

VA Cooperative Studies Program:

A Legacy of Achievement



1997

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Cooperative Studies Program

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VA Cooperative Studies Program: A Legacy of Achievement

The VA is uniquely suited for research efforts at the national level because the VA operates a high quality, national health care system. The VA research effort focuses on medical problems that are common and relevant to the veteran population we serve. These national research studies influence the course of disease and improve the survival and quality of life of our veteran patients. However, the high frequency in the larger U.S. population of the health conditions we study, and the import of the research questions posed, makes VA study results highly relevant to the entire country. Often, the quality of research conducted in the VA establishes the standard of care for the entire U.S. health care system, and for the world.

Medical experts frequently comment editorially about the results of VA Cooperative Studies because of their impact on medical practice, and because they so frequently provide definitive answers to medical questions of national concern. Good words are used commonly to describe the products of the VA research effort. Such words as “the first,” “a landmark study,” “standard setting results,” and “innovative” describe the research effort and the research products that address issues so critical to the health of our veterans and our nation.

Members of Congress have recognized VA studies as having value for our veterans, and adding value to our society as a whole. Such recent studies as the evaluation of implantable insulin pump technology for patients’ with type 2 diabetes, and medical treatment for patients with symptomatic enlargement of their prostate glands, represent two recent examples of landmark studies that define the standard of care for medical problems common to all our citizens.

Most gratifying to us in Research and Development in the VA is that our research so clearly improves the survival and quality of life for our veteran patients. Our research demonstrably improves the effectiveness and efficiency of our national health care system. Studies compare surgery with medical treatment, evaluate the most appropriate use of health care services (especially expensive hospital care), and assess the cost effectiveness of competing treatment strategies. These studies not only inform our patients and providers about the best treatment choices, but also in-

form our policy makers and managers about the cost and consequences of new and existing treatments.

Our Research Program faces the challenges of the 1990's and the next century with hope and anticipation. The Research Program brings tremendous intellectual capital to the challenge posed by the diseases and disabilities that effect our veteran patients. We know that their health care future is in our hands, at least in part. We understand that the answers to today's health care questions reside in tomorrow's research products. We accept that challenge eagerly and with resolve to improve health and to provide the best return possible for the precious resources conferred upon us by our Congress on behalf of our nations citizens.

John R. Feussner, M.D.
Chief Research and Development Officer

Cooperative Studies Program

Introduction

The Cooperative Studies Program is a research organization in the Veterans Health Administration's Office of Research and Development that conducts large scale, , definitive clinical research on health issues vital to our nations' veterans. The Program supports a network of VA clinicians and researchers that identifies important medical and health services questions and performs scientific investigations to discover the answers to these questions. Our findings improve the health of veterans and the efficiency of the VA health care system, and often result in new standards of care that benefit the health of the nation as a whole.

Cooperative Studies has an illustrious past, and is responsible for over five decades of major health advances including:

- treatment for tuberculosis
- saving lives by treating high blood pressure
- using aspirin to prevent heart attacks, stroke, and death
- pioneering work in drug treatment for mental illness

This document describes important impacts of the Cooperative Studies Programs and the programs influence on the practice of medicine both within the VA system and in the larger health care community. The document is organized into two sections. The first section describes impacts of completed Cooperative Studies and the second section describes Cooperative Studies that are currently underway or planned and their potential impacts on VA and the larger health care community.

Heart

■ **80% of strokes in patients with irregular heart beats can be prevented by a blood thinning drug**

Irregular heartbeat (atrial fibrillation) is a common condition that affects as many as 9 percent of the elderly. Patients with this condition are at a high risk for stroke. Low doses of a drug that thins the blood, warfarin, decreased by 79% the rate of strokes among these patients, without increasing the risk of bleeding. This represents a low cost treatment that prolongs life, increases the quality of life, and reduces the cost of caring for stroke patients, saving the VA medical care system millions of dollars. This treatment is now accepted as the standard of care throughout the world.

■ **Surgery can prevent stroke in patients with a blocked carotid artery**

Every year nearly 500,000 individuals in the United States die or are disabled by a stroke and direct and indirect costs to society are estimated at more than 7 billion dollars annually. Cerebral infarction represents approximately three-fourths of all strokes, and at least 15% of cerebral infarctions have been related to blockage of the carotid artery.

Patients with carotid artery blockages experiencing early warning signals of stroke often suffer major stroke or death if not treated. Other patients with blockages may not have symptoms, but are still at risk for stroke.

Cooperative Studies conducted two major studies of a surgical procedure, called carotid

endarterectomy, that clears the blockage of the carotid artery (called carotid stenosis). One study focused on patients with warning symptoms, and the other focused on patients with carotid stenosis who nevertheless did not have symptoms.

Prior to these studies, the effectiveness of surgical removal of the blockage had not been proven even though the surgery was widely used. The surgery was particularly controversial for patients who did not have prior neurologic symptoms including minor stroke and temporary “mini strokes” (transient ischemic attacks).

Both studies showed that surgery was effective in preventing stroke and/or “mini stroke”. These two studies, combined with the results of three other studies in the United States and Europe led to the consensus of surgically treating patients with especially high levels of carotid stenosis to prevent stroke. Surgical treatment has become the standard of care for such patients. This treatment is now accepted as the standard of care throughout the world.

■ **Aggressive treatment of moderate hypertension works well for older patients**

Hypertension (high blood pressure) should be treated in all patients to prevent serious complications such as stroke, heart failure, and kidney disease. However, antihypertensive medications can interfere with the patient’s quality of life, particularly for elderly patients.

The purpose of this study was to compare different high blood pressure medications in the elderly population in terms of reduction in blood pressure and effects on patient’s quality

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of life. In general, the drugs were found to be effective and not to markedly reduce the patient's quality of life. Aggressive treatment of mild to moderate hypertension in the elderly does not adversely affect their activities of daily living, mental acuity, cognitive function, sense of well being, and mood. This study demonstrated that the beneficial effects of therapy could be achieved without effecting adversely older persons' daily lives.

■ **Discovered the optimal strategy for prescribing the correct drug for hypertension**

Over 40 million Americans have hypertension (high blood pressure), but less than 50% of people with hypertension are adequately treated. This disease is a direct or contributing cause for stroke, coronary heart disease and kidney failure. In an early VA cooperative study done in the 1960's, it was proven that treatment of mild to moderate hypertension prevented the long-term morbidity and mortality of the disease. Concern about the side effects of the most widely used antihypertensive medications in the 1970's and the emergence of several new classes of medications in the 1980's resulted in a need to develop guidelines about the optimal treatment for an individual patient.

Cooperative Studies conducted a trial comparing representatives of six different classes of antihypertensive drugs. Striking differences were found in the beneficial effects of the drugs in different age and race groups. The results of the study provide physicians with valuable guidelines on which drugs to use first in patients according to the patient's characteristics. The results of this study allow physicians to

tailor drug therapy to optimize the patients blood pressure control while minimizing unwanted side effects.

■ **Long term effects of coronary artery bypass surgery were defined in the most extensive study on record**

VA studies were the **first in the world** to evaluate whether giving coronary bypass surgery right away was better than giving heart drugs to patients who have chest pain because of blockages in their arteries. Bypass surgery uses veins from the legs or arteries near the heart to go around the blockages and improve the heart's blood supply.

Heart drugs worked for most veterans to stop chest pain. Only a small number of people with many blocked arteries did better with surgery. These results had a major impact on establishing who should get bypass surgery in this country. Although surgery does help a small number of patients who have very bad hearts, most don't need surgery right away and can be given drugs to stop their chest pain. This landmark study generated over 50 journal articles, including several in the *New England Journal of Medicine*. These study results reduced the costs and risks involved with this major surgical procedure and determined the standard of practice in North America and Europe.

■ **Low dose aspirin can prolong the lives of patients who have had coronary artery bypass surgery**

This landmark study showed that aspirin reduces deaths and heart attacks by 50% in

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patients with unstable chest pain. The results of this study were included in an international effort to evaluate the effects of this therapy in treating patients with heart attacks and stroke, and in preventing death.

The combined analysis of this information was published in the *British Medical Journal* in 1994. This provided unquestionable evidence of the remarkable health benefits of aspirin. This low cost medicine is now widely and routinely prescribed for patients with heart disease.

■ **Angioplasty prevents chest pain in patients with mild heart disease and allows them to exercise more**

Patients with blocked heart arteries can have chest pain, heart attacks or even die. This VA study was the first study to evaluate a method of opening blocked arteries called angioplasty. Angioplasty is done by inserting a balloon into the blocked artery and then inflating it. The study focused on people with one blocked artery.

Patients given angioplasty had less pain and were able to exercise for longer periods of time than the people given only heart medications. The people treated with angioplasty, however, did not live any longer than the people given the heart medications.

The results were published in the *New England Journal of Medicine* in 1992, and received national press coverage. A follow-up cost analysis will provide patients, physicians and policy makers with information on the benefit of this procedure and the related costs.

■ **Patients with heart failure can be saved with optimal drug therapy**

Congestive heart failure is a medical condition in which the heart is weakened and cannot pump blood properly to the rest of the body. Two studies in veterans with heart failure provided definitive evidence that heart drugs can improve the heart's ability to pump blood and keep patients from dying from this condition.

The first large study found out that drugs called vasodilators helped the heart and prevented people from dying. The second study found that drugs called ACE inhibitors were even better in preventing deaths. These results were published in the *New England Journal of Medicine* in 1991. An entire issue of the heart journal *Circulation* was devoted to additional important results in 1993.

The results of these VA studies revolutionized the treatment of heart failure because they saved patients' lives and improved their quality of life. This information is being used to obtain a license from the Food and Drug Administration to make a combination of these drugs available for treating patients with heart failure.

■ **Determined the optimal device for patients who require heart valve replacement surgery**

Replacement of patients' natural heart valves with artificial valves has been an extremely successful operation since the 1960's, extending the lives of patients by decades and greatly improving their functional abilities. This long term study compared two types of heart valve

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replacements, a completely mechanical valve and an animal valve.

The study found that veterans with the mechanical valve had more bleeding, but that this valve lasts longer than the animal valve. The 11 year follow-up paper was published in the *New England Journal of Medicine* in 1993. These results provide critical information for patients and physicians that permits them to choose the replacement heart valve that best suits their medical condition.

This study is also producing information that will determine when it is best to operate on patients with this disease. The long term results will provide definitive information to match the best valve device with the best timing for replacement.

Infectious Disease

■ **Progression of HIV infection to full blown AIDS can be delayed with the drug AZT**

This study tested a new drug called AZT to prevent people with HIV infection from getting AIDS symptoms. HIV is an infection caused by a virus that affects the body's immunity, and over time will result in AIDS, a condition nearly always fatal. Half of the people in the study were given AZT right away and the other half got AZT later, after the infection worsened.

The study showed that giving the drug AZT right away to veterans with HIV disease kept people from getting symptoms of AIDS, but they did not live any longer. The study also showed that giving HIV patients AZT right

away cost more than giving it later and that there were some harmful side effects of the drug. These findings were published in the *New England Journal of Medicine* in 1992 and in the *British Medical Journal* in 1993. The results of this study received world-wide press coverage and have made a substantial impact on how people with HIV infection are treated.

■ **Discovered which blood tests best determine if treatment for AIDS is effective**

This study determined which specialized blood tests were related to more serious AIDS disease and death. There are cells in the blood that are very important in fighting the HIV virus. When the HIV virus attacks and kills enough of these cells, a person with HIV becomes sicker. This was the first study to relate this information and either worsening disease or death.

The results from this study are very important for testing new drugs to treat HIV because studies can be done much quicker by studying the cell changes instead of studying sicker patients. This study showed that blood tests can be used to determine whether a drug is preventing patients from becoming sicker without actually waiting for it to happen. This allows for the faster development of new AIDS drugs that are so critically needed for treating this disease. The paper was published in the *New England Journal of Medicine* in 1996. This information has also been presented at both national and international AIDS meetings and received with great enthusiasm.

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■ Patients with septic shock should not be given steroid therapy

Patients in intensive care units with severe (life threatening) septic shock infections have a high risk of dying. This VA study was only one of two studies done in the U.S. to see if treating patients with powerful drugs called steroids would improve their chances of surviving in spite of the life threatening infection.

The study results were published in the *New England Journal of Medicine* and subsequent papers were published in *Critical Care Medicine* (1990) and *Archives of Internal Medicine* (1991). Before results were available from this VA Cooperative Study, the best medical practice was to administer steroid medications to these critically ill patients. The study showed clearly that giving steroids did not improve patient survival from their infections. This study dramatically changed the practice of medicine. Steroids are no longer used to treat life-threatening infections in the U.S.

Cancer

■ Patients treated with chemotherapy and radiation rather than surgery for advanced throat cancer can keep their voice boxes

Standard treatment for advanced cancer of the larynx (voicebox) is surgical removal, in which case the patient loses his/her natural voice. This Cooperative Study compared a new non-surgical treatment to surgery for this disease. The non-surgical treatment consisted of chemotherapy to reduce the tumor combined with radiation therapy to completely eliminate the tumor.

Study results (published in the *New England Journal of Medicine* in 1991) showed that for 2/3 of the patients, the voicebox could be saved without adversely affecting the patient's chances for survival. This treatment not only improves the patient's survival with this cancer but also gives them the option of keeping their own voice. This has a tremendous impact on the quality of life of patients afflicted with this cancer.

Prostate

■ Discovered which medical treatment for enlarged prostate works best

Enlarged prostate, known as benign prostatic hyperplasia (BPH) is a common problem in older men. Approximately 50% of men may have BPH by the age of 60 years, and the frequency approaches 90% in octogenarians. We estimate that a 50-year-old man has a 20-25% chance of undergoing a prostatectomy operation for BPH during his lifetime. This operation represents the second most commonly performed operation under Medicare. Approximately 400,000 prostatectomies are performed annually in the U.S., representing a substantial economic burden for health care delivery in our country.

The primary objective of this VA Cooperative Study was to critically evaluate medications for the treatment of symptomatic benign prostatic hyperplasia (BPH). The results of this study were reported in the August 22, 1996 issue of the *New England Journal of Medicine*.

The drug terazosin (marketed as Hytrin) effectively relieved symptoms and signs of BPH. Finasteride (marketed as Proscar) was not found to be effective. Combining the two

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drugs was no more effective than terazosin alone.

In this landmark study, the VA Cooperative Studies Program defined the ultimate medical treatment for prostatic disease. There is now a proven effective medical therapy for BPH and men no longer have to undergo surgery with all of its inherent risks and side effects.

■ **For patients with moderately symptomatic benign prostate enlargement, watchful waiting can be an acceptable alternative to surgery**

In an earlier study, Cooperative Studies examined surgery for BPH. Although the lifetime risk of surgical treatment for benign prostatic hyperplasia (BPH) is 30%, transurethral resection of the prostate (TURP), the most common surgical intervention, had never been evaluated in a controlled trial. Prior to this study, considerable disagreement existed whether the benefits of surgery outweigh the risks for men with moderately symptomatic BPH, and whether delaying surgery as long as possible was a reasonable alternative.

The purposes of the study were to compare the effectiveness of TURP to watchful waiting in moderately symptomatic men above age 55, and to compare the cost-effectiveness of the two treatment regimens. A wide range of outcomes were evaluated including symptom reduction, quality of life, and cost of care.

The results were published in the *New England Journal of Medicine* in 1995. The results showed that TURP is highly effective in relieving the symptoms and signs of bladder outlet obstruction caused by BPH. Complications were infrequent, and surgery did not cause impotence or urinary incontinence.

However, for men who are able to cope with their symptoms and prefer not to have surgery, watchful waiting is an effective treatment strategy.

Diabetes

■ **An implanted insulin pump is preferred by diabetic patients and controls blood sugar better than multiple daily insulin injections**

This study tested a hockey puck-sized insulin pump, implanted in the abdomen and controlled by a computer to deliver insulin into the blood stream. In the first large scale study of the implanted insulin pump, 121 patients from 7 VA medical centers were treated with either the insulin pump or daily multiple injections of insulin.

Study results were published in the *Journal of the American Medical Association* in 1996 and showed that with the pump patients had:

- better blood sugar levels
- reduced hypoglycemia (low blood sugar)
- better weight control
- significantly better quality of life

This study was initiated from interest of members of the House of Representatives Veterans Affairs Committee. Congress asked the VA Cooperative Studies Program to conduct a large-scale, multi-center trial evaluating the safety and efficacy of the implantable insulin pump in patients with Type II, adult-onset diabetes. Accordingly, Cooperative Studies Program completed this landmark study, giving new hope for ending diabetics' need for daily injections.

Hearing

■ Discovered the most effective cochlear implant to help totally deaf patients hear and understand speech

Cochlear implants are electronic devices implanted into patients who are totally deaf for the purposes of enabling them to hear again. Hearing ability in patients after implantation varies; some patients can hear only environmental sounds, while others can actually hear speech and talk on the telephone. Several different types of cochlear implant devices exist, and it is important to scientifically evaluate their effectiveness.

The Cooperative Studies Program conducted the first large scale randomized trial comparing the effectiveness of advanced cochlear implant devices. The multi-channel implant devices were found to be superior to the single-channel device. One particular multi-channel device was found to be most effective, when used in conjunction with a new speech processor developed for that device. The study should demonstrate to physicians and patients the potential value of this exciting and innovative technology.

Substance Abuse

■ Determined the best treatment for alcoholic patients with bleeding in the esophagus

Alcoholic veterans who are very sick commonly bleed in the esophagus. The usual therapy for these patients was sclerotherapy (injecting a solution into the vein via an endoscope to stop

the bleeding). The results showed that patients who had bled before were helped by this treatment but that those who had not bled before were not helped.

The information on patients who had not bled before was published in the *New England Journal of Medicine* in 1991. The results on prior bleeders was published in *Hepatology* in 1994. This study changed the practice of medicine by defining the patient groups which most benefit this treatment. The treatment is now limited to patients who have previous bleeding.

Epilepsy

■ Determined an effective alternative drug treatment for epilepsy

Epilepsy is one of the most common chronic, disabling medical conditions. We estimate that approximately two million people in the United States are affected and that at least 50,000 veterans are being treated in VA medical centers for seizure disorders.

Cooperative Studies conducted the first large scale, randomized comparison of the new seizure drug, divalproex sodium, with a standard drug. The results of this study, published in the September 10, 1992 issue of the *New England Journal of Medicine*, demonstrated that a new anti-seizure drug, divalproex sodium, was equally effective as a treatment for grand mal seizures as a standard drug, carbamazepine. Thus, physicians now have another single drug treatment option for the treatment of grand mal seizures. This is important since as many as 10% of patients cannot tolerate the standard drugs.

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The study also showed that the standard drug was more effective than divalproex sodium for petit mal seizures, indicating that this new drug should not be used as a front-line drug therapy for those types of seizures. The results of this study also demonstrated the need for better tolerated, more effective treatments for epilepsy.

As with several other conditions, results from this study more clearly defined which patient groups benefit most from different drugs. These results refine and improve medical practice and optimize treatments to match the patient's unique conditions and needs.

Gastrointestinal

■ Surgery is an effective alternative to long term medical therapy for severe heartburn

Gastroesophageal reflux or severe heartburn is one of the most prevalent clinical conditions affecting the gastrointestinal tract. Heartburn is the primary symptom of gastroesophageal reflux disease, and about 40 percent of adult Americans suffer from heartburn at least once a month. The impact on the Department of Veterans Affairs may be even greater than that on the general population, since factors which predispose to reflux (e.g., cigarette smoking, alcohol consumption, and use of certain medications) are common among veteran patients. Among patients who seek medical attention for this disease, 10 to 20 percent have serious complications.

The primary goal of the study was to compare the efficacy of two different strategies of

medical therapy with surgical therapy for gastroesophageal reflux disease. The two medical strategies were "intensive" (patients took medication daily) and "symptomatic" (patients took medicine only when symptoms arose). The surgical procedure involved wrapping a portion of the stomach around the end of the esophagus to prevent the reflux of stomach acids into the esophagus. This was the first long-term comparison of surgery versus medical treatment.

This study, published in the March 19, 1992 issue of the *New England Journal of Medicine*, concluded that in men with complicated gastroesophageal reflux disease, surgery is significantly more effective than conventional medical therapy. Medical therapy is also effective, but to a significantly lesser degree.

An economic analysis accompanied this clinical trial. It determined that besides being clinically advantageous, surgery was less expensive than the best medical strategy for men up to age 48 years. However, by age 69 years, initial medical therapy is clinically superior and less expensive than surgery for men.

These results suggest that antireflux surgery performed by a skilled surgeon is a valid alternative to protracted medical therapy, particularly for patients up to 48 years of age. The results of this study offer hope to those patients with complicated gastroesophageal reflux who need relief and do not want long-term, costly medical therapy.

This VA Cooperative Study again definitively established the benefits of radically different treatments (medical and surgical), defined which patient groups would do better with the several treatment options, and above all, presented our patients with choices among several beneficial treatments.

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Surgery

■ **Most malnourished surgical patients can be treated without expensive intravenous nutrition**

The number of nutritionally-based complications in surgical patients is extremely high. If an effective modality existed to avoid these complications, it would be extremely helpful to our patients.

Total parenteral nutrition (TPN) is a system in which all fluids, electrolytes, micronutrients and macronutrients are provided to the patient by the intravenous route. Initially, TPN was reserved for those patients in whom death from starvation was imminent, but was expanded to include malnourished surgical patients also. However, the effectiveness of this expensive treatment on improving patient outcomes of surgery was not established at the time of this study. This VA Cooperative trial, the first large scale trial of TPN, assessed the efficacy of seven to ten days of preoperative TPN in reducing complications and death in malnourished patients undergoing major operations.

The study, published in the August 22, 1991 issue of the *New England Journal of Medicine*, found that only severely malnourished patients benefitted from TPN. Mildly malnourished patients had no demonstrable benefit from preoperative TPN, and actually experienced an increased rate of infections.

An economic analysis of the study results concluded that preoperative TPN did not reduce costs in any subgroup of patients. Preoperative TPN, a very costly therapy,

should be limited to severely malnourished patients.

The study result defined a select patient group who would benefit from the treatment. The resulting economic analysis demonstrated that future use should be limited to only severely malnourished patients since the treatment was not only costly, but somewhat harmful to less ill veterans.

Primary Care

■ **Rapid access to high quality primary care for patients discharged from the hospital with severe chronic illnesses greatly improves patient satisfaction with care but may actually lead to an increase in future hospital readmissions**

Hospital readmissions are prevalent, and account for a major portion of total health care expenditures. They are usually related to problems that arose during the original admission and may frequently be preventable. Readmissions may account for half of all hospitalizations and 60% of hospital costs. In addition to their expense, readmissions may be a marker of poor quality care. It is therefore important to implement interventions that may avert readmissions. The purpose of this study was to determine whether an intervention of rapid access to high quality primary care for patients discharged from the hospital would reduce hospital readmissions.

In a multi-center randomized, controlled trial at nine VA Medical Centers, 1,396 veterans with diabetes, chronic obstructive pulmonary

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disease, or congestive heart failure were randomly assigned to receive either usual care or an intensive primary care intervention. The intervention involved close follow-up by a nurse and a primary care physician, beginning before discharge and continuing for the next six months.

On admission to the study, the patients were severely ill. Half of those with congestive heart failure had disease in the NYHA class III or IV; 30 percent of those with diabetes had end-organ damage; and a quarter of those with chronic obstructive pulmonary disease required home oxygen treatment or oral corticosteroids.

The patients had extremely poor quality-of-life scores.

Although they received more intensive primary care than the controls, the patients in the intervention group had significantly higher rates of readmission and more days of rehospitalization. The patients in the intervention group were more satisfied with their care, but there was no difference between the study groups in quality-of-life scores, which remained very low. The results of the study were published in *New England Journal of Medicine* in 1996.

Current research is being conducted by the Cooperative Studies Program in the areas described below.

Heart

❑ **Discover if taking beta-blocker drugs can prolong and improve the lives of millions of patients with advanced heart failure**

“Beta-Blocker Evaluation of Survival Trial (BEST)” will determine if beta-adrenergic drugs can lengthen the lives of patients with heart failure. If the therapy proves successful, it will also improve the health and quality of life of patients suffering from this common ailment. Also, the VA may avoid hospitalizing many patients with heart failure and save millions of dollars in costs. In 1990, heart failure accounted for over 22,000 VA hospital discharges, at a cost of nearly \$100 million.

The National Heart Lung and Blood Institute has recognized the great national importance of this study by joining the VA in funding this research. Because of special efforts to include women, this study will have special impact on women with heart failure and help close that knowledge gap.

❑ **Discover the genetic basis of heart failure and the genetic factors that influence response to treatment**

The BEST DNA substudy will establish a large bank of DNA samples from patients with heart failure. This will make it possible to study the genes that govern the way the heart responds to stress, and ultimately fails under the strain. Understanding the genetic basis of the vulnerability to heart failure is the key to developing

new therapies targeted directly at the responsible mechanisms.

❑ **Point the way to new therapies for heart failure by relating changes in the heart’s shape, the activation of genes, and the blood’s hormonal signals**

The development of new therapies for heart failure will require basic scientific understanding of the effects of treatment on the shape of the heart muscle and the activation of genes that send chemical signals through the blood. Recent progress in heart failure treatment has come from exploiting such understanding to relieve the burden on the failing heart. Beta-blocker drugs are a promising new therapy that offers the exciting chance to help the heart to actually repair itself. These studies will determine if the treatment actually works by returning the heart muscle to a more functional shape, and controlling the harmful overstimulation of the heart by the hormones in the blood.

❑ **Discover if computer analysis of the heart’s electrical signals can help avoid unnecessary surgery for patients with symptoms of heart attack**

The diagnosis and subsequent treatment of suspected heart attack involves a series of life-and-death decisions to employ more and more invasive, risky, and expensive diagnostic procedures.

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This study (“Quantitative Exercise Testing and Angiography - QUEXTA”) is developing a method to obtain the greatest possible information from the electrical signals produced by the heart during an exercise test. To help avoid unnecessary surgical procedures, save money, and improve care in thousands of veterans, it will determine the best way to diagnose patients without more invasive coronary artery catheterization (taking pictures of the blockage of the heart’s blood supply by inserting a camera through a tube placed in the patient’s veins).

The impact of the results will extend beyond the VA system, as suspected heart attacks are one of the most common and costly reasons for seeking emergency care in the United States.

❑ **Learn if it is safe to postpone risks and costs associated with invasive diagnostic tests for patients with heart attack**

“VA Non-Q Wave Infarction Strategies in Hospital (VANQWISH)” will determine if a less invasive and expensive diagnostic strategy (exercise stress testing) can be substituted for a more invasive and expensive strategy (immediate angiography by cardiac catheterization) in about half of all heart attack victims. This will settle a major controversy about the management of patients who have a particular type of heart attack, with enormous consequences to the cost and risk of care.

Every year, about 750,000 persons in the US have the kind of heart attack that we are studying, making this study one of the most important initiatives in evidence-based medicine, with a potential impact measured in thousands of patients’ lives and billions of dollars.

❑ **Determine the best drug for improving cholesterol levels in patients with heart disease**

Coronary heart disease affects over 7 million people in this country and is a major concern for our veterans. A study in 2,500 veterans will determine the best treatment for patients with low values for “good” cholesterol (HDL) and high levels for triglycerides. Patients with these levels of blood lipids (fats) are at high risk for heart attack even though they have relatively normal overall cholesterol.

The study will follow patients for 5 years to see if they suffer from heart attacks or die. The occurrence of stroke is also being studied. The results of the study are expected to have important cost implications, improve the quality of care of veterans, and identify ways to slow progression of coronary heart disease.

❑ **Determine if aspirin and a blood thinner (warfarin) prevent deaths in patients with heart disease**

About one and half million people have a heart attack in this country every year and 500,000 of them die. Aspirin is a common drug used to treat people with heart attacks. This VA study is evaluating whether giving people a blood thinner (warfarin) in addition to aspirin will decrease the chance of dying and potentially save about 20,000 lives a year. Eight thousand people will be followed for six years to determine whether this combination of drugs works better than aspirin alone.

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❑ Evaluate the role of digitalis in the modern treatment of heart failure

Congestive heart failure (CHF) continues to be a major public health problem. For over 200 years, digitalis has been used for the treatment of CHF. Digitalis is the second most commonly prescribed drug in the United States and in 1986 accounted for over 12 million prescriptions. Approximately 70% of CHF patients regularly use digoxin, and despite the newer treatments now available for CHF, there has been little decline in the drug's use over the past five years. However, despite the continued widespread use of digoxin, there is controversy regarding the appropriateness of its role and value in treating CHF patients.

The primary objective of this trial is to determine whether digitalis prevents death in patients with congestive heart failure. A secondary objective is to determine whether digitalis treatment prevents worsening of heart failure and reduces the need for rehospitalization.

The Cooperative Studies Program is collaborating with the National Heart Lung and Blood Institute to conduct this study, which is the first large scale randomized clinical trial of digitalis. With over 300 participating medical centers in the United States and Canada, it is the largest international congestive heart failure clinical trial.

The results of this study should answer many outstanding questions regarding the use of this 200-year-old drug. It is scheduled for publication in the February 20, 1997 issue of the *New England Journal of Medicine*.

❑ Test the idea that excess iron in blood causes hardening of the arteries, opening the possibility that drawing blood might prevent thousands of deaths from heart disease and avoid billions of dollars of health costs

“Ferritin Adjustment Study (FeAST)” will determine if it is feasible to test a remarkable new hypothesis about the way that iron in the blood acts to promote chemical reactions leading to “hardening of the arteries”. If this study is successful, and if the larger study that would follow comes to a positive conclusion, the results would be a revolution in the prevention of circulatory diseases and in human nutrition. Although success is far from certain, the potential consequences would be dramatic.

Iron has been regarded as a nutrient, needing supplementation in the elderly. The premise of this study, however, is that most adult men have too much iron in storage, and that it acts as part of the pathologic process converting cholesterol into arterial and venous plaques that block the flow of blood. The removal of the excess iron by regular blood donation, less than the amounts typically given in “blood drives”, is simple and safe, but the proposed benefit is controversial. This study will set the stage for a definitive test.

Cooperative Studies Program

Current Studies

❑ **Determine what medication works best for keeping the heart beat regular in patients with an irregular heart beat**

Atrial fibrillation is now the commonest cardiac rhythm disturbance (irregular heart beat) encountered in clinical practice, leading to significant mortality and morbidity. It affects 1.0 to 1.5 million Americans and is responsible for more than 75,000 strokes a year. Atrial fibrillation affects more than 3.5% of people 70 years or older. It is an established risk factor for congestive heart failure and stroke, impairs the ability to exercise, and may produce disabling palpitations and other associated symptoms. Atrial fibrillation is the basis for hospitalization twice as often as all other arrhythmias combined, and the average hospital stay is five days.

The best approach to standardized therapy for atrial fibrillation remains uncertain. The main goals of treatment are to relieve symptoms (usually due to a fast heart rate), prevent the development of stroke and improve the patient's functioning. Agents that are effective in maintaining normal heart rhythm are very important. This study will compare two of the most promising agents - amiodarone and sotalol - to determine how effective they are in maintaining normal heart rhythm in patients with atrial fibrillation.

❑ **Discover how to improve hospital care for patients undergoing heart surgery**

There has been a renewed emphasis on measuring and improving the quality of health care. Quality can be defined as "the degree to which

health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." There are 3 major elements to the study of quality of care: structure, process, and outcome.

— *Structure of care* refers to the overall context in which care to a group of patients is delivered, e.g., the facilities, equipment, services, and manpower available for care and the credentials and qualifications of the health professionals involved.

— *Process* may be defined as the set of procedures and skills with which health care technology of proven or accepted efficacy is delivered to individual patients.

— *Health outcome* is defined as the measurable end-results of an episode of health care.

This study will examine linkages between processes and structures of cardiac care and outcomes. About 5,000 veterans undergoing cardiac surgery at 14 VA medical centers will participate. Data are collected on patient risk factors and on the structures and processes of the operation. Patients are followed for 6 months to observe their outcomes of mortality, morbidity, quality of life, and patient satisfaction with care.

The study will identify which structures and processes of care are important to good and adverse patient outcomes. This is essential information for VA health care managers to improve patient care, and therefore, the health and quality of life of veterans.

Cancer

❑ **Determine if patients with early prostate cancer can forgo invasive surgery**

Cancer of the prostate is the second leading cause of cancer death in men. While there is no cure for cancers which have spread, a cure is possible if cancer is confined to the prostate. For these cases, the most frequent treatment approach is surgical removal of the prostate. However, there currently is no conclusive evidence that surgery can prevent the spread of cancer or extend life. The risks and complications of surgery are serious and real and affect quality of life.

The objective of this study is to determine conclusively one way or the other if radical prostatectomy or just symptomatic treatment gives the best result overall for men with early, localized prostate cancer.

This study, the “Prostate Cancer Intervention Versus Observation Trial (PIVOT)” will be the largest clinical trial of radical prostatectomy ever done. Based on past efforts by the National Cancer Institute in this area, this may be a study that can only be done in the VA.

The results of this study will impact all men. The risk of prostate cancer increases with age so that if a man lives long enough, he probably will develop the disease. In many cases such men will die “with” but not “of” prostate cancer. This study will provide the critical answer for each man whether surgery is worth the risk.

If this study finds surgery is not the better option, the savings to the health care system could amount to billions of dollars, and the risks of surgery can be justifiably and confidently avoided as men decide their treatment preferences.

❑ **Identify who is at high risk for colon cancer in order to target screening tests, saving lives and health care dollars**

Colon cancer is a leading cause of cancer death in the United States. Mortality remains high because most colorectal cancers are not detected until after they have spread, making surgical removal impossible.

Most colon cancers begin as colon polyps. Cancer can be prevented if polyps can be removed by colonoscopy. However, colonoscopy is very expensive. Since health care dollar resources do not exist to screen all patients, resources should be focused on those patients known to have the highest risk of polyps and eventually cancer.

This is the first large study to examine historical and environmental risk factors in order to identify the highest risk patients. Targeting high risk patients for effective, but costly, screening would be the most efficient and powerful program for prevention of colon cancer. Removal of polyps in all high risk patients will likely lead to an overall eradication of colon cancer in the general population.

Cooperative Studies Program

Current Studies

Post-Traumatic Stress Disorder

❑ **Develop improved tests in the diagnosis of Post-Traumatic Stress Disorder (PTSD)**

Post-traumatic stress disorder is a serious health problem for many veterans, including those who served in the Vietnam war. This study is developing psychological and physiological tests that can provide the means to accurately diagnose this condition and evaluate the progress of patients who are being treated.

❑ **Determine if a new form of group psychotherapy relieves the suffering of veterans afflicted by the effects of combat stress experienced in the Vietnam war**

The “Treatment of PTSD” study will determine the most appropriate kind of psychotherapy for Vietnam veterans with Post-Traumatic Stress Disorder. The study should have a profound impact on treatment of these patients. It will test the specific value of a therapy that includes “reliving” of combat trauma in a controlled group therapy setting.

If successful, this treatment will provide renewed hope for the veterans who continue to be devastated by the consequences of their combat experiences. It will also set a standard for treatment of other veterans and other patients with PTSD.

Mental Illness

❑ **Decide if Clozapine, a new drug for schizophrenia, is cost effective**

Schizophrenia is the most disabling, prolonged and costly of all mental illnesses. In 1990, schizophrenia patients occupied 36% of all psychiatric inpatient beds at VA medical centers. While short-term studies have shown the novel antipsychotic drug, Clozapine, to be superior to standard drugs in reducing symptoms for patients unresponsive to traditional treatment, its long-term efficacy is not known.

Clozapine shows great promise for reducing the need for hospitalization among the most treatment resistant patients and for improving their social adjustment. Unfortunately, the drug is expensive and causes a potentially fatal blood disorder (agranulocytosis) in 1% of patients. This potential side effect necessitates weekly blood testing of patients taking the drug and adds to its already high cost, a significant barrier to its widespread use.

The primary purposes of this study are: 1) to determine if health care savings (due primarily to reduced time in the hospital) will offset the additional cost of Clozapine treatments, and 2) to determine if there will be a significant long-term reduction in symptoms of schizophrenia in patients treated with Clozapine or a substantial improvement in social and vocational functioning.

The study is targeting a population of refractory schizophrenics with a recent history of frequent hospitalization. Four hundred twenty three patients were entered from 15 VA medical centers. The final manuscript from the study is currently under review at *New England Journal of Medicine*.

❑ **Discover if vitamin E reduces debilitating side-effects of the drugs used for patients with schizophrenia and improves their functioning and quality of life**

Schizophrenia is a severe and chronic mental disorder that afflicts about 1% of all Americans. It is most commonly treated with anti-psychotic medications. A severe side effect called “tardive dyskinesia” causes debilitating symptoms of involuntary, disfiguring facial movements. This terrible side effect interferes with the treatment of schizophrenia in many patients. Up to now, the condition has been untreatable, but the “Vitamin E Treatment of Tardive Dyskinesia” study will determine if a promising new treatment can help. This would be a long-awaited advance in the treatment of a catastrophic mental illness made even more unbearable by a disfiguring side effect of medication.

❑ **Identify the gene that causes schizophrenia, to develop more effective treatments for this devastating disease**

The importance of this investigation to schizophrenic patients and their families cannot be overemphasized. Schizophrenia is one of the most common diagnoses in the VA patient population. It is a devastating, debilitating disease, but current treatments are not always effective and have significant side-effects. Quality of life is substantially reduced in patients with schizophrenia.

Identification of a gene responsible for the development of schizophrenia will make it possible to develop more effective drugs with less severe side-effects. This study is one of the largest genetic linkage studies of schizophrenia in the world. It will be a landmark investigation and will make a major contribution to the understanding of the genetics of schizophrenia. Combining efforts with other researchers and collaborating with private industry will ensure that useful products will be developed from study results.

Substance Abuse

❑ **Collaborate with the National Institute on Drug Abuse to rapidly evaluate treatments for cocaine addiction, the most critical part of the nation’s drug abuse epidemic**

The health consequences, social disruptions, and economic costs of the epidemic of drug abuse, especially cocaine, need no elaboration. Mounting a medical response to this pressing national emergency, the National Institute on Drug Abuse (NIDA) has enlisted the help of the VA Cooperative Studies Program to provide the statistical infrastructure in support of rapid development of new treatments. Success will result in new treatment options and renewed hope of reversing the epidemic. The Cooperative Studies Program can provide the unique clinical and scientific resources to help NIDA to rapidly and accurately screen addiction treatment compounds.

Cooperative Studies Program

Current Studies

❑ **Evaluate drugs for treating heroin addiction which are less addictive than methadone and cannot be abused, to expand the ability of VA to treat these patients**

Substance abuse is a major health service issue for the VA. At many VA programs, up to one-half of the neuropsychiatric beds are occupied by patients with substance abuse. Treatment can be helpful, however, for opiate dependent patients (including patients addicted to heroin). Participation in opiate substitution therapy programs has led to substantial improvements in health and reductions in mortality for opiate dependent patients. However, current treatments (for example, methadone) are addictive too, and regulations limit their availability. Because of this, only the most severely affected patients receive therapy.

Two studies, both joint projects of the National Institute on Drug Abuse (NIDA) and the Cooperative Studies Program, propose to expand treatment options for opiate substitution therapy. The first is a study of buprenorphine, a drug that is less addictive than methadone, and may make it easier for patients to become totally free from all opiate drugs. The other is designed to test the safety and effectiveness of a combination of buprenorphine and naloxone, which should give the benefit of opiate substitution therapy without the risk of abuse. Data from these projects will be used to support New Drug Applications to the Food and Drug Administration (FDA).

If these treatments are proven safe and effective, treatment of opiate dependent patients could occur in an office based setting rather than a substance abuse clinic as is presently

done. Treatment could be available to many more patients than can now be served in methadone clinics. This could also remove the stigma of attending substance abuse clinics, which would encourage abusers to seek treatment sooner and to stay with treatment.

❑ **Discover if liver cirrhosis, a life threatening complication of alcoholism, can be prevented by taking a purified vitamin called lecithin**

Cirrhosis of the liver is a leading cause of death in the United States. Alcoholic cirrhosis is the most common form of the disease and is a significant problem among veterans. It ranks as the 7th leading cause of death in 25-44 year olds and 6th among the 45-64 year age group. There is currently no way to prevent or cure alcoholic cirrhosis. However, for the first time there is reason to believe, based on highly successful animal studies, that a preventive agent, lecithin, has been found. Lecithin is a vitamin, and the objective of this study is to determine if it can prevent cirrhosis in patients with alcoholic fibrosis.

This study, "Effect of Polyunsaturated Lecithin on Liver Fibrosis", is designed to prevent the development of cirrhosis in alcoholics with alcoholic fibrosis (a precursor to cirrhosis). If polyunsaturated lecithin is found to be effective, it will be the first treatment ever to provide an effective but simple approach to preventing cirrhosis. The impact on suffering and death, and the associated health care costs (estimated at \$15 billion in 1983), would be substantial.

Cooperative Studies Program

Current Studies

❑ **Identify the first effective therapy for treating alcoholic patients who have cirrhosis of the liver**

Currently there is no accepted therapy for alcoholic cirrhosis other than abstinence and proper nutrition. In the United States, cirrhosis of the liver is the ninth leading cause of death overall and chronic alcohol use causes up to 95% of liver cirrhosis. In addition to the heavy costs related to mortality, many millions of dollars are lost annually because of direct medical expenses and lost man-hours of work. Because the incidence of cirrhosis is two to three times higher in men than women, cirrhosis may be an even more common cause of death in middle-aged veterans.

Cirrhosis due to chronic alcoholism is an end-stage liver disease. Patients have only a 50/50 chance of living for 2-3 years after confirmed diagnosis. There currently is no proven effective treatment to prevent progression to death. Colchicine is known to have certain effects which suggest that it can be an effective treatment in extending survival time.

This study will be the definitive trial of colchicine for the treatment of alcoholic cirrhosis of the liver, a condition for which abstinence and nutrition are the only known treatments. Because alcoholic cirrhosis is a disabling disease with high rates of associated morbidity and mortality, an effective treatment will significantly reduce the financial burden of the disease on the health care system.

❑ **Determine if medication helps alcoholic veterans stop drinking over the long term - to prevent many medical, social and economic consequences of problem drinking**

Alcoholism is a tenacious, chronic illness with devastating consequences for an individual's mental and physical health. In Fiscal Year 1994, VA spent \$507 million for substance abuse treatment, while overall costs to society at large were approximately \$85 billion. Thus, there is a compelling need to evaluate new treatments.

Naltrexone is the most promising new medication in the search for an effective treatment for alcoholism. Although it was approved for short-term use by the Food and Drug Administration, we need to extend our limited knowledge about the long term use of this treatment.

This major, ongoing multi-hospital study will evaluate the efficacy (Does it work?), cost-effectiveness (How much does it cost?), and durability (Need for short-term or long-term treatment?) of naltrexone in the treatment of alcohol-dependent veterans. The results of this study could have an enormous impact on the health of alcohol-dependent veterans and others, as well as provide a significant reduction in overall health care costs.

Cooperative Studies Program

Current Studies

Health Systems/Quality Issues

- ❑ **Show if hospital based home care is a less expensive alternative for very ill patients who have had many hospitalizations**

The primary objective of the study, “A Multi-site Randomized Trial of Team-Managed Hospital Based Home Care” is to determine whether total health care costs for severely disabled and terminally ill veterans is less for the team-managed hospital based home care model compared to customary care.

A previous study conducted at Hines VA Hospital found significant increases in patient and caregiver satisfaction with care with this model. This increase in satisfaction was accompanied by an overall net cost savings of 13%. This multi-site study will try to determine whether greater satisfaction and increased cost savings can be generalized to all VA programs nationwide.

If this study finds that team managed hospital based home care is more cost-effective than traditional forms of care, and that patient outcomes and satisfaction are enhanced, this is a win-win situation for VA and for veterans - and VA would rely more heavily on this home based service in the future.

- ❑ **Determine if providing computerized reminders on standards of care to clinic doctors improves the quality of care to veterans**

The primary objective of this study is to determine if computer-generated reminders can increase health care practitioners' adherence to standards of ambulatory care. Results from baseline data have shown that, without reminders, practitioners adhere to certain accepted standards of care about 50% of the time. We hypothesize that reminders will increase adherence by about 20%.

Improvements in adherence to standards of care will have a direct and important impact on the quality of health care provided within VA ambulatory care clinics. If the computer reminders are successful in increasing adherence, broad implementation of the system should result in improved quality of care.

- ❑ **Show if it is possible to lower the dose of an expensive drug (erythropoietin) given to all kidney dialysis patients, simply by changing the way the medication is administered**

Over 90% of dialysis patients experience a lowering of red blood cell count and anemia, the predominant complication in these patients. A new drug, recombinant human erythropoietin, approved for use in 1989, effectively combats this anemia. Its cost is significant, totaling \$5,000-\$10,000 per patient per year.

A few small studies have suggested that the dosage of the drug could be reduced by 30-50% by injecting it under the skin (subcutane-

ously), rather than giving it intravenously. The lowered dose seems to achieve the same beneficial effects for the patient. However, patient discomfort and inconvenience may be increased. Although most medical centers initially gave the drug intravenously, many are switching methods without the benefit of certain knowledge about the effects of the subcutaneous route.

This large-scale, multi-center trial is comparing the methods of administration of erythropoietin. If the subcutaneous route is found to lower the dose of the drug without sacrificing therapeutic effect, the study could reduce expenditures for erythropoietin by as much as \$3.5 million in VA. Potential savings for Medicare are \$110 million.

❑ **Substituting telephone appointments for clinic visits may lower cost of care without diminishing quality of care**

This study will compare standard scheduling of follow up visits to a modified schedule including telephone appointments. With telephone care, the interval between regularly scheduled clinic visits will be doubled, but patients will receive three scheduled telephone appointments with their health care provider during this time.

We expect that telephone care will be less expensive than frequent visits, and patients' health will be just as good as with usual care. In fact, the more frequent contact by telephone may even increase patient satisfaction. If a significant number of visits can be replaced by telephone contacts, VA will be able to deploy scarce health care resources more efficiently.

Aging

❑ **Discover whether specialized care for frail elderly patients saves lives and improves quality of life**

“Geriatric Evaluation and Management Units and Geriatric Follow-up” (GEM) will determine if specialized inpatient and outpatient units are the best way for the VA to care for the most rapidly growing group of veterans, the elderly. The proportion of veterans over 65 years of age will increase from 26% in 1990 to 46% in 2020, and the VA must be prepared to serve their needs, following evidence-based policy.

The impact of this study will extend far beyond the VA, as millions of older Americans come under managed care. No other study, completed or planned, can provide the conclusive and incontrovertible evidence needed to guide policy in this area, which is so central to the current reorganization of American medicine. Patient outcomes (mortality, quality of life, functional status) and health systems outcomes (use of services, cost, process of care) will be evaluated in this study.

Surgery

❑ **Select the best method for surgical anesthesia in major abdominal operations**

Major abdominal surgery, such as operations involving the aorta, colon, stomach, and biliary system, can be performed under general or regional (epidural) anesthesia. This study will determine which of these ways of administer-

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ing anesthesia results in the lowest rates of death and major complications. Special focus will be given to patients who are at higher risk for poor surgical outcomes.

The results of this study will provide the evidence doctors and patients need to make an informed selection of the best method of anesthesia.

Vascular

❑ **Determine the best material for grafts for treating blocked vessels in the leg, helping veterans avoid amputation**

Many veterans suffer from blockages of leg arteries, a painful condition that can cause the death of tissue and lead to amputation. This study will determine if Dacron, Teflon, umbilical vein, or the patient's own vein is a more effective material for surgical grafts that bypass these blockages.

The results of this study will help surgeons select the best possible bypass graft to use when repairing a patient's blood vessels. This will lead to more successful operations, and fewer patients will have to lose their legs.

❑ **Determine the best timing for surgical repair of abdominal aneurysms, by conducting a study that has provided ultrasound screening to over 100,000 veterans**

The Cooperative Studies Program is conducting 2 studies on patients with abdominal aortic aneurysms (AAA). The first addresses the

question of immediate surgery vs. selective surgery, where the aneurysm is not repaired until it grows significantly or becomes symptomatic. If postponing surgery is safe, many unnecessary operations, with their attendant cost and complications, will be avoided. An ultrasound screening program associated with this study has already screened over 100,000 veterans.

A companion study is designed to follow the natural history of large AAA. This study will track patients who have large aneurysms but for whom surgical repair is not planned (due to contraindications or patient refusal). This study should determine the livelihood of aneurysm ruptures based on size, and will provide important decision making information for managing patients with large AAA.

❑ **Show whether blood thinning drugs help patients with serious circulation problems avoid leg amputation**

The World War II veteran is approaching 70 years of age. This age group is at a high risk for developing peripheral vascular disease, particularly involving the legs. As the veteran population ages, we expect that an ever larger group of veterans will have arterial insufficiency of their lower legs and will be at risk for amputation. Vascular reconstruction can be performed, but the grafts have a high failure rate.

This study will evaluate whether a blood thinning drug, warfarin, improves the patency of bypass grafts that are currently at high risk of failure. It represents the first North American attempt to examine systematically the use of oral anticoagulation to improve the long term results of arterial revascularization proce-

dures. This study could provide a substantial improvement in the lives of patients undergoing these operations. It also has the potential to reduce costs since these patients would not need additional surgery to deal with the consequences of failed grafts.

Epilepsy

❑ **Identify which treatments are best to alleviate life-threatening prolonged epileptic seizures**

Status epilepticus is characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition. It is a neurologic emergency that must be stopped as quickly as possible to prevent death or severe, permanent brain damage. We estimate that between 60,000 and 250,000 cases of generalized convulsive status epilepticus occur in the United States each year, and many of these occurrences are in veterans.

This study will compare the relative efficacy and toxicity of four standard intravenous treatment regimens as the initial treatment for generalized status epilepticus. This is the largest study on the treatment of status epilepticus ever undertaken, and when published will be the definitive study on the preferred treatment of this life threatening condition.

❑ **Find which drugs work best to treat epileptic seizures in older patients without serious side effects**

New onset epilepsy in the elderly occurs in 45,000 - 50,000 elderly patients each year.

These patients are especially vulnerable to side effects from medications because of changes caused by the aging process. Also, these patients often have other medical conditions and take other drugs, so the likelihood of drug interactions is increased.

This study will test two newly approved drugs for the treatment of seizures, gabapentin and lamotrigine, for seizure control and tolerability in comparison to a standard drug, carbamazepine. It will focus on patients over 65 years of age. These new drugs reportedly have fewer side effects or known drug interactions.

If one of the drugs being studied is more effective in the elderly with fewer side effects, this will allow elderly seizure patients to live a better, more seizure-free, more toxicity-free life. Such a drug would also prevent some of the injuries caused by falls during seizures which can result in savings for the health care system. Potentially, hospitalizations and clinic visits related to drug toxicity and drug-drug interactions can be prevented as well.

Vision

❑ **Determine the best lens implant for veterans who have complications during cataract surgery, enabling them to better regain their vision**

With 1.2 million procedures annually, cataract extraction is the most common surgical procedure in the United States and the biggest single cost in Medicare. Vitreous loss, the most common complication of cataract surgery, occurs in about 1,000 VA patients each year. About a third of these patients will become

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surgical failures and experience visual handicap for the rest of their lives. Thus, determining the best procedure (anterior or posterior chamber lens implants) to use in the face of vitreous loss is an important clinical question.

This study will identify the most effective response to vitreous loss caused by cataract surgery. It is the only nationally funded, multicenter prospective clinical trial on cataract surgery to have ever taken place. Improved vision for patients who have complications during cataract surgery could save VA \$500,000 per year because patients will not need low-vision services.

Analysis of the data will provide unequaled data on outcomes of cataract surgery. In addition to data on the patients suffering vitreous loss, this study has collected data on over 15,000 cataract operations over the last five years. These data will be critical in making the difficult decisions necessary to provide the best care in the setting of national health care reform.

three types of hearing aids. It will help identify which hearing aids work well for different types of patients, and is the first ever large-scale study in this area. Patients in the study will wear each hearing aid for a three month period. The hearing aids will be manufactured to appear identical, so that the patient and audiologist providing hearing tests will not know which one the patient is using. The study will provide previously unavailable, unbiased, scientific results about hearing aids.

Hearing

❑ Undertake the first large-scale trial to determine the most effective hearing aids in patients with severe hearing loss

There are approximately 25 million Americans with hearing impairment. More than 14 million of them could benefit from a hearing aid. However, there is a scarcity of sound scientific data on the relative safety and efficacy of different types of hearing aid circuits.

This study, jointly funded by the VA and by the National Institute on Deafness and Other Communication Disorders, aims to compare

