug availability and drug cost. For each therapeutic class, common factors reported in the literature that quantitatively describe individual drug attributes and which are utilized for evaluating drug agents were identified. Tables 11a and 11b list some of the most common drug attributes (drug efficacy and drug safety) and their related factors addressed in the literature, for each of the six therapeutic classes. Additionally, the tables list two other drug attributes (drug availability and drug cost), which are commonly cited in the literature as essential drug characteristics that are also taken into consideration by most P&T committees during formulary development.

Table 11a: List of drug attributes and factors for different therapeutic drug classes used in the study

Drug Attributes	**Drug Factors**		
	Antidepressants (SSRIs)	**ACE-Inhibitors**	**Beta Blockers**
Drug Efficacy	Response rate, % Total drop-out rate, %	All cause mortality rate (cardiovascular and non-cardiovascular causes) Percent improvement in functional capacity	Percent all cause mortality Percent mortality and hospitalization rate Percent improvement in functional capacity
Drug Safety	Drop-out rate (due to adverse drug reactions), % # of treatment-limiting severe adverse drug reactions # other adverse drug reactions # Drug interactions	Drop-out rate (due to adverse drug reactions) # Adverse drug reactions # Drug interactions	Percent discontinuation rate (due to adverse drug reactions) # of treatment-limiting severe adverse drug reactions # of other adverse drug reactions # Drug interactions
Drug Availability	Number of dosage forms available Number of doses available Common dosing frequency	Number of dosage forms available Number of doses available Common dosing frequency	Number of dosage forms available Number of doses available Common dosing frequency
Drug Cost	Price of the drug as purchased by the EAMC Pharmacy	Price of the drug as purchased by the EAMC Pharmacy	Price of the drug as purchased by the EAMC Pharmacy

Table 11b: List of drug attributes and factors for different therapeutic drug classes used in the study

Drug Attributes	Drug Factors		
	Loop Diuretics	**ARBs**	**Nitrates**
Drug Efficacy	Percentage improvement in NYHA functional class	Percent all cause mortality	Percent reduction in Pulmonary Capillary Wedge Pressure (PWP)
	Reduction in mean body weight	Percent hospitalization rate	Percent increase in Cardiac Index (CI)
	Percentage improvement in edema	Mean improvement in the Left Ventricular Ejection Fraction (LVEF)	Percent reduction in Pulmonary Arterial Pressure (PAP)
		Percent total drop-out rate	Percent reduction in Systemic Vascular Resistance (SVR)
Drug Safety	# Mild to moderate Adverse drug reactions	Percent drop-out rate (due to adverse drug reactions)	Percent drop-out rate (due to adverse drug reactions)
	Percentage of patients experiencing treatment-limiting adverse drug reactions	# of treatment-limiting severe adverse drug reactions	# of treatment-limiting severe adverse drug reactions
	# Drug interactions	# of adverse drug reactions	# Drug interactions
Drug Availability	Number of dosage forms available	Number of dosage forms available	Number of dosage forms available
	Number of doses available	Number of doses available	Number of doses available
	Common dosing frequency	Common dosing frequency	Common dosing frequency
Drug Cost	Price of the drug as purchased by the EAMC Pharmacy	Price of the drug as purchased by the EAMC Pharmacy	Price of the drug as purchased by the EAMC Pharmacy

Definitions for the different drug attributes and factors included in Tables 14a and 14b for each therapeutic class are included in Chapter 3 page nos. 106-113

4.1.4. Step4: Compiling literature-based factor values for all study drugs and drug classes

A total of 472 articles for the five therapeutic classes used for CHF management and 273 articles for antidepressants were identified and extracted during the initial search. All relevant articles (from selected systematic review articles, randomized clinical trials, meta-analysis type of studies) were identified and reviewed. For each therapeutic class, factor values that were reported in the articles were compiled and then weighted averages for each factor were computed and summarized in tabular formats.

The factor values obtained for drugs in the six therapeutic classes such as antidepressants, ACE-Inhibitors, beta blockers, loop diuretics, ARBs and nitrates have been summarized in Tables 12 through 17 respectively along with the number of review articles and studies from which the factor values for the different factors were derived.

Table 12: Summary table of the drug attributes and factors for Antidepressant (SSRIs) class of drugs:

Drug Attributes	Factors	Citalopram [*1a]	Fluoxetine [*1b]	Paroxetine [*1c]	Sertraline [*1d]
		Weighted factor values obtained from literature (Range)			
Drug efficacy	Response rate	**53.08** (36-82)	**50.28** (14-74)	**51.51** (19-78)	**59.13** (14.5-76)
	Total drop-out rate, %	**22.9** (7.2-48)	**33.66** (27.1-40.6)	**32.35** (20-42.6)	**25.12** (8-26)
Drug safety	Drop-out rate (due to adverse drug reactions), %	**11.51** (5.6-17.3)	**15.23** (3.7-30)	**19.37** (9.7-20)	**14.85** (7-28)
	# of treatment-limiting severe adverse drug reactions	**6** (5-7)	**5**	**3** (2-5)	**5** (3-7)
	# other adverse drug reactions	**4** (1-7)	**4** (1-7)	**3.5** (1-6)	**3.5** (3-6)
	# Drug interactions	**5**	**22**	**5**	**6**
Drug availability	Number of dosage forms available	**2** (Tablet, Solution)	**3** (Tablet, Capsule, Solution)	**2** (Tablet, Suspension)	**2** (Tablet, Solution)
	Number of doses available	**4** (10mg, 20mg, 40mg Tablets, 10mg/5mL solution)	**5** (10mg, 20mg Tablet/Capsule, 40mg Tablet, 90mg-CR Capsule, 20mg/5mL solution)	**8** (10mg, 12.5mg, 20mg, 25mg, 30mg, 37.5mg, 40mg, Tablet, 10mg/5mL suspension)	**4** (25mg, 50mg, 100mg Tablet, 20mg/5mL solution)
	Common dosing frequency	Once Daily	Once Daily	Once Daily	Once Daily
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	0.05/Tab	0.19/Tab	0.08/Tab	1.54/Tab

[* 1a] Information compiled from 10 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*1b] Information compiled from 17 Randomized Clinical Trial and 4 Review articles published in scientific journals

[*1c] Information compiled from 12 Randomized Clinical Trial and 3 Review articles published in scientific journals

[*1d] Information compiled from 12 Randomized Clinical Trial and 2 Review articles published in scientific journals.

Table 13: Summary table -Drug attributes and factors for ACE-Inhibitor class of drugs

Drug Attributes	**Factors**	**Enalapril** [*2a]	**Lisinopril** [*2b]	**Ramipril** [*2c]	**Fosinopril** [*2d]	**Quinapril** [*2e]	**Benazepril** [*2f]
		Weighted factor values obtained from the literature (Range)					
Drug efficacy	All cause mortality rate (cardiovascular and non-cardiovascular causes)	**21.75** (0-39.3)	**2.84** (0-3.57)	**12.62** (1-20.75)	**2.39** (1.63-3.44)	**1.02** (0-2.7)	**2.39** (0-6.89)
	Percent improvement in functional capacity	**14** (9.4-28.4)	**26.8** (12.6-58.6)	**7.2** (2-15.6)	**15.0**	**20.5** (10.9-25.8)	**15.0**
Drug safety	Drop-out rate (due to adverse drug reactions)	**8.53** (3.3-15.2)	**11.42** (6.2-17)	**16.29** (14-18.5)	**5.0** (2-8)	**8.78** (0-20)	**4.3**
	# Adverse drug reactions	**5** (0-9)	**4** (0-7)	**5** (0-9)	**2** (1-3)	**6** (0-11)	**4** (0-7)
	# Drug interactions	**11**	**4**	**2**	**2**	**2**	**5**
Drug availability	Number of dosage forms available	**2** (Tablet, Inj)	**1** (Tablet)	**1** (Capsule)	**1** (Tablet)	**1** (Tablet)	**1** (Tablet)
	Number of doses available	**5** (2.5mg, 5mg, 10mg, 20mg Tablets, and 1.25mg/mL Inj)	**6** (2.5mg, 5mg, 10mg, 20mg, 30mg, and 40mg Tablets)	**4** (1.25mg, 2.5mg, 5mg, and 10mg Capsules)	**3** (10mg, 20mg, and 40mg Tablets)	**4** (5mg, 10mg, 20mg, and 40mg Tablets)	**4** (5mg, 10mg, 20mg, and 40mg Tablets)
	Common dosing frequency	BID	Once Daily	BID	Once Daily	BID	Once Daily
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	0.04/Tab	0.18/Tab	0.29/Cap	1.10/Tab	0.143/Tab	0.176/Tab

[*2a] Information compiled from 11 Randomized Clinical Trial and 3 Review articles published in scientific journals

[*2b] Information compiled from 7 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2c] Information compiled from 10 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2d] Information compiled from 4 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2e] Information compiled from 6 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2f] Information compiled from 4 Randomized Clinical Trial and 1 Review articles published in scientific journals

Table 14: Summary table of the drug attributes and factors for Beta blocker class of drugs:

Drug Attributes	**Factors**	**Carvedilol** [*3a]	**Metoprolol** [*3b]
		Weighted factor values obtained from the literature (Range)	
Drug efficacy	Percent all cause mortality	**10.12** (0-14)	**7.7** (0-11.8)
	Percent mortality and hospitalization rate	**19.6** (11.1-50)	**31.53** (24.7-32.2)
	Percent improvement in Functional capacity	**5.9** (2.6-11.1)	**17.8** (5.4-40)
Drug safety	Percent discontinuation rate (due to adverse drug reactions)	**9.3** (5.3-16)	**11** (10.8-11.2)
	# of treatment-limiting severe adverse drug reactions	**4** (1-6)	**3**
	# of other adverse drug reactions	**12** (4-18)	**8**
	# Drug interactions	**3**	**0**
Drug availability	Number of dosage forms available	**1** (Tablet)	**2** (Tablet, Injection)
	Number of doses available	**4** (3.125mg, 6.25mg, 12.5mg, and 25mg Tablets)	**4** (25mg, 50mg, 100mg, Tablets, and 1mg/mL Inj)
	Common dosing frequency	BID	Once Daily
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	1.15/Tab	0.023/Tab

[*3a] Information compiled from 11 Randomized Clinical Trial and 4 Review article published in scientific journals

[*3b] Information compiled from 11 Randomized Clinical Trial and 3 Review articles published in scientific journals

Table 15: Summary table of the drug attributes and factors for Loop diuretics class of drugs:

Drug Attributes	Factors	Furosemide [*4a]	Torsemide [*4b]	Bumetanide [*4c]
		Weighted factor values obtained from the literature (Range)		
Drug efficacy	Percentage improvement in NYHA functional class	**33.45** (24-37.2)	**43.8** (38-45.8)	**33**
	Reduction in mean body weight	**1.04** (0.7-2.07)	**1.45** (0.9-3)	**1.6** (1.5-1.7)
	Percentage improvement in edema	**74.2** (48-92)	**78.2** (55-97)	**78**
Drug safety	# Mild to moderate Adverse drug reactions	**15** (3-27)	**16** (31)	**8** (2-11)
	Percentage of patients experiencing treatment-limiting adverse drug reactions	**12.2**	**19.7**	**22.2**
	# Drug interactions	**12**	**1**	**2**
Drug availability	Number of dosage forms available	**3** (Tablet, Solution, Injection)	**2** (Tablet, Injection)	**2** (Tablet, Injection)
	Number of doses available	**6** (20mg, 60mg, 80mg Tablets, 10mg/mL Injection, 10mg/mL and 40mg/5mL solution)	**5** (5mg,10mg, 20mg, and 100 mg Tablets, and 10mg/mL injection)	**4** (0.5mg, 1mg, and 2mg Tablets, 0.25mg/mL injection)
	Common dosing frequency	Once daily	Once daily	Once daily
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	0.008/Tab	0.647/Tab	0.05/Tab

[*4a] Information compiled from 8 Randomized Clinical Trial and 1 Review article published in scientific journals

[*4b] Information compiled from 6 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*4c] Information compiled from 3 Randomized Clinical Trial and 2 Review articles published in scientific journals

Table 16: Summary table of the drug attributes and factors for ARBs class of drugs:

Drug Attributes	**Factors**	**Irbesartan** [*5a]	**Valsartan** [*5b]	**Losartan** [*5c]
		Weighted factor values obtained from the literature (Range)		
Drug efficacy	Percent all cause mortality	**13.33** (0-16.9)	**19.53** (17.3-19.7)	**11.6** (1.1-17.7)
	Percent hospitalization rate	**4.55** (4-4.7)	**13.75** (13-13.8)	**15.00** (5.7-17.1)
	Mean improvement in the Left Ventricular Ejection Fraction (LVEF)	**3.36** (1.9-4.4)	**4.06** (4-5)	**1.70** (1.2-2.3)
	Percent total discontinuation rate	**18.13** (12.3-19.7)	**16.2** (16.1-17.3)	**18.00** (7.1-18.5)
Drug safety	Percent drop-out rate (due to adverse drug reactions)	**13.75** (5.3-16)	**9.8** (9.7-9.9)	**8.9** (1.9-12.2)
	# of treatment-limiting severe adverse drug reactions	**3**	**2-3**	**10** (7-13)
	# of adverse drug reactions	**3** (2-5)	**2** (2)	**4** (0-7)
Drug availability	Number of dosage forms available	**1** (Tablet)	**1** (Tablet)	**1** (Tablet)
	Number of doses available	**3** (75mg, 150 mg, and 300mg Tablets)	**4** (40mg, 80mg 160, and 320 mg Tablets)	**3** (25mg, 50mg, and 100mg Tablets)
	Common dosing frequency	Once Daily	BID	Once Daily
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	0.694/Tab	1.44/Tab	0.820/Tab

[*5a] Information compiled from 2 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*5b] Information compiled from 2 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*5c] Information compiled from 8 Randomized Clinical Trial and 3 Review articles published in scientific journals.

Table 17: Summary table of the drug attributes and factors for Nitrates class of drugs:

Drug Attributes	Factors	Isosorbide Dinitrate [*6a]	Isosorbide Mononitrate [*6b]	Nitroglycerin [*6c]
		Weighted factor values obtained from literature (Range)		
Drug efficacy	Percent reduction in Pulmonary Capillary Wedge Pressure (PWP)	**41.26** (37.5-45.5)	**41.26**	**39.9** (36.3-48.1)
	Percent increase in Cardiac Index (CI)	**16.1** (11.7-22.3)	**16.1**	**18.4** (13-19)
	Percent reduction in Pulmonary Arterial Pressure (PAP)	**36** (35-36.6)	**36**	**33.9** (28.7-34.8)
	Percent reduction in Systemic Vascular Resistance (SVR)	**13.7**	**13.7**	**25.9** (14.1-28.0)
Drug safety	Percent drop-out rate (due to adverse drug reactions)	**6.7**	**11** (7-12)	**5.5**
	# of treatment-limiting severe adverse drug reactions	**3**	**3**	**1**
	# Drug interactions	**0**	**1**	**4**
Drug availability	Number of dosage forms available	**2** (Tablet, Capsule)	**1** (Tablet)	**6** (Tablet, Capsule, Solution, Ointment, Injection, and Patch)
	Number of doses available	**3** (20mg, 30 mg Tablets and 40mg Tablet/Capsule)	**5** (10mg, 20mg Tablets, 30mg, 60mg, and 120mg ER Tablets)	**8** (2mg Tablet, 2.5mg, 6.5mg, and 9mg Capsule-ER, 0.4mg/spray, 2% ointment, 5 mg/mL Injection, 0.1 mg/hour, 0.2 mg/hour, 0.3 mg/hour, 0.4 mg/hour, and 0.6 mg/hour Patch)
	Common dosing frequency	Once Daily	Once Daily	Patch: 0.4-0.8mg/hr
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	0.01850/Tab	0.033/Tab	0.317/Patch

[*6a] Information compiled from 5 Randomized Clinical Trial and 1 Review article published in scientific journals

[*6b] Information compiled from 3 Randomized Clinical Trial and 1 Review article published in scientific journals

[*6c] Information compiled from 6 Randomized Clinical Trial and 1 Review article published in scientific journals

4.1.5. Step5: Conducting first focus group meeting for evaluating and determining rankings and weightings of different drug selection criteria

Two focus group meetings were scheduled with the drug selection committee members at the hospice for developing formularies for the two medical conditions. The members listed in Table 18 comprised the ad hoc drug selection committee at the hospice who participated in the drug selection process.

Table 18: First focus group meeting involving the drug selection committee members

FIRST FOCUS GROUP MEETING
Meeting date: Wednesday, June 15, 2005 (11:00am-2:00 pm)
Meeting place: Hospice of EAMC, Auburn, AL
Facilitated by: Researcher and Academic Advisor
Participants of the focus group meeting
Physician and Medical Director, Hospice of EAMC
Pharmacy Manager, EAMC Home Care Pharmacy
Admission Nurse, Hospice of EAMC
Manager, Hospice of EAMC
Director, Hospice and Oncology Services of EAMC
Clinical Coordinator, Hospice of EAMC
Pharmacist, EAMC Home Care Pharmacy

The following action items were followed during the first focus group meeting:

- Review pharmacologic classes used for managing CHF and depression conditions
- Present summary tables for drugs within each therapeutic class
- Explain detailed drug selection procedures
- Obtain rankings and weightings on different drug attributes and factors

4.1.5.1 Review pharmacologic classes used for managing CHF and depression conditions:

For CHF, the recommendations and suggestions reported by the ACC/AHA guidelines were presented to the committee members. All information listed in Tables 8, 9, 10 and Figures 4, and 5 were presented. Since the drug classes that contained all single medications were included in the guidelines as a part of drug therapy management for CHF patients in certain circumstances, those agents were directly selected for the CHF formulary by consensus of the committee. Drugs in the therapeutic classes listed in Table 19 were directly selected for CHF formulary.

Table 19: Drug agents directly selected for the CHF formulary

Therapeutic class for CHF drug management	**Drug agents included**
Calcium channel blockers	Amlodipine
Cardiac glycosides	Digoxin
Vasodilators	Hydralazine
Aldosterone receptor antagonists	Spironolactone
Anticoagulants	Warfarin
Thiazide diuretic	Hydrochlorthiazide
Thiazide-like diuretics	Metolazone

4.1.5.2. Present summary tables for factor values for drugs within each therapeutic class:

All those classes of drugs that contained multiple drug agents and which required selection of appropriate drugs for the formulary were considered for detailed selection process. Summary Tables (Tables 20 through 25) were presented to the group, which contained information regarding the range of factor values that were obtained across different factors for each of the six therapeutic classes respectively

4.1.5.3. Explain the detailed drug selection procedures:

In the next step, the researcher and his academic advisor, who were the facilitators, explained the protocol and detailed procedures for drug selection to the group. To ensure that the group members clearly understand the selection procedure, a practice session was conducted with the help of a dummy example. Any questions or doubts that were raised during the practice session were cleared by the facilitators. Because of the practice nature of the dummy example, which served as an opportunity for the members to get a hands on experience on how to assign rank and weight to their own preferences, the responses obtained from them (through the dummy example) were not collected and reported.

Table 20: Range of factor values for Antidepressant drug class:

Drug Attributes	**Factors**	**Citalopram** *1a	**Fluoxetine** *1 b	**Paroxetine** *1 c	**Sertraline** *1 d
		Range of weighted factor values obtained from literature			
Drug efficacy	Response rate	50-59%			
	Total drop-out rate, %	23-37%			
Drug safety	Drop-out rate (due to adverse drug reactions), %	11.5-19			
	# of treatment-limiting severe adverse drug reactions	3-6			
	# other adverse drug reactions	1-5			
	# Drug interactions	5-22			
Drug availability	Number of dosage forms available	2-3			
	Number of doses available	4-8			
	Common dosing frequency	Once Daily			
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	($4.67/100 = 0.05/Tab To $77.06/50 = 1.54/Tab)			

*1a Information compiled from 10 Randomized Clinical Trial and 2 Review articles published in scientific journals
*1b Information compiled from 17 Randomized Clinical Trial and 4 Review articles published in scientific journals
*1c Information compiled from 12 Randomized Clinical Trial and 3 Review articles published in scientific journals
*1d Information compiled from 12 Randomized Clinical Trial and 2 Review articles published in scientific journals

Table 21: Range of factor values for ACE-Inhibitors drug class:

Drug Attributes	**Factors**	**Enalapril** [*2a] **Lisinopril** [*2b] **Ramipril** [*2c] **Fosinopril** [*2d] **Quinapril** [*2e] **Benazepril** [*2f]
		Range of weighted factor values obtained from literature
Drug efficacy	All cause mortality rate (cardiovascular and non-cardiovascular causes)	1.0-21.7
	Percent improvement in functional capacity	7.2-26.8
Drug safety	Drop-out rate (due to adverse drug reactions)	4.3-16.3
	# Adverse drug reactions	0-6
	# Drug interactions	2-11
Drug availability	Number of dosage forms available	1-2
	Number of doses available	3-6
	Common dosing frequency	Once Daily-BID
Drug cost ($/pill)	Price of the drug as purchased by the EAMC Pharmacy	$0.67/100 = 0.007/Tab To $99.28/90 = 1.10/Tab

[*2a] Information compiled from 11 Randomized Clinical Trial and 3 Review articles published in scientific journals

[*2b] Information compiled from 7 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2c] Information compiled from 10 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2d] Information compiled from 4 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2e] Information compiled from 6 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*2f] Information compiled from 4 Randomized Clinical Trial and 1 Review articles published in scientific journal

Table 22: Range of factor values for Beta Blockers drug class:

Drug Attributes		**Carvedilol** [*3a]	**Metoprolol** [*3b]
	Factors	**Range of weighted factor values obtained from literature**	
Drug efficacy	Percent all cause mortality	7.7- 10.12	
	Percent mortality and hospitalization rate	19.6 - 31.5	
	Percent improvement in Functional capacity	5.9 -17.8	
Drug safety	Percent discontinuation rate (due to adverse drug reactions)	9.3 - 11	
	# of treatment-limiting severe adverse drug reactions	3 - 4	
	# of other adverse drug reactions	8- 12	
	# Drug interactions	0-3	
Drug availability	Number of dosage forms available	1 - 2	
	Number of doses available	4	
	Common dosing frequency	Once Daily - BID	
Drug cost	Price of the drug as purchased by the EAMC Pharmacy	$ 2.14/100 = 0.021/tab To $ 115.40/100 = 1.15/tab	

[*3a] Information compiled from 11 Randomized Clinical Trial and 4 Review article published in scientific journals
[*3b] Information compiled from 11 Randomized Clinical Trial and 3 Review articles published in scientific journals

Table 23: Range of factor values for Loop Diuretics drug class:

Drug Attributes		**Furosemide** [*4a]	**Torsemide** [*4b]	**Bumetanide** [*4c]
	Factors	**Range of weighted factor values obtained from literature**		
Drug efficacy	Percentage improvement in NYHA functional class	33.45 - 43.8		
	Reduction in mean body weight	1.0 - 1.6		
	Percentage improvement in edema	74.2 - 78.2		
Drug safety	# Mild to moderate Adverse drug reactions	2-27		
	Percentage of patients experiencing treatment-limiting adverse drug reactions	12.2 -22.2		
	# Drug interactions	1-12		
Drug availability	Number of dosage forms available	2-3		
	Number of doses available	4-6		
	Common dosing frequency	Once Daily		
Drug cost	Price of the drug as purchased by the EAMC Pharmacy	$0.48/100 = 0.005/Tab To $94.16/100 = 0.942/Tab		

[*4a] Information compiled from 8 Randomized Clinical Trial and 1 Review article published in scientific journals

[*4b] Information compiled from 6 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*4c] Information compiled from 3 Randomized Clinical Trial and 2 Review articles published in scientific journals

Table 24: Range of factor values for Angiotensin Receptor Blocker drug class:

Drug Attributes		**Irbesartan** [*5a] **Valsartan** [*5b] **Losartan** [*5c]
	Factors	**Range of weighted factor values obtained from literature**
Drug efficacy	Percent all cause mortality	13.3 - 19.5
	Percent hospitalization rate	4.5 - 15
	Mean improvement in the Left Ventricular Ejection Fraction (LVEF)	1.7 - 4.06
	Percent total discontinuation rate	16.2 - 18.13
Drug safety	Percent drop-out rate (due to adverse drug reactions)	8.9 - 13.7
	# of treatment-limiting severe adverse drug reactions	2-10
	# of adverse drug reactions	2-7
Drug availability	Number of dosage forms available	1
	Number of doses available	3-4
	Common dosing frequency	Once Daily-BID
Drug cost	Price of the drug as purchased by the EAMC Pharmacy	$62.49/90 = 0.694/tab To $136.30/90 = 1.51/Tab

[*5a] Information compiled from 2 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*5b] Information compiled from 2 Randomized Clinical Trial and 2 Review articles published in scientific journals

[*5c] Information compiled from 8 Randomized Clinical Trial and 3 Review articles published in scientific journals

Table 25: Range of factor values for Nitrates drug class:

Drug Attributes	Factors	Isosorbide Dinitrate [*6a]	Isosorbide Mononitrate [*6b]	Nitroglycerin [*6c]
		Range of weighted factor values obtained from literature		
Drug efficacy	Percent reduction in Pulmonary Capillary Wedge Pressure (PWP)		39.9- 41.3	
	Percent increase in Cardiac Index (CI)		16.1 -18.4	
	Percent reduction in Pulmonary Arterial Pressure (PAP)		33.9- 36	
	Percent reduction in Systemic Vascular Resistance (SVR)		13.7-25.9	
Drug safety	Percent drop-out rate (due to adverse drug reactions)		5.5 -11	
	# of treatment-limiting severe adverse drug reactions		1-3	
	# Drug interactions		0 -4	
Drug availability	Number of dosage forms available		1-7	
	Number of doses available		5-14	
	Common dosing frequency		Once Daily- QID	
Drug cost	Price of the drug as purchased by the EAMC Pharmacy	$1.77/100 = 0.018/tab To $9.70/30 = 0.323/patch		

[*6a] Information compiled from 5 Randomized Clinical Trial and 1 Review article published in scientific journals
[*6b] Information compiled from 3 Randomized Clinical Trial and 1 Review article published in scientific journals
[*6c] Information compiled from 6 Randomized Clinical Trial and 1 Review article published in scientific journals

4.1.5.4. Obtain rankings and weightings on different drug attributes and factors:

For each therapeutic class, the group was asked to give their consensus on the list of important drug attributes and factors which resulted from literature review process. Additionally, the group was asked to add other drug attributes or factors that did not appear on the list, that they believed were important drug features, and should be considered for making drug selection decisions. For all six therapeutic classes, there was complete consensus on the list of attributes and factors that were presented to them. In addition, the group did not have any additional drug attributes or factors to add to that list. Each member of the group ranked and then weighted the listed drug attributes that they considered most important for selecting appropriate therapies for their patients.

4.1.5.5. Determine level of agreement for the assigned rankings and weightings:

Rankings and weighting for the different drug attributes and factors were obtained from each member of the group. Since individual member was asked to give his/her preference, every person in that group may not have similar preferences for different drug attributes or factors. Therefore, in order to test the degree of agreement among all participating members, inter-rater reliabilities were conducted and analyzed using the intraclass correlation coefficients (ICC) tests. ICC tests are usually used to measure inter-rater reliability for continuous data, and are preferred over other tests such as Pearson's r only when the sample size is less than 15. The ICC assesses rating reliability by comparing the variability of different ratings of the subject to the total variation across all ratings and all subjects. In other words ICC may be conceptualized as the ratio of between-groups variance to total variance (McGraw & Wong, 1996).

Intraclass correlation coefficients for drug attributes:

Intraclass correlation tests were conducted to determine the level of agreement between all committee members on the ratio weights computed for all drug attributes. In all of the six therapeutic drug classes that were subjected to MAUT methodology, significantly high correlation coefficients were obtained for attributes in the descending order of drug efficacy, drug safety, drug cost, and drug availability ($p<0.005$). Regardless of the therapeutic drug class, highest ratio weights were reported for drug efficacy while the least ratio weights were reported for drug availability [Appendix D-Table D1].

Intraclass correlation coefficients for factors:

For individual drug class, separate intraclass correlation tests were conducted to determine the level of agreement on the ratio weights assigned by the members for different factors specified under each drug attribute. The results obtained from intraclass correlation coefficient tests for factors are summarized in Appendix D [Tables D2-D7].

For factors included under efficacy, significant levels of inter-rater agreement were obtained for SSRIs ($r=0.932$, $p< 0.009$), ACE-Inhibitors ($r = 0.838$, $p= 0.009$), and Beta-Blockers ($r = 0.829$, $p= 0.046$) classes of drugs. This indicates that, for these drug classes, members of the drug selection committee had greater agreement on their preferences for different factors considered for attribute "efficacy."

For factors included under safety, significant levels of inter-rater agreement were obtained for loop diuretics ($r = 0.706$, $p=0.038$) class of drugs, indicating that, for loop diuretics, members of the drug selection committee had greater agreement on their preferences for different factors considered for the attribute "safety."

Similarly, for factors included under availability, significant levels of inter-rater agreement were obtained for Ace-Inhibitors ($r = 0.869$, $p=0.038$), Beta-Blockers ($r = 0.793$, $p=0.029$) and Angiotensin Receptor Blockers ($r = 0.787$, $p=0.031$) class of drugs, indicating that, for these drug classes, members of the drug selection committee had greater agreement on their preferences for different factors considered for attribute "availability."

Thus, results from the ICC tests conducted for factors in each drug class showed different levels of agreement, suggesting that members of the selection committee did differ in their preferences on the individual criteria considered important under each drug attribute.

4.1.6. Calculating factor utility and total utility scores for individual study drug (Steps 6 and 7):

After obtaining the ranks and weights from individual group members for the drug attributes and factors in each therapeutic class, the next important step in formulary development was to calculate a composite score for each drug agent within a therapeutic class. These composite scores, also referred to as "total utility score," were calculated for each individual drug, using the weighted average factor values (obtained for that drug through literature review process) and the drug attributes ratio weights and drug factors ratio weights (obtained from individual members' ranks and weights). The calculation of total utility score values are broadly divided into two parts:

- Computation of Factor Utility Scores
- Computation of Total Utility Scores

Procedures for calculating the factor utility scores and the total utility scores were followed and the respective values were obtained. For each therapeutic class, sensitivity analysis was performed by changing the utility scales values related to all drug attributes and factors and then the changes in the relative rankings for drugs in each class were observed. Although, $\pm$ 10% of the factor value range was considered for the utility scales instead of $\pm$ 20%, no changes in the relative rankings were observed for the drugs in all six therapeutic classes. Finally, summaries of such rankings and the different combination of rankings that were observed across the group were organized in tabular formats. Rankings for the group were determined in terms of how many out of seven members ranked a particular drug as number one, number two, and so on. Additionally, number of members that ranked the top two drugs as either number one or number two was reported. Different combinations for ranking of the drugs that were observed were also reported.

Rankings obtained for drugs in each of the six therapeutic classes are summarized in Tables 26 through 31. Tables 26a, 27a, 28a, 29a, 30a, and 31a represent the final rankings obtained for the six classes, while Tables 26b, 27b, 28b, 29b, 30b, and 31b summarizes these rankings, whereas Tables 26c, 27c, 28c, 29c, 30c, and 31c represent the different rank combinations observed for the six therapeutic classes respectively.

Table 26a: Total utility scores and final rankings obtained from the drug selection committee members for Antidepressant drug class

ANTI-DEPRESSANTS	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Citalopram	80.71	66.67	60.48	67.78	62.59	62.54	68.11	54.49
Paroxetine	80.23	64.88	63.30	68.98	64.09	60.42	64.99	50.93
Sertraline	70.05	54.05	52.99	55.29	49.17	52.59	62.06	44.05
Fluoxetine	56.97	54.30	51.70	55.00	55.54	56.18	49.23	42.84
RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG								
Citalopram	1	1	2	2	2	1	1	1
Paroxetine	2	2	1	1	1	2	2	2
Sertraline	3	4	3	3	4	4	3	3
Fluoxetine	4	3	4	4	3	3	4	4

Table 26b: Summary of rankings obtained for Antidepressant drug class

	Number of members (Out of 7)	Percentage of Members
Citalopram ranked as Number 1 choice of drug	**4**	**57**
Paroxetine ranked as Number 2 choice of drug	**4**	**57**
Sertraline ranked as Number 3 choice of drug	**4**	**57**
Fluoxetine ranked as Number 4 choice of drug	**4**	**57**
Citalopram ranked as one of the top 2 drug agents	**7**	**100**
Paroxetine ranked as one of the top 2 drug agents	**7**	**100**

Table 26c: Summary of different ranking combinations obtained for Antidepressant drug class

	Number of members (%)		Number of members (%)		Number of members (%)		Number of members (%)
Citalopram Paroxetine Sertraline Fluoxetine	2/7 (29%)	Citalopram Paroxetine Fluoxetine Sertraline	2/7 (29%)	Paroxetine Citalopram Sertraline Fluoxetine	2/7 (29%)	Paroxetine Citalopram Fluoxetine Sertraline	1/7 (14%)

Table 27a: Total utility scores and final rankings obtained from drug selection committee members for ACE-Inhibitors class

ACE-INHIBITORS	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Lisinopril	59.89	57.87	57.27	61.54	60.22	57.32	64.33	57.27
Quinapril	56.89	57.30	55.58	60.72	58.08	55.56	60.72	50.45
Benazepril	56.36	55.95	55.68	56.35	57.56	59.56	54.67	53.48
Fosinopril	50.29	44.27	50.04	51.55	48.47	53.04	49.55	49.59
Enalapril	48.77	48.40	47.31	45.52	49.99	55.55	45.42	49.28
Ramipril	44.94	43.05	41.39	49.71	42.69	46.24	51.83	40.27
	RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG							
Lisinopril	1	1	1	1	1	2	1	1
Quinapril	2	2	3	2	2	3	2	2
Benazepril	3	3	2	3	3	1	3	3
Fosinopril	4	5	4	4	5	5	4	4
Enalapril	5	4	5	6	4	4	6	5
Ramipril	6	6	6	5	6	6	5	6

Table 27b: Summary of rankings obtained for ACE-Inhibitors drug class

	Number of members (Out of 7)	Percentage of Members
Lisinopril ranked as Number 1 choice of drug	**6**	**86**
Quinapril ranked as Number 2 choice of drug	**5**	**71**
Benazepril ranked as Number 3 choice of drug	**5**	**71**
Fosinopril ranked as Number 4 choice of drug	**4**	**57**
Enalapril ranked as Number 5 choice of drug	**2**	**29**
Ramipril ranked as Number 6 choice of drug	**5**	**71**
Lisinopril ranked as one of the top 2 drug agents	**7**	**100**
Quinapril ranked as one of the top 2 drug agents	**5**	**71**

Table 27c: Summary of different ranking combinations obtained for ACE-Inhibitors drug class

	Number of members (%)		Number of members (%)		Number of members (%)		Number of members (%)		Number of members (%)
Lisinopril Quinapril Benazepril Fosinopril Enalapril Ramipril	1/7 (14%)	Lisinopril Quinapril Benazepril Fosinopril Ramipril Enalapril	2/7 (29%)	Lisinopril Quinapril Benazepril Enalapril Fosinopril Ramipril	2/7 (29%)	Lisinopril Benazepril Quinapril Fosinopril Enalapril Ramipril	1/7 (14%)	Benazepril Lisinopril Quinapril Fosinopril Enalapril Ramipril	1/7 (14%)

Table 28a: Total utility scores and final rankings obtained from the drug selection committee members for Beta blockers drug class

BETA BLOCKER	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Metoprolol	**67.35**	**69.32**	**64.65**	**68.96**	**69.82**	**64.46**	**72.10**	**65.69**
Carvedilol	**42.60**	**36.79**	**40.28**	**38.32**	**38.35**	**49.35**	**41.52**	**47.48**
	RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG							
Metoprolol	1	1	1	1	1	1	1	1
Carvedilol	2	2	2	2	2	2	2	2

Table 28b: Summary of rankings obtained for Beta blockers drug class

	Number of members (Out of 7)	Percentage of Members
Metoprolol ranked as Number 1 choice of drug	**7**	**100**
Carvedilol ranked as Number 2 choice of drug	**7**	**100**

Table 29a: Total utility scores and final rankings obtained from the drug selection committee members for Loop diuretics drug class

LOOP DIURETICS	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Torsemide	64.45	51.71	64.46	63.84	63.20	63.60	76.71	58.74
Furosemide	61.02	63.07	61.27	56.58	62.71	63.24	56.07	63.81
Bumetanide	59.70	56.47	56.30	64.15	63.53	55.42	69.41	56.15
	RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG							
Torsemide	1	3	1	2	2	1	1	2
Furosemide	2	1	2	3	3	2	3	1
Bumetanide	3	2	3	1	1	3	2	3

Table 29b: Summary of rankings obtained for Loop diuretics drug class

	Number of members (Out of 7)	Percentage of Members
Torsemide ranked as Number 1 choice of drug	**3**	**43**
Furosemide ranked as Number 2 choice of drug	**2**	**29**
Bumetanide ranked as Number 3 choice of drug	**3**	**43**
Torsemide ranked as one of the top 2 drug agents	**6**	**86**
Furosemide ranked as one of the top 2 drug agents	**4**	**57**

Table 29c: Summary of different ranking combinations obtained for Loop diuretics drug class

	Number of members (%)		Number of members (%)		Number of members (%)		Number of members (%)		Number of members (%)
Torsemide Furosemide Bumetanide	2/7 (29%)	Bumetanide Torsemide Furosemide	1/7 (14%)	Bumetanide Torsemide Furosemide	2/7 (29%)	Torsemide Bumetanide Furosemide	1/7 (14%)	Furosemide Torsemide Bumetanide	1/7 (14%)

Table 30a: Total utility scores and final rankings obtained from the drug selection committee members for ARBs drug class

ARBs	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Irbesartan	**62.16**	**66.14**	**65.03**	**60.34**	**60.06**	**55.70**	**70.65**	**54.30**
Valsartan	**51.48**	**48.92**	**53.23**	**49.43**	**53.82**	**46.69**	**52.30**	**49.70**
Losartan	**45.05**	**47.68**	**43.13**	**45.64**	**42.84**	**48.66**	**42.56**	**41.50**
	RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG							
Irbesartan	1	1	1	1	1	1	1	1
Valsartan	2	2	2	2	2	3	2	2
Losartan	3	3	3	3	3	2	3	3

Table 30b: Summary of rankings obtained for Angiotensin Receptor Blockers (ARBs) drug class

	Number of members (Out of 7)	Percentage of Members
Irbesartan ranked as Number 1 choice of drug	**7**	**100**
Valsartan ranked as Number 2 choice of drug	**6**	**86**
Losartan ranked as Number 3 choice of drug	**6**	**86**
Irbesartan ranked as one of the top 2 drug agents	**7**	**100**
Valsartan ranked as one of the top 2 drug agents	**6**	**86**

Table 30c: Summary of different ranking combinations obtained for Angiotensin Receptor Blockers (ARBs) drug class

	Number of members (Percentage)		Number of members (Percentage)
Irbesartan Valsartan Losartan	6/7 (86%)	Irbesartan Losartan Valsartan	1/7 (14%)

Table 31a: Total utility scores and final rankings obtained from the drug selection committee members for Nitrates drug class

NITRATES	TOTAL UTILITY SCORES							
	GROUP	MEMBER 1	MEMBER 2	MEMBER 3	MEMBER 4	MEMBER 5	MEMBER 6	MEMBER 7
Nitroglycerin	58.03	52.45	52.78	48.71	66.08	0.00	62.70	60.72
Isosorbide Dinitrate	54.50	56.57	55.57	67.82	41.30	0.00	37.73	52.50
Isosorbide Mononitrate	49.20	50.54	50.80	59.11	35.56	0.00	36.64	46.32
	RANKINGS BASED ON THE TOTAL UTILITY SCORES FOR EACH DRUG							
Nitroglycerin	1	2	2	3	1	0	1	1
Isosorbide Dinitrate	2	1	1	1	2	0	2	2
Isosorbide Mononitrate	3	3	3	2	3	0	3	3

Table 31b: Summary of rankings obtained for Nitrates drug class

	Number of members (Out of 7)	Percentage of Members
Nitroglycerin ranked as Number 1 choice of drug	**3**	**43**
Isosorbide Dinitrate ranked as Number 2 choice of drug	**2**	**29**
Isosorbide Mononitrate ranked as Number 3 choice of drug	**5**	**57**
Nitroglycerin ranked as one of the top 2 drug agents	**5**	**57**
Isosorbide Dinitrate ranked as one of the top 2 drug agents	**6**	**86**

Table 31c: Summary of different ranking combinations obtained for Nitrates drug class

	Number of members (%)		Number of members (%)		Number of members (%)
Nitroglycerin Isosorbide Dinitrate Isosorbide Mononitrate	3/7 (43%)	Isosorbide Dinitrate Nitroglycerin Isosorbide Mononitrate	2/7 (29%)	Isosorbide Dinitrate Isosorbide Mononitrate Nitroglycerin	1/7 (14%)

4.1.7. Step 8: Conducting the second focus group meeting for making final drug selection for the two condition-specific hospice formularies.

Three weeks after the first focus group meeting, the second meeting was scheduled involving the same group members. The second meeting that was held on July 6, 2005 was also facilitated by the same facilitators and included all members of the drug selection committee that were present in the first focus group meeting.

The drug rankings summarized for each individual member as well as for the whole group were presented to the group during the second meeting. The rankings for the drugs in each drug class were determined by combining the individual member's preferences (weightings) for the drug selection criteria, weighted factor values obtained from the literature, and the drug price information (acquisition cost) obtained from the EAMC hospice pharmacy database. The drug selection committee reviewed the rankings and then followed the protocol for identifying and selecting drugs for the final inclusion list.

In each therapeutic class, after including the top 2 drugs in the final inclusion list, the group was asked to add to add other agents to that list only if they believed the drug was needed. Out of the six therapeutic classes, the group added only one agent (i.e. isosorbide mononitrate as a nitrate) in the final inclusion list. The pros and cons for all drug agents that were included in the final list were discussed. Table 32 lists the different pros and cons discussed by the group for the six therapeutic classes. Based on the pros and cons discussion, a final consensus on specific drug agents in each therapeutic class to be selected for the two condition-specific formularies was obtained.

Table 32: List of pros and cons discussed for drugs within each therapeutic class during second focus group meeting

Therapeutic class	Drug agent	Pros discussed	Cons discussed
Antidepressants (SSRIs)	Citalopram	➢ Low cost ➢ Efficacious ➢ Less drug interactions ➢ Less side effects	None
	Paroxetine	➢ Low cost ➢ Less drug interactions ➢ Less side effects ➢ More # of doses available ➢ Used for anxiety, OCD, PTSD	➢ High number of drop-outs ➢ Causes weight gain
ACE-Inhibitors	Lisinopril	➢ Daily dosing ➢ Efficacious	None
	Quinapril	➢ Low cost	None
Beta Blockers	Metoprolol	➢ Low cost ➢ Efficacious	None
	Carvedilol	➢ Efficacious	None
Loop Diuretics	Furosemide	➢ Low cost	
	Torsemide	➢ Less drug interactions	➢ Cost
ARBs	Valsartan	➢ Heart failure indications	➢ Cost
	Irbesartan	➢ Low cost ➢ Daily dosing	
Nitrates	Nitroglycerine	➢ More # of doses available	
	Isosorbide dinitrate		➢ Dosing frequency
	Isosorbide mononitrate	➢ Also used in cardiac events such as angina	

Table 33 represents the summary of procedures followed for the final drugs to be selected for the two condition-specific hospice formularies. For antidepressants, loop diuretics, and beta-blockers classes of drugs, pros and cons were discussed for those agents that were among the top two lists, and all those agents were selected for the

formulary. For ACE-Inhibitors, and angiotensin receptor blockers (ARBs) class of drugs, pros and cons were discussed for those agents that were listed as one of the top two agents, but only one agent was selected for the formulary in each class. Lisinopril was selected as the ACE-Inhibitor, while valsartan was selected by the group as the ARB agent. Unlike for the above five therapeutic classes (antidepressants, ACE-Inhibitors, beta-blockers, loop diuretics, and ARBs) where the group only considered the top two drug agents to be included in the final inclusion list, the group included a third agent (Isosorbide mononitrate) to be considered in the nitrates class of drugs. After discussing the pros and cons for the three drug agents in nitrates class, a consensus was reached to include Nitroglycerin and isosorbide mononitrate in the formulary.

Table 33: Summary of the final drug selection process for formulary development

Drug Class	Drugs included for final selection process	Listed as the top 2 drug agents	Discussed Pros and Cons	Selected for the Formulary
Antidepressants (SSRIs)	Citalopram	√	√	√
	Paroxetine	√	√	√
ACE-Inhibitors	Lisinopril	√	√	√
	Quinapril	√	√	
Loop diuretics	Furosemide	√	√	√
	Torsemide	√	√	√
Beta blockers	Metoprolol	√	√	√
	Carvedilol	√	√	√
ARBs	Irbesartan	√	√	
	Valsartan	√	√	√
Nitrates	Nitroglycerin	√	√	√
	Isosorbide Dinitrate	√	√	
	Isosorbide Mononitrate		√	√

The final drug agents that were selected for depression and CHF formulary at the center are shown in Table 33.

4.1.8. Special Considerations for Final Drug Selections:

For the final hospice formularies for depression and CHF conditions, decisions regarding specific drug agents as well as number of drugs in each drug class to be included for the formulary were taken. The special considerations for the specific drug agents in each drug class were discussed during the pros and cons session. Some of the considerations that were taken into account for the different drug classes are outlined below:

Antidepressants (SSRIs):

In the antidepressant (SSRIs) class of drugs, both citalopram and paroxetine were selected for the formulary inclusion. Pros and cons for both these agents were discussed. During discussion, both agents were considered to be equally efficacious; however, paroxetine was noted to be advantageous in special populations. Paroxetine is available in two dosage strengths and additionally is indicated in anxiety disorder, obsessive compulsive disorder, and post traumatic stress disorder patients, thereby making it beneficial in patients experiencing depression in combination with one of these disorders. The committee also discussed and agreed that both SSRI agents had similar adverse effects (weight gain) and had very similar drop out rates. Selection of both these agents is indicative that the committee members focused on the “efficacy” aspect of the drugs, despite the fact that they were associated with certain negative features.

ACE-Inhibitors:

In the ACE-Inhibitor class of drugs, lisinopril was the only agent that was selected for the formulary. Although, both lisinopril and quinapril were included in the final inclusion list, and both had an advantage of daily dosing, only lisinopril was selected as the final agent for the formulary, because it was noted to be more efficacious than quinapril.

Beta-Blockers:

In the beta-blocker class of drugs, both metoprolol and carvedilol were selected for the formulary. Both these agents were discussed as being efficacious. Although, metoprolol and carvedilol have different modes of action, they both produce the same effect (i.e. they cause vasodilation). Metoprolol is a "pure" or "specific" beta-blocker, while carvedilol is an alpha/beta-blocker. For patients with Left Ventricular Dysfunction, carvedilol is preferred, as it is noted to be more efficacious and is better tolerated, while for other patients, metoprolol is preferred. Additionally, both these agents were included in the guidelines for treating CHF and have been shown to decrease morbidity and mortality as compared to other beta blockers. Selection of these agents once again suggests that the selection committee considered efficacy as an important parameter in making their drug selection decisions.

Loop Diuretics:

Both furosemide and torsemide were selected for the formulary. For the loop diuretic class of drugs, the committee discussed the cost and safety-related issues. Furosemide was selected because it was the lowest cost agent. Although drug cost for torsemide was discussed as a negative point, it was selected since fewer number of drug

interactions were reported for this agent. Moreover, it was noted that some patients become resistant to the diuretic effect of furosemide over time and therefore fail to respond to adequate doses of furosemide. Therefore, it was decided that in such cases torsemide would only be administered as a second line agent. Thus, both furosemide and torsemide were selected for the formulary.

Angiotensin Receptor Blockers (ARBs):

In the ARBs class of drugs, valsartan was the only agent selected for the formulary. As compared to irbesartan which is a lower cost drug, valsartan was preferred because it has been shown to reduce hospitalization and mortality in patients with CHF. Although irbesartan is low-cost drug, clinical trials have not shown to produce similar benefits in patients with CHF as compared to valsartan. Selection of valsartan over irbesartan is suggestive of the fact the selection committee preferred efficacy over cost as an important parameter for making their drug selection decisions.

Nitrates:

In the nitrate class of drugs, a total of three agents were discussed during the pros and cons session. Apart from the top two agents i.e. nitroglycerin, and isosorbide dinitrate, the committee also included isosorbide mononitrate in the final inclusion list. Nitrates are generally given in combination with hydralazine to those patients who continue to have persistent symptoms of CHF even after taking ACE-Inhibitors or ARBs along with a beta-blocker, or to those patients that are unable to tolerate an ACE-Inhibitor or ARBs (due to drug intolerance, hypotension or renal insufficiency). In addition, nitrates are effective in controlling symptoms of angina which is sometimes present along with CHF. For this class of drugs, committee members discussed convenience issues such

as dosing frequency, availability of drugs in different doses as well as efficacy-related issues. Nitroglycerin was selected for the formulary as it was available in different dosage strengths and forms (topical, SL as well as oral). Isosorbide mononitrate was selected because it can be dosed once or twice a day (that aids in improving patient compliance) as opposed to three or four times a day for the dinitrate salt. Therefore, because of the dosing-frequency convenience, isosorbide mononitrate was chosen over isosorbide dinitrate.

4.1.9. Formulary Implementation and Compliance:

The formularies for CHF and depression drugs at the hospice were officially implemented on September 1, 2005. Information about the formulary drug agents were circulated among all the clinical and non-clinical staff at the center. In order to verify whether the condition-specific hospice formularies that were developed in this study was appropriately followed and that non-formulary agents were not being prescribed or used, drug utilization patterns six months before and after the implementation of the formulary were studied. In the pre-formulary period, out of 26 patients with depression, 9 patients (35%) were found to be using non-formulary depression agents, while out of 20 patients with CHF, 6 patients (30%), were found to be using non-formulary CHF agents. Out of 25 patients who were included in the post-formulary depression group, two patients (8%) received one non-formulary agent i.e. sertraline. Of these two patients, one patient was enrolled in the center during the washout period, during which sertraline was initiated. The second individual who was enrolled in the center after the formulary was officially implemented received sertraline

for depression management. This suggests that depression formulary was successfully being followed by the clinicians at the hospice.

Out of 15 patients who were included in the post-formulary CHF group, two patients (13%) received one non-formulary agent (i.e. enalapril). Out of two patients, one patient was enrolled in the center during the washout period, during which enalapril was initiated. The second patient who was enrolled in the center after the formulary was officially implemented received enalapril for CHF management. This suggests that CHF formulary was successfully being followed by the clinicians at the hospice.

4.2. PHASE-II: Evaluating the economic impact of drug agents selected for the two condition-specific hospice formularies

Information regarding drug utilization, demographics, and resource utilization was gathered and analyzed to examine the economic impact of the formularies developed in Phase-I of the study. Separate samples of patients who were seeking care six months prior to, and six months after the washout period following implementation of the formulary at the EAMC hospice for CHF or depression conditions were selected for the second phase of the study. The drug utilization report included only those drugs agents that were prescribed and provided by the hospice. It did not include other drugs or medications that the patients could be taking for managing their medical conditions. In addition to drug utilization data, patients' demographic and resource utilization data were also collected. This phase of the study was sub-divided into the following sections:

4.2.1. Collect pre-formulary data for hospice patients diagnosed with CHF or depression six-months prior to implementing the formulary

Pre-formulary depression patients: Hospice patients who were seeking care at the hospice of EAMC and who were taking antidepressants medications to manage their depressive symptoms between January 1, 2005 through June 30, 2005 were identified as the pre-formulary depression patients for the study. A total of 32 patients who filled their antidepressant prescriptions during this time frame were identified with the help of the drug utilization data that were extracted from the pharmacy database system. Out of 32, only 28 patients met the inclusion criteria (listed in Chapter 3, pages 99 to 101) and were included in the study. Out of these 28 patients, data on 26 patients were included for analysis and two patients were excluded because they were identified as outliers.

Pre-formulary CHF patients: Hospice patients with a primary diagnosis of CHF condition who were seeking care at the hospice of EAMC from January 1, 2005 through June 30, 2005 were identified as the pre-formulary CHF patients. These patients were identified with the help of an appropriate diagnosis code. A total of 27 patients were identified, out of which only 22 patients met the inclusion criteria and were included in the study (listed in Chapter 3, pages 99 to 101). Out of these 22 patients, data on 20 patients were included for analysis, while two patients were excluded because they were identified as outliers.

4.2.2. Collect post-formulary data for hospice patients diagnosed with CHF or depression six-months after implementation of the formulary

Post-formulary depression patients: Hospice patients who were seeking care at the hospice of EAMC and who were taking antidepressants medications to manage their depressive symptoms between September 1, 2005 through February 28, 2006 were identified as the post-formulary depression patients. A total of 31 patients who filled their antidepressant prescriptions during this time period were identified with the help of the drug utilization data that was extracted from the pharmacy database system. Out of 31, only 25 patients met the inclusion criteria and were included in the study (listed in Chapter 3, pages 98 and 99). Table 34 describes the demographics and other general characteristics for pre as well as post-formulary depression patients.

Post-formulary CHF patients: Hospice patients with a primary diagnosis of CHF condition who were seeking care at the hospice of EAMC from September 1, 2005 through February 28, 2006 were identified as the post-formulary CHF patients.

Table 34: Demographic and other clinical characteristics for pre and post-formulary depression group:

Patient Characteristics	**Pre-Formulary (N=26)**	**Post-Formulary (N=25)**	**p-value**
*Gender, (%)	Males: 14 (54%) Females: 12 (46%)	Males: 15 (60%) Females: 10 (40%)	0.889
*Ethnicity, (%)	Caucasian: 18 (69%) African-American: 8 (31%)	Caucasian: 17 (68%) African-American: 8 (32%)	0.851
Mean Age ± S.D.	72.35 ± 24.35	67.68 ± 13.41	0.546
Mean Length of Treatment ± S.D.	121.08 ± 52.07	106.98 ± 51.05	0.604
Average # of co-morbid conditions ± S.D.	2.69 ± 1.25	2.58 ± 0.87	0.311
Average # of medications	11.65 ± 4.30	13.52 ± 4.19	0.685
Primary diagnosis, (%)	Cancer (all forms): 17 (65%) Congestive Heart Failure (CHF) : 3 (11.5%) End-Stage Renal Disorder (ESRD): 2 (8%) Chronic Obstructive Pulmonary Disorder (COPD): 1 (4%) Failure to Thrive: 3 (11.5%)	Cancer (all forms): 18 (72%) Congestive Heart Failure (CHF) : 2 (8%) End-Stage Renal Disorder (ESRD): 1 (4%) Chronic Obstructive Pulmonary Disorder (COPD): 1 (4%) ALS: 1 (4%) Parkinson's Disease: 1 (4%) General Debility: 1 (4%)	

* Chi-square test was used to compare the gender or ethnicity differences across groups Other (continuous) variables were compared using t-tests

The post-formulary CHF patients were identified with the help of an appropriate diagnosis code. A total of 21 patients were identified, out of which only 15 patients met the inclusion criteria and were included in the study. Table 35 describes the demographics and other general characteristics for pre as well as post-formulary CHF patients.

Table 35: Demographic and other clinical characteristics for pre and post-formulary CHF group:

	Pre-Formulary (N=20)	**Post-Formulary (N=15)**	**p-value**
*Gender, (%)	Males: 10 (50%) Females: 10 (50%)	Males: 7 (53%) Females: 8 (47%)	0.745
*Ethnicity, (%)	Caucasian: 11 (55%) African-American: 9 (45%)	Caucasian: 9 (60%) African-American: 6 (40%)	0.693
Mean Age $\pm$ S.D.	81.70 $\pm$ 10.65	78.00 $\pm$ 12.70	0.355
Mean Length of Treatment $\pm$ S.D.	103.30 $\pm$ 62.34	104.1 $\pm$ 69.40	0.991
Average # of co-morbid conditions $\pm$ S.D.	4.00 $\pm$ 1.45	3.65 $\pm$ 1.25	0.236
Average # of medications	10.55 $\pm$ 3.30	10.66 $\pm$ 3.79	0.423

* Chi-square test was used to compare the gender or ethnicity differences across groups
Other (continuous) variables were compared using independent 2-sample t-tests

4.2.3. Data Analyses:

4.2.3.1. Pre and Post-formulary depression patients' characteristics:

Table 34 describes the demographic and clinical characteristics of the pre and post-formulary depression patients. The majority of the pre and post-formulary patients with depression were males (54% and 60%) and Caucasians (69% and 68%) respectively. While the pre-formulary depression patients had a mean age of about 72 (S.D.= $\pm$ 24.3) years, the mean age for post-formulary depression group was about 68 (S.D.= $\pm$ 13.4) years. On average, both pre and post-formulary groups reported approximately three co-morbid conditions, for which they were prescribed an average of about 12 (S.D.= $\pm$ 4.30) and 13 (S.D.= $\pm$ 4.19) different medications to control their conditions respectively. The average length of treatment for the pre-formulary depression group was found to be about 121 days, whereas for the post-formulary depression group it was about 107 days. The majority of the patients in both the pre and post-formulary depression groups had a diagnosis of cancer (65% and 72%) or congestive heart failure (12% and 8%). Differences in categorical variables (gender, ethnicity) across the pre and post formulary depression groups were compared using chi-square tests, while differences in continuous variables (age, length of treatment, co-morbid conditions, and number of prescribed medications) were compared using t-tests. Differences in the aforementioned clinical and demographic parameters across pre and post-formulary depression groups were tested using two-tailed tests. The two depression groups were found to be comparable as they had similar demographic and clinical characteristics and none of these variables were found to be statistically significant at $\alpha = 0.05$. In other words, the two groups did not differ in any of clinical and demographic parameters (Refer to Table 34).

4.2.3.2. Pre and Post-formulary CHF patients' characteristics:

Table 35 depicts the demographic and clinical characteristics of the pre and post-formulary CHF patients. While a majority of the pre and post-formulary patients with CHF were Caucasians (55% and 60%), approximately half of them were males (50% and 54%) respectively. The mean age for both pre and post-formulary patients with CHF was about 82 (S.D.= $\pm$ 10.65) and 78 (S.D.= $\pm$ 12.70) years respectively. On average, both pre and post-formulary groups reported approximately four co-morbid conditions for which they were prescribed an average of about 11 different medications to control their conditions respectively. The average length of treatment for pre-formulary CHF group was found to be about 103 days, whereas for post-formulary CHF group it was about 104 days. Differences in categorical variables (gender, ethnicity) across the pre and post formulary depression groups were compared using chi-square tests, while differences in continuous variables (age, length of treatment, co-morbid conditions, and number of prescribed medications) were compared using t-tests. Differences in the aforementioned clinical and demographic parameters across pre and post-formulary depression groups were tested using two-tailed tests. The two groups were found to be comparable as none of the demographic and clinical variables were found to be statistically significant at $\alpha = 0.05$ (Refer to Table 35).

4.2.3.3. Computation of drug costs:

Using the operational definitions provided in chapter 1, different types of drug costs were computed for pre and post-formulary depression or CHF patients. All types of drug costs were computed using per patient day. Table 36 summarizes the total,

condition-specific, and other drug costs for the pre and post-formulary depression groups. The total drug costs [5.10 (± 5.13); 7.38 (± 6.80)], condition-specific drug costs [0.19 (± 0.47); 0.36 (± 0.44)], and other drug costs related to the condition [4.90 (± 5.00); 7.02 (± 6.80)] for the post-formulary depression group were found to lower than those obtained for the pre-formulary depression group.

Table 36: Difference in different types of mean drug costs (in dollar amount), expressed as per patient day drug costs obtained for pre and post-formulary depression groups

Type of drug costs	Pre-formulary group (n=26)	Post-formulary group (n=25)	p-value
Depression- Total Drug Cost	7.38 (± 6.80)	5.10 (± 5.13)	0.1840
Depression-Other Drug Cost	7.02 (± 6.80)	4.90 (± 5.00)	0.2123
Depression-Specific Drug Cost	0.36 (± 0.44)	0.19 (± 0.47)	0.0209*

*$p<0.05$

Table 37 summarizes the total, condition-specific, and other drug costs for the pre and post-formulary CHF groups. The total drug costs [3.32 (± 2.19); 3.52 (± 2.65)], and condition-specific drug costs [1.27 (± 1.24); 1.52 (± 1.62)], for the post-formulary CHF group were found to lower than those obtained for the pre-formulary CHF group. Although, the different types of costs in the post-formulary period were found to be lower than the pre-formulary period, the differences were not found to be statistically significant.

Table 37: Difference in different types of mean drug costs (in dollar amount), expressed as per patient day drug costs obtained for pre and post-formulary CHF depression groups

Type of drug costs	Pre-formulary group (n=20)	Post-formulary Group (n=15)	p-value
CHF- Total Drug Cost	3.52 (± 2.65)	3.32 (± 2.19)	0.8187
CHF-Other Drug Cost	1.99 (± 2.07)	2.05 (± 1.78)	0.6258
CHF-Specific Drug Cost	1.52 (± 1.62)	1.27 (± 1.24)	0.6462

4.3 Research Hypotheses and Questions:

In the present study, a total of six research questions were answered, for which six research hypotheses were tested. The first three research questions and hypotheses pertain to depression condition (Refer to Table 38), whereas the remaining three are related to CHF condition (Refer to Table 39). To test the study hypotheses, both parametric and non-parametric tests were conducted.

Research Question 1:

Is there a difference in the total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary?

For answering the first research question, the following sub-hypotheses were tested:

Null Hypothesis:

H_{01A}: There is no difference in the total drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary.

H_{01}: There is no difference in the log-transformed total drug costs values for managing depression per patient enrollment day before and after implementation of the depression formulary.

Research Question 2:

Is there a difference in the other drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary?

For answering the third research question, the following sub-hypotheses were tested:

Null Hypothesis:

H_{02A}: There is no difference in the other drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary.

H_{02B}: There is no difference in the log-transformed other drug costs values for managing depression per patient enrollment day before and after implementation of the depression formulary.

Research Question 3:

Is there a difference in the specific drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary?

For answering the second research question, the following sub-hypotheses were tested:

Null Hypothesis 03:

H_{03A}: There is no difference in the specific drug costs for managing depression per patient enrollment day before and after implementation of the depression formulary.

H_{03B}: There is no difference in the log-transformed specific drug costs values for managing depression per patient enrollment day before and after implementation of the depression formulary.

The sub-hypotheses under each major hypothesis were tested using two-tailed parametric statistical tests such as independent 2-sample t-test, as well as by non-parametric statistical tests such as Wilcoxon 2-sample test. The results for the first three research hypotheses are outlined in Table 38.

Table 38: Research hypotheses tested for differences in the mean drug costs obtained across pre and post-formulary depression groups

Statistics	Null Hypothesis	Sub-hypothesis	p-value	Action
Parametric	Hypothesis 01	H_{01A}	0.1840	Fail to reject null
		H_{01B}	0.5646	Fail to reject null
	Hypothesis 02	H_{02A}	0.2123	Fail to reject null
		H_{02B}	0.6704	Fail to reject null
	Hypothesis 03	H_{03A}	0.0209*	Rejected null
		H_{03B}	0.0026*	Rejected null
Non-parametric	Hypothesis 01	H_{01A}	0.3913	Fail to reject null
		H_{01B}	0.3913	Fail to reject null
	Hypothesis 02	H_{02A}	0.4233	Fail to reject null
		H_{02B}	0.4233	Fail to reject null
	Hypothesis 03	H_{03A}	0.0014*	Rejected null
		H_{03B}	0.0014*	Rejected null

* Significant at $\alpha = 0.05$

Statistical significance was observed in both the parametric and non-parametric statistics tests related to depression-specific drug costs, indicating that the pre and post-depression groups differed significantly in their depression-specific drug costs. However, the pre and

the post-depression groups did not demonstrate statistical significance in their total and other drug costs related to depression.

Research questions 4 though 6 are related to the differences in the mean drug costs between the pre and post-formulary CHF groups.

Research Question 4:

Is there a difference in the total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary?

For answering the fourth research question, the following sub-hypotheses were tested:

Null Hypothesis 04:

H_{04A}: There is no difference in the total drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

H_{04B}: There is no difference in the log-transformed total drug costs values for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

Research Question 5:

Is there a difference in the other drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary?

For answering the fifth research question, the following sub-hypotheses were tested:

Null Hypothesis 05:

H_{05A}: There is no difference in the other drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

H_{05B}: There is no difference in the log-transformed other drug costs values for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

Research Question 6:

Is there a difference in the specific drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary?

For answering the sixth research question, the following sub-hypotheses were tested:

Null Hypothesis 06:

H_{06A}: There is no difference in the specific drug costs for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

H_{06B}: There is no difference in the log-transformed specific drug costs values for managing CHF per patient enrollment day before and after implementation of the CHF formulary.

The sub-hypotheses under each major hypothesis were tested using two-tailed parametric statistical tests such as independent 2-sample t-test, as well as by non-parametric statistical tests such as Wilcoxon 2-sample test. The results for the last three research hypotheses are outlined in Table 39. Across both parametric as well as non-parametric statistical tests, pre and the post-CHF groups did not demonstrate statistical significance in their total, specific, and other drug costs related to CHF, indicating that the two groups did not differ significantly in any of the drug costs categories.

Table 39: Research hypotheses tested for differences in the mean drug costs obtained across pre and post-formulary CHF groups

Statistics	Null Hypothesis	Sub-hypothesis	p-value	Action
Parametric	Hypothesis 04	H_{04A}	0.8187	Failed to reject null
		H_{04B}	0.7661	Failed to reject null
	Hypothesis 05	H_{05A}	0.6258	Failed to reject null
		H_{05B}	0.5764	Failed to reject null
	Hypothesis 06	H_{06A}	0.9366	Failed to reject null
		H_{06B}	0.6462	Failed to reject null
Non-parametric	Hypothesis 04	H_{04A}	0.9899	Failed to reject null
		H_{04B}	0.9899	Failed to reject null
	Hypothesis 05	H_{05A}	0.9336	Failed to reject null
		H_{05B}	0.9336	Failed to reject null
	Hypothesis 06	H_{06A}	0.7015	Failed to reject null
		H_{06B}	0.7015	Failed to reject null

* $p<0.05$

4.4. Further Analysis:

Further analysis was conducted as a part of this research in order to explore the differences between the pre and post-formulary drug costs and to get a detailed understanding about the data. The present study focused on developing drug formularies for depression and CHF and also assisted in choosing appropriate drug agents from specific therapeutic classes. Since this study was primarily aimed at selecting appropriate condition-specific agents, it is important to explore the economic or financial impact of those condition-specific drug agents. In order to accomplish this goal, the drug utilization

pattern for both pre and post-formulary groups were noted. This information included total quantity, cost, and total number of patients taking those drugs. Similar information was gathered for all pre and post-formulary depression and CHF groups. Table 40 and Table 41 summarize the drug utilization patterns for pre and post-formulary depression and CHF groups respectively.

Table 40: Drug utilization pattern reported for all depression patients seeking care at hospice of EAMC during pre and post-formulary period

Name of the drug	Pre-formulary period (n=26)			Post-formulary period (n=25)		
	Total Quantity	Total Cost	Number of Patients	Total Quantity	Total Cost	Number of Patients
Antidepressants						
* Citalopram 20 mg Tab	973	$256.10	9	1959	$66.20	17
Fluoxetine 20 mg Tab	70	$2.65	1			
* Paroxetine 10 mg Tab	378	$30.25	6	485	$38.80	6
* Paroxetine 20 mg Tab	128	$12.30	2			
Sertraline 25 mg Tab	318	$490.10	3	14	$13.30	1
Sertraline 50 mg Tab	232	$357.50	5	112	$177.00	1
Total	**2227**	**$1148.90**	**26**	**2570**	**$295.30**	**25**

* Drug agents selected for EAMC hospice formulary

The total depression-specific drug costs obtained in the pre-formulary time period was found to be $1148.90, while that for post-formulary time period it was $295.30. Similarly, the total CHF-specific drug costs in the pre and post-formulary time periods were found to be $2836.70 and $1479.00 respectively. Breakdown of these total CHF-specific costs by individual therapeutic class is shown in Table 41. More detailed information about the overall specific drug costs; specific-costs per patient; and specific-costs per patient day for both medical conditions are listed in Table 42.

Table 41: Drug utilization pattern reported for all CHF patients seeking care at hospice of EAMC during pre and post-formulary period

Name of the drug	Pre-formulary period			Post-formulary period		
	Total Quantity	Total Cost	# of Patients	Total Quantity	Total Cost	# of Patients
Ace Inhibitors						
* Benazepril Tab				140	$24.65	1
Captopril Tab	60	$0.60	1			
Enalapril Tab	28	$0.80	2	56	$1.55	1
* Lisinopril Tab	28	$20.45	1	20	$7.55	1
Total	**116**	**$21.40**	**4**	**216**	**$33.75**	**3**
Beta-Blockers						
* Carvedilol (Coreg)	1003	$1160.60	8	905	$723.25	7
* Metoprolol (Toprol)	45	$1.10	2	308	$5.60	3
Total	**1048**	**$1161.70**	**10**	**1213**	**$728.85**	**10**
Loop Diuretics						
Bumetanide Tab	562	$32.30	2			
* Furosemide Tab	1106	$10.15	12	612	$9.75	7
* Furosemide Injection	11	$12.60	4	5	$3.10	2
* Torsemide Tab	84	$73.90	2			
Total	**1763**	**$128.95**	**20**	**617**	**$12.85**	**9**
Angiotensin-Receptor Blockers (ARBs)						
Losartan (Cozaar)	14	$11.50	1			
* Valsartan (Diovan)				14	$20.15	1
Total	**14**	**$11.50**	**1**	**14**	**$20.15**	**1**
Nitrates						
* Isosorbide Mononitrate Tab	538	$16.60	5	84	$2.80	1
Isosorbide Dinitrate Tab	1142	$21.80	3			
* Nitroglycerin Transdermal	290	$98.45	5	383	$132.10	6
* Nitro-Bid Ointment	10	$37.80	1	8	$26.95	1
* NitroQuick Tab	475	$414.40	6	225	$216.45	3
Total	**2455**	**$589.1**	**20**	**700**	**$378.3**	**11**
Calcium-Channel Blockers (CCBs)						
Verapamil (Diltiazem) Tab	180	$127.45	2			
* Amlodipine (Norvasc) Tab	182	$153.10	1	140	$117.80	1
Total	**362**	**$280.55**	**3**	**140**	**$117.80**	**1**
Cardiac Glycosides						
* Digoxin (Digitek) Tab	**526**	**$26.80**	**6**	**86**	**$4.55**	**3**
Vasodilators						
* Hydralazine Tab	**126**	**$2.45**	**2**	**364**	**$10.50**	**3**
Aldosterone receptor antagonist						
* Spironolactone Tab	**336**	**$30.60**	**3**	**210**	**$17.40**	**2**
Oral Anticoagulants						
* Warfarin (Coumadin) Tab	**182**	**$42.80**	**2**			
Thiazide Diuretic						
* Hydrochlorthiazide Tab				**112**	**$11.50**	**2**
Thiazide-like Diuretic						
* Metolazone (Zaroxolyn) Tab	**92**	**$109.40**	**3**	**42**	**$49.90**	**2**

* Drug agents selected for EAMC hospice formulary

Table 42: Summary of condition-specific drug costs during pre and post-formulary time periods

Condition	Type of drug costs	Pre-formulary costs	Post-formulary costs
Depression	Total drug costs for specific agents	$1148.90	$295.40
	Average specific drug costs, per patient	$44.20	$11.80
	Average specific drug costs, per patient day	$0.36	$0.11
Congestive Heart Failure	Total drug costs for specific agents	$2836.70	$1479.00
	Average specific drug costs, per patient	$141.80	$98.60
	Average specific drug costs, per patient day	$1.36	$0.95

The total drug costs for specific agents; average specific drug costs per patient; and average specific drug costs per patient were all found to be lower for both post groups than their corresponding pre-formulary groups. The average specific-drug costs per patient for the pre and post-formulary depression groups were found to be $44.20 and $11.80, while the average specific-costs per patient day for the two groups were $0.36 and $0.11 respectively. The average specific-drug costs per patient for the pre and post-formulary CHF groups were found to be $141.80 and $98.60, while the average specific-costs per patient day for the two groups were $1.36 and $0.95 respectively.

Change in drug prices during post-formulary period:

The pharmacy at the hospice participates in two different pharmaceutical buying groups and therefore as a result, may actually have different types of contracts for the different drugs and pharmaceutical agents they buy. As a consequence of this event, the differences reported in the total drug costs for specific drugs; average specific drug costs

per patient; and the average specific drug costs per patient day does not reflect the true difference in the costs only because of formulary. The differences between these costs could be due to the formulary as well as the contract. To observe the precise impact of the formularies on the differences in the drug costs between the pre and the post-formulary groups, it is necessary to exclude the effect of contracts. In order to remove this effect, all drug cost computations were carried out utilizing the pre-formulary drug prices. All pre-formulary drug prices were used during the post-formulary period, and then the total drug costs for specific drugs; average specific drug costs per patient; and average specific drug costs per patient day for the post-formulary periods were calculated. This is summarized in Table 43.

Table 43: Summary of condition-specific drug costs during pre and post-formulary time periods (drug costs computed using the pre-formulary drug prices)

Condition	Type of drug costs	Pre-formulary drug costs (X)	Post-formulary drug costs (Y)	Drug cost savings (X-Y)
Depression	Total drug costs for specific agents	$1148.90	$748.60	$400.30
	Average specific drug costs, per patient	$44.20	$29.95	$14.25
	Average specific drug costs, per patient day	$0.36	$0.28	$0.08
Congestive Heart Failure	Total drug costs for specific agents	$2836.70	$1427.35	1409.35
	Average specific drug costs, per patient	$141.80	$95.15	$46.65
	Average specific drug costs, per patient day	$1.36	$0.92	$0.44

Potential drug cost savings can be calculated on three different levels such as:

- Level 1: Overall drug cost savings – obtained by subtracting overall specific drug costs in the post-formulary period from the pre-formulary period
- Level 2: Drug cost savings achieved at a per patient level – obtained by subtracting average specific drug costs per person in the post-formulary period from that of the pre-formulary period
- Level 3: Drug cost savings achieved at a per patient day level – obtained by subtracting specific drug costs per patient day incurred for individual patient in the post-formulary period from that of the pre-formulary period.

In the first level, the cost savings achieved do not reflect the number of patients and average length of treatment into consideration and demonstrates the overall drug cost savings. Although, cost savings in the second level takes into account total number of patients, it still does not account for the average length of treatment. The third level of drug cost savings is the only approach that takes total number of patients as well as the average length of treatment into consideration, and thus far provides the best estimate for the actual difference in the pre and the post-formulary drug costs due to formulary implementation.

Assuming that the pharmacy at the hospice did not enter into any type of contracts or special pharmaceutical buying groups, the difference in the overall specific drugs agents for pre and post-formulary groups was $400.30 [$1148.90-$748.60]. However, on an individual patient level, the differences in depression specific drug costs reported between pre and post groups was found to be $14.25 [$44.20-$29.95]. Moreover, if the average specific drug costs on a per patient per day level is taken into consideration, then

the differences reported between the pre and the post-formulary depression groups was found to be $0.08 [$0.36-$0.28].

Similarly, for CHF, the difference in the overall specific drugs agents; average specific drug costs per patient; and specific drug costs per patient per day; for pre and post-formulary groups were found to be $1409.35 [$2836.70-$1427.35]; $46.65 [$141.80-$95.15]; and $0.44 [$1.36-$0.92] respectively.

4.5. Projected formulary drug cost savings:

Table 44 represents drug cost savings that could be achieved by the hospice as a result of formulary development. Projected drug cost savings are calculated on an annual basis, for which key information such as total number of patients and their average length of treatment for each condition from the present study were taken into consideration. In this study, the pre-formulary and post-formulary periods were each six-month periods, therefore for the annual cost savings calculations, data were extrapolated to one year period. The projected drug cost savings that could be achieved by the hospice as a result of implementing depression and CHF formularies were computed using the average drug cost savings that were obtained on a per patient day level for the respective condition multiplied by the average number of patient treatment days per year as demonstrated in Table 44. Thus, the hospice of EAMC could achieve an annual projected drug costs savings of about $456.00 and $1813.00 as a result of implementing depression and CHF formularies.

Table 44: Projected annual drug cost savings from depression and CHF formularies

Condition	Type of drug costs	Difference in pre and post formulary costs (A)	Average number of patients treated per year (B)	Average length of treatment (C)	Average number of patient treatment days per year D = (B*C)	Projected annual drug cost savings [A*D]
Depression	Average specific drug costs, per patient day	$0.08	50	114	5700	$456.00
Congestive Heart Failure	Average specific drug costs, per patient day	$0.44	40	103	4120	$1812.80

* Average numbers from the present study finding are extrapolated to one-year period.

5. DISCUSSION

This chapter will review the findings of this study discuss the limitations, and describe the practical applications of the study for hospice organizations. This chapter will conclude providing recommendations for future research in this area.

5.1. General Overview of the Study:

The study primarily focused on developing hospice drug formularies for two specific medical conditions; depression and Congestive Heart Failure (CHF) using the Multi-Attribute Utility Theory (MAUT) methodology. It also examined the economic impact of the drug agents selected through the MAUT methods. The study addressed six major research questions concerning the economic impact of the formularies that were developed using scientific methodology. The present study was conducted in two phases:

- Phase-I: Develop hospice formularies using MAUT method
- Phase-II: Evaluate economic impact of the condition-specific hospice formularies by examining the difference in the drug costs in the pre and post-formulary groups.

5.2. PHASE-I: Developing Hospice Formularies Using the MAUT Method:

Very few studies have been found in the literature that have addressed the issue of providing optimum pharmaceutical care to hospice patients and none of them have addressed the use of appropriate drugs or pharmaceutical agents for patients who seek

hospice care. Although, clinical practice guidelines have provided drug class recommendations, they do not provide suggestions or recommendations on the use of specific agents in each class: nor do they specify any special considerations for hospice patients. Therefore, the decisions to choose the most appropriate agents for managing medical conditions in hospice patients is not straightforward. Moreover, for selecting agents for drug formularies, drugs are typically assessed and chosen on the basis of predefined criteria. For this formulary development process, the criteria for making drug selections are usually categorized into drug attributes and their corresponding factors, which are quantitatively measured on different scales. Since the decisions to select the most appropriate agent are based on different criteria that are assessed on disparate measures, it becomes difficult for decision makers to choose the best drug option. Thus, there was a need to select a decision-making tool that would provide a framework to compare drugs on disparate measures. This study has used the MAUT method, which has been reported to offer an advantage of making such comparisons easier has also been successfully applied in formulary decision making processes (Brennan & Anthony, 2000; Schumacher, 1991; McCoy, 1998; Schapira, 2004).

The MAUT method has been previously employed by several researchers as a decision-making tool for making formulary selections for certain therapeutic classes to be used for general population. However, this method has never been applied for developing formulary in a specialized patient setting such as hospice. Therefore, the present study has attempted to explore the usefulness of the MAUT method as a decision-making tool for the purpose of developing formularies for hospice setting. The usefulness and limitations of using this method for creating hospice formularies are addressed next.

5.2.1. Usefulness of MAUT Method:

The MAUT method helped in breaking down complex decisions into simple and understandable components and thereby assisted the drug selection committee to select appropriate drug agents from each of the therapeutic drug class. This was accomplished by:

1. *Identifying important drug attributes and factors to be considered for making comparisons across different drug agents*

For the purpose of creating an evidence-based hospice formulary, comprehensive literature reviews were conducted for each study drug class, which were followed by the different steps in that MAUT method in a sequential manner. The literature reviews assisted in identifying important characteristics (drug attributes and factors) for the different drug agents that were typically used for managing depression or CHF conditions.

Within each drug class, only those drugs attributes and factors which were consistently addressed in the literature were identified and selected for this study. Although for each drug class, a pool of key factors corresponding to drug attributes was chosen, all of those factors may or may not be relevant to the hospice setting. To ensure that the factors selected through the literature review process were appropriate, consensus was obtained during the first focus group meeting. The group was also asked to include any factors or attributes they thought would be more appropriate for drug evaluation and comparison purposes. However for each study drug class, no additional parameters were added to the existing list of drug attributes or factors, suggesting that the literature

compilation of all key attributes and factors was comprehensive for making rationale decisions regarding appropriate drug selection.

2. Evaluating (ranking and weighting) each attribute and related factors of a decision

For individual drug classes, attributes and factors that were chosen from the literature review process were evaluated by individual drug selection committee members. Relative rankings or preferences were obtained from each member of the group on the various attributes and factors that they regarded as the most important characteristic of a drug considered for formulary inclusion. Every person in the group might have different preferences for different drug attributes or factors while choosing appropriate therapy for their patients. Therefore, in order to test the degree of agreement among all participating members for their assigned rankings or weightings, inter-rater reliabilities were conducted and analyzed using the intraclass correlation coefficients (ICC) tests. To determine the degree of agreement for the different drug attributes and factors separate ICC tests were conducted.

Intraclass correlation coefficients for drug attributes:

Results from the intraclass correlation coefficients for drug attributes showed significantly high correlation coefficients for attributes in the descending order of drug efficacy, drug safety, drug cost, and drug availability [Appendix D-Table D1]. High correlation coefficients demonstrated that all committee members considered efficacy to be the most important attribute and drug availability to be the least preferred attribute for selecting appropriate therapeutic agent for their patients.

Intraclass correlation coefficients for factors:

For individual drug class, separate ICC tests were conducted to determine the level of agreement on the ratio weights assigned by the members for different factors specified under each drug attribute. The results obtained from intraclass correlation coefficient tests for factors are summarized in Appendix D [Tables D2-D7]. Results from the ICC tests conducted for factors in each drug class demonstrated different levels of agreement, suggesting that members of the selection committee did differ in their preferences on the criteria considered important for making appropriate drug selections.

The results from ICC tests suggest that regardless of differences in preferences found for the different factors considered under each drug attribute, members of the drug selection committee did show similar preferences for the major drug attributes. The group considered efficacy to be the most important drug attribute followed by safety, cost and drug availability. These findings are consistent with the literature where experts have reported that efficacy and safety are the two most important considerations taken into account by several drug selection committees or P&T committees (AMCP, 1997; Rational Pharmaceutical Management Plus Program (n.d.).

3. *Ranking drugs in each therapeutic class based on a composite score computed for multiple parameters*

Because drugs are assessed on several parameters that are measured on different scales, it has been reported that most P&T committees often face difficulties while making decisions for selecting appropriate agents for the formulary. They do not have a common basis or measure to compare the different drug alternatives and then choose the best available option. The MAUT method which is a systematic identification and analysis

method offers a solution to this problem. For each drug agent the MAUT method assists in combining the literature-based factor values with the committee members' preference weighted values into a single composite score. Computation of a single unitary measure for each drug would enable one to rank the different drug alternatives with much ease. In the present study such composite score (total utility score) was computed for each drug agent which assisted the drug selection committee in determining a systematic ranking for the different drug alternatives.

5.2.2. Limitations of MAUT Method:

The MAUT method assisted the drug selection committee in systematically identifying and reducing choices to the top two drug alternatives in each drug class. In order to choose agents for the formulary, the MAUT method was complemented by a nominal group technique, which allowed members of the committee to discuss certain features of the drugs which may or may not have been captured through the MAUT method. Those drugs identified as the top two agents based on the composite score (total utility scores) were directly included in the final inclusion list, along with other agents if the committee felt the need to include others in the list. The nominal group technique facilitated the committee to discuss the pros and cons of the comparative drugs that helped them in making the final drug selection. This allowed the committee members to lead further discussions regarding some salient features of the different drugs that were being considered for the formulary inclusion. In all six therapeutic drug classes (except for the nitrates class), committee members included the top two agents identified through MAUT method for the pros and cons discussion. Isosorbide mononitrate was the only

agent in the nitrates class of drugs that was not ranked as one of the top two agents but was included in the final inclusion list. This suggests that there might have been some important features associated with isosorbide mononitrate that may not have been captured through the MAUT method, which the group members wanted to discuss so that they could justify its inclusion or exclusion from the formulary. For the nitrates drug class although the members of the drug selection committee ranked 'efficacy' to be the most important attribute and 'drug availability' to be the least important attribute, the group considered drug availability issue (such as dosing frequency) to be an important consideration during the pros and cons discussion. Isosorbide mononitrate was selected because it could be dosed once or twice daily as opposed to three or four times daily requirements for the dinitrate salt. Therefore, because of the dosing-frequency convenience, isosorbide mononitrate was chosen over isosorbide dinitrate. Thus, this study showed that the drug agents identified as the top agents by the MAUT method were not always chosen by the drug selection committee for the final formulary.

Implementation of the MAUT method for the purpose of developing a systematic formulary is a time consuming process. It not only involves conducting a comprehensive literature search and review process for drugs in each therapeutic class but also involves conducting focus group meetings with the drug selection committee members. The literature review process for six study drug classes and scheduling the two focus group meetings was conducted over several months. Thus developing formulary through MAUT method can be a time consuming process.

5.3. Implementation of Hospice Formularies:

In order to verify whether the clinicians were complying with the formulary agents chosen in this study, drug utilization patterns were studied six months before and after the implementation of the formulary. Drug utilization patterns observed in the post-formulary period showed that for each of the condition-specific formulary group, a lower percentage of patients were on non-formulary agents than in the pre-formulary period. In the pre-formulary period, the percentages of patients that were prescribed non-formulary agents were 30% and 35% in CHF and depression patients respectively. However, in the post-formulary period about 13% and 8% of the CHF and depression patients received non-formulary agents respectively, indicating that the clinicians adhered to using the formulary agents for their patients in the post-formulary period. Thus, the formularies were successfully implemented and were being followed at the hospice at a higher rate after the MAUT method.

5.4. Phase-II: Evaluating the Economic Impact for the Condition-specific Hospice Formularies:

The second phase of the present study investigated the economic impact of the individual condition-specific hospice formulary that was developed in the Phase-I of the study. The primary purpose of this study phase was to investigate the differences in the drug costs per patient day, six-months before and after implementing the formulary. The drug costs computed in this study were categorized into three types: *total drug costs* which included costs of specific as well as auxiliary drug agents; *specific drug costs* which included costs of specific drugs that are used to manage the condition; and *other*

drug costs which took into account the costs for all auxiliary agents used for managing the condition. Drug cost savings that could be achieved as a result of implementation of the formularies were also examined. Investigation of the economic or financial impact of the formularies was conducted from the hospice organizations' standpoint. In other words, the question addressed in Phase-II of the study was whether or not the formularies impacted the drug costs incurred by the hospice.

5.4.1. Study Design Considerations for Economic Impact Evaluation of Formularies: Although, terminally-ill patients who seek hospice care have less than six-months of life, generally the national average length of stay that has been reported for these patients is around 58 days (CMS, 2005). The limited life expectancy of patients enrolled in hospices is one of the major challenges for conducting research in such type settings. For assessing the impact of formularies, it would be ideal to measure and compare drug costs or other factors before and after the formulary implementation using the same patient group. However, in this study the economic impact of individual condition-specific formularies used two separate pre and post samples, since we did not want to change the regimen once the patient's symptoms were controlled given the short life expectancy.

Since separate samples were utilized for economic impact evaluation, it was important to investigate the patient characteristics of both pre and post-formulary groups. Such comparisons determined whether the two groups in each condition differed in any of the patient characteristics, which further allowed us to provide validity to the economic impact findings of this study.

The hospice of EAMC provides services to terminally-ill patients belonging to all age groups, most are either Caucasians or African-Americans, and about half of them are

male patients. Descriptive statistics conducted across both pre and post-formulary depression as well as CHF groups showed that each group was a representative sample of the patients typically cared for by this hospice (Refer to Tables 34 and 35). For each condition, no differences were observed in the demographic parameters (such as age, gender and ethnicity) or other clinical characteristics (such as length of treatment days and co-morbid conditions), suggesting that the two groups were comparable.

5.4.2. Economic Impact of Hospice Formularies on Drug Costs:

In this study, the impact of each condition-specific formulary on the drug costs related to respective condition was evaluated and the potential drug cost savings were computed.

5.4.2.1. Economic Impact of Depression Formulary:

The economic impact findings obtained from this study were found to have mixed results. All the three categories of drug costs: total drug costs, other drug costs and specific drug costs associated with depression were found to be lower in the post-formulary period as compared to the pre-formulary period. Only the differences in the depression-specific drug costs were found to be statistically significant in the post-formulary period as compared to the pre-formulary period. Although, a decrease in the total drug costs or the other drug costs incurred per patient day was observed in the post-formulary period, this difference was not found to be of statistical significance. However the tests dealing with the comparisons of drug costs across pre and post-formulary depression analyses did not have sufficient statistical power to detect significant changes

in the drug costs that might have been observed with a larger sample size. An elaboration of this limitation has been described in details under the heading of study limitations.

Even though the study did not show any statistical significance in the drug costs computed across pre and post-formulary depression groups, the implementation of the depression formulary did result in drug cost savings which are pragmatically significant. With an intention to further explore the decrease in the drug costs that occurred in the post-formulary period as compared to the pre-formulary period, post-hoc analysis for the depression-specific agents were conducted. Results from the post-hoc analysis demonstrated that on a per patient day level, the hospice of EAMC saved about eight cents as a result of implementing depression formulary. Consequently, the analysis also showed that the projected annual pharmacy savings that could be achieved by the hospice was estimated to be about $456.00. Although, the economic impact findings concerning the total drug costs, specific-drug costs and the other drug costs related to depression incurred by the hospice were found to have mixed results, pharmacy savings were achieved as a result of selecting specific agents for managing depression. The depression formulary that was established in this study resulted in financial savings for the hospice.

5.4.2.2. Economic Impact of CHF Formulary:

All the three categories of drug costs: total drug costs, other drug costs and specific drug costs associated with CHF condition were found to be lower in the post-formulary period as compared to the pre-formulary period. Although, a decrease in the different types of costs per patient day was observed in the post-formulary period, these differences were not found to be of statistical significance. In other words, the

implementation of the CHF formulary did not have any financial/economic impact on the drug costs related to the condition. However the tests dealing with the comparisons of drug costs across pre and post-formulary CHF analyses did not have sufficient statistical power to detect significant changes in the drug costs that might have been observed with a larger sample size. A more detailed explanation of this limitation has been described under study limitations.

Similarly even for CHF formulary, although the study did not show any statistical significance in the drug costs computed across pre and post-formulary CHF groups, the implementation of the CHF formulary did result in drug cost savings which are pragmatically significant. Results from the post-hoc analysis showed that on a per patient day level, the hospice of EAMC saved about forty-four cents as a result of implementing CHF formulary. Consequently, the analysis also demonstrated that the projected annual pharmacy savings that could be achieved by the hospice was estimated to be about $1813.00. Although, the total drug costs, specific-drug costs and the other drug costs related to CHF incurred by the hospice in the post-formulary period were not found to be significantly different than from the pre-formulary costs, pharmacy savings were achieved as a result of selecting specific agents for managing CHF. The CHF formulary that was established in this study showed financial savings that could be achieved by the hospice.

5.4.2.3. Issues Related to Economic Impact of Drug Formularies:

The economic impact results obtained from this study were consistent with the literature findings which are also found to be mixed. There are numerous studies found in

the literature which have addressed the issue of whether or not formulary acts as an effective cost containment tool in controlling the drug costs as well as overall healthcare costs. Conflicting results concerning the economic impact of the formularies have been found in the literature. Several researchers have found that formularies can reduce the drug costs of overall healthcare costs (Bloom, & Jacob, 1985; Hefner, 1979). For example the study conducted by Bloom and Jacob, showed that the drug cost per patient month reduced by 78.9%, as a result of formulary implementation. However, there are few studies found in the literature which have found that formularies can sometime cause an increase in the drug costs or the overall healthcare costs because of the higher drug utilization or resource utilization related to the formulary agents (Dranove, 1989; Horn, 1996). A study conducted by Dranove showed that due to inclusion of antibiotics in the Medicaid formulary resulted in an increased drug costs. Similarly the study conducted by Horn et al showed that formulary implementation were significantly and positively related to higher rates of emergency department visits and hospital admissions, and positively, but not always significantly related to drug cost, drug count and physician office visits.

5.5. Study Limitations:

Certain limitations were identified in this study and therefore the interpretations of the findings of this study should be viewed in the light of those limitations.

The study was primarily conducted at a specific community hospice. The findings of this study therefore are applicable to that hospice, and the findings cannot be generalized to other hospices. For this study, Multi-Attributes Utility Theory (MAUT) technique was

utilized as a tool for making formulary decisions. As this method required acquiring preferences from members of the drug selection committee, responses obtained in this study are highly reflective of their own experience and knowledge about using the drug agents to manage their patients' condition, which may vary if we ask for preferences from a different committee belonging to other hospice setting. Although, the MAUT method can be applied to some other hospice or healthcare setting, the drugs included in the hospice formularies through this study may or may not be the same if formularies for the same conditions were to be developed for other hospices or healthcare institution.

The drug factors that were consistently addressed or assessed across all studies were included in the study. Some factors were excluded because they were reported in a few studies and were assessed for certain drugs within that therapeutic class. Some of the efficacy-related factors that were excluded include quality of life, hospitalization, and duration of hospitalization. Disease-contraindications and worsening of condition due to drug withdrawal were some of the safety-related factors that were excluded. The need for medication preparation, level of comfort associated with drug delivery, monitoring requirements, and need for dosage and rate calculations are some of the convenience or drug availability factors that were excluded from this study. If all the factors mentioned in the literature were taken into account, the final rankings of the drugs could have been different, which could alter some of the findings of this study.

Two separate samples pre-test post-test design, which is a quasi experimental study design, was employed for Phase-II of the study. The primary aim of the second phase was to examine the economic impact of the drug agents that were selected in Phase-I. As compared to using a true experimental design such as controlled studies, this

study has employed a quasi-experimental design, which is therefore associated with some of the threats to internal validity. This study could have been subjected to several potential threats to internal validity that includes history; maturation; differential selection of participants; mortality; and selection-maturation interaction and will be discussed in this section.

History is a limitation in this study because an unexpected event (a change in drug contract) occurred between the pre-test and the post-test period. This affected the appropriate measurement of drug costs as drugs were priced differently in the two periods. The hospice of EAMC participates in two major pharmaceutical buying groups that offer different prices for drugs and pharmaceuticals. However, in the time period between the pre and post-formulary period the contract prices were changed and therefore the changes in the drug costs that were initially computed in the post-formulary period could have been accounted by two factors: the contract change or the formulary implementation. This may have either lead to overestimation or underestimation of the actual differences in the drug costs incurred during the post-formulary period. Therefore, it was necessary to remove the effect of contract change on the differences in the drug costs computed in the post period. To achieve this, the pre-formulary drug prices were used for calculating the post-formulary drug costs, which thereby ensured that drug prices remained unchanged for both the periods.

Since two separate samples were used for this study, maturation could have occurred in individuals in each sample thereby affecting the internal validity. Moreover, the clinical condition of hospice patient populations is so critical, that there is a high probability that maturation would have occurred in both pre and post samples.

Differential selection of pre and post samples is another threat to internal validity as the subjects in the two samples may have different characteristics (such as different co-morbid conditions), that could affect the type of drug, its usage and also the costs in the two samples. Moreover, since the patients selected within each group have different maturation rates, selection-maturation also posses a potential threat to this study.

Except for depression-specific drug costs, no statistical significance was found in the differences in the various types of drug costs measured in the pre-formulary and post-formulary for depression as well as CHF patients. Although, a reduction in the different types of drug costs per patient day were observed in the post-depression and post-CHF patients, these differences were not found to be of statistical significance. Non-significant results can be attributed to low sample size for pre and post depression as well as CHF groups. A small sample size can decrease the power of the test, so that small differences are also less likely to be detected. Statistical power analyses were performed using the pre and post depression as well as CHF patients by Power and Precision software tool. (Power-Analysis). The power for the pre and post-formulary depression analysis was found to be around 28%, while that for CHF analysis was about 22%, which are extremely low compared to the desired power of 80%. Even after conducting non-parametric statistics, non-significant findings were observed in the different types of drug costs (except for depression-specific drug costs) for both depression and CHF patients. With a larger sample size, the results could have been different.

The economic impact of the formulary agents were examined on the basis of calculating the difference in the drug costs found in the pre and the post-formulary periods. There are few studies that have shown that the drug costs may actually increase

as a result of formulary development, as the utilization of those formulary agents increases in the post-formulary period (Horn et al, 1996). However, these studies have shown that even though there is an increase in the drug costs, there is a reduction in the overall healthcare costs. In this study, the overall healthcare costs were not measured, which would have given a better understanding and a holistic view of the economic impact of the formularies.

The economic impact of the formulary agents was only examined by calculating the differences in the drug costs found in the pre and the post-formulary periods. Instead of assessing the overall healthcare costs, only the drug costs were taken into consideration for the economic impact evaluation. The study did not assess the overall healthcare costs which included the medical costs (such as drug costs, hospitalization costs, costs of other healthcare resources that were utilized such as oxygen, medical equipments, etc or the costs associated with services provided by the physicians, skilled nurses, other clinical and non-clinical personnel) and non-medical costs (such as transportation costs). Further insights about the overall economic impact of the formularies could have been observed if the study would have assessed an overall impact of formularies of the total healthcare costs and/or resource utilization.

Additionally, the study did not assess the clinical impact of the formulary agents as to whether or not the drug agents that were selected in the formulary had better, worse or no effects on the patient's condition. An understanding of the impact of formulary agents on the clinical as well as humanistic outcomes such as quality of life could have given further insights about the impact of formularies of the quality of care that is being provided as the hospice.

Although, the present study used the MAUT method as a decision-making tool for developing hospice formulary, the usefulness of this method was not evaluated in terms of participant's satisfaction or the worth of utilizing this method, given the limitations such as time constraint and comprehensiveness of the method. Additionally, the economics of conducting this method in this type of healthcare setting was not evaluated.

5.6. Study Implications:

The first and foremost goal of any decision making process is to make the best possible decision. However, the goal of MAUT is to provide insights into the process of making good decision. The MAUT method is a process that aids decision makers in systematically organizing, weighing, and quantifying the different parameters upon which they make their decisions. This process has previously been applied for formulary development process. However, it has never been applied in a hospice setting. The present study is an exploratory study that used the MAUT method to develop hospice drug formularies for specific clinical conditions such as depression and CHF, and also aimed at examining the economic impact of the drug agents that were selected by this process. In this study, drug agents for depression and CHF conditions were selected based on the combination assessment of evidence on important drug factors addressed in the literature as well as drug selection committee members' preferences for drug factors which they consider important for drug selection. The MAUT assisted the formulary decision makers to understand information related to different drug agents. .

The MAUT method was successfully employed as a decision-making tool in selecting agents for the depression and CHF formularies. Similar methodology can be

further applied for the purpose of developing formularies related to other clinical conditions and even at different hospice settings.

As a result of developing and implementing drug formularies, fewer drug agents had to be stocked by the hospice of EAMC. Limiting the total number of drugs may help the EAMC hospice control their inventory costs. Additionally, this may also enable the hospice to have better contract prices for formulary drug agents from the participating buying groups, which will further allow the hospice to reduce the overall drug costs.

5.7. Suggestions for Future Research:

The present study successfully used the MAUT method for developing formularies in a hospice setting. Additionally, the study showed that potential pharmacy savings could be achieved as a result of implementing formularies that were developed by the MAUT method. In order to increase the reliability of the formulary development method used in this study and to validate the economic impact findings, similar research could be replicated at other hospices. Based on the findings and implications of this study certain questions were raised, which could be answered by future studies in this area.

One of the major limitations identified in this study was the small sample size. Moreover, the statistical power for both depression and CHF analyses were found to be lower than desired. Thus, in order to have a statistical power of around 80%, it would be necessary to collect data from 80-100 patients for each pre and post-formulary group. A requirement of 100 subjects for the future study would therefore equate to having at least five hospice facilities participate in future studies (assuming each center has patient enrollment similar to that of hospice of EAMC).

Future research using procedures similar to those in this study, conducted at multiple hospices. The same clinical data could be used to replicate the MAUT process in each hospice to determine how consistent the formularies would be if they were all developed using the same method. This would also enable the researcher to compare the rankings and weightings (or examine the inter-rater reliabilities) assigned by one hospice for drug attributes and factor to another hospice or to other hospices. This would also give additional insights into the preferences of the drug selection committees at different hospices which could be used to identify the most important criteria for formulary development across different hospices.

In addition to measuring the impact of each of the condition-specific formularies on drug costs, future research should include overall healthcare costs or resource utilization measures. This will give an overall picture of the impact of formularies on the total healthcare costs and resource utilization. If future studies are conducted at multiple sites, then could the data could be collected and analyzed centrally. The overall economic impact of the formularies developed at multiple hospices can be evaluated by employing a nested cohort study design. The differences in the drug costs as well as the overall healthcare costs including the medical and non-medical costs associated with the therapy would be measured and then compared across the pre and post-formulary patient groups.

This study did not examine the total costs that were involved for implementing the formulary at the hospice, which included the researcher's time as well as other costs associated with the formulary implementation. Therefore, it would be interesting to examine the total cost of implementing the formulary, which would give us further insights about the overall potential savings that could be achieved as a result of

developing and implementing formularies by MAUT method. Additionally, this study did not assess the acceptability of the MAUT method by the participating members. Therefore, studies dealing with the assessment of the acceptability of the MAUT method should also be conducted, which will give further insights about the actual worth of developing the formulary based on this method.

5.8. Conclusion:

This was an exploratory study investigating whether the MAUT tool can be used to develop a formulary in the hospice setting, and whether the decisions to include specific drugs for the formulary have an impact on the economic outcomes. The MAUT method was successfully used as a decision making tool for formulary development process. Additionally, drug cost savings were achieved as a result of implementing the formularies. In this study, MAUT method was therefore found to be an effective tool for reaching consensus and selecting drugs for developing hospice formularies for congestive heart failure and depression. The study also showed that, annually the hospice of EAMC could achieve an estimated drug cost savings of about $456.00 and about $1813.00 as a result of implementing depression and CHF formularies respectively. Thus, the study has a methodological value as it has illustrated the usefulness of MAUT method for the purpose of supporting a formulary decision at the hospice.

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APPENDIX A: Institutional Review Board [Auburn University]

Auburn University

Auburn University, Alabama 36849

Office of Human Subjects Research
307 Samford Hall

Telephone: 334-844-5966
Fax: 334-844-4391
hsubjec@auburn.edu

May 13, 2005

MEMORANDUM TO:	Nikhil Khandelwal Pharmacy
PROTOCOL TITLE:	"Developing the Condition-Specific Hospice Formularies For Congestive Heart Failure (CHF) and Depression and Evaluating Their Economic Impact"
IRB FILE:	05-092 EP 0505
APPROVAL DATE: EXPIRATION DATE:	May 12, 2005 May 11, 2006

The above reference protocol was approved by IRB Expedited procedure under Expedited Category #5 on May 12, 2005. You should report to the IRB any proposed changes in the protocol or procedures and any unanticipated problems involving risk to subjects or others. Please reference the above authorization number in any future correspondence regarding this project.

If you will be unable to file a Final Report on your project before May 11, 2006, you must submit a request for an extension of approval to the IRB no later than April 25, 2006. If your IRB authorization expires and/or you have not received written notice that a request for an extension has been approved prior to May 11, 2006, you must suspend the project immediately and contact the Office of Human Subjects Research for assistance.

A Final Report will be required to close your IRB project file. You are reminded that consent forms must be retained at least three years after completion of your study.

If you have any questions concerning this Board action, please contact the Office of Human Subjects Research at 844-5966.

Sincerely,

Peter W. Grand jean, Chair
Institutional Review Board for the Use of Human Subjects in Research

cc: Dr. Bruce Berger
Dr. Kem Krueger

APPENDIX B: Institutional Review Board [East Alabama Medical Center]

05-07-E

LETTER OF APPROVAL
Institutional Review Board

TO: Nikhil Khandelwal, M.S
Principal Investigator

FROM: Michael J. Lisenby, M.D.
Chairperson, IRB

DATE: May 6, 2005

The research project submitted for Expedited Review and approval entitled, "Developing the Condition-Specific Hospice Formularies for Congestive Heart Failure (CHF) and Depression Conditions and Evaluating Their Economic Impact" was reviewed and approved with the following stipulations:

A. Investigators acknowledge and accept their responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable thereof.

B. Investigators must report promptly to the IRB:

(1) Any proposed changes in IRB approved research and acknowledge such research may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.
(2) Any unanticipated problems involving risks to human subjects or others.
(3) Any instance of serious or unexpected adverse events arising during the research.

C. The above titled project is approved May 6, 2005 through May 5, 2006.
If the project is to continue beyond the ending date of approval, application for renewal must be made as of March 4, 2006 to be further approved by the IRB.

D. Approval is contingent upon modifications, if any, of the protocol or waiver and approved documentation of such modifications.

_____ 5/11/05
IRB Chairperson Date

Please acknowledge your agreement to abide by these stipulations by your signature, keep a copy and return the original to the IRB office.

_____ 5/12/05
Principal Investigator Date

May 23, 2005

Nikhil Khandelwal, MS
128 Miller Hall
Pharmacy Care Systems Department
Auburn University
Auburn, Alabama 36849

Re: Non-Disclosure Agreement

Dear Mr. Khandelwal:

Enclosed you will find a fully executed copy of the non-disclosure agreement that you signed with East Alabama Medical Center. This copy is being sent to you for your files. If you have any questions or need further assistance, please do not hesitate to call me at 705-1322.

Sincerely,

Marcilla C. Gross
HIPAA Privacy Officer

Enclosure

NON-DISCLOSURE AGREEMENT

THIS NON-DISCLOSURE AGREEMENT ("Non-Disclosure Agreement") is made and entered into as of this 4 day of May, 2005 ("Effective Date"), by and between **EAST ALABMA MEDICAL CENTER** (hereinafter referred to as "Provider") and **Nikhil Khandelwal, MS** (hereinafter referred to as "Student").

WHEREAS, Provider has agreed to permit Student to observe the delivery of health care in Provider's facility as a learning experience. In connection with Student's observations, Student has possible access to Confidential Information; and

WHEREAS, Provider requires that Student protect the privacy and confidentiality of the Confidential Information.

NOW, THEREFORE, in consideration of the foregoing and of the covenants and agreements set forth herein, the parties, intending to be legally bound, agree as follows:

1. **Confidential Information.** For purposes of this Non-Disclosure Agreement, "Confidential Information" means information whether oral, written or recorded in an electronic format or other medium (other than that which is public knowledge) about the business, activities, operations, or facilities of Provider, including but not limited to its methods, techniques, and processes; development, costs and pricing of its products and services; business and marketing strategies and plans; financial data, personnel data; all trade secrets pertaining in any respect to Provider's business; and other non-public information furnished to or obtained by Student form or on behalf of Provider. "Confidential Information" shall also include Protected Health Information ("PHI") as that term is defined in 45 CFR 164.501, including, without limitation, any information, whether oral or recorded in any form or medium: (i) that relates to the past, present or future physical or mental condition of an individual; or (ii) the provision of health care to an individual; or (iii) the past, present or future payment for the provision of health care to an individual; and (iv) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual. Any notes, papers, databases or other items that contain, embody, discuss, describe, refer or relate to Confidential Information shall likewise be considered Confidential Information within the meaning of this Non-Disclosure Agreement. All Confidential Information shall at all times and for all purposes be considered the property of Provider.

2. **Non-Disclosure Covenants.** Student acknowledges that he is in a position of trust and confidence. In particular, Provider and Student recognize that Student may come into contact with or have access to Confidential Information. During the term of this Non-Disclosure Agreement, Student agrees as follows:

a. Student shall not use or disclose Confidential Information in any manner other than while observing the delivery of healthcare at Provider's facility. Further, Student shall not use Confidential Information in any manner that would constitute a violation of any local, state or federal laws, rules or regulations.

b. Student acknowledges that Provider has a duty under law to keep Protected Health Information confidential and secure and that any unauthorized use or disclosure of Protected Health

Information may subject Provider to substantial fines, penalties and damages. Student agrees to use reasonable care to avoid the disclosure or dissemination of any Confidential Information.

c. The obligations set forth in this Section 2 shall survive termination of this Non-Disclosure Agreement, regardless of the reasons for termination.

3. Return of Provider Property. Upon termination or expiration of the Agreement and immediately upon request by Provider, Student will return to Provider all documents, materials and other property belonging to Provider, including but not limited to all Confidential Information, in Student's possession or control. Notwithstanding the above, upon termination of this Agreement for any reason, Student shall return or destroy all PHI (regardless of form or medium), including all copies thereof and any data compilations derived from PHI and allowing identification of any Individual who is the subject of PHI.

4. Term and Termination. This Non-Disclosure Agreement shall commence on the Effective Date and will remain effective for the entire duration of Student's observations. In the event of a material breach by Student of any of its obligations hereunder, Provider shall have the right, as specifically recognized by Student, to terminate the Agreement at any time by providing Student written notice of termination setting forth a description of the breach and the effective date of termination.

5. Injunctive Relief. In the event of a breach by Student of any of its obligations hereunder, Provider shall have, in addition to any other rights and remedies available at law or in equity, the right to obtain injunctive relief without the necessity of proving actual damages or that any irreparable harm would or might result from a failure to obtain injunctive relief, it being acknowledged and agreed to by all parties hereto that any such breach will cause irreparable harm to Provider and that monetary damages alone will not provide an adequate remedy.

6. Indemnification. Student shall indemnify and hold Provider, and its employees, officers, directors, independent Students, agents and representatives, harmless from and against all claims, liabilities, judgments, fines, assessments, penalties, awards or other expenses, of any kind or nature whatsoever, including, without limitation, attorneys' fees, expert witness fees, and costs of investigation, litigation or dispute resolution, relating to or arising out of any breach or alleged breach of this Non-Disclosure Agreement by Student. The obligations set forth in this Section 6 shall survive termination or expiration of this Non-Disclosure Agreement, regardless of the reasons for termination.

7. Governing Law and Venue. This Non-Disclosure Agreement shall be governed by, and interpreted in accordance with the internal laws of the State of Alabama, without giving effect to any conflict of laws provisions. Any action at law, suit in equity, or other judicial proceeding for the enforcement of this Non-Disclosure Agreement, or any provision hereof, shall take place in the State of Alabama in the County in which Provider has its place of business. Student hereby consents to the personal jurisdiction of the state and federal courts in such County, in any dispute arising from or related to this Non-Disclosure Agreement.

8. Binding Effect; Modification. This Non-Disclosure Agreement shall be binding upon, and shall enure to the benefit of, the parties hereto and their respective permitted successors

and assigns. This Non-Disclosure Agreement may only be amended or modified by mutual written agreement of the parties.

9. **Waiver.** The failure of either party at any time to enforce any right or remedy available hereunder with respect to any breach or failure shall not be construed to be a waiver of such right or remedy with respect to any other breach or failure by the other party.

10. **Severability.** In the event that any provision or part of this Non-Disclosure Agreement is found to be totally or partially invalid, illegal, or unenforceable, then the provision will be deemed to be modified or restricted to the extent and in the manner necessary to make it valid, legal, or enforceable, or it will be excised without affecting any other provision of this Non-Disclosure Agreement, with the parties agreeing that the remaining provisions are to be deemed to be in full force and effect as if they had been executed by both parties subsequent to the expungement of the invalid provision.

11. **Assignment.** This Non-Disclosure Agreement and the rights and obligations hereunder shall not be assigned, delegated, or otherwise transferred by either party without the prior written consent of the other party and any assignment or transfer without proper consent shall be null and void.

12. **No Third-Party Beneficiaries.** Nothing express or implied in this Non-Disclosure Agreement is intended to confer, nor shall anything herein confer, upon any person or entity other than Provider, Student and their respective successors or permitted assigns, any rights, remedies, obligations or liabilities whatsoever.

IN WITNESS WHEREOF, Provider and Student have each caused this Non-Disclosure Agreement to be executed in their respective names by their duly authorized representatives, as of the day and year first above written.

"PROVIDER"

EAST ALABAMA MEDICAL CENTER
2000 PEPPERELL PARKWAY
OPELIKA, ALABMA 36801

Signature _____

Print Name: Janice J. Baker

Title: Vice President of Medical Staff & Legal Affairs

"STUDENT"

Nikhil Khandelwal, MS
128 Miller Hall
Pharmacy Care Systems Department
Auburn University
Auburn, Alabama 36849

Signature: _____

Print Name: NIKHIL KHANDELWAL

APPENDIX C: PowerPoint Presentation Slides [First Focus Group Meeting]

Developing Condition-specific Hospice Formularies For CHF And Depression & Evaluation of Their Economic Impact

Phase 1
Hospice of East Alabama Medical Center
Focus Group Meeting

June 15, 2005

Nikhil Khandelwal, MS
Auburn University

Study Objectives

- The purpose of this study is to develop a condition-specific partial hospice formulary for CHF and depression, using the Multi-Attribute Utility Theory (MAUT).
- This study will also evaluate the economic impact of the medications selected for the condition-specific hospice formulary.

Study Phases

- PHASE I: Developing condition-specific hospice formulary, using the Multi-Attribute Utility Theory (MAUT) method.
  - Literature Review
  - Focus Group Meeting
- PHASE II: Evaluating the economic impact of drug agents selected in the condition-specific hospice formulary.

Study Procedures – Formulary Development

- Step 1: The major drug selection criteria that are consistently reported in the literature were identified and classified into:
  - Drug attributes (efficacy, safety, availability, cost)
  - Factors describing the drug attributes

Examples of Drug Attributes and Factors

Study Procedures – Formulary Development

- Step 2: Factor values (and ranges) for each medication were obtained for each factor/attribute
  - Databases searched: MEDLINE, IPA, CINAHL, PsycINFO, and Cochrane Database
  - Types of articles included: Systematic reviews, RCTs, meta-analysis, and guidelines

Study Procedures – Formulary Development

- Step 3: Focus Group Meeting
  - Consensus on the relevant attributes and factors to be considered for drug evaluation and selection
  - Rank and Weight different drug attributes and factors
- Step 4: Economic Evaluation
  - Compare costs and utilization prior to and after the formulary change

Ranking & Weighing

Ranking and Weighing Criteria

Rank	Selection Criteria (Drug Attributes)	Ratio Weight
2	Drug Safety	
1	Drug Efficacy	
4	Drug Availability	
3	Drug Cost	

First, rank the criteria according to its importance to you in selecting a drug for your patients.
Rank selection criteria from 1 - 4
(1=most important to 4 = least important)

Ranking and Weighing Criteria

Rank	Selection Criteria (Drug Attributes)	Ratio Weight
2	Drug Safety	
1	Drug Efficacy	
4	Drug Availability	1
3	Drug Cost	

Set the ratio weight of the least important criteria as 1

Ranking and Weighing Criteria

Rank	Selection Criteria (Drug Attributes)	Ratio Weight
2	Drug Safety	
1	Drug Efficacy	
4	Drug Availability	1
3	Drug Cost	2

Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
(i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

Ranking and Weighing Criteria

Rank	Selection Criteria (Drug Attributes)	Ratio Weight
2	Drug Safety	
1	Drug Efficacy	
4	Drug Availability	1
3	Drug Cost	2

Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
(i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

Ranking and Weighing Criteria

Rank	Selection Criteria (Drug Attributes)	Ratio Weight
2	Drug Safety	4
1	Drug Efficacy	8
4	Drug Availability	1
3	Drug Cost	2

Determine the ratio weights for the remaining criteria by order of increasing importance ending with the most important criteria.
Remember to always compare the criteria currently being evaluated against the least important criteria in setting ratio weights.

You Try!

Imagine you are ranking the attributes for tri-cyclic antidepressants

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

Depression

Class: SSRI
Measures of Efficacy

- **Response Rate:** The proportion of individuals that demonstrate a mean reduction of at least 50 percent of the depressive symptoms from the baseline after 4 or more weeks of antidepressant treatment as measured by the:
  - Hamilton Rating Scale for Depression (HAM-D) or
  - Montgomery Asberg Depression Rating Scale (MADRS)
- **Total Drop-out Rate:** The proportion of individuals who discontinued drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or serious adverse drug events.

Class: SSRI
Measures of Safety

- **Drop-out Rate (ADRs):** Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs:** Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions:** Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions:** Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: SSRI
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

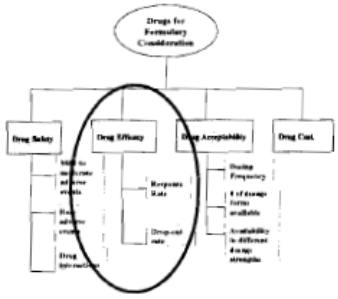
Class: SSRI
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

Examples of Drug Attributes and Factors



Calculating the Total Score for a Single Medication

Factor	Value from literature (average or median)	Average Ratio Weight (Focus Group)	(Value) x (Weight)
Response Rate	54	.9	48.6
Drop out rate	21	.1	2.1
Sum			50.7

Calculating the Total Score for a Single Medication

Attribute	Calculated value from previous slide	Average Ratio Weight (Focus Group)	(Value) x (Weight)
Efficacy	50.7	.70	35.5
Safety	26.4	.20	5.3
Availability	35.8	.15	5.4
Cost	23.2	.10	2.3
Sum			48.5

NYHA CLASS III-IV CHF MANAGEMENT

Diuretic + ACE-Inhibitor + Digoxin + Beta Blocker

- Diuretic: Evidence of Fluid Retention; Improves Cardiac function, and symptoms
- ACE-Inhibitor: Reduces mortality and morbidity; Patients not tolerant to ACE-Inhibitors → ARBs + Hydrazaline + Nitrates
- Digoxin: Reduces symptoms and enhances functional capacity
- Beta Blocker: Reduces mortality and morbidity, improves clinical status and overall well-being

Severe CHF: Loop Diuretic + Thaizide/Metolazone

CHF MANAGEMENT

Diuretic + ACE-Inhibitor + Digoxin + Beta Blocker

STANDARD THERAPY

Spironolactone
- Reduces mortality
- Contraindicated in renal failure patients and patients with pre-existing hyperkalemia

Anticoagulants
Reduces the risk for developing thromboembolic events

Antiplatelet (Low-dose Aspirin)

SPECIFIC GUIDELINE RECOMMENDATIONS

Hypertension/Hyperlipidemia or Diabetes

- Treatment should be followed for concomitant conditions, as if the patients did not have CHF
- Drugs that both control Blood Pressure and treat CHF should be preferred (Diuretics, ACE-Inhibitors, and Beta-Blockers)
- AVOID CALCIUM CHANNEL BLOCKERS

SPECIFIC GUIDELINE RECOMMENDATIONS

Coronary Artery Disease

- Drugs that both relieve angina and treat CHF should be preferred
- Nitrates and Beta Blockers
- AVOID CALCIUM CHANNEL BLOCKERS (except

Myocardial Infarction: (Without Heart Failure/Angina)

- ACE-Inhibitors + Beta Blockers
- Aspirin or Clopidogrel (Antiplatelet agents)

SPECIFIC GUIDELINE RECOMMENDATIONS

Atrial Fibrillation (Supraventricular Arrhythmia)

- Digoxin is the most commonly used agent
- Beta Blockers (Carvedilol, Buisoprolol, or Metoprolol) are more effective than Digoxin
- AVOID CALCIUM CHANNEL BLOCKERS (such as Verapamil or Diltiazem)
- If Beta Blockers are ineffective, or contraindicated, then AMIODARONE is recommended

SPECIFIC GUIDELINE RECOMMENDATIONS

Ventricular Arrhythmia

- Beta Blockers (Timolol or Propranolol) are recommended
- Amiodarone is recommended, increases Ejection Fraction, and decreases worsening heart failure conditions

ACE Inhibitors

Class: ACE Inhibitors
Measures of Efficacy

- **All Cause Mortality Rate:** The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **Functional Capacity:** The percent improvement in the baseline exercise scores as measured by different exercise tests such as treadmill exercise tests or bicycle at the end of the study period.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

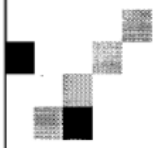
Loop Diuretics

Class: Loop Diuretics
Measures of Efficacy

- **NYHA Functional Status:** The proportion of individuals that have shown improvement in at least one NYHA functional class during the study period.
- **Mean Body Weight:** The mean reduction in body weight obtained at the end of the study period.
- **Edema Improvement:** The percentage of individuals that have shown improvement in the edema conditions at the end of the study.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)



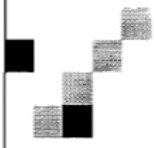
Beta Blockers

Class: Beta Blockers
Measures of Efficacy

- **All Cause Mortality Rate:** The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **All Cause Mortality Rate:** Composite measure of the proportion of individuals who have died or have been hospitalized for heart failure during the study
- **Functional Capacity:** The percent improvement in the baseline exercise scores as measured by the 6-minute walk test at the end of the study period.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)



ARBs

Class: ARBs
Measures of Efficacy

- **All Cause Mortality Rate:** The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **Hospitalization Rate:** The proportion of individuals that were re-hospitalized during the study period as a result of increased morbidity or worsening heart failure conditions.

Class: ARBs
Measures of Efficacy (Continued)

- **Left Ventricular Ejection Fraction:** Percent improvement in left ventricular ejection fraction from baseline.
- **Total Drop-out Rate:** The proportion of individuals who discontinued drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or serious adverse drug events.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)

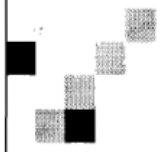
Nitrates

Class: Nitrates
Measures of Efficacy

- **Pulmonary Capillary Wedge Pressure:** The percent reduction in pulmonary capillary wedge pressure (PWP), from baseline.
- **Cardiac Index:** The percent improvement in the Cardiac Index (CI) values, from baseline.
- **Pulmonary Arterial Pressure:** The percent reduction in Pulmonary Arterial Pressure (PAP) from baseline.
- **Systemic Vascular Resistance:** The percent reduction in Systemic Vascular Resistance (SVR) from baseline.

Ranking and Weighing Criteria

- First, rank the criteria according to its importance to you in selecting a drug for your patients.
  Rank selection criteria from 1 - 4
  (1=most important to 4 = least important)
- Set the ratio weight of the least important criteria as 1
- Determine the ratio weight of next least important criteria in the list with respect to the ratio weight of the least important criteria.
  (i.e. if criteria ranked 3 is twice as important as criteria ranked 4 (least important), then the ratio weight of criteria 3 =2)



Questions?

Thank you for your participation!

- THE SLIDES THAT FOLLOW ARE HANDOUTS

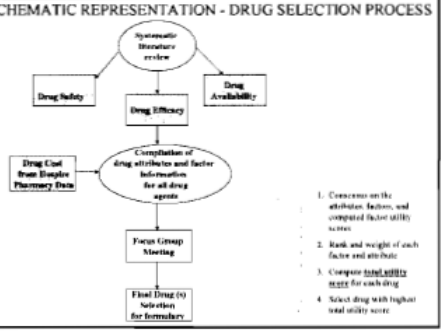
Overall Study Objectives

- The purpose of this study is to develop a condition-specific partial hospice formulary for CHF and depression, using the Multi-Attribute Utility Theory (MAUT).
- This study will also evaluate the economic impact of the medications selected for the condition-specific hospice formulary.

Today's Focus Group Objectives

- Come to consensus on the relevant attributes and factors to be considered for drug evaluation and selection
- Rank and weight the different drug attributes and factors for seven pharmacologic classes

SCHEMATIC REPRESENTATION - DRUG SELECTION PROCESS



Class: SSRI
Measures of Efficacy

- **Response Rate:** The proportion of individuals that demonstrate a mean reduction of at least 50 percent of the depressive symptoms from the baseline after 4 or more weeks of antidepressant treatment as measured by the:
  - Hamilton Rating Scale for Depression (HAM-D) or
  - Montgomery Asberg Depression Rating Scale (MADRS)
- **Total Drop-out Rate:** The proportion of individuals who discontinued drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or serious adverse drug events.

Class: SSRI
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: SSRI
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: SSRI
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Class: ACE Inhibitors
Measures of Efficacy

- **All Cause Mortality Rate:** The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **Functional Capacity:** The percent improvement in the baseline exercise scores as measured by different exercise tests such as treadmill exercise tests or bicycle at the end of the study period.

Class: ACE Inhibitors
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: ACE Inhibitors
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: ACE Inhibitors
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Class: Loop Diuretics
Measures of Efficacy

- **NYHA Functional Status:** The proportion of individuals that have shown improvement in at least one NYHA functional class during the study period.
- **Mean Body Weight:** The mean reduction in body weight obtained at the end of the study period.
- **Edema Improvement:** The percentage of individuals that have shown improvement in the edema conditions at the end of the study.

Class: Loop Diuretics
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: Loop Diuretics
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: Loop Diuretics
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Class: Beta Blockers
Measures of Efficacy

- **All Cause Mortality Rate**: The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **All Cause Mortality Rate:** Composite measure of the proportion of individuals who have died or have been hospitalized for heart failure during the study
- **Functional Capacity:** The percent improvement in the baseline exercise scores as measured by the 6-minute walk test at the end of the study period.

Class: Beta Blockers
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: Beta Blockers
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: Beta Blockers
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Class: ARBs
Measures of Efficacy

- **All Cause Mortality Rate:** The proportion of individuals that have died due to cardiovascular events (such as progressive heart failure, sudden death, recurrent cardiac events and cardiac rupture) or non-cardiovascular causes (such as cerebrovascular events, pulmonary embolism, and nonvascular causes) at the end of the study period.
- **Hospitalization Rate:** The proportion of individuals that were re-hospitalized during the study period as a result of increased morbidity or worsening heart failure conditions.

Class: ARBs
Measures of Efficacy (Continued)

- **Left Ventricular Ejection Fraction:** Percent improvement in left ventricular ejection fraction from baseline.
- **Total Drop-out Rate:** The proportion of individuals who discontinued drug therapy during the study period, for reasons such as lack of efficacy, non-compliance, or serious adverse drug events.

Class: ARBs
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: ARBs
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: ARBs
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

Class: Nitrates
Measures of Efficacy

- **Pulmonary Capillary Wedge Pressure:** The percent reduction in pulmonary capillary wedge pressure (PWP), from baseline.
- **Cardiac Index:** The percent improvement in the Cardiac Index (CI) values, from baseline.
- **Pulmonary Arterial Pressure:** The percent reduction in Pulmonary Arterial Pressure (PAP) from baseline.
- **Systemic Vascular Resistance:** The percent reduction in Systemic Vascular Resistance (SVR) from baseline.

Class: Nitrates
Measures of Safety

- **Drop-out Rate (ADRs)**: Proportion of individuals who discontinued drug therapy after experiencing one or more adverse drug reactions (ADRs).
- **Treatment Limiting ADRs**: Number of serious ADRs occurring during the study period, that may have led subjects to discontinue the drug or seek special medical attention (including hospital admission or an ER visit).
- **Other Adverse Drug Reactions**: Average number of mild to moderate ADRs occurring during the study period.
- **Drug Interactions**: Number of possible drug interactions associated with the drug molecule that had a rating of 1, 2, or 3 in Hansten & Horn's Drug Interactions. These ratings indicate that some action is necessary to minimize or avoid risk.

Class: Nitrates
Measures of Drug Availability

- **Availability in different dosage forms**: The number of different commercial preparations marketed for the medication such as tablet, capsule, oral solution, injection, etc.
- **Availability in different doses**: Defined as the number of different doses or strengths in which the drug is available in the market.
- **Dosing Frequency**: Defined as the total number of times, a drug is recommended to be either administered or given to the patient on a day for the purpose of managing the condition.

Class: Nitrates
Measures of Drug Cost

- **Drug Cost**: The cost of the medication after adjusting for discounts or incentives as received by the Hospice Pharmacy at EAMC.

APPENDIX D: Ranking and Weighting Protocol For Drug Attributes And Factors

PART (A) - Ranking and weighting different selection criteria (Drug Attributes):

Rank (I)	Rank (II)	Selection Criteria (Drug Attributes)	Ratio Weight (I)	Ratio Weight (II)
		Drug Safety		
		Drug Efficacy		
		Drug Availability		
		Drug Cost		

PART (B) - Ranking and weighting different factors for drug efficacy:

Rank (I)	Rank (II)	Drug Efficacy Factors	Ratio Weight (I)	Ratio Weight (II)
		Response Rate		
		Total Drop-out Rate		

PART (C) - Ranking and weighting different factors for drug safety:

Rank (I)	Rank (II)	Drug Safety Factors	Ratio Weight (I)	Ratio Weight (II)
		Drop-out rate (due to adverse drug reactions)		
		Treatment limiting adverse drug reactions		
		Other (mild to moderate) adverse drug reactions		
		Drug interactions		

PART (D) - Ranking and weighting different factors for drug availability:

Rank (I)	Rank (II)	Drug Availability Factors	Ratio Weight (I)	Ratio Weight II)
		Availability in different dosage forms (tablets, capsules, liquids, etc)		
		Availability in different doses or strengths		
		Dosing Frequency (# of times drug is taken per day)		

APPENDIX E: INTRACLASS CORRELATION COEFFICIENTS

APPENDIX [D-Table D1]
Intraclass Correlation Coefficients for the Ratio Weights Obtained for all Drug Attributes for Individual Drug Class:

Drug Attributes	Drug Class	Correlation Coefficients	Confidence Interval	p-value
Drug efficacy Drug safety Drug availability Drug cost	Antidepressants (SSRIs)	0.979	0.917-0.999	< .000 *
	ACE-Inhibitors	0.983	0.931-0.999	< .000 *
	Beta blockers	0.954	0.820-0.997	< .000 *
	Loop Diuretics	0.927	0.711-0.995	< .000 *
	ARBs	0.984	0.939-0.999	< .000 *
	Nitrates	0.867	0.447-0.991	< .003 *

* p-value significant at $\alpha = 0.05$

APPENDIX [D- Table D2]
Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (Antidepressants drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
Antidepressants (SSRIs)	Drug efficacy	Response rate	0.932	0.398-1.000	< .009 *
		Total drop-out rate			
	Drug safety	Drop-out rate (due to adverse drug reactions)	0.161	-2.319-0.914	0.314
		# of treatment-limiting severe adverse drug reactions			
		# other adverse drug reactions			
		# Drug interactions			
	Drug availability	Number of dosage forms available	0.524	-1.425-0.988	0.165
		Number of doses available			
		Common dosing frequency			

* p-value significant at $\alpha = 0.05$

APPENDIX [D- Table D3]

Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (ACE-Inhibitors drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
ACE-Inhibitors	Drug efficacy	All cause mortality rate	0.838	-0.426-1.000	0.009 *
		Percent improvement in functional capacity			
	Drug safety	Drop-out rate	0.624	-0.915-0.990	0.111
		# Adverse drug reactions			
		# Drug interactions			
	Drug availability	Number of dosage forms available	0.869	-0.175-0.994	0.038 *
		Number of doses available			
		Common dosing frequency			

* p-value significant at α = 0.05

APPENDIX [D- Table D4]

Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (Beta Blockers drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
Beta Blockers	Drug efficacy	Percent all cause mortality	0.829	-0.379-0.993	0.046 *
		Percent mortality and hospitalization rate			
		Percent improvement in functional capacity			
	Drug safety	Percent discontinuation rate (due to adverse drug reactions)	0.595	-0.602-0.971	0.095
		# of treatment-limiting severe adverse drug reactions			
		# of other adverse drug reactions			
		# Drug interactions			
	Drug availability	Number of dosage forms available	0.793	-0.054-0.995	0.029 *
		Number of doses available			
		Common dosing frequency			

* p-value significant at α = 0.05

APPENDIX [D- Table D5]

Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (Loop Diuretics drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
Loop Diuretics	Drug efficacy	Percentage improvement in NYHA functional class	0.362	-2.252-0.984	0.249
		Reduction in mean body weight			
		Percentage improvement in edema			
	Drug safety	# Mild to moderate Adverse drug reactions	0.706	-0.500-0.993	0.038 *
		Percentage of patients experiencing treatment-limiting adverse drug reactions			
		# Drug interactions			
	Drug availability	Number of dosage forms available	0.375	-2.435-0.996	0.286
		Number of doses available			
		Common dosing frequency			

* p-value significant at $\alpha = 0.05$

APPENDIX [D- Table D6]

Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (ARBs drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
ARBs	Drug efficacy	Percent all cause mortality	0.392	-1.404-0.957	0.249
		Percent hospitalization rate			
		Mean improvement in the Left Ventricular Ejection Fraction (LVEF)			
		Percent total drop-out rate			
	Drug safety	Percent drop-out rate (due to adverse drug reactions)	0.301	-2.562-0.982	0.277
		# of treatment-limiting severe adverse drug reactions			
		# of adverse drug reactions			
	Drug availability	Number of dosage forms available	0.787	-0.87-0.995	0.031 *
		Number of doses available			
		Common dosing frequency			

* p-value significant at $\alpha = 0.05$

APPENDIX [D- Table D7]

Intraclass Correlation Coefficients for Ratio Weights for Factors Describing Individual Drug Attribute (Nitrates drug class)

Drug Class	Drug Attribute	Drug Factors Describing Attributes	Correlation Coefficient	Confidence Interval	p-value
Nitrates	Drug efficacy	Percent reduction in Pulmonary Capillary Wedge Pressure (PWP)	0.514	-0.922-0.966	0.142
		Percent increase in Cardiac Index (CI)			
		Percent reduction in Pulmonary Arterial Pressure (PAP)			
		Percent reduction in Systemic Vascular Resistance (SVR)			
	Drug safety	Percent drop-out rate (due to adverse drug reactions)	0.365	-2.105-0.945	0.264
		# of treatment-limiting severe adverse drug reactions			
		# Drug interactions			
	Drug availability	Number of dosage forms available	0.344	-2.464-0.987	0.289
		Number of doses available			
		Common dosing frequency			

* p-value significant at $\alpha = 0.05$