Protocol

for

PEACE

PREVENTION OF EVENTS WITH ANGIOTENSIN CONVERTING ENZYME INHIBITION

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LIST OF ABBREVIATIONS

ACE..... Angiotensin Converting Enzyme

CABG..... Coronary Artery Bypass Surgery

CAMI ..... Canadian Assessment of Myocardial Infarction

CARE ..... Cholesterol and Recurrent Events Trial

CCS ..... Canadian Cardiovascular Society

CSCC..... Clinical and Statistical Coordinating Center

DSMB..... Data and Safety Monitoring Board

EF ..... Ejection Fraction

GISSI..... Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico

ICD-CM ..... International Classification of Diseases-Clinical Modification

IRB ..... Institutional Review Board

ISIS..... International Study of Infarct Survival

LV..... Left Ventricular

LVEF..... Left Ventricular Ejection Fraction

MI..... Myocardial Infarction

MMRC ..... Mortality and Morbidity Review Committee

NHLBI..... National Heart, Lung, and Blood Institute

PAI-1 ..... Plasminogen Activator Inhibitor-1

PASC..... Publications and Ancillary Studies Committee

PCC ..... Pharmacy Coordinating Center

PTCA..... Percutaneous Transluminal Coronary Angioplasty

PEACE ..... Prevention of Events with Angiotensin Converting Enzyme Inhibition

SAVE ..... Survival and Ventricular Enlargement Trial

SOLVD..... Studies of Left Ventricular Dysfunction

tPA..... Plasminogen Activator

TRACE..... TRAndolapril Cardiac Evaluation

TITLE

Prevention of **E**vents with **A**ngiotensin **C**onverting **E**nzyme Inhibition, **PEACE**

OBJECTIVE

To determine whether the addition of an angiotensin converting enzyme (ACE) inhibitor to standard therapy in patients with known coronary artery disease and preserved left ventricular function will reduce the risk of cardiovascular mortality, myocardial infarction, the occurrence of a coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty.

I. INTRODUCTION

The mortality and morbidity attributed to coronary artery disease remains the major public health problem in the United States. Decades of studies and the major implementations of risk factor modification (primary prevention) have clearly led to impressive reductions in the age-adjusted risk of coronary heart disease and death.[1] In many respects, these important lifestyle modifications have postponed the clinical manifestation of coronary heart disease to a more advanced age. However, coronary heart disease still remains the leading cause of death and morbidity in the United States.[2] In 1992 alone there were 650,000 hospital discharges coded for acute myocardial infarction. Concomitant major strides in the management of acute infarct patients with the prompt use of aspirin, beta blockers, and reperfusion regimens (thrombolytic therapies and/or primary percutaneous transluminal coronary angioplasty) have resulted in major reductions in in-hospital mortality, which translates into more survivors of myocardial infarction.[3]

This shift in demographics towards more survivors of myocardial infarction (MI) is apparent from the marked reductions in acute myocardial infarction mortality rates from 22% in the 1970s to 16% and 10% in the early and late 1980s, respectively. This progress can also be readily illustrated from the survival experience of recent major clinical trials of acute myocardial infarction. In ISIS-2 (Second International Study of Infarct Survival), conducted between 1985 and 1987, the 35-day mortality rate with conventional therapy was 13.2%, whereas the aspirin and thrombolytic group mortality rate was only 8.0%.[4] In the recently completed ISIS-IV trial (randomizations between 1990 and 1992), a comparable overall mortality rate for over 58,000 patients in 30 participating countries had further decreased to 7.1%.[5] This favorable trend is also reflected in the Italian experience in the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico) trials.[6,7] The 42-day mortality in GISSI-1 (n=11,806; 1984-85), GISSI-2 (n=12,490; 1988-89), and GISSI-3 (n=19,394; 1991-93) was 13.0 to 10.7, 9.3 to 8.3, and 7.2 to 6.0%, conventional to active therapy, respectively. Although these studies are considered to have broad inclusion criteria, the exclusion of hemodynamically unstable patients may yield a more optimistic view of overall mortality in acute myocardial infarction. The Canadian Assessment of Myocardial Infarction (CAMI) study group provided a more thorough determination of survival of all patients presenting to nine institutions from 1990 to 1992. Their combined 9.9% in-hospital mortality rate includes unstable patients as well as deaths in the emergency units.[8]

These major accomplishments in acute myocardial infarction therapy are coupled with population-based improvements in risk factor modification to produce larger segments of elderly individuals in the population with coronary artery disease, many as survivors of acute myocardial infarction. Patients who have already experienced a myocardial infarction continue to receive benefits of contemporary therapy with even greater attention directed towards modification of the known risk factors. This so called "secondary prevention" is generally viewed as of major public health importance since therapeutic modalities directed towards a higher risk population achieve a greater tangible benefit when assessed as the number of individuals that need to be treated in order to extend one life. Treatment of hypertension, hypercholesterolemia, cessation of smoking and other lifestyle modifications have been highly effective in secondary prevention. In addition to conventional risk factor modification, there is a strong though yet unproven rationale that ACE inhibitor therapy may provide a complementary means to produce an even further reduction in the risk of subsequent coronary heart disease events.

ACE inhibitor therapy is widely used in the treatment of asymptomatic patients with systemic hypertension. On the other end of the spectrum, ACE inhibitor therapy is of proven value and is considered a "cornerstone" of pharmacologic therapy for symptomatic congestive heart failure.[9] More recently, the clinical effectiveness of ACE inhibitors for secondary prevention in patients that experienced a myocardial infarction with residual left ventricular dysfunction has been demonstrated.[10,11] Results of SOLVD (Studies of Left Ventricular Dysfunction) (prevention) and SAVE (Survival and Ventricular Enlargement Trial) demonstrated that the long-term use of ACE inhibitor therapy in patients with left ventricular dysfunction without overt heart failure not only reduced mortality and the manifestations of congestive heart failure, but, importantly, resulted in a reduction in the incidence of myocardial infarction and other clinical manifestations of coronary artery disease. Both studies validated their initial rationale that chronic ACE inhibitor therapy would attenuate ventricular enlargement and a further deterioration in ventricular function.[12,13] Importantly, both studies independently demonstrated a previously unknown finding, that the long-term administration of ACE inhibitor therapy also reduced mortality and morbidity from manifestations of coronary artery disease.

The similarities between these two large studies in both the magnitude of the reduction in the risk of myocardial infarction with ACE inhibitor therapy (SAVE: 24%; 95% confidence interval, 5 to 40% and SOLVD: 23%; 95% confidence interval, 11 to 34%) as well as the comparability of the chronicity of therapy required to observe these benefits, strongly suggest a consistent action of ACE inhibitor therapy in reducing myocardial infarction in these patients with depressed left ventricular function (see Figures 1A and 1B on page 4). In the SOLVD studies, ACE inhibitor assigned patients were also less likely to be hospitalized for unstable angina[11], whereas in the SAVE study, ACE inhibitor assignment was associated with reduced need for revascularization procedures (coronary artery bypass surgery and percutaneous transluminal coronary angioplasty).[14] In both studies this favorable effect of ACE inhibitor therapy on coronary artery associated endpoints was only manifest after long-term administration. These observations are consistent with comparatively short-term, randomized trials of ACE inhibitors (such as MARCATOR) to prevent restenosis following coronary angioplasty, and underscore the importance of long-term follow up for clinical outcomes. During six-month follow up, ACE inhibitors had no effect on restenosis, death, nonfatal myocardial infarction or recurrent angina.[15, 16]

Although these studies were limited to patients with left ventricular (LV) dysfunction, findings from both SAVE and SOLVD support the hypothesis that these important benefits will be observed in the even broader population of patients with coronary artery disease and more preserved left ventricular function. As anticipated, in both studies the lower the baseline ejection fraction (EF), the greater the risk of experiencing cardiovascular death or complications of congestive heart failure. In contrast, this baseline left ventricular ejection fraction (LVEF) was not a significant predictor of the risk of experiencing a subsequent myocardial infarction. Moreover, the efficacy of ACE inhibitor therapy in reducing the risk of myocardial infarction was not dependent on the baseline left ventricular ejection fraction. This lack of a significant or even strong trend for an interaction between the level of LV dysfunction and reduction in risk of myocardial infarction suggests that ACE inhibitor therapy will also be of benefit to the much larger group of patients with coronary artery disease and preserved LV function.

Although ACE inhibitor therapy has been widely studied in other patient populations (hypertension, symptomatic congestive heart failure), the observation of a reduction in coronary artery disease related events had not previously been demonstrated. The SAVE and SOLVD trials were the first studies that followed large numbers of patients on ACE inhibitor therapy for more than three years. Since reduction of coronary artery disease events with ACE inhibitor therapy did not occur until after one year of therapy, it could be anticipated that trials with shorter periods of observation would be unable to demonstrate this important action of ACE inhibitor therapy.

Since the SOLVD and SAVE studies demonstrated a reduction in coronary heart disease related events, there has been a great deal of speculation of the possible mechanism for these clinical benefits. Although the chronicity of therapy required for this action would appear to exclude the acute hemodynamic effect of ACE inhibitor therapy, the long-term hypotensive actions could have a favorable influence on the subsequent development of myocardial infarctions. The SOLVD investigators directly addressed this and reported that the magnitude of blood pressure lowering was insufficient in and of itself to explain the observed magnitude of the reduction in myocardial infarctions.[11] Similarly, in SAVE, blood pressure differences between therapy arms of only 3 mmHg in these normotensive or appropriately treated hypertensives would not be anticipated to result in the 23% reduction in myocardial infarctions and 24% decrease in coronary revascularization procedures. Therefore, more specific mechanisms for the ACE inhibitor mediated reductions in coronary events "beyond blood pressure control" need to be invoked.

Several mechanisms by which the renin-angiotensin-aldosterone-bradykinin systems could contribute to coronary atherosclerosis and conversely explain these benefits of ACE inhibitors are currently proposed. Activation of the renin-angiotensin-aldosterone-bradykinin system has been associated with increased risk of myocardial infarction. In a hypertensive population, a greater activation of the renin-angiotensin system as assessed by plasma renin activity related to urinary sodium excretion (an index of dietary sodium) was associated with increased likelihood of experiencing a coronary event.[17] Although this observation has not been universally accepted[18] there is considerable support for the concept that local elevation in angiotensin II promotes unfavorable cardiovascular remodeling. At the tissue level, elevation in angiotensin II promotes vascular smooth muscle proliferation.[19] A polymorphism due to either a deletion (D) or insertion (I) of 287 base pair segments in the intron region in the ACE inhibitor gene results in three readily distinguishable genotypes. Those homozygous for DD phenotypically have a more rapid local

Figure 1A

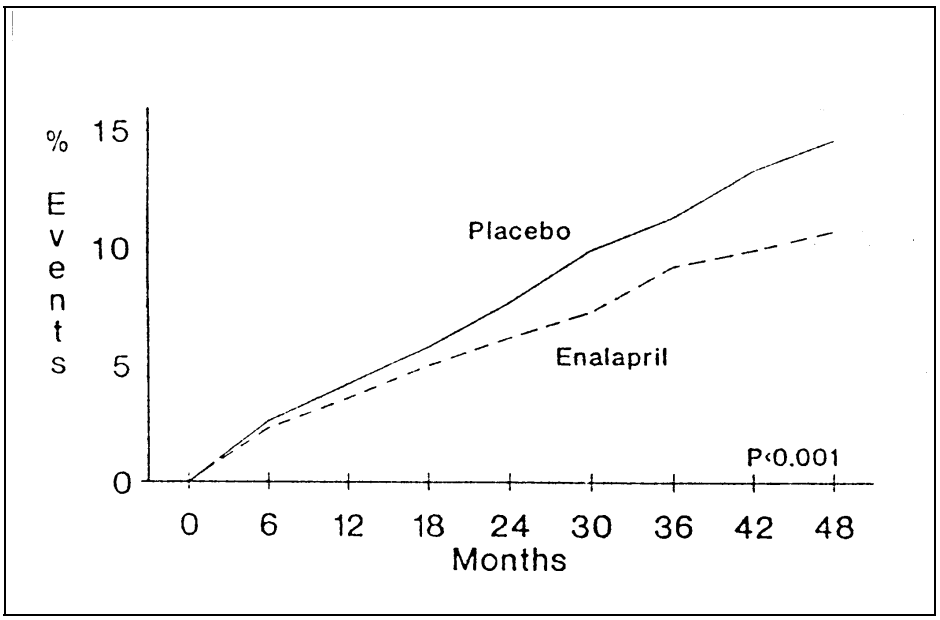
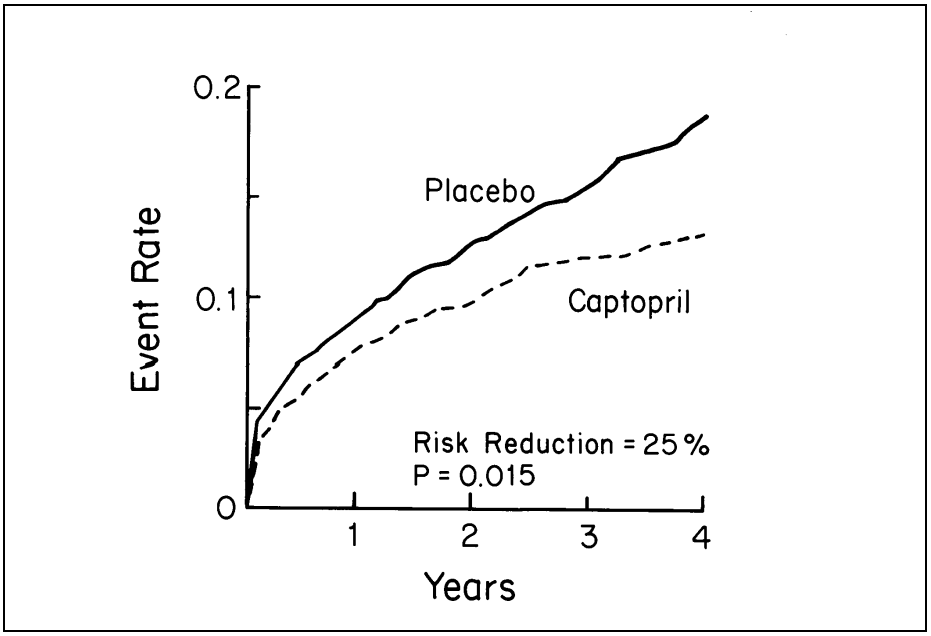


Figure 1B



The number of patients experiencing a myocardial infarction following randomization in the SOLVD study, Figure 1A; or the SAVE study, Figure 1B. Note the similar magnitude of the reduction of risk of experiencing an MI following randomization to either of the ACE inhibitors.[10,11]

conversion of angiotensin I to II,[20] and it is this genotype that has been associated with an increased risk of myocardial infarction unexplained by more conventional risk factors.[21] Of interest, no relationship was found between this ACE inhibitor gene polymorphism marker and the risk of having other manifestations of coronary artery disease.[22]

It is now apparent that the activity of the renin-angiotensin system cannot be adequately assessed by measurement of plasma hormones alone. The importance of the local conversion of angiotensin II by tissue ACE has been well demonstrated in experimental models, particularly in the heart.[23,24] This local angiotensin II production is now believed to have an important trophic influence which can adversely alter the delicate balance between myocytes, connective tissue, and vascular components of the myocardium.[25] The potent acute vasoconstrictor action of angiotensin II in some respects may be less important than these chronic mitogenic influences. Indeed, in animal models of myocardial infarction and hypertrophy, local cardiac ACE activity was enhanced even though systemic determination of plasma renin activity was not augmented.[26, 27] This local activation of ACE gene expression can alter vascular growth independent of hemodynamic stimulus.

Even the obvious direct vasoconstrictor actions of angiotensin II must be reconsidered in light of the newly emerging integrative aspects with local tissue activity. ACE inhibitor therapy, by both reducing angiotensin II and enhancing local bradykinin, potentiates endothelial-derived nitric oxide[28] and thereby restores appropriate vaso-responsiveness of the atherosclerotic vasculature. The role of bradykinin in this restoration of vasodilator function serves to underscore that some important actions of ACE inhibitors may not be duplicated by the newly developed more specific angiotensin antagonists.[29] In addition to these vasoactive and vasotrophic influences, ACE inhibitors have a direct favorable effect on the atherosclerotic process and the hemostatic triggers of acute thrombotic episodes. The atherosclerotic burden in cholesterol-fed rabbits has been reduced by chronic ACE inhibitor therapy.[30] Angiotensin II unfavorably alters the balance between the promoter of thrombosis plasminogen activator inhibitor-1 (PAI-1) and the natural thrombolytic tissue type plasminogen activator (t-PA).[31] This observation linking the renin-angiotensin system to fibrinolytic function offers another plausible mechanism whereby ACE inhibitor therapy may exert a favorable influence on major coronary ischemic events.

In summary, patients with coronary artery disease are at heightened risk for major cardiovascular events. With current advances, a larger segment of our population is manifesting coronary artery disease at a more advanced age. The majority of these patients have preserved left ventricular function. Prior studies with ACE inhibitor therapy in patients with depressed EF have demonstrated that their long-term administration leads to improved survival and reduced risk of myocardial infarction over and above conventional therapy. There is sufficient rationale and experience to indicate that these benefits will apply to the larger group of patients with coronary artery disease and preserved LVEF and therefore have even broader public health implications. A definitive trial is needed to assess the effects of ACE inhibitor therapy on the incidence of cardiovascular mortality, myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty in patients with coronary disease and preserved left ventricular ejection function. This clinical outcome trial will be coupled with smaller mechanistic studies to elucidate the mechanisms for the presumed improvement in outcome with long-term ACE inhibitor therapy.

II. OVERVIEW OF STUDY DESIGN

A. Primary Objective

The primary objective of the **P**revention of **E**vents with **A**ngiotensin **C**onverting **E**nzyme Inhibition (PEACE) trial will be to test whether the addition of the angiotensin converting enzyme (ACE) inhibitor trandolapril to standard therapy will reduce the incidence of cardiovascular mortality, non-fatal myocardial infarction, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty in patients with coronary artery disease, but with preserved left ventricular function.

B. Secondary Objectives

The effect of trandolapril on the following hierarchy of clinical cardiovascular events will be evaluated.

1) Coronary heart disease death, non-fatal myocardial infarction, or a coronary revascularization procedure (CABG or PTCA).

2) The primary outcome or unstable angina (requiring hospitalization).

3) Any of the outcomes in (2) or congestive heart failure (requiring hospitalization).

4) Any of the outcomes in (3) or stroke.

5) Any of the outcomes in (4) or peripheral vascular disease (requiring intervention, angioplasty, bypass surgery, or aneurysm repair).

6) Any of the outcomes in (5) or cardiac arrhythmias (requiring hospitalization).

In addition, the effect of trandolapril on the risk of total mortality, cause-specific mortality, as well as the individual components of the hierarchy of clinical cardiovascular events, will be estimated.

C. Patient Eligibility

The eligibility and exclusion criteria are as broad as possible to increase the generalizability of the results, while maintaining patients' safety and the scientific integrity of the trial. In attempting to be representative of the population with this disease, the trial has set a goal of including 40% women and 20% minority. Participants must meet all inclusion criteria and have none of the exclusion criteria. All potential participants with any single exclusion characteristic must be excluded. However, such patients may be reconsidered for eligibility at a later time (e.g., if a patient

had an MI less than three months prior to randomization, they may be reconsidered at a later time). However, **all** inclusion and exclusion criteria must be reevaluated at that time.

1. Inclusion Criteria

1) Men and women ≥ 50 years of age at the time of randomization.

2) Coronary artery disease documented as at least one of the following:
   a) A documented myocardial infarction at least three months prior to randomization.

   b) A CABG or PTCA at least three months prior to randomization.

   c) A coronary angiogram demonstrating the presence of at least one native coronary obstruction (non-bypassed) of ≥ 50% luminal diameter. The qualifying lesion(s) will be based on the most recent study.

3) Left ventricular function:
   a) Ejection fraction > 40% as determined by contrast ventriculography, radionuclide ventriculography, or echocardiography performed less than 18 months prior to the date of randomization.

   OR

   b) A qualitatively normal echo or angiogram of the LV in the absence of wall motion abnormality. If regional dysfunction is present or the LVEF is compromised, a quantitative ejection fraction would still be required.

2. Exclusion Criteria

1) Potential participant is currently prescribed an ACE inhibitor which cannot be discontinued.

2) Contraindication to the use of an ACE inhibitor (e.g., prior adverse experience with an ACE inhibitor, current or planned pregnancy, any angioedema, or hyperkalemia).

3) Current clinical condition(s) requiring the use of an ACE inhibitor (e.g., symptomatic congestive heart failure, hypertension requiring ACE inhibitor for adequate control).

4) Current clinical requirement for use of an angiotensin II receptor antagonist.

5) Hospitalization for unstable angina occurring less than two months prior to the date of randomization.

6) Valvular heart disease which, in the assessment of the treating physician, is likely to require surgical intervention.

7) Coronary artery bypass surgery within three months prior to the date of randomization.

8) Percutaneous transluminal coronary angioplasty within three months prior to the date of randomization.

9) Plans for elective coronary revascularization procedure.

10) Serum creatinine > 2.0 mg/dL (177μmol/L) (measured within 12 months prior to the date of randomization). If last serum creatinine was ≥ 1.5 and ≤ 2.0 mg/dL (≥133 and ≤177μmol/L), recheck after run-in and prior to randomization. If serum creatinine > 2.0 mg/dL (177μmol/L) at that time, patient is excluded.

11) Serum potassium ≥ 5.5 mEq/L (5.5 mmol/L) from most recent laboratory assessment within 12 months prior to the date of randomization.

12) Other concurrent medical conditions thought likely to limit five-year survival (e.g., certain cancers, cirrhosis, severe chronic obstructive pulmonary disease).

13) Psychosocial conditions not conducive to adherence to the long-term requirements of this trial.

14) Inability or unwillingness to provide written informed consent.

15) Women of childbearing potential not using adequate contraception.

16) Current use of non-FDA or non-HPB approved medication in a research trial (see Manual of Operations for details).

D. Informed Consent and Institutional Review Board (IRB)

Each participating site will be required to submit the PEACE trial protocol to its local IRB for approval. As part of this process, an appropriate informed consent form will be developed at each site. A copy of the IRB approval letter and a copy of the consent form approved by the local IRB will be forwarded to the PEACE Clinical and Statistical Coordinating Center (CSCC). No screening, run-in visits, randomizations or study drug shipments will be allowed prior to the receipt of these documents. The consent form will, at a minimum, meet the guidelines from the Code of Federal Regulations, part 46 - Protection of Human Subjects. A sample Informed Consent Form is included as Appendix A.

E. Screening, Randomization and Follow Up

Potentially eligible and interested subjects identified through screening of outpatient clinics, coronary care units, cardiac catheterization records and other appropriate sources will be scheduled for a pre-randomization visit. At or prior to this visit the respective participant may be given the

patient brochure describing the study. Prior to the pre-randomization visit, the patient's physician will be contacted to discuss the study and the patient's potential participation. The importance of obtaining the local physician's commitment and support in maintaining long-term adherence and follow up cannot be overemphasized.

1. Pre-Randomization Visit

a) Study requirements will be reviewed with the potential participant, and the Screening Form will be completed for eligible patients who will participate in run-in or who may be eligible based on ECG.

b) The Informed Consent Form will be read by (or to) all eligible candidates and signed by those willing to continue. Any questions by the candidates will be addressed by the clinical staff.

c) A baseline blood pressure will be taken and a 20-day supply of run-in trandolapril (2 mg taken once daily) with a page of instructions and possible adverse effects will be given to consenting participants.

d) An appointment for the Randomization Visit will be made.

e) The Screening Form will be transmitted to the CSCC.

f) Participants whose most recent serum creatinine was ≥ 1.5 and ≤ 2.0 mg/dL, will have their serum creatinine checked after at least one week of run-in medication and before randomization. If creatinine is now > 2.0 mg/dL, the participant is ineligible and his/her primary care physician will be notified of the results.

g) Baseline blood (serum, plasma) and urine samples will be collected.

2. Randomization Visit

a) The patient will be asked about possible adverse events attributable to trandolapril which may have occurred during the run-in. In addition, they will be asked about the occurrence of any PEACE primary or secondary study outcomes. Any reported adverse events and the capsule count will be recorded on the Randomization Form. If run-in was not tolerated, or adherence < 80%, the candidate will be thanked and excused. If run-in medication was tolerated and adherence was adequate, the patient will be invited to participate in the PEACE trial. A study-directed medical history and blood pressure evaluation will be performed, and the Randomization Form completed.

b) The personal information on the Patient Tracking Form will be completed and a general medical release authorizing access to medical records including death certificate will be signed. These will be filed with the patient's PEACE records at the clinical site.

c) Randomization to placebo or trandolapril (2 mg), taken once daily, will be carried out by using an 800 telephone number as described in the Manual of Operations. A 200-day supply of study medication will be dispensed with an instruction sheet.

d) Plans will be made for the first post-randomization visit at six months.

e) The Pre-Randomization and Randomization Forms will be transmitted to the CSCC.

3. Follow Up Visits

a) Follow up visits will be conducted every six (±1) months. At the first Semi-Annual visit, study medication dose will be increased to 4 mg taken once daily, unless blood pressure is < 110 mmHg systolic or the patient has symptomatic hypotension. Participants will have been instructed to notify the clinical site promptly of adverse events such as cough or dizziness. If participants have not reported any adverse events by one week after the first six month visit, the study coordinator will contact the participant. If significant adverse side effects are reported, the dose may be reduced to 2 mg daily. A supply of 2 mg capsules and an updated pill instruction sheet will be mailed to the participant with instructions to return the 4 mg capsules. All changes in study medication administration will be recorded on the Follow Up Visit Form and transmitted to the CSCC. If at any time the patient reports side effects while on 2 mg daily, the dose may be reduced to 1 mg daily.

b) At all Semi-Annual and Annual Visits, capsule counts of previously issued study medication will be recorded and a new 200-day supply of study medication dispensed. The Follow Up Visit Form will be completed, or if contact cannot be made, the reason for no contact will be recorded on the Follow Up Visit Form, and the form transmitted to the CSCC.

F. PEACE Design Synopsis

Mode of Support:	Contract from the National Heart, Lung, and Blood Institute
Period of Support:	November 1995 to June 2004
Clinical Centers:	160 (approx)
Clinical and Statistical Coordinating Center:	1
Recruitment Goal:	8,100 patients

Major Patient Selection Criteria:	Men and women ≥ 50 years of age and either coronary angiography with at least one epicardial coronary obstruction (non-bypassed) ≥ 50% luminal diameter or MI ≥ 3 months or CABG ≥ 3 months or PTCA ≥ 3 months and preserved left ventricular function (LVEF > 40%).
Length of Recruitment:	3 years
Length of Follow-up:	Minimum of 4 years; Maximum of 7 years
Outcomes Measures	
Primary:	Cardiovascular mortality, non-fatal myocardial infarction, CABG or PTCA
Secondary:	1) Coronary heart disease death, non-fatal MI, CABG or PTCA 2) The primary outcome or unstable angina (requiring hospitalization) 3) Any of the outcomes in (2) or congestive heart failure (requiring hospitalization) 4) Any of the outcomes in (3) or stroke 5) Any of the outcomes in (4) or peripheral vascular disease (requiring intervention, angioplasty, bypass surgery, or aneurysm repair) 6) Any of the outcomes in (5) or cardiac arrhythmias (requiring hospitalization)
Method Treatment Assignment:	Randomized permuted block
Stratification Variable:	Clinic
Level of Masking	
Treatment Group:	Masked to medical team and patient
Aggregate Data:	Masked to medical team and patient Monitored by independent Data and Safety Monitoring Board
Type of Trial:	Randomized placebo controlled, large, simple
Study Treatment:	Run-in trandolapril (2 mg taken once daily) for two weeks. Randomization to placebo or trandolapril (2 mg taken once daily) taken for 6 months. After first 6-month visit, medication dose will be increased to placebo or trandolapril (4 mg taken once daily). Patients with side effects may be placed on a reduced dose of 2 mg or, if necessary, 1 mg.
Schedule of Evaluations:	See Table 1

Table 1: Schedule of Patient Evaluations

Evaluation	Pre-randomization	Randomization	Months from Randomization	
		10/96 - 10/99	Semi-Annual	Annual
Inclusion Criteria	X	X		
Exclusion Criteria	X	X		
Informed Consent	X			
Adverse Events		X	X	X
Study Medication	X	X	X	X
Cardiovascular Medical History		X		
Weight		X		X
Height		X		
Blood Pressure	X	X	X	X
Baseline Blood (Serum, Plasma), Urine	X			
Serum Creatinine	X	(a)		
Serum Cholesterol	X			
Serum Potassium	X			
CCS Functional Classification		X		X
Current Medication		X		X
Interim Medical History		X	X	X

(a) Conducted only if pre-randomization value is ≥ 1.5 and ≤ 2.0 mg/dL.

III. INTERVENTION

A. Trandolapril

In the SOLVD and SAVE trials, the respective ACE inhibitors, enalapril and captopril, were shown to reduce the incidence of death and myocardial infarction in patients selected for reduced ejection fraction. The fact that these two ACE inhibitors had similar favorable outcomes supports, but does not prove, the concept that similar benefits could be achieved with other ACE inhibitors.

Even if this action could be attributed to ACE inhibitors as a class of agents, the important issue of appropriate dose selection would still have to be resolved.

A requirement for the ACE inhibitor selected for PEACE was that it be well studied and have proven efficacy in a major cardiovascular morbidity and mortality trial to ensure that the PEACE study effort would be based on not only a proven agent, but also an effective dosage regimen.

The TRAndolapril Cardiac Evaluation (TRACE) study was a placebo-controlled trial in 1749 Danish infarct survivors at 27 sites. Participants were randomized three to seven days after index infarction, with wall motion index ≤ 1.2 by echocardiography, corresponding to a global ejection fraction ≤ 35%. At two-year follow up, randomization to trandolapril resulted in a 22% mortality reduction,[32] and a favorable trend (14% reduction) in recurrent myocardial infarctions. The trandolapril dose was titrated from the initial 1 to 2 mg and then to the target of 4 mg (once daily). This effective dose was well tolerated, and, as anticipated, a higher incidence of cough, hypotension and hyperkalemia were experienced in the trandolapril group. Thus, trandolapril represents a once-a-day ACE inhibitor with a dosing regimen that has been effectively used in a major morbidity/mortality trial in patients with acute myocardial infarction.

After oral administration, trandolapril is rapidly absorbed and converted to its active form, trandolaprilat, in the liver. Peak plasma concentrations of trandolaprilat are achieved in 4-6 hours, and steady-state in four days. Concomitant food intake did not alter trandolaprilat bioavailability. Trandolapril is excreted in the urine (33%) and bile (66%), thus dose reduction is recommended in severe renal or hepatic dysfunction. Elimination half-life of trandolaprilat is biphasic, with the prolonged terminal elimination phase being 16-24 hours.[33]

In clinical trials involving more than 2200 hypertensive patients, trandolapril has been well tolerated, with an adverse effect profile similar to that of other ACE inhibitors. In a trial of 786 subjects treated with 2 or 4 mg of trandolapril for up to 12 months, cough was reported by <3%; other less frequently reported side effects included headache (1.9%), dizziness (1.8%), weakness (1.4%), palpitations (0.4%), hypotension (0.5%), nausea (0.6%), gastrointestinal disorders (0.5%), pruritis (0.4%), and rash (0.5%).[34]

As with other ACE inhibitors, trandolapril should not be administered to pregnant or breast feeding women, to patients with a history of angioedema, or in conjunction with potassium-sparing diuretics.

B. Concomitant Medications

Study medication will be added to conventional therapy, including management of hyperlipidemia, hypertension and diabetes, as well as aspirin (unless contraindicated). Concomitant medications are recorded on the Randomization and Annual Visit Forms. Except for the recommendation of non-use of potassium-sparing diuretics, there will be no protocol restrictions on other concomitant medications.

IV. STATISTICS

A. Statistical Analysis

The primary endpoint on which the sample size determination was based is the combined incidence of non-fatal myocardial infarction, death attributed to a cardiovascular etiology, CABG or PTCA. The hypothesis of equal time to event distributions in the two treatment arms will be tested using a two-sided logrank test at the overall 0.05 (2-tail) significance level. An intention to treat analysis will be used. It is assumed that the trial will accrue patients uniformly over the first three years, with a minimum follow-up of four years.

1. Sample Size and Power

To estimate the sample size, the following assumptions were made: the incidence of the primary outcome will be 19% in the placebo group; the study should have a power of 90%; use of trandolapril will result in at least an 18% relative reduction in the incidence of the primary outcome; 15% of the trandolapril treated group will discontinue active therapy (drop out, 10% in year one); 15% of the placebo group will initiate the use of active therapy (drop in); drop-in will occur uniformly during the trial; and there will be no lag between the initiation of therapy and the start of the treatment effect. This resulted in an estimated sample size of 8,100 patients (e.g., 4,050 per group).

2. Interim Analyses

Interim analyses of the primary endpoint are expected to occur approximately every six months in the course of the trial coincident with meetings of the Data and Safety Monitoring Board (DSMB). The DSMB will have the final decision on the frequency and method of statistical monitoring. While these sample size calculations do not account for any interim analyses, the use of the Lan-DeMets procedure[35] with an O'Brien and Fleming spending function would decrease the overall power only minimally.

3. Stratification and Randomization

After eligibility is established, patients will be stratified by clinical center. Randomization will be by the method of randomized permuted blocks.[36]

4. Secondary Analyses

Survival and other time-to-event distributions will be estimated by the method of Kaplan and Meier.[37] Overall survival will also be compared. Time to secondary endpoints will use a specific hierarchy (see page 6, Secondary Objectives) and will be estimated by the Kaplan-Meier procedure and evaluated by the log rank test. Incidence of hospitalizations for primary cardiovascular complications will be compared using the Wilcoxon test.[38] In order to lower the likelihood of false positive results, a two-sided p-value of 0.01 will be used for all secondary analyses.

5. Subgroup Analyses

Important subgroups will be pre-specified based on clinical demographics and mechanistic considerations. Interaction between each of these subgroups and treatment will be tested using the procedure of Gail and Simon.[39] For these tests, a p-value of 0.05 will be used. The importance of the subgroups will be to test for heterogeneity of the overall treatment effect. Predetermined subgroups will be tested for the primary outcome and for the declared secondary endpoints. The major subgroups that will be evaluated will be based on the primary eligibility criteria of previous myocardial infarction, documented obstructive coronary disease, CABG or PTCA. Other risk factors to be evaluated are gender, age above and below the median, ejection fraction above and below the median, prior history of hypertension, and prior therapy for diabetes. The efficacy of therapy will also be evaluated in conjunction with mechanistic studies that assess the ACE gene genotype with respect to the deletion or insertion polymorphism. Relevant practice issues of potential differential efficacy with respect to a patient's gender will be evaluated.

V. DATA COLLECTION

All required trial information will be recorded on standardized data collection forms. A Manual of Operations will be compiled and distributed to the staff of each clinical center as a guide to the implementation of the PEACE Protocol. Training sessions will be held prior to beginning recruitment in order to assure that patient management and data collection procedures are uniform and to train the investigators in study procedures.

The Study Coordinator at each clinical site will assemble completed data forms weekly. Copies of the forms will be kept at the office of the Principal Investigator at each clinical site and originals will be sent to the Clinical and Statistical Coordinating Center (CSCC) every two weeks. The timely submission of all study information will be the responsibility of the individual clinical center.

The importance of the visit schedule will be stressed to both the patient and the staff of the clinical center. Ideally, no visits should be missed; the one month windows on either side of the target visit date provide scheduling flexibility. If, however, a visit is missed, the visit should be rescheduled as soon as possible.

Every effort will be made to follow all study subjects according to the PEACE Protocol even when they make temporary or permanent moves to another city. When a patient moves into a geographic area served by a PEACE clinical center other than the one in which the patient was originally enrolled or is currently being served, the patient will be reassigned to the care of the new center. If the patient moves into a geographic area not served by a PEACE clinical center, the patient will be placed on phone contact and the follow-up information should be obtained every six months. Resupply of medication will be mailed to the patient.

Primary outcomes will be recorded on the Outcomes Form and sent to the CSCC. For all deaths, a copy of the death certificate will be obtained. If hospitalized at the time of death, a copy of the hospital face sheet with ICD-CM code(s), or hospital discharge summary and autopsy report, if

any, will be obtained. If not hospitalized, a copy of the emergency medical services or ambulance report will be obtained. Documentation will be forwarded to the CSCC for classification by the Mortality and Morbidity Review Committee (MMRC). Two members of the committee will independently code the death as cardiovascular or non-cardiovascular.

For non-fatal myocardial infarction, a copy of the hospital face sheet with ICD-CM code(s), hospital discharge summary, cardiac enzyme laboratory report, and initial and last electrocardiograms will be obtained. Documentation will be forwarded to the CSCC for adjudication by the MMRC. Two members of the committee will independently code the event as a confirmed myocardial infarction or as not meeting the specified study criteria.

For PTCA or CABG, a copy of the hospital face sheet with ICD-CM code(s) or the hospital discharge summary will be obtained and forwarded to the CSCC.

For the primary endpoints cardiovascular death and non-fatal myocardial infarction if the adjudicators' opinions are in agreement, they constitute the final outcome determination. If the two opinions differ, a third opinion will be obtained from the MMRC Chairperson.

VI. SUBSTUDIES AND ANCILLARY STUDIES

A. Introduction

In order to derive full benefit from the data collected and to provide fair access to all study participants, the Publications and Ancillary Studies Committee (PASC) will review applications for ancillary studies, coordinate the formation of writing groups on each topic and make recommendations to the Steering Committee regarding these activities.

B. Ancillary Studies

An ancillary study will be defined as a study in which PEACE patients are used in an investigation that requires additional data not collected as part of the main protocol. Such studies may be carried out independently by PEACE investigators either as a single center or in collaboration with other PEACE investigators. Although outside funding may be sought for ancillary studies, all of these must be approved by the PEACE Publications and Ancillillary Studies Committee. This committee will assess the quality of the science proposed and determine whether conducting the ancillary study has any potential to adversely affect the main study. The contribution of the requestors of ancillary projects to the overall study will be considered. A recommendation will then be transmitted from the PASC to the Steering Committee. The Steering Committee will make the final recommendation for each report.

C. Data Storage and Analysis

Originals of each data form will be stored at the Clinical and Statistical Coordinating Center and data will be entered into their computer system. Data will be analyzed at the CSCC unless other arrangements have been recommended by the PASC and approved by the Steering Committee. All data designated as representing the PEACE study must be derived from and verified by the CSCC.

D. Application Review Process

The Publications and Ancillary Studies Committee will review proposals at each of the annual meetings as well as between meetings, if necessary. If several applications for similar studies are received, the PASC will request that the applicants resolve differences in their proposals and submit a joint application. If irreconcilable differences exist between similar applications or if the applicants cannot resolve differences or do not wish to collaborate, the PASC will individually grade the applications based upon scientific merit and feasibility, previous investigator experience, balance of projects in the overall study (to be certain that all investigators have a chance to pursue studies that they choose) and past recruitment and follow-up performances.

In order to assure that all sites have an equal opportunity to develop and participate in analyses, proposals will be circulated to each of the Principal Investigators to invite their participation. The proposer will make recommendations to the Steering Committee regarding the participants and their responsibilities in the substudy. Final decisions regarding participation rest with the Steering Committee which will receive a recommendation from the PASC.

Applications from non-PEACE investigators and institutions are welcomed but will be accorded secondary priority for approval and must be in the format that a PEACE investigator would use to make application.

All ancillary studies will be reviewed for approval by the Data and Safety Monitoring Board.

VII. PUBLICATION POLICY

The Publications and Ancillary Studies Committee will review all proposed publications and presentations and report its recommendations to the Steering Committee.

A. Data Analysis and Release of Results

The scientific integrity of the study requires that the data from all of the clinical centers be analyzed study-wide and reported as such. Thus, an individual center may not report the data collected from only that center. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee. Additionally, all presentations and publications are expected to protect the integrity of the major objectives of the study; data endpoints by randomization group will not be available to clinical center investigators until the completion of the study. Recommendations about the timing of presentation of such

endpoint data and the meetings at which the data are presented will be discussed and approved by the Steering Committee.

B. Review Process

Each proposed manuscript, abstract, or presentation must be submitted to the Publications and Ancillary Studies Committee. The PASC may recommend changes to the authors. The PASC will make a recommendation to the Steering Committee regarding suitability of the proposed submission and the recommendation of the Steering Committee will be conveyed to the authors.

C. Primary Outcome Papers

The primary outcome papers of the PEACE trial are defined as papers that present outcome data for the entire PEACE trial (such as papers dealing with the primary and secondary endpoints). The final determination of whether a particular manuscript is a primary outcome paper rests with the Steering Committee which will receive a recommendation from the Publications and Ancillary Studies Committee.

Authorship on primary outcome manuscripts and abstracts will be "The PEACE Investigators." For such manuscripts, there will be an appendix containing the names of the organizational units and their Principal Investigators and Co-investigators. Organizational units will include the CSCC, Clinical Centers, Office of the Study Co-chairmen, and the National Heart, Lung, and Blood Institute.

D. Other PEACE Manuscripts, Abstracts and Presentations

All studies other than those designated as "primary outcome" fall into this category. The authorship of papers or abstracts resulting from these studies will name the individuals involved, ending with the phrase "for the PEACE Investigators." In addition, these manuscripts will have the same appendix as described above for primary outcome papers.

VIII. STUDY ORGANIZATION

A. Introduction

PEACE study organization includes the following components: the NHLBI, the Data and Safety Monitoring Board, the Steering Committee and its subcommittees, the Executive Committee, the Clinical and Statistical Coordinating Center, the Clinical Centers, Pharmacy Coordinating Center and the Central Biochemistry Laboratory. In the following section each component and the interrelationship among these components will be described. The organization structure that is depicted in Appendix B was developed to facilitate the conduct of the study by ensuring careful and uniform adherence to the Protocol and the Manual of Operations.

B. Structure

The Director of the National Heart, Lung and Blood Institute (NHLBI) is responsible for the use of Institute funds and the management of Institute programs. He has ultimate responsibility for the conduct of PEACE and serves as the final decision-maker for all major decisions affecting PEACE. The Institute Director appoints the Chair and members of the Data and Safety Monitoring Board (DSMB). The Principal Investigator of the NHLBI represents the Director of the NHLBI and is responsible for ensuring that the scientific and technical objectives of the study are consistent with the mission and responsibilities of the NHLBI. The Principal Investigator, or his designate, is a member of the study's Executive and Steering Committees and a voting member of each of the subcommittees (PASC and MMRC) of the Steering Committee.

1. Data and Safety Monitoring Board

The Data and Safety Monitoring Board is appointed by the Director of the NHLBI. The members are independent of the conduct of the study. They include experts in cardiology, biostatistics and bioethics. The DSMB reviews the Protocol for the main study, any proposed major modifications to the Protocol or the Manual of Operations, and the protocols for all proposed ancillary studies.

The members of the DSMB will monitor the progress of recruitment, adherence, data quality, endpoint data and side effects. Any serious event occurring during the run-in phase will be monitored by the DSMB in the same way as events occurring during the randomization phase of the trial. Summary endpoint data presented by randomization group is confidential and shared only with the DSMB. The DSMB will review reports twice a year and make its recommendations concerning the conduct of PEACE directly to the Director of the NHLBI. The Study Co-chairmen, the Principal Investigator and Co-investigators of the Clinical and Statistical Coordinating Center, and a representative of the NHLBI Project Office are ex-officio members of the DSMB.

2. Steering Committee

The Steering Committee is the representative body of study participants. The voting members of the Steering Committee include the Study Co-chairmen (Eugene Braunwald, M.D. and Marc A. Pfeffer, M.D., Ph.D.), the NHLBI Principal Investigator (Michael Domanski, M.D.), the Clinical and Statistical Coordinating Center Principal Investigator (Joel Verter, Ph.D.), two clinical center Principal Investigators (Bernard J. Gersh, M.B., Ch.B., D.Phil. and Jean L. Rouleau, M.D.), and five others who will be clinical center Principal Investigators. The Co-Investigators from the CSCC will be non-voting members of the Committee. The Steering Committee provides overall scientific direction for the study through consideration of recommendations from the subcommittees. The business of the Steering Committee will be conducted in accordance with customary parliamentary procedures. The Steering Committee will meet at least once each year to review the progress of the study and to monitor non-endpoint data. The Steering Committee will not have access to endpoint data and treatment group differences until the trial is completed. The Steering Committee will establish subcommittees to support its objectives. The subcommittees are the Publications and Ancillary Studies Committee (PASC), and the Mortality and Morbidity Review Committee (MMRC). The members of the subcommittees are appointed from among the clinical

centers, CSCC, and NHLBI Principal Investigators. The chairman of each subcommittee will be a member of the Steering Committee.

All subcommittees have specific responsibilities outlined below and assume other responsibilities as requested by the Steering or Executive Committees.

a) Publications and Ancillary Studies Committee decides on the timing and content of publications and presentations. They will review all study manuscripts prior to submission. They will review all research requests for use of study patients or accumulating study data. They will forward their recommendation for each proposal to the Steering Committee.

b) Mortality and Morbidity Review Committee establishes classification procedures for cardiovascular and coronary heart disease mortality and definite non-fatal myocardial infarction. This subcommittee classifies endpoints on the basis of a masked review.

3. Executive Committee

The Executive Committee will consist of the Study Co-chairmen, the NHLBI Principal Investigator, and the Principal Investigator of the CSCC. In addition, the Co-investigators from the CSCC and other NHLBI investigators will be ex-officio members. They will provide study direction between meetings of the Steering Committee, develop an agenda for the annual meeting of the Steering Committee, and coordinate the activities of the two subcommittees. During the first two years, they will hold monthly conference calls or face-to-face meetings to review recruitment and patient follow-up, adherence to the Protocol with respect to drug compliance, and follow-up visit timeliness and data quality. After the recruitment phase, they will meet every six months between the annual Steering Committee meetings.

4. Clinical and Statistical Coordinating Center

The Clinical and Statistical Coordinating Center (CSCC) provides overall coordination for all aspects of the study. They participate in all aspects of the design and implementation of the PEACE trial. The Principal Investigator is a voting member of the Steering Committee and the Executive Committee. The Principal Investigator and Co-investigators provide scientific and technical service to the Steering Committee and each of its subcommittees. The CSCC has the responsibility for implementing the systems necessary for randomization, drug distribution, data collection, editing, management and statistical analyses. They are responsible for providing appropriate and timely data reports to the DSMB, the Steering Committee and its subcommittees, and the Executive Committee. The CSCC will oversee all aspects of the clinical centers' performance. They assist in the selection of the centers, train and certify the centers' staff, and coordinate the fiscal aspects of the study.

5. Clinical Centers

The clinical centers are staffed by a primary Study Coordinator and a Principal Investigator. The Principal Investigator works with the CSCC and the other members of the Executive Committee to conduct the study in accordance with the Protocol and Manual of Operations. The clinical center is expected to perform the following functions:

a) Screen, recruit, obtain informed consent and randomize acceptable numbers of eligible patients.

b) Dispense study medication in the manner outlined in the PEACE Protocol.

c) Maintain contact with patients.

d) Schedule and perform follow-up visits, submit data collection forms to the CSCC, and respond to data queries in an appropriate manner, as outlined in the protocol and the Manual of Operations.

e) Obtain Protocol-required validating information on endpoints.

f) Attend study meetings.

6. Knoll Pharmaceutical

Knoll Pharmaceutical Company will provide the study medication to the Pharmacy Coordinating Center (PCC). Knoll Pharmaceutical will have no access to study data prior to the termination of the trial.

7. Pharmacy Coordinating Center

The Pharmacy Coordinating Center will receive the study medication from Knoll Pharmaceutical. They will store, process and distribute the drugs to the Clinical Centers. In addition they will create, install and monitor the PEACE Trial's automated randomization and drug assignment system.

8. Central Biochemistry Laboratory

The Central Biochemistry Laboratory (CBL) will coordinate the collection, local processing and shipment of baseline blood and urine specimens from each collaborating clinic. The CBL will serve as the long term storage repository of these specimens.

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APPENDIX A - INFORMED CONSENT FORM

November 21, 1997

CAVEAT TO IRB

Please note that this sample language does not preempt or replace local IRB review and approval. Investigators are required to provide the local IRB with a copy of this sample language along with the language intended for local use. Local IRBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval.

Any deletion or substantive change of information concerning risks or alternative treatments must be justified by the investigator, approved by the local IRB, and noted in the IRB minutes. Justification and IRB approval of such changes must be forwarded to the PEACE Clinical and Statistical Coordinating Center. Sponsor approved changes in the PEACE Protocol must be approved by the Local IRB before use unless intended for the elimination of apparent immediate hazard. New information shall be shared with existing subjects at next encounter, with all new subjects prior to involvement, or as the local IRB may otherwise additionally require.

SAMPLE CONSENT LANGUAGE

INFORMED CONSENT FORM
RESEARCH STUDY

Prevention of **E**vents with **A**ngiotensin **C**onverting **E**nzyme Inhibition
The PEACE Trial

INTRODUCTION

You are being asked to take part in a research study. Before you decide to take part, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent. This consent form provides information about the research study which has been explained to you. Once you understand the study and the tests it requires, you will be asked to sign this form if you want to take part. You are entirely free to choose if you will take part.

PURPOSE

(Local Institution) and the National Heart, Lung and Blood Institute are carrying out a research study to determine whether trandolapril, a drug used to treat high blood pressure and heart failure, can also prevent heart attacks and death in patients with coronary heart disease. The PEACE study will enroll about 8,100 participants at 160 or more sites in the U.S., Canada and Italy. It will last 4-7 years depending on when you join the study.

Trandolapril is one of a group of drugs called angiotensin converting enzyme inhibitors, or ACE inhibitors. Trandolapril has been approved by the US Food & Drug Administration for use in the United States for use as an anti-hypertensive. A reduction in heart attacks has been observed in research studies looking at the effect of ACE inhibitors in patients with heart failure, but the ability of ACE inhibitors to prevent heart attack and coronary death has not previously been studied directly.

To be eligible for this research study, you must have coronary heart disease and your heart's ability to pump blood must be normal or near normal. If you cannot take ACE inhibitors or should definitely be taking ACE inhibitors for health reasons, you should not participate in PEACE. Also if you have abnormal kidney function, high blood potassium, or are pregnant, you may not join the study.

DESCRIPTION OF PROCEDURES

To identify candidates for PEACE, medical staff of this clinic reviewed hospital or office medical records for patients with coronary heart disease, and discussed study participation with potential candidates' physicians. Medical staff of this clinic then contacted PEACE candidates such as yourself to find out if they were interested in joining the PEACE study.

If you agree to participate, your height, weight and blood pressure will be measured, a blood sample (approximately 2 tablespoons) and a urine sample will be collected in order to measure cardiovascular risk factors (such as clotting functions, lipid values and homocysteine), you will be asked some questions about your health and medications, and you will be given a 20-day supply of trandolapril capsules (2 mg taken once daily) to see if you are able to take the medication. This visit will take about 1 hour.

You will be asked to return for a second visit which will last about 1 hour. If you have no problems with the study medication, you will be randomly assigned (like flipping a coin) to receive either trandolapril or placebo (inactive) capsules at this second visit. You have an equal chance of being assigned to trandolapril (2 mg) or placebo, and neither you nor the investigators will know which you are receiving.

Thereafter, you will be asked to return to the clinic every 6 months for the duration of the study to update your health records and receive a new supply of study medication. These visits will take about ½ hour. The dose of study medication may be increased to 4 mg (placebo or trandolapril) at the first semi-annual visit.

After PEACE is completed, the results will be analyzed and reported. If you wish, you will be notified of the results of PEACE.

BENEFITS AND RISKS

You may receive no direct benefit for participating in the research study. If trandolapril reduces heart attacks and coronary death, and you are assigned to trandolapril, you may benefit from the reduced chance of having a heart attack or coronary death. Benefits to others include an improved understanding of the effectiveness of trandolapril for protection against heart attack and coronary death.

There is a risk with drawing blood. You may feel discomfort as the needle goes through the skin. There may be some bruising at the site where blood is drawn. Pressing hard on the spot for 1 or 2 minutes after the needle is removed will help to prevent a bruise. Very rarely, the arm may become infected. Occasionally a person may feel lightheaded or even faint when blood is drawn.

Side effects associated with trandolapril in European studies are similar to other ACE inhibitors such as enalapril (Vasotec), captopril (Capoten), and lisinopril (Zestril) which are approved for use in the United States. Among 1049 participants in a research study of trandolapril, these side effects included cough (3.9%), wheezing or shortness of breath (2 patients), dizziness (5), headache (2), fatigue (2), rash (2), palpitations (2), impotence (2), insomnia (1), abdominal pain (1), diarrhea (1), swelling (1), low white blood cell count (1), and worse kidney function (1).

ACE INHIBITORS MUST NOT BE TAKEN BY WOMEN WHO ARE PREGNANT OR WHO MIGHT BECOME PREGNANT while taking the drug, because ACE inhibitors can cause serious birth defects. If you are a premenopausal woman, have not been surgically sterilized (hysterectomy or tubes tied) and wish to participate in this research study, you must not be pregnant and must use a reliable birth control method for the duration of your participation in the study and for at least 60 days after stopping the study drug. Acceptable ways to prevent pregnancy are barrier methods (sponge with spermicide, diaphragm with spermicide, cervical cap with spermicide), birth control pills, intrauterine device (IUD), injectable or implantable contraceptives (Depo-Provera, Norplant) or abstinence. Pregnancy tests are not required at the outset or during the study. If, during the study, you believe that you may be pregnant, immediately contact the study coordinator and stop taking study medication until such time as the pregnancy is or is not confirmed.

ALTERNATE TREATMENTS

Usual actions to prevent coronary heart disease include maintaining a healthful lifestyle, control of risk factors such as smoking, diabetes and high blood pressure, coronary angioplasty or bypass surgery. In middle-aged and older men, aspirin has been shown to reduce the risk of coronary heart disease. Your participation in this research study does not affect your ability to receive any of these interventions.

COSTS

The tests and visits that are a part of this study will cost only your time and travel.

PAYMENT FOR INJURY OR HARM

As the description of risks shows, taking part in this research study may result in injury or harm to you. If you require medical care, you should go to an emergency room. Otherwise the doctor in charge of this study will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance. Neither The George Washington University nor the National Heart, Lung, and Blood Institute will pay for your care. You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in the study. This position does not prevent you from pursuing whatever appeals may be available under the law.

PRIVACY
The results of this research study will be given to the research study's Coordinating Center at the George Washington University, and to the National Heart, Lung and Blood Institute, and may be asked for by the Food and Drug Administration or the United States Department of Health and Human Services. Except for these people, records from this study will be kept private unless required by law. Any reports on this study will not use your name or identify you.

RIGHT TO WITHDRAW
You may decide to stop this study at any time. Your care and relations with the doctors and nurses working on this research study will not be changed in any way if you decide not to participate in the study or to stop the study.

VOLUNTARY CONSENT
Your participation in this research study is voluntary. If you have any questions about the study, you should contact (the Clinical Principal Investigator), the person in charge of the study. Also, if you have any questions about your rights as a participant in this study, please call (local IRB contact), who is not affiliated with this research study.

SIGNATURES
By signing this consent form you are agreeing that you understand this consent form, have had an opportunity to ask questions, have had your questions answered to your satisfaction, and agree to take part. You will be given a copy of this consent form.

_____ _____
Signature of Participant Date

_____ _____
Signature of person obtaining consent Date

_____ _____
Signature of Principal Investigator or Designee Date

APPENDIX B - ORGANIZATIONAL FLOW CHART

PEACE
Organizational Chart