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I. INTRODUCTION

Background

Congestive heart failure (CHF) is a major and growing public health problem. It has been estimated that approximately 2 million Americans suffer from heart failure. Moreover, since its prevalence is known to increase with age, improvements in the average life expectancy of the general population would be expected to increase the number of such patients over the next few decades. For example, the number of hospitalizations, partly or wholly due to CHF, almost tripled between 1970 and 1982: from 570,000 in 1970 to 1,557,000 in 1982.

Approximately 250,000 new cases of CHF are diagnosed every year in the U.S. The mortality among these patients is reported to be between 10% and 20% a year, so that about 100,000 to 200,000 deaths per year can be attributed to CHF in the U.S. alone, and worldwide the numbers of deaths may be between one and two million per year. Little is known about the impact of any long-term drug treatment or other preventive measure on survival. Even digitalis and diuretics, which have been the mainstay of treatment for many years, have never been critically evaluated in this respect.

The recognition that patients with congestive heart failure often have elevated peripheral vascular resistance has led to the introduction of vasodilator therapy which has emerged as an important component of treatment of heart failure. These drugs include direct acting vasodilators such as nitrates, hydralazine and minoxidil; neurohumoral antagonists such as prazosin and angiotensin converting enzyme (ACE) inhibitors; and calcium channel blockers.

Of the vasodilators, the ACE inhibitors appear to be the most promising as they counteract some of the "key" adverse hormonal and vasoconstrictor mechanisms, and they appear to produce symptomatic relief, improve exercise capacity and ejection fraction, in short (<3 mos.) but well controlled randomized double-blind studies.[1,2] In one randomized controlled study with captopril in rats with large infarcts, a significant prolongation of survival was observed. A pooled analysis of the few hundred patients entered into the randomized trials suggests a favorable trend toward a lower mortality but the data are so scant that no reliable assessment of these effects is possible.[4] No controlled clinical study has examined the effects of these agents when administered over several years on physiological parameters, symptoms, mortality and safety. There may be several reasons why no previous study has convincingly demonstrated a beneficial effect of medical treatment on survival in CHF:

1. Once a patient develops overt CHF, the pathophysiologic changes may be irreversible, and intervention at this stage may be too late to prevent death.

2. The pathophysiologic changes of CHF may be reversible but the currently available drugs (diuretics, inotropic agents and vasodilators) may be ineffective.
3. The completed trials may not have been large enough or of adequate duration to have reliably detected plausible reductions in mortality.

Previous Randomized Clinical Trials of Chronic Treatment with Vasodilators in Heart Failure

There have been at least 17 randomized trials of the use of oral vasodilators in patients with chronic heart failure.[4] The period of treatment has varied from 6 to 52 weeks. Prazosin or trimazosin (8 trials), isosorbide-dinitrate (2 trials), captopril and enalapril (4 trials), hydralazine (2 trials) and minoxidil (1 trial) have been evaluated in a total of just under 900 patients. The average trial enrolled only about 50 patients, and the largest study was of 388 patients. Most trials included patients who were in New York Heart Association Functional Classes II to IV.

Several important conclusions can be drawn from the available data. First, the mortality rate in the control groups of these studies was around 15% over an average follow-up of 12 to 15 weeks; this confirms the poor prognosis of these patients. Second, no study on its own revealed a significant reduction in mortality. All were too small to detect even large risk reductions (e.g., 50 or 60%), let alone medically realistic and biologically plausible risk reductions of 15% to 20%. Third, most studies followed patients for too short a duration to be useful in assessing long-term responses to vasodilator therapy. Thus, in order to determine the effects of vasodilators on survival, a large trial consisting of several thousands of patients followed for a few years is required. Despite the paucity of data regarding the effects of most treatments on mortality, the combined results of the short term studies of ACE inhibitors appear promising (4% deaths among treated patients compared with 10% deaths among the control subjects). These analyses are retrospective and it is possible that the true effects of the ACE inhibitors when evaluated in a study of adequate size, will prove to be small, although still worthwhile. The currently available results provide us with the hypothesis that ACE inhibitors may reduce mortality.

Two Important Considerations in Designing Trials that Assess the Effects of ACE Inhibitors on Mortality

Two important considerations have influenced the concept of SOLVD:

(a) Need to study asymptomatic and symptomatic patients with left ventricular dysfunction

First, it is possible that drug treatment given when CHF is overt may not be as beneficial, as compared with earlier treatment. It is therefore proposed that patients with left-ventricular dysfunction but without overt CHF need to be studied in addition to a group of patients with overt CHF. Accordingly, two concurrent but separate trials are planned: a "Prevention Trial" that would include patients with a low ejection fraction and no overt CHF; and a "Treatment Trial" that would include patients with a low ejection fraction and symptoms and signs of overt CHF. Patients in the former group would have come to medical attention for reasons other than CHF, such as myocardial infarction, other ischemic heart disease, hypertension, etc. However, the patients must not have had obvious symptoms or signs of CHF, although the patient may have been treated with drugs such as diuretics or long acting nitrates for indications other than CHF, e.g., hypertension or angina. It is recognized that some of these patients may develop CHF, if withdrawn from such treatment or may have limited exercise capacity if objective measures such as treadmill tests are performed. However, the fundamental aim is to enroll patients without overt CHF (in whom additional treatment with a vasodilator or an inotropic agent is not normal practice). For the purposes of the protocol these patients would be enrolled into the "Prevention Trial."

(b) Only moderate reductions on mortality are plausible

Second, it would be reasonable to expect only modest (10 to 20%) but not large (40 to 50%) reductions in the risk of death with pharmacologic therapy such as ACE inhibitors. This does not, of course, apply to its effects on various physiologic measures, e.g., ventricular function or symptoms. For example, it is relatively simple to demonstrate whether or not these drugs improve exercise tolerance, just as it is relatively easy to demonstrate whether or not a particular cancer treatment temporarily shrinks a tumor. However, in CHF, as in cancer, it is likely to be extremely difficult to prevent (or substantially delay) a large proportion of deaths. Indirect support for this conclusion comes from many sources, including (a) the previous few decades of slow progress in the curative treatment of the common chronic cardiovascular diseases of middle and old age including CHF; (b) the heterogeneity of each single disease such as CHF, as evidenced by the unpredictability of survival duration even when apparently similar patients are compared with each other; (c) the variety of different mechanisms in patients with CHF that can lead to death, only one or two of which may be appreciably influenced by one particular therapy; and

(d) experience with many earlier trials, both in CHF and other cardiac conditions, review of which suggests that the true risk reductions being studied were probably only of the order of 5, 15 or 25 per cent, rather than, 40, 50 or 60 per cent.[5]

Moderate Reductions in Mortality Can Be Worthwhile

Having accepted that only moderate reductions in mortality using currently available treatments are plausible, how worthwhile might such effects be, if they could be reliably detected? To some clinicians, reducing the risk of death in patients with CHF from about 30 per 100 patients to about 25 per 100 patients treated may not seem worthwhile. Indeed, if such a reduction were achievable only at the expense of prolonged treatment by an expensive or toxic agent, this might be an appropriate view. On the other hand, since death from CHF is common, a simple, non-toxic, widely practicable treatment that reduced the risk of death by 10 or 20 per cent could, on a national (or international) scale, have substantial public health implications and might prevent or substantially delay several tens of thousands of deaths a year. Many of the patients who would benefit would still be in middle, rather than old age, with a reasonable expectation of an enjoyable life. These absolute gains may be substantial and could considerably exceed the numbers of lives that would hypothetically be saved by a simple cure for all patients with some less common disease such as acute myeloid leukemia.

Strategies in Reliably Detecting Moderate But Worthwhile Reductions in Mortality

The Overall Strategy

The chief aim of this study is to reliably distinguish between two medically plausible alternatives: either there is no worthwhile difference in survival, or treatment confers a moderate, but worthwhile, benefit (e.g., 15 or 20 per cent fewer deaths). Of course, if larger treatment effects were apparent, then either of the two trials could be discontinued prematurely. However, unrealistic over-optimism of treatment effects in previous studies has often led to clinical trials of inadequate size with inconclusive results. Reliable monitoring of these moderate effects therefore requires trials of several thousands of patients in which a total of one or two thousand deaths occur.

Since the number of patients to be entered in the SOLVD study is over 10 times the number entering any previous study of CHF, a similar order of simplicity is required in order to make this study practicable. Fortunately, studies

in which mortality is the chief outcome can be conducted validly with very little data. The large size of the study and the process of randomization ensures reasonable comparability of the groups, so that only data pertinent to certain key subgroup hypotheses need be collected. Since the assessment of most outcomes of interest in SOLVD (total and cardiovascular mortality, myocardial infarction, stroke, overt CHF in the Prevention Trial) do not require elaborate investigations, complicated and intensive tests can easily be minimized in the majority of patients without any appreciable loss of essential information. Therefore, since very little data per patient is required, this overall simplicity can engender a very large study at a practicable effort.

The Substudy Strategy

While simplicity in overall study design facilitates answering reliably the main question of drug effect on mortality, it could result in a lack of mechanistic information of the effects of such treatment on intermediate physiologic outcomes. However, such studies do require specialized tests at repeated intervals, but usually need to be performed only on smaller numbers of patients. Such studies can be carried out satisfactorily in a few centers. These detailed studies will be called substudies and will be implemented in addition to the overall main study. This philosophy of a two-tiered study--an overall simple and large study and several small and detailed studies--overcomes some of the common pitfalls of previous clinical trials: of either not being large enough to answer the mortality questions reliably or of not being truly detailed enough to shed light on mechanisms.

References

1. Cannon PJ, Powers ER, Reison DS et al. A placebo controlled trial of captopril in refractory chronic heart failure. J Am Coll Cardiol 2:755-63, 1983.

2. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: A placebo-controlled, randomized, double-blind study. Circulation 70:271-78, 1984.

3. Pfeffer MA et al. Survival after an experimental myocardial infarction: Beneficial effects of long term therapy with captopril. Circulation 2(2):406-412, 1985.

4. Furberg CD and Yusuf S. Effect of vasodilators on survival in chronic heart failure. Am J Cardiol 55:1110-1113, 1985.

5. Yusuf S, Collins R and Peto R. Why do we need some large and simple trials? Statistics in Medicine 3:409-420, 1984.

II. OVERVIEW OF STUDY DESIGN

In this section, a brief simplified description of the SOLVD study design is given, with the details given in subsequent sections.

A. Program Objective

The primary objective of SOLVD is to answer the following questions:

1. In patients with left ventricular dysfunction (resting ejection fraction equal to or less than 35%) and no overt heart failure, can survival be improved by taking an ACE inhibitor?
2. In patients with left ventricular dysfunction (resting ejection fraction equal to or less than 35%) and with overt heart failure, can survival be improved by taking an ACE inhibitor?

A secondary but very important key analysis is the effect of treatment on survival in all participants in the study (Prevention and Treatment Trials combined). To answer these questions, two concurrent but distinct randomized double blind controlled trials will be conducted. The first is a placebo controlled Prevention Trial. The second is a Treatment Trial and participants will be randomized to "standard" treatment + placebo or "standard" treatment + active agent. "Standard" treatment may vary from center to center but could include digitalis, other inotropic agents, diuretics, or vasodilators other than ACE inhibitors.

Subsidiary objectives of the Study are to assess the effects of treatment in each trial and with combined trials on:

1. Cardiovascular mortality
2. Sudden death including nonfatal cardiac arrest
3. Myocardial infarction
4. Stroke
5. Hospitalization for cardiac failure
6. Quality of life

In addition, development of congestive heart failure will be assessed in the Prevention Trial.

Subgroup Hypotheses

The effects of treatment in each trial may be different in the following subgroups:

1. Low, intermediate and high plasma sodium.
2. Participants on and off a vasodilator at baseline. In addition an analysis will be carried out based on the intent to use vasodilators if the participant's condition worsens.
3. Low, intermediate and high baseline ejection fraction.
4. Participants with ischemic heart disease, hypertensive heart disease and other etiologies of heart disease.

B. Participant Eligibility

All study participants will have an ejection fraction of 35% or less with "symptomatic" participants being randomized into the Treatment Trial and "asymptomatic" participants randomized into the Prevention Trial. Entry criteria are broad in order to facilitate recruitment of as wide a population as possible in whom no qualitative treatment interactions are thought likely. Patients with definite indications or contraindications to ACE inhibitors will be excluded.

C. Medication Tolerance

The administration of medications during the medication tolerance period (from Visit 1 to Visit 2) and the placebo run-in period (from Visit 2 to Visit 3) will be single blind, while during the post-randomization period (after Visit 3) the study will be double blind.

D. Treatment

This double blind study will evaluate the effect of an ACE inhibitor (enalapril) on mortality. The drug will be available in low, intermediate and high doses. This will facilitate using lower doses in those unable to tolerate the higher dose of the agent.

E. Outcomes

The primary outcome of interest for both trials is mortality due to any cause. Subsidiary outcomes for both trials are cardiovascular mortality, sudden death including successfully resuscitated cardiac arrest, incidence of myocardial infarction, stroke, need for cardiac transplantation, hospitalization for heart failure and quality of life. In the Prevention Trial, onset of CHF is an additional outcome of interest.

F. Study Size and Duration

4,600 participants will be randomized to the Prevention Trial and 2,500 participants to the Treatment Trial. Participants will be recruited over a 3 year period and followed for a minimum of two and maximum of five years. This study will have 90% power to detect a 20% apparent[1] reduction in mortality in the Prevention Trial and a 19% apparent mortality reduction in the Treatment Trial.

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[1]The term "apparent" is used to denote the effect that is actually observed in the trial after including non-adherers. The "real" benefit among those who actually take all medications is likely to be somewhat larger.

G. Sample Size Considerations

Sample size requirements for SOLVD are estimated based on the following assumptions:

1. A 3-year mortality in the control group of the Prevention Trial of 17% [10.2%, 3.4%, and 3.4% during the first, second and third years of follow-up, respectively].
2. A 3-year mortality in the control group of the Treatment Trial of 32% [16%, 8%, and 8% during the first, second and third years of follow-up, respectively].
3. A 25% reduction in mortality, given 100% adherence with treatment.
4. A 3-year adherence rate of 85% in the Prevention Trial.
5. A 3-year adherence rate of 80% in the Treatment Trial [dropouts and dropins of 10%, 5%, 5% during 3 years].
6. Non-adherers revert to event rates of the other Treatment group.

Therefore, the expected mortality rates are as follows:

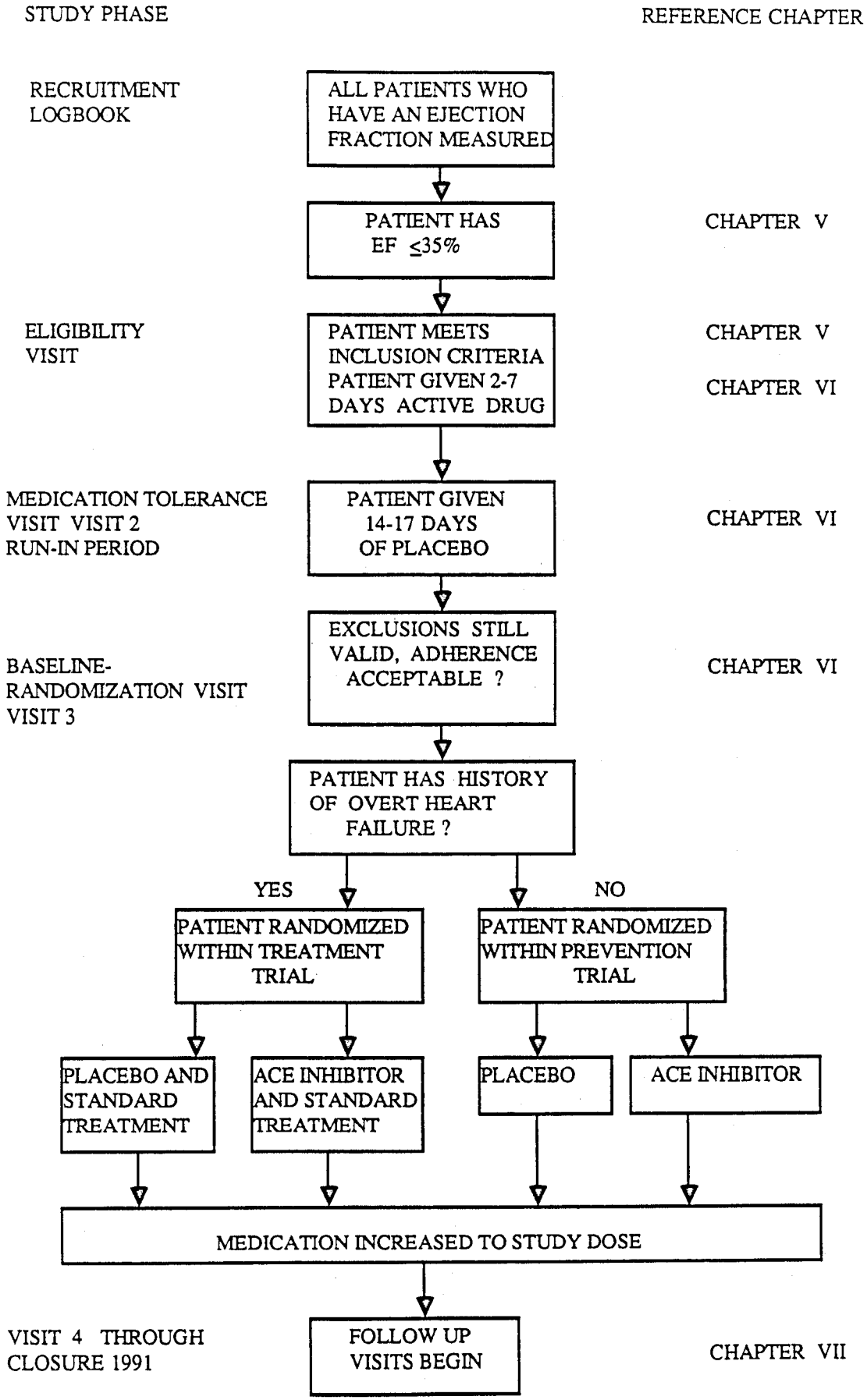
	Prevention Trial	Treatment Trial
Mortality in the control group	17%	31%
Mortality after ACE inhibitors	13%	25%
Effective mortality reduction	20%	19%

The number of participants needed to detect these actual differences with an alpha = .025 (1-sided) and power of 90% are 4,600 and 2,500 participants for the Prevention and Treatment trials, respectively.

These calculations are sensitive to the adherence and mortality rate assumptions. Greater adherence or higher mortality rates would lead to greater power, whereas less adherence or lower mortality rates would lead to lower power. Both of these assumptions will be reviewed during the course of the trial and adjustments in study size may be required to maintain the power at the originally planned level.

A "true" mortality reduction of 25% is a degree of benefit that would be important to detect. To the extent that the two trials can be considered together, a common or average "true" reduction of 18% could be detected with high probability (i.e., an "apparent" 13% mortality reduction).

SOLVD


STUDY PHASE
REFERENCE CHAPTER
RECRUITMENT LOGBOOK
ALL PATIENTS WHO HAVE AN EJECTION FRACTION MEASURED
PATIENT HAS EF ≤35%
CHAPTER V
ELIGIBILITY VISIT
PATIENT MEETS INCLUSION CRITERIA PATIENT GIVEN 2-7 DAYS ACTIVE DRUG
CHAPTER V
CHAPTER VI
MEDICATION TOLERANCE VISIT VISIT 2 RUN-IN PERIOD
PATIENT GIVEN 14-17 DAYS OF PLACEBO
CHAPTER VI
BASELINE-RANDOMIZATION VISIT VISIT 3
EXCLUSIONS STILL VALID, ADHERENCE ACCEPTABLE ?
CHAPTER VI
PATIENT HAS HISTORY OF OVERT HEART FAILURE ?
YES
NO
PATIENT RANDOMIZED WITHIN TREATMENT TRIAL
PATIENT RANDOMIZED WITHIN PREVENTION TRIAL
PLACEBO AND STANDARD TREATMENT
ACE INHIBITOR AND STANDARD TREATMENT
PLACEBO
ACE INHIBITOR
MEDICATION INCREASED TO STUDY DOSE
VISIT 4 THROUGH CLOSURE 1991
FOLLOW UP VISITS BEGIN
CHAPTER VII

III. STUDY ORGANIZATION

A. Steering Committee

The Steering Committee is composed of the Principal Investigators from each of the Clinical Centers, the Coordinating Center, the Central Laboratory and the Project Office. The chairperson of the Committee is appointed by the NHLBI director. The Steering Committee will oversee all aspects of the studies. This includes design of the protocol and manual of operations, monitoring of the progress of the trials and analysis and publication of the study results. The Steering Committee will also consider and act on any special issues related to the studies that may arise. The Steering Committee will establish subcommittees to develop procedures and report their recommendations for approval to the full committee. An Executive Committee comprised of the Chairperson of the Steering Committee (Dr. Bertram Pitt), two Principal Investigators from Clinical Centers (Dr. Jay Cohn and Dr. William Hood), the Principal Investigator of the Coordinating Center (Dr. C.E. Davis) and the NHLBI Project Officer (Dr. Salim Yusuf) will develop Steering Committee agenda and recommendations for consideration and provide study direction between meetings of the Steering Committee.

The Steering Committee will meet twice each year to monitor the progress of the studies and review non-endpoint selected data. The Steering Committee will not have access to the endpoint data until the trials are completed. The current sub-committees are: Recruitment and Screening, Drug Selection, Follow-up, and Publications and Substudies. Other subcommittees can be established by the Steering Committee as needed. The Chairpersons and Co-Chairpersons of each of these committees will be appointed by the NHLBI. In any votes of the Steering Committee each Clinical Center, the Central Laboratory and the Coordinating Center will have one vote. In case of a tie vote, the NHLBI Project Officer will cast the deciding vote. Representatives of the drug company may normally attend the Steering Committee meetings; they may be asked to absent themselves from the discussion when the Committee feels it to be appropriate. The drug company representative is not a voting member of the Steering Committee.

B. Data and Safety Monitoring Board

A Data and Safety Monitoring Board appointed by the National Heart, Lung, and Blood Institute will review the protocols of the main study and substudies during the planning phase and thereafter periodically monitor progress, data, outcomes, toxicity, safety, and other confidential data. Under guidelines provided by NHLBI staff, the Board will indicate when changes should be made in the conduct of the study. This committee is comprised of experts in relevant biomedical fields, biostatistics, and bioethics who

have no direct relationship with the study. Outcome data will be privileged and shared only with the Data and Safety Monitoring Board during Phase II. The chairman of the Steering Committee, staff from the Coordinating Center and Project Office will attend meetings of the Data and Safety Monitoring Board but will not vote on issues brought to the Board. No member of the drug company staff will attend the Board meetings. The Board will meet twice a year during the studies. The Board will make its recommendations concerning study conduct, the feasibility of substudies and ancillary studies including premature ending of the studies, directly to the NHLBI. The members of the Data and Safety Monitoring Board are:

Eugene Braunwald, MD
Chairman
Brigham, Women`s and Beth Israel Hospital

Byron W. Brown, PhD
Stanford Medical Center

Lawrence J. Cohen, MD
Yale - New Haven Medical Center

Max Halperin, PhD
George Washington University

Milton Packer, MD
Mount Sinai Hospital

Elliot Rapaport, MD
University of California

Leroy Walters, PhD
Georgetown University

C. Clinical Centers

There are 23 Clinical Centers in SOLVD. The Principal Investigator and location of each clinic is:

Thierry LeJemtel, MD
Albert Einstein College of Medicine
Bronx, New York

Robert Capone, MD
Brown University
Providence, Rhode Island

Mariell Likoff, MD
Hahnemann University
Philadelphia, Pennsylvania

James Young, MD
Baylor College of Medicine
Houston, Texas

David Johnstone, MD
Dalhousie University
Halifax, Nova Scotia

Kevin McIntyre, MD
Harvard University
West Roxbury, Massachusetts

Martial Bourassa, MD
Montreal Heart Institute
Montreal, Quebec

Michael Herman, MD
New York Medical College
Valhalla, New York

Robert Kohn, MD
State University of
New York
Buffalo, New York

William Rogers, MD
University of Alabama
Birmingham, Alabama

Carl Pepine, MD
University of Florida
Gainesville, Florida

Hubert Pouleur, MD
University of Louvain
Brussels, Belgium

Bertram Pitt, MD
University of Michigan
Ann Arbor, Michigan

Barry Greenberg, MD
University of Oregon
Portland, Oregon

Douglas Stewart, MD
University of Washington
Seattle, Washington

Philip Kirlin, MD
Michigan State University
East Lansing, Michigan

John Gregory, MD
Overlook Hospital
Summit, New Jersey

Deeb Salem, MD
Tufts University
Boston, Massachusetts

Jeffrey Shanes, MD
University of Illinois
Chicago, Illinois

John Kostis, MD
Robert Wood Johnson Medical
Institute
New Brunswick, New Jersey

Jay Cohn, MD
University of Minnesota
Minneapolis, Minnesota

William Hood, MD
University of Rochester
Rochester, New York

Gottlieb Friesinger, MD
Vanderbilt University
Nashville, Tennessee

Coordinating Center:
C.E. Davis, PhD
University of North Carolina
Chapel Hill, North Carolina

Project Office:
Salim Yusuf, MRCP, DPhil
National Heart, Lung
and Blood Institute
Bethesda, Maryland

A complete listing of the Co-Principal Investigators and other SOLVD personnel is in Appendix E.

IV. DRUG SELECTION

A. Introductory statement

An Angiotensin Converting Enzyme (ACE) inhibitor, enalapril, will be used for the Prevention Trial and Treatment Trial. (Detailed justification for drug selection is in Appendix D.) All participants will receive the active agent and placebo during a run-in period, and then if the drug is tolerated and adherence is satisfactory, patients will be randomized to receive either the active drug or placebo. In the Treatment Trial, "standard treatment" with digitalis, diuretics, or non-ACE inhibitors vasodilators may be maintained and adjusted at the discretion of the attending physician.

B. "Standard Treatment"

In the Prevention Trial, the control group will receive only placebo medication in addition to other drugs that they may receive for indications other than CHF. In the Treatment Trial, most participants will already be receiving digitalis and diuretics as "standard treatment," and some will be receiving non-ACE vasodilators as well. Participants in the Treatment Trial will be allowed to continue receiving other medication, including non-ACE vasodilators, and these should be adjusted by the attending physician as necessary. However, if the use of non ACE-inhibitors is not clearly indicated in these participants, an attempt should be made to discontinue these medications during the compliance time period. If a potential participant is stable without these vasodilators, he or she should be randomized. If, however, the participant's health deteriorates and there a clear need for an non ACE-inhibitor vasodilator, the drug should be reinstituted before randomization. The indication for the continued use of the drug should be documented for this participant.

On rare occasions, initiation of treatment with an ACE inhibitor may result in symptomatic hypotension which may persist for several hours. This generally occurs in participants with hyponatremia, hypovolemia, low arterial pressure, or those on high doses of diuretics especially if these have been increased in the previous week. It may also be more common when congestive failure is advanced, i.e., Class IV. The frequency of this problem may be minimized if diuretic dose is reduced prior to treatment and/or a lower dose of ACE inhibitor is used. There is only minimal experience, however, with the use of ACE inhibitor in participants who are already taking other potent vasodilators, other than long acting nitroglycerin (such as prazosin, hydralazine, nifedipine, etc.); and it is not known whether these participants will also have an excessive tendency to develop significant hypotension. This problem should be minimized if not obviated by gradually and carefully initiating active drug therapy at a low dose and

progressing to the higher maintenance dose, while reducing the dose of the non-ACE vasodilator or stopping it altogether if hypotension develops.

Patients with Class IV CHF, hyponatremia and those on other vasodilators other than isosorbide are to be hospitalized for about 24 hours to assess the hypotensive response to the first and possibly the second 2.5 mg dose of enalapril. (The data from the first 100 such patients will be reviewed and a decision whether or not to continue to hospitalize these patients will then be made.)

V. PARTICIPANT ELIGIBILITY AND EXCLUSION CRITERIA, SCREENING AND PRE-RANDOMIZATION VISITS

A. Eligibility Criteria

Participants to be considered for inclusion into this study must satisfy the following two criteria:

1. Age on the day of randomization is between 21 and 80 years, inclusive.
2. Left Ventricular Ejection Fraction (EF) of less than or equal to 35% performed within three (3) months of the day of consent (Visit 1, the Eligibility Visit).

Notes:

i. The EF must be assessed by one of the following techniques:
   a. Radionuclide left ventricular angiography (MUGA or first pass)
   b. Left ventricular contrast angiography (RAO or biplane)
   c. 2-D echocardiogram (either by area-length method or by modified Simpson's rule.)

ii. If more than one method has been performed to determine an EF, or if an EF has been performed several times within the previous three months, the investigator should choose the most recent EF or if using a previous EF, the subsequent ones must be less than 40%. If more than one technique to determine EF has been used within the previous 3 months, then angiographic or radionuclide techniques are preferable to echocardiograms.

iii. The EF to be considered for eligibility may not be performed within seven (7) days of an acute myocardial infarction, reperfusion therapy or cardiac surgery (i.e., CABG or valve replacement).

iv. If the investigator feels that the participant's clinical condition has remained stable since an earlier EF measurement, this need not be repeated just prior to randomization. Otherwise, the investigator may obtain another measurement of EF to assess participant eligibility.

B. Exclusion Criteria

The intent of the following criteria is to exclude only those prospective participants with non-cardiac conditions or diseases likely to independently limit their long-term survival. Furthermore, certain cardiac conditions have been excluded in an attempt to study myocardial disease (pump dysfunction) as opposed to other specific cardiac diseases. Deliberately, exact guidelines have not been specified. Prospective participants meeting any of the following criteria should be excluded from enrollment into the studies:

1. Medical history of intolerance to enalapril.
2. Prospective participant already on an ACE-inhibitor and unable to discontinue.

3. Myocardial infarction in the last 30 days. (This is only a temporary exclusion.)
4. Hemodynamically significant primary valvular or outflow tract obstruction (e.g., mitral valvular stenosis, aortic valvular stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).
5. Constrictive Pericarditis.
6. Complex congenital heart disease.
7. Syncopal episodes presumed to be due to life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion).
8. Any prospective participant in whom cardiac surgery including transplantation is likely in the near future (e.g., participant's name is on cardiac transplant list). In particular, if a potential participant is likely to need CABG surgery in the immediate future, he or she should be excluded, but can be reassessed for eligibility after surgery.
9. Unstable angina pectoris (defined as angina at rest) or severe stable angina (more than an average of 2 attacks per day) despite treatment.
10. Uncontrolled hypertension at the time of randomization (uncontrolled blood pressure shall be defined as systolic blood pressure over 140 <u>AND</u> diastolic blood pressure over 95).
11. Cor pulmonale (right ventricular failure secondary to pulmonary disease).
12. Advanced pulmonary disease ($FEV_1/FVC = \leq 50$, peak expiratory flow rate less than 200 mls/sec, FVC less than 60% of predicted).
13. Major neurologic diseases which could lead to early death (i.e., Alzheimer's disease, advanced Parkinson's disease).
14. Cerebrovascular disease (e.g., significant carotid-artery stenosis) that could potentially be complicated or rendered unstable by administration of an ACE inhibitor (N.B. Prospective participants who may be at increased risk for stroke should their blood pressure drop excessively. The mere presence of a carotid bruit need not in itself exclude participants.)
15. Collagen vascular disease other than rheumatoid arthritis (i.e., systemic lupus erythematosus polyarteritis nodosa, scleroderma).
16. Suspected significant renal artery stenosis.
17. Renal failure (i.e., creatinine > 2.5 mg/dl or dialysis patients).
18. Malignancies, except for surgically cured skin cancer, carcinoma-in-situ, or 5 years free of disease after the diagnosis of solid-tumors.

19. Requirement for immunosuppressive therapy. (The use of steroids for non-life threatening diseases such as arthritis is not an exclusion.)
20. Active myocarditis.
21. Significant primary liver disease.
22. Likelihood of a prospective participant being nonadherent due to chronic alcoholism, lack of a fixed address, drug addiction, etc.
23. Other life threatening disease or prospective participant who is not realistically expected to be discharged alive from the hospital.
24. Pregnant woman or woman of child-bearing potential who is not protected from pregnancy by any method.
25. Prospective participant who is simultaneously on other investigational drug protocols (other than for compassionate use).
26. Failure to give consent.

C. Recruitment, Screening and Pre-randomization Visits

Prospective participants to be considered for the studies are to be recruited from among the participating hospitals and physicians identified by each of the collaborating Clinical Centers. The enrollment process will consist of four steps:

(i) Initial screening procedures.
(ii) Eligibility visit
(iii) Medication tolerance visit
(iv) Baseline (Randomization) visit

Participant eligibility will be evaluated at each step and those completing all four steps will be randomized.

1. Initial Screening

At the initial screening, investigators are to identify the pool of potential study participants. This can be achieved by either reviewing past medical records, logs of invasive and non-invasive laboratories, referrals by private physicians, or other sources of recruitment. All participants that have an EF of $\leq$ 40% or entered the hospital for congestive heart failure will be entered into a standardized logbook to be provided to each Clinical Center by the Coordinating Center.

The logbook will contain basic screening criteria such as the prospective participant's name, age, EF, date of EF, as well as other necessary identifying information (name of hospital or physician). If the participant is potentially suitable for the study, he/she is to be scheduled for the Eligibility Visit. All centers must start maintaining the log from 2/1/86 onwards in order to facilitate early participant recruitment. However, wherever possible, Clinical Centers are encouraged to maintain participant logs even prior to this. During the recruitment phase, a monthly summary table that outlines the number of

participants newly entered into the logbook, the number with an EF $\leq$ 35%, the number with an EF > 35% but $\leq$ 40%, the number with CHF but an EF $\geq$ 40%, the number with CHF but EF not available, and the number of participants invited to attend the Eligibility Visit, is to be mailed to the Coordinating Center from each Clinical Center.

2. Eligibility Visit (Visit 1)

Participants attending the Eligibility Visit will have laboratory determinations, a simple physical examination, and an Eligibility Visit Form completed. The laboratory determinations (henceforth to be called the standard laboratory battery) include hematocrit, total white blood count, percentage of neutrophils, percentage of lymphocytes, sodium, potassium, blood urea nitrogen, creatinine and the number of positives on proteinuria. Informed consent will be obtained from all eligible prospective participants for the entire study. A 20 ml blood sample is to be drawn and spun down and the plasma frozen and transported to a central laboratory if the participant is randomized (Appendix A). Supine and sitting heart rate and systolic and diastolic blood pressures will be recorded. Participants will then be provided with 2.5 mg. BID enalapril for the medication tolerance period. They will then be scheduled for their next visit, which should take place 2 to 7 days later.

Potential participants who are NYHA Class IV or who have known sodium values less than 130 meq/l must be hospitalized for 24 hours for blood pressure monitoring while taking the 2.5 mg BID enalapril. 24 hour hospitalization for monitoring is also required for potential participants who are taking vasodilators other than isosorbide as indicated for treatment for congestive heart failure. (See also section 1.3.10 in the Manual of Operations, Hospitalization of Participants at High Risk of Hypotension.) Participants who are taking a calcium channel blocker for angina or vasodilators for angina or hypertension, are not required to be hospitalized. Continued use of a non-study vasodilator (isosorbide, calcium blockers, hydralazine,prazosin, etc.) in participants should be documented. Physicians are encouraged to discontinue such drugs wherever feasible in order to minimize the number of participants on non-study vasodilators in SOLVD.

3. Medication Tolerance Visit (Visit 2)

At the Medication Tolerance visit, any adverse symptoms (such as symptomatic hypotension) will be checked. Participants that adhered to the medication regimen (75% or better with at least some medication taken in the two days prior to this visit date), will have the standard battery of laboratory determinations performed. Participants who do not tolerate the active

agent may be completely excluded or may be rescreened after modification of appropriate ancillary drug therapy. Participants who are still eligible to continue will then be provided with matching placebo to assess adherence and scheduled for their next visit, which should take place in about two weeks (14-17 day window). Any participants who have a clearly indicated need to continue on the use of non ACE-inhibitor vasodilators will have this documented on the form at this visit.

4. Baseline (Randomization) Visit (Visit 3)

At the Baseline visit, the participant's adherence with the placebo during the run-in period will be evaluated by pill count. If 80% or more of the tablets have been taken, no reasons for exclusions have occurred or have been detected in the preceding two weeks, the participant appears to be stable, and is willing to participate, then the participant is to be randomized. Any participants who have a clearly indicated need to continue on the use of non ACE-inhibitor vasodilators will have this documented on the form at this visit. All entry data will then be collected and entered on the visit form. Participants will then be classified as eligible for either the Prevention or Treatment Trial according to the criteria outlined in section D.

Participants who are found to meet all of the study entry criteria are randomly allocated to either enalapril or placebo. Each Clinical Center is provided with packages of medication identified only by the study identification number. Clinic personnel enter the pill count data for the placebo run-in period, other information to verify that the participant is eligible and the trial (Prevention or Treatment) into the Center's personal computer (PC). The PC then assigns a randomization number which is identical to one of the study identification numbers on the packages of medication. The participant is given the medication corresponding to this number.

ONCE RANDOMIZED THE PARTICIPANT SHOULD BE FOLLOWED THROUGHOUT THE DURATION OF THE STUDY, EVEN IF HE/SHE STOPS STUDY MEDICATION.

Every attempt should be made to maintain the participant on the study drug throughout the study although in certain cases (such as safety), the study drug may be discontinued. It should, however, be possible to keep this group of participants to a very small number as low doses of all medication will be available. Any such participants should be followed

and would be part of the analysis of all randomized participants (Intention to Treat).

D. Stratification Criteria

Randomization will be stratified by Clinical Center and by whether the participant is eligible for the Prevention or Treatment Trial.

The Prevention Trial is to be comprised of participants with no overt heart failure, that is, participants with little or no limitation of exercise tolerance due to dyspnea or fatigue and who do not require digitalis, diuretics or vasodilators for heart failure. The participants in the Prevention Trial can be viewed as belonging to one of the following two groups (which are not formal stratification criteria for randomization but may well be used for retrospectively stratified analyses):

IA. Participants with EF $\leq$ 35% and who are not on any cardiac medications.

IB. Participants with EF $\leq$ 35% who require medications for cardiovascular problems other than heart failure.

Such participants may be on beta-blockers, calcium channel-blockers, or even diuretics or vasodilators, but these drugs should have been used for indications other than CHF; e.g., hypertension or angina pectoris. While it is recognized that an occasional participant may be on digitalis only for control of atrial fibrillation, investigators are encouraged to acknowledge that atrial fibrillation in the setting of poor left ventricular function usually co-exists with other symptoms of heart failure and are urged to consider whether such participants are more appropriately entered into the Treatment Trial. In sedentary patients, if there is doubt as to whether they are truly asymptomatic, investigators are urged to perform either a formal or informal exercise test (such as walking the patient one flight of stairs).

The Treatment Trial is to be comprised of participants with overt heart failure, that is, participants who have currently or in the past had clear clinical evidence of CHF (e.g., shortness of breath on exertion or at rest, evidence of fluid retention such as peripheral edema, pulmonary congestion, jugular venous distension and who currently require treatment with diuretics, and/or inotropic drugs and/or vasodilators for symptomatic relief). The participants in the Treatment Trial can be viewed as belonging to one of the following two groups:

IIA. Participants with EF $\leq$ 35% and who require digitalis and/or diuretics for heart failure.

IIB. Participants with EF $\leq$ 35% and who require vasodilators (usually in addition to digitalis and/or diuretics) for heart failure.

Note: Minimizing the number of participants entering the SOLVD on non-study ACE-inhibitors is critical to maintain a treatment differential and statistical power. Therefore, physicians are encouraged to withdraw vasdilators during the run-in period. If a participant clearly needs vasodilators, this should be documented.

VI. INTERVENTION

A. Drug Administration

After participants are identified as potentially eligible for the SOLVD Study by having an ejection fraction $\leq$ 35%, they will be screened for exclusions. At Visit 1, the Eligibility Visit, eligibility will be ascertained, written consent will be obtained, key clinical data will be recorded, blood will be obtained for storage and determinations which will be measured centrally, and for the standard battery of laboratory determinations to be done locally (see section V.C.2.), and 2-7 days of 2.5 mg. BID enalapril will be dispensed (see the Manual of Operations section 1.3.10 for Hospitalization of Patients at High Risk of Hypotension). Participants are not to be told that they are receiving active medication at this stage (the study is single blind). The participant will be instructed to take the study drug for 2-7 days and the appointment for the next visit will be made. Twenty-four hours after the initial dose is given, a phone call should be made to the participant to assess any adverse symptoms.

At Visit 2,[1] the Medication Tolerance Visit, an assessment of whether or not the participant has suffered adverse reactions will be done. Additionally, blood will be drawn for the standard battery of laboratory determinations. If the participant has not experienced any adverse symptoms, he/she will be started on 14-17 days placebo (single blind) to assess adherence. 24 hours after the second dose is given, a phone call should be made to the participant to assess any adverse symptoms. The participants are not to be told that they are receiving placebo. (The study remains single blind.) The laboratory results would usually be available the next day, and will alert the physician to possible pre-renal azotemia. The participant will be excluded from the study if he/she had a significant hypotensive bout secondary to the active agent that cannot be controlled with other measures or if major changes in renal function are detected. If the participant was only moderately or mildly symptomatic, several treatment options could be considered. These might include decreasing concomitant diuretics or other vasodilators, or liberalizing the intake of sodium if the participant was on a restricted sodium diet. If the participant is felt to be a reasonable candidate for either Trial, a new medication tolerance period could be tried after modifying his/her ancillary drug regimen. If no adverse reactions during the medication tolerance period occur and adherence to the test dose is at least 75% during the 2-7 day medication tolerance period (with at least some drug taken in the last 2 days of the

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[1] Some potential participants will be using non-study vasodilators. At Visit 1 or Visit 2, discontinuation of the use of these vasodilators should be considered.

test period), then the participant will be started on placebo BID to assess adherence. There is only one recycling procedure allowed for each prospective participant for the medication tolerance or the placebo run-in periods.

At Visit 3, the Randomization Visit, adherence to the placebo run-in period will be assessed and attention directed to discovering whether or not the participant`s health is stable and he/she meets the inclusion criteria. If the participant's adherence during the placebo run-in period is at least 80%, then a clinical history will be taken, medications currently used will be assessed and a physical examination will be performed.

At this time the participant will be randomized and given enalapril 5 mg. BID or placebo (Dose 2). If the clinic physician considers the participant to be at high risk, the recommended beginning dose for this participant should be 2.5 mg. BID. If the participant tolerates the beginning dose for a week, the dosage should then be increased to 5 mg. BID. At this stage the study becomes double blind for the rest of this participant's involvement. The participant will be instructed to take his/her medication on the day of the clinic visit and 24 hours later a phone call will be made to assess any symptoms. If the participant has dizziness or fainting, modification of other treatments as detailed above could be made. If the participant tolerates that dose, he/she will then continue on (Dose 2) for 2 weeks, until Visit 4.

Visit 4 will occur 2 weeks after randomization (Visit 3). A history will be taken and physical examination performed with attention paid to symptoms of orthostatic hypotension, such as syncope and the aggravation or new onset of angina. Blood for the standard battery of laboratory tests will be drawn and clinical data will be obtained. This optional visit may occur at the clinic or the participant's private physician's office. Only laboratory data are required for this visit. If the participant is not tolerating medication, further modification of nonstudy drugs may have to be made. At Visit 4 the physician has the option to increase, decrease or maintain the dose of the study medication. If the participant tolerates Dose 2, enalapril or placebo will be increased to 10 mg BID (Dose 3) and again a phone call 24 hours later will be made to review the results of laboratory tests done on the preceding day and any new symptoms. If the participant tolerates Dose 3, this will be continued for a 4-week period and thereafter throughout the study.

Dosage options will include Doses 1, 2 or 3, taken once or twice daily. The dose of the study medication may be increased or decreased at the discretion of the investigator, but whenever possible investigators are encouraged to maintain participants on 10 mg. BID or the highest possible dose tolerated. Should a participant develop azotemia, hyperkalemia, mild proteinuria, or symptoms of orthostatic hypotension, investigators are

encouraged initially to modify the dose of any nonstudy drugs such as diuretics, vasodilators or potassium supplements rather than modifying the study drug.

Specific guidelines for identifying adverse effects, either at the Medical Toleration Visit (Visit 2) or subsequently are as follows: Azotemia is defined as an increase in serum creatinine by 1.0 mg/dl or greater over the previous value, not to exceed 4.0 mg/dl. Hyperkalemia is defined as an increase in serum potassium level to 5.5 mEq/L or greater. Proteinuria is defined as the appearance of two-plus protein in the urine when it was previously absent, or an increase by two grades if already present, e.g., three-plus instead of one-plus. Symptomatic hypotension is defined as any unexplained syncopal episode, or any episode of dizziness or lightheadedness experienced in the upright position, whether or not a blood pressure measurement could be made at the time of the symptoms. Ordinarily a decline in upright blood pressure should be demonstrable in such patients if they are under observation when the symptoms occur. Occurrence of one or more of these adverse effects requires reduction in the dose of study medication, or stopping study medication with restarting at a lower dose, or reduction in the dose of other medications such as diuretics and/or non-ACE vasodilators. The exact method of treating an adverse reaction will be at the discretion of the patient's physician, and should depend upon the severity of the adverse reaction and the clinical setting in which it occurs.

B. Some suggested alterations in other drugs at onset of active drug treatment

At the physician's discretion, participants may need some modification of their usual medication. For example, those participants who recently had an increase in diuretic dosage, or who are dehydrated or hyponatremic (<130 mq/l), could have their diuretic discontinued for a period of about 24 hours. If the participant can tolerate being off diuretics for 2-3 days, earlier discontinuation may further minimize first dose hypotension.

In order to avoid hyperkalemia secondary to a drop in aldosterone levels, some physicians may wish to consider temporarily withholding potassium sparing diuretics during treatment initiation and rechecking serum potassium one week later.

C. Management of Study Drug During an Intercurrent Event

It is anticipated that intercurrent events may necessitate either no change in study drug administration, transient stopping of the study drug or, in some cases, irreversible termination of the study drug. It is recommended that unless clear contraindications arise, the study drug should be continued at the same or lower dose or only briefly interrupted for the duration of the

intercurrent event and then reinstituted as soon as possible. Some typical situations are outlined below:

1) Worsening congestive heart failure: Study drug can usually be continued although it may be stopped or continued at the discretion of the attending physician. The participant's heart failure should be treated utilizing conventional pharmacologic measures (other than an "open-label" ACE inhibitor) and, once the participant is stable, the participant should be continued on the same dose of the study drug (and additional pharmacologic therapy, if needed). Physicians are encouraged to maximize the doses of diuretics or digitalis before using any vasodilator. If these drugs do not control symptoms, then vasodilators (first non ACE-inhibitor drugs, then ACE-inhibitors) or inotropic agents may be tried.

2) Acute myocardial infarction: The protocol does not require stopping study drug should the participant develop an MI during the study. However, during the study, at the discretion of the attending physician, the study drug may be stopped during the early phase of convalescence following acute myocardial infarction. If the drug had been discontinued, the physician is encouraged to restart the study drug in low doses as soon as possible and preferably within 2 weeks. The dose can then be gradually increased to the maximum tolerated level.

3) Hospitalization for other medical illnesses, cardiac or non-cardiac surgery (other than cardiac transplantation): Although it may be necessary to discontinue the study drug during the course of the acute medical illness or surgical convalescence, it is hoped that the study drug will be cautiously reinstituted prior to the participant's discharge, increasing the dosage to the previous maintenance dose as tolerated.

Certain events may necessitate stopping the study drug for a more prolonged period. Examples are as follows:

1) Cardiac transplantation: The study drug will not be continued after transplantation.

2) Participant request: Participants should be encouraged to continue on their treatment regimens throughout the trial. However, should the participant insist on being withdrawn from the study drug, the study drug can be discontinued. These participants should be encouraged to keep their regular clinic appointments and whenever possible, the study drug should be reinstituted.

3) Suspected adverse drug reaction: If a severe adverse reaction thought to be related to the study drug occurs, the study medication may be discontinued temporarily, and then if medically feasible, reinstituted.

4) Need for ACE-inhibitor therapy: While management of an exacerbation of symptomatic CHF with non ACE-inhibitor therapy is strongly encouraged, it is recognized that the referring physician may insist on the use of an open-label ACE inhibitor. The study drug should then be terminated. Individual clinical center Principal Investigators should

share in the decision for starting patients on open-label ACE inhibitor therapy, whenever possible. Institution of open-label ACE-inhibitor therapy should only commence after all other pharmacologic means of controlling heart failure have failed (e.g. increasing diuretics, adjustment of digoxin dosage, use of other vasodilators, etc.) and should be documented on the appropriate form.

D. Time Frame for SOLVD Visits

Visit #	Visit Name (if any)	Medication to be given	Time period until next visit	Time period from Randomization
1*	Eligibility	2.5 mg BID enalapril	2-7 days	Minus 16-24 days
2*	Medication Tolerance	placebo BID	14-17 days	Minus 14-17 days
3	Baseline (randomization)	5.0 mg BID enalapril or placebo bid	2-3 weeks	0
4**	Follow-Up	10 mg BID enalapril or placebo BID	3-4 weeks ± 1 week window	2-3 weeks
5	Follow-Up	Maintenance dose	2.5 mos.	6 weeks
6 etc.	Follow-Up	Maintenance dose	Every 4 months	4 months, etc.

* An attempt should be made to minimize the use of non-study vasodilators in participants by discontinuing their use during this period.

** Optional clinic visit but mandatory laboratory determinations.

VII. DATA COLLECTION

A. Overview

The data to be collected will be kept to the minimum needed to achieve the main goals of the study. This section will outline the data to be collected for study purposes. Additional data may be needed for ancillary studies, substudies or local participant management (but are not covered here).

The data collected will be of two types: 1) data to be entered into the central data base (left hand side of a printed form) and 2) data recorded for local clinic use only (right-hand side of a printed form), as an aid to clinic personnel but not entered centrally. Study forms will clearly separate the two, and only the study data will be transferred into the main database. Thus, the computer screen will include only the items required for the study.

Data collection falls into 5 basic categories: 1) eligibility data, 2) medication tolerance data, 3) entry (baseline) data, 4) regular post-randomization follow-up data, and 5) special post-randomization follow-up data (death and hospitalizations).

B. Eligibility Data

1. Screening Log. Each center will keep a log of prospective participants with their ejection fractions, some identifying information (name, age, sex). This information would not be entered into the computer by the clinics. A summary of this log is sent monthly to the Coordinating Center as a means of monitoring recruitment, as well as describing the broader population of low EF patients.

2. Eligibility Form. Participants thought to be eligible for SOLVD will have a pre-randomization visit at which key eligibility and identifying information will be obtained (Form in Appendix B). Chapter V contains a complete list of the eligibility criteria.

C. Medication Tolerance Data

Each prospective participant will go through a medication tolerance period (2-7 days). This is to test for acute toxic reactions to the active drug. Reasons for medication intolerance are recorded and the standard battery of laboratory data are determined to monitor specific hematologic and biochemical abnormalities which may take place. (See Chapter V and Appendix B)

D. Entry Data

After the two-week run-in phase following the Medication Tolerance visit, participants who meet adherence standards and continue to be eligible are randomized. At this point, baseline data are collected. (See Baseline Form, Appendix B.)

E. Regular Followup Visit Data

1. Followup Schedule. The followup visits should occur at 2 weeks and 6 weeks post-randomization and then at 4, 8 and 12 months. Thereafter (years 2 to the end of the study), clinic visits will be required at 4 month intervals. Because of the high probability of death or complications in the Treatment Trial, participants should be contacted by telephone at least once between visits to ascertain if any study "event" had occurred and to encourage adherence. Likewise, participants in the Prevention Trial who become symptomatic should also be contacted by telephone between visits.

Any participant who misses a study visit shall be contacted by telephone as soon as possible to reschedule the regular followup visit before the participant runs out of tablets. If the participant has died or was hospitalized since the last visit, the appropriate forms should be completed. Each visit after the first six weeks (i.e., after Visit 5) shall have a designated "time window" of plus/minus 3 weeks, and an attempt should be made to complete the clinic visit in this window even if only telephone contact is made. In extraordinary circumstances, if the participant cannot be seen in the time window, sections A, B and C of the followup forms can be completed by telephone (See Appendix B).

2. Followup Procedures. The current address and telephone number of the participant, the participant's employer and physician should be verified by the study nurse at each visit.

At two and six weeks post-randomization and every annual visit after randomization, the standard battery of laboratory data will be obtained (see Chapter V).

Data concerning toxicity of and adherence to study treatment, discontinuation or change in study drug dosage, use of non-study medications, occurence of angina or syncope, and hospitalizations should be collected by the study nurse at each visit and entered on the study followup forms.

Blood pressure, heart rate and weight may be recorded by either the study nurse or physician at each visit. The study physician should determine and record whether there has been a change in the severity of CHF since the last visit

The above data will be collected on the Follow-up Interview and Examination Form.

If there has been discontinuation or alteration of the study drug dosage, hospitalization, or death during the interval since the last visit, then one or more of the three special study forms should be completed by the study nurse and validated by the study physician.

(a) Adherence measures. Pill counts will be used to determine adherence which will be reported on the followup form. Every effort to maximize adherence should be encouraged at every visit. If adherence is less than 90%

and this is not due to discontinuation or change in the dosage of the study drug at the request of a physician, then the participant should be counselled to determine the reason for poor adherence. If it is determined that reducing the dose or altering the frequency of administration to once a day may improve medication adherence by reducing side effects or for any other reason, then consideration should be given to reducing the drug dose or frequency of drug administration. In general, only in cases of extreme adverse reactions should the study drug be withdrawn completely. When there are no medical reasons for non-adherence, strategies for increasing adherence should be discussed with the patient.

(b) Study drug side effects. Enalapril is well tolerated but some adverse effects have been reported. Symptomatic hypotension has been observed in some patients. Azotemia is also not uncommon, especially in patients with hypovolemia or impaired renal function. A very small percentage of patients experience skin rash, cough and very rerely laryngeal edema. These changes are generally reversible with reduction in drug dose or cessation of therapy. Suspected adverse reactions should be documented on the Followup form. (See pages 36-41, 43-46 of the Manual of Operations for details.)

(c) Change in the severity of symptoms of CHF

(i) New onset of CHF in patients of the Prevention Trial:

The onset of congestive heart failure in a participant in the Prevention Trial will constitute a secondary endpoint and will be defined by the onset of symptoms and/or signs of congestive heart failure which, in the opinion of the Principal Investigator, are sufficiently severe to warrant pharmacologic treatment. This definition is the same as that used to stratify participants at baseline to the Prevention or Treatment Trials. For those participants in the Prevention Trial in whom pharmacologic treatment, consistent with treatment for CHF has been instituted in the interval since the last visit by a non-study physician, the study physician will be responsible for ascertaining the reason for initiation of therapy. If there is documented clinical or radiographic evidence of peripheral or pulmonary congestion, this should be recorded.

(ii) Exacerbation or amelioration of symptoms of congestive heart failure:

In participants of the Treatment Trial and participants of the Prevention Trial who have developed CHF, the study physician should document changes in the presence or severity of symptoms.

d) Quality of Life

The Quality of Life Form is a self-administered test. It should be completed by each participant at Baseline (Visit 3), 6 weeks (Visit 5), and 12 months post-randomization (Visit 8), and at the end of the study.

The study nurse should check the form after completion to make sure each item has been answered.

E. Special Followup Visit Data

(1) A Hospitalization Form should be completed for each hospitalization since the last visit. Study nurses should request hospital records for each hospitalization, and the study physician should determine and document the events leading to hospital admission.

(2) Alteration in Study Drug Dosage

If, at the request of a physician, the study drug has been discontinued or the dose reduced since the last visit, the Alteration in Study Drug Dosage Form should be completed. This will require information regarding the reason for the alteration in drug dosage. This information may be obtained from hospital records but might also require personal contact with the responsible physician.

If the study physician wishes to reinstitute or increase the dose of the study drug, the Alteration in Study Drug Dosage Form should also be completed, providing information about the new doses and reason for alteration.

(3) Mortality

The First Notification of Death Form should be completed immediately following ascertainment of the death of a study patient. The vital status of all participants who fail to attend scheduled visits should be determined as quickly as possible. Deaths should be reported immediately to the Coordinating Center using the First Notification of Death Form, even if supporting documents are not yet available.

Once the cause of death is ascertained, the Final Designation of Death Form should be completed. On the basis of all available clinical information, each death should be classified as cardiovascular or non-cardiovascular. If cardiovascular, the study physician using whatever information is available, should state his or her belief as to whether the death was cardiac, stroke or other and if the death was cardiovascular, whether the death was sudden or not should also be specified.

F. Monitoring Data Quality

Since the integrity and credibility of the study results depend on data quality, data collection will be monitored on a regular basis during the study. The data management system provided by the Coordinating Center will perform the majority of edit checks on the data as they are entered at the clinical sites. Reports will be generated for the Steering Committee that depict (for each clinic) timely receipt of data, consistency of data over forms, error rates, screening and randomization rates, and participant follow-up.

Quality assurance measures will be initiated before the start of the study with training and certification of clinic staff in operational procedures. Periodically throughout

the study, the Coordinating Center staff will provide additional retraining and recertification as necessary. Staff from the Coordinating Center will provide assistance to the Clinical Centers in answering questions about the protocol and helping to solve operational problems. On visits to the Clinical Centers, Coordinating Center staff will compare data from randomly selected data forms with data on the central files. (A hard copy record of key data should be maintained locally at each Clinical Center.) The Coordinating Center staff will also coordinate data collection activities with the other program agencies.

It is the responsibility of the Principal Investigator to insure that all data for SOLVD from his or her Center are representative and accurate. Since the entry criteria and possible endpoints are crucial to the study, the Principal Investigator will meet with the staffs of the participating hospitals on a regular basis to review the entry criteria, (particularly the validity of the ejection fraction measurements) for all patients entered, and to review the mortality information on any participant who dies.

Any Clinical Center which uses echocardiograms for the measurement of ejection fraction will submit data to the Coordinating Center which demonstrates a good correlation in ejection fraction measurements by echocardiogram and one of the other two methods. Alternatively the first five echocardiograms done at a Center will be recorded on a video cassette tape and sent to the Echocardiogram Core Lab at the Houston Clinical Center. The Coordinating Center will identify a 5% random sample of participants entered. The Clinical staff will ensure that the ejection fraction measurement data are copied and made available for re-reading by the Coordinating Center cardiologist. If there are questions concerning the eligibility of the ejection fraction, a cardiologist from one of the other centers will be asked to provide a third reading. The analysis of this random 5% check will be made available to the DSMB and Executive Committee annually.

VIII. PARTICIPANT SAFETY AND CONFIDENTIALITY

A. Introduction

Assuring safety and confidentiality of participant data are essential components of the SOLVD protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his/her care, while the Data and Safety Monitoring Board will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in mortality and drug toxicity.

B. Exclusions

Persons with contraindications to the study drug will not be eligible to be enrolled. Exclusions are detailed on page 2 in Section V.

C. Initiation of Treatment

Two to seven days of enalapril will be given to all potential participants at the end of the first pre-randomization visit to screen for early intolerance to the study drug. For participants subsequently enrolled, dosage may be adjusted up or down within the range of 2.5-10 mg. QD or BID at the discretion of the study physician. (Details in Section VI)

D. Adverse Reactions and Discontinuation of Study Drug

At all follow-up visits, possible adverse effects of the study drug will be assessed. The study physician may, at his/her discretion, reduce or stop administration of the study drug. Depending on the situation, the change may be temporary or permanent. Examples of situations which may require a temporary reduction or elimination of the study medication include: worsening congestive heart failure, acute myocardial infarction, or hospitalization for other illnesses. Events which may require permanent cessation of the study drug include: cardiac transplantation, adverse drug reaction, need for active therapy with closely related compounds, and participant request. (Details in Section VI)

E. Unblinding Procedure

Unblinding should not usually be necessary. However, treating physicians have the option of removing participants from the study who are suspected of having intolerable side effects from an ACE inhibitor. Similarly, participants who are felt clinically to be unresponsive to their "standard" therapy, and in need of an ACE inhibitor can have the study drug stopped, and then be started on a known ACE inhibitor. (See Section VI). These participants, however, will continue to be part of the study and will need to be followed until termination of the study. Participants who are to undergo surgical procedures should be treated as if they are on the active drug. This may result in temporary

drug withdrawal but should not necessitate unblinding. Under unusual circumstances chiefly relating to participant safety, unblinding may be necessary. This should usually be done after consultation with the Principal Investigator of the clinic involved, the Chairman of the Steering Committee or the Project Officer.

In extreme emergencies (i.e., accidental overdosage, etc.) the hospital pharmacy will be able to identify treatment assignments. The Coordinating Center must be notified within 24 hours that a code has been broken.

F. Confidentiality

The confidentiality of all participant information must be protected, both at the Clinical Centers and at the Coordinating Center. Paper records and computer files must be appropriately safeguarded from unauthorized access.

Paper records for study participants will be stored only at the Clinical Centers. These records should receive the same care as would ordinary medical records. If it is not possible for the study forms to be handled by the hospital's medical record room, they should be stored in locked filing cabinets within secure office space. Only study personnel who have completed SOLVD training and certification in data handling should have access to study forms.

Similar care is needed in the handling of the computer records of study data stored in each Clinical Center. All data files created by the study data management system (DMS) will be encrypted using a software implementation of the National Bureau of Standards Data Encryption Algorithm, using a key known only to the Coordinating Center staff. This will prevent any access to the data using software other than the DMS.

Access to the data using the DMS will be controlled by a system of user IDs and passwords. Each Clinical Center staff member must complete the SOLVD data handling training and certification program before being given an ID and password to use the DMS by the SOLVD Clinic Data Coordinator. The privileges allowed to each ID can be individually set by the Data Coordinator. The DMS will require each user to change his/her password every month, and obvious passwords (e.g., the person's name, common words, etc.) will not be accepted as passwords. All passwords stored within the DMS will be encrypted using the DES algorithm mentioned above; decrypted passwords will never be displayed or stored within the system.

Confidentiality of information within the Coordinating Center will be protected through a variety of procedures and facilities:

1. The confidential nature of the data collected, processed, and stored at the Coordinating Center is explained to all new personnel, who must sign a "confidentiality certification" after discussion with their supervisor.

2. All access to Coordinating Center office space containing data is controlled through a single reception area. All visitors are screened and cannot enter the area without a Coordinating Center escort. All office space is locked after working hours.

3. All participant data sent to the Coordinating Center is encrypted as described above. All diskettes containing participant data are stored in a single suite of interior rooms within the Coordinating Center. This suite is accessible only to authorized staff and is locked when unattended.

4. All participant data stored on the University's mainframe computers are likewise encrypted. In addition, all such datasets are protected by passwords which must be supplied before the data can be accessed. Passwords are released only to Coordinating Center staff with a need to use the particular file, and are changed on a regular schedule.

5. Copies of all data received are stored off-site by a commercial data security firm. The data are stored in an environmentally controlled bank vault, protected 24 hours a day by automated security systems and human security personnel. All personnel employed by this firm are bonded, and required to sign confidentiality agreements analogous to those signed by Coordinating Center staff.

6. All printouts, plots, and reports containing individually identifiable data are produced on printers and plotters within the Coordinating Centers secure office space. All such reports are kept in locked storage cabinets within the Coordinating Center.

7. No participant identifiers will be present on any data for files transmitted to the Data Monitoring Committee or the Government.

IX. ADHERENCE

A. Background and Rationale

Adherence to the prescribed medication regimen will be monitored by means of pill count. The aim of such monitoring is to maintain the highest possible level of adherence in individual participants. Adherence will be maintained at acceptable levels by a combination of educational efforts and behavioral modification techniques. The techniques are designed (a) to inform the participant of his/her responsibilities to the protocol, (b) to determine causes of nonadherence, and (c) to apply remedies to improve unacceptable adherence.

B. Specifics of Proposed Methodology

1. Protocol for Determining Adherence Potential. At Visit 1, the eligibility Visit, all participants will be given 2 to 7 days of enalapril, 2.5 mg. BID. At Visit 2, the medication tolerance visit, a pill count of the drug will be done to see that the medication was taken. Once renal function is assessed, participants will be given a 14 to 17 day supply of placebo. At Visit 3, the participant's adherence to the approximately two week placebo regimen will be expressed as the number of pills actually taken as a percentage of those expected to be taken. If the adherence rate is less than 80%, then the subject will be ineligible for enrollment.

2. Protocol for Monitoring Adherence. The measurement of adherence will be based on pill count. The adherence rate will be determined by computer calculation at each visit by comparing the number of tablets actually taken to the number that were supposed to have been taken. The adherence rate will be determined from the dose that the participant currently is prescribed.

3. Standard Procedures. Following initial evaluation, participants will be instructed at the eligibility visit in procedures required of them for successful participation. Participants will be provided with information on congestive heart failure and treatment effects, expectations for personal benefit from participation, motivation for adherence with treatment regimens and research protocols, and previous experience with medical treatment for chronic diseases.

4. Special Procedures. Minimum standards for adherence will be established by the Steering Committee with respect to the performance of individual participants as well as average values across centers. However, with individual participants the goal is always to achieve 100% adherence at each visit. Coordinators will be alerted to possibilities of poor adherence in association with dosage increases, change in regimen, toxic side effects, multiple drug

regimens, and hospitalizations affecting medication usage. When participants do drop out of the study, intensive efforts, including telephone and personal contact, will be made to retrieve participants for clinic visits and, where possible, to reinstitute medication. Whenever adherence falls below a critical level (e.g., <80%), the clinic physician should additionally be involved to ascertain remediable causes of poor adherence and to institute appropriate measures that can improve adherence.

X. SUBSTUDIES AND ANCILLARY STUDIES

A. Introduction

It is the expressed intent of the Steering Committee and the NHLBI to derive the maximum amount of scientific information from the SOLVD database via Primary Endpoint analyses and to encourage the development of Ancillary Studies, Databank and Substudies. An equal opportunity will exist among the SOLVD units to participate in the analysis and presentation of the data pertaining to the major objectives of the study as well as to the proposal and performance of Ancillary Studies, Databank and Substudies. Participation in these activities will be open equally to the Principal Investigators of all SOLVD sites, the Coordinating Center and the NHLBI Program Office. With the approval of the Principal Investigators, the Co-Investigators at the various sites are encouraged to participate in this process.

In order to assure that these activities will proceed with a high level of scientific merit and with fairness to all participants, the Publications and Substudies Subcommittee will review applications for nonprotocol studies, will coordinate the formation of the writing groups on each topic, and will make recommendations to the Steering Committee for both of these activities.

B. Ancillary Studies

An ancillary study uses SOLVD participants in an investigation which is not described in the SOLVD protocol and involves data which is not collected as part of the routine SOLVD data set. Such studies may be carried out independently by the applicant investigators or in conjunction with other SOLVD investigators or units, and require independent (non-SOLVD) funding.

Ancillary studies must be approved by the Steering Committee on the recommendation of the Publications and Substudies Subcommittee. All applications for ancillary studies must be submitted in writing to that Subcommittee. They will be assessed on the appropriateness of the question(s) being asked and must assure that the investigation will not interfere with the main objectives of SOLVD. They should be implemented only after recruitment and performance in the main study are satisfactory at the relevant clinical centers.

C. Substudies

Like the ancillary study, a substudy uses SOLVD participants in an investigation which is not part of the routine SOLVD studies. It is, however, considered to be of such general interest to the study investigation that it is carried out with SOLVD NHLBI funding, usually on a portion of the SOLVD participants enrolled at one or more Clinical Centers.

Substudies must be approved by the Steering Committee on the recommendation of the Publication and Substudies Subcommittee. All applications for substudies must be submitted in writing. They will be graded on scientific merit as well as the appropriateness of the question(s) being asked and must assure that the investigation will not interfere with the main objectives of SOLVD. They will be implemented only after recruitment and performance in the main study are satisfactory at the relevant Clinical Centers.

D. Databank Studies

A databank study utilizes data which has been routinely collected as part of the main SOLVD study in order to answer questions other than those proposed in the main protocol. It involves only the analysis of data and is generally not funded since it uses resources at the Coordinating Center. However, such studies must be approved by the Steering Committee at the recommendation of the Publications and Substudies Subcommittee. All applications for databank studies will be graded by the Subcommittee for scientific merit and the appropriateness of the question being asked, and must assure that the timing of publication will not interfere with the main objectives of SOLVD.

E. Other ("Non-SOLVD") Projects

Simultaneous participation of the SOLVD participants in an unrelated study is strongly discouraged since this may result in interference with SOLVD objectives or place demands on the participant that may diminish his/her availability, cooperation or willingness to participate in additional SOLVD-related studies. In certain circumstances, it may be desirable, for clinical reasons, to enter a SOLVD participant into a compassionate use protocol in order that this participant may receive an investigational drug or device. This decision will be made by the Principal Investigator of a Clinical Center and will be based on the clinical needs of the participant. Prior approval is not required. However, the principal investigator is required to notify the Coordinating Center of this action within 10 days. Simultaneous participation of a SOLVD participant in a non-SOLVD prospective investigation requires the prior approval of the Executive Committee.

F. Data Storage and Analysis

The Coordinating Center will be responsible for the collection and analysis of Substudy data and for the analysis of Databank Studies. In the case of Ancillary Studies, the proposing investigator will assume responsibility for data storage and analysis.

Analyses of the databank and substudies will be performed by the Coordinating Center in the order in which requests are received. Prior to major abstract or other deadlines, the Coordinating Center will inform SOLVD sites of a final date for receipt of such

requests. Should the Coordinating Center, because of the number of requests received, be unable to process all requests, it will initially process one designated request from each site.

G. Application Review Process

The Subcommittee will review proposals at each of the semi-annual meetings as well as between meetings as necessary. If several applications for similar Ancillary, Substudy, or Databank studies are received, the Subcommittee will request the applicants to resolve differences in their proposals and resubmit a joint application. If irreconcilable differences exist between the applications or if the applicants are unwilling to cooperate, the Subcommittee will individually grade the applications according to the following criteria:

1. Scientific merit and feasibility
2. The previous experience of the investigator(s)
3. Balance and fairness. This is an attempt to assure that, as nearly as possible, projects are spread among all centers and investigators.
4. Recruiting and follow-up performance. This will be applied only in those cases where an applicant is seriously behind in his/her recruiting commitment or follow-up performance is poor (e.g., incomplete data forms, poor compliance, etc.) and is meant to assure that additional studies do not undermine the major objectives of SOLVD at any site.

In order to assure that all centers have an equal opportunity to develop and participate in the analyses, proposals will then be circulated through the Chairman of the Publication and Substudies Subcommittee to each of the Principal Investigators to invite their participation. In the case of Substudies, the proposer (the first name on the application) will recommend participants and their level of responsibility to the Project Office. Once the concept of a substudy has been approved, the protocol will be developed by the particular investigator(s) and one member each from the Coordinating Center and Project Office. In the case of Ancillary or Databank studies, the proposer (the first name on the application) will be responsible for selecting participants and their level of responsibility.

Applications from non-SOLVD investigators or institutions are welcomed but will be accorded secondary status should a similar application be received from a qualified SOLVD investigator.

XI. STATISTICAL ANALYSES

A. Statistical Reports

The Coordinating Center will be responsible for preparing reports to monitor the progress of the study for the Steering Committee and the Data and Safety Monitoring Board. Each type of report will include information on different aspects of the trials.

1. Steering Committee Reports

To assess the progress of the daily operation of the study, the Coordinating Center will prepare routine reports for the Steering Committee. These reports will focus on the general status of 1) participant recruitment, 2) participant adherence, 3) "effective adherent person years," 4) quality control, and 5) clinical performance data at each center. Special attention will be paid to the recruitment of participants during that phase of the study and maintaining high adherence. These reports will include summaries of the monthly Clinical Center reports on participant screening as well as relevant statistics from the screening and randomization visits. Data detailing the recruitment status at the Clinical Center will be forwarded to the Coordinating Center to produce a weekly recruitment report. In addition the number of participants on a vasodilator will be monitored. This report will contain data no more than two weeks old when received by the Steering Committee. If required, the data can be transmitted via telephone lines. No endpoint or side effect data will be included in the Steering Committee Reports.

2. Data and Safety Monitoring Board Reports

The Data and Safety Monitoring Board reports will be prepared twice a year. These will be tailored to meet the needs of the committee. The report will consist of seven major sections for each trial: 1) General Progress of Study and Recruitment, 2) Endpoints, 3) Quality of Life, 4) Possible Toxicity and Side Effects, 5) Adherence, 6) Number of Participants on Vasodilators, 7) Data Quality, and 8) Substudies. The General Section will outline participant recruitment and effective person-years of follow-up in comparison to targets stated in advance. The section on endpoints will contain treatment comparisons with respect to both the major outcome of mortality and the secondary outcomes of this protocol. The Quality of Life section will compare the two groups with respect to the quality of life questionnaire. The Possible Toxicity and Side Effects section will compare the treatments with respect to hospitalizations, specified clinical chemistries, and other measures of side effects. Adherence to study medications and comparisons of observed versus projected measures will be reported in the fifth section. This will include reports of the average pill count in the treatment groups and other measures of adherence. The sixth section will contain quality control reports which will aid the committee in evaluating the data of the preceding sections. In each of

these sections, data will be provided for the study as a whole and separately for each clinic.

Four weeks prior to the scheduled meetings of the committee a thoroughly edited data file will be created by the Coordinating Center. At this point a random sample of the records on the analysis file will be compared directly with the computer records which were submitted by the Clinical Centers. This check will insure that the records have not been altered by the processing. In addition, statistical tabulations of the distributions of the important variables will be inspected to detect unusual values which might not have been detected by the editing process. After the file has been thoroughly checked, the tables and graphs of the data will be produced. These tables will be compared with the previous report(s). This check will identify major changes in the data which might be indicative of computational or processing errors. The final report will be mailed to the members of the committee two weeks prior to the meeting. Steps will be taken to insure security and confidentiality, including distribution by certified mail and enactment of a return policy of all reports. The tables comparing the treatments with respect to the major outcomes will be updated two days before the meeting so that the committee will have the most up-to-date data possible at the time of the meeting.

B. Statistical Analysis

1. Criteria for Efficacy

The primary measure of efficacy for the Prevention and Treatment trials will be mortality from any cause. A secondary objective for both trials will be to evaluate the effect of treatment on cardiovascular mortality. Other analyses will relate to the onset of CHF in the Prevention Trial, worsening CHF in the Treatment Trial, new myocardial infarction, stroke, and reasons for hospitalizations. All analyses will be done for each separate trial and for both trials combined.

2. Interim Analyses

For both the Prevention and Treatment Trials, it is essential that the data be analyzed by the Coordinating Center at regular intervals and the study terminated or extended if warranted. There are three potential reasons for ending either or both of these trials early: 1) efficacy of the treatment may be proved, 2) harmful effects of the drug may be discovered, or 3) there may be no hope for a reasonable evaluation of the proposed hypotheses. In certain circumstances (for example, where recruitment is behind schedule or the "power" of the study is lower than anticipated, for example, due to lower than expected event rates but not based on the apparent treatment effect), extension of the study may be considered. Conversely, if little treatment differential exists in the use of ACE

inhibitors, power may be seriously compromised and early termination of one or both trials will be considered.

In monitoring for efficacy or harmful effects, a number of methods for the repeated analysis of accumulating data have been proposed and used (Chatterjee and Sen, 1973; Halperin and Ware, 1974; Peto, 1977; Davis, 1978; and O'Brien and Fleming, 1979). Since these procedures generally use time to the occurrence of an event as the response variable, they can be applied to both the Prevention and Treatment Trials. When considering the stopping of a trial in which efficacy of the experimental treatment is claimed, the method used for monitoring the trial should be conservative in the sense that the trial should be stopped before its planned end only if the treatment is clearly superior. Thus early stopping should be considered only if the difference is great. The O'Brien-Fleming type boundary or the method of Peto (Peto et al., 1977) provide such a conservative approach. For this reason, these methods will be used to guide decisions in the individual SOLVD trials. In addition, while viewing the combined data from both trials, even more conservative boundaries may have to be considered. The statistic to be used will be the logrank statistic, which is appropriate since it has independent increments (Tsiatis, 1981).

In addition, the method proposed by Halperin (Halperin M., et al., 1982), will be used to determine if the trial(s) should be continued if the difference between the two treatments is small. This method computes the conditional probability of rejecting the null hypothesis given a specific alternative and the data at the time of the analysis. If this probability is too small, one may choose to discontinue the trial.

Although the above outlines the statistical methods which will be used, the actual recommendation concerning stopping or continuing the trials will be made by the Data and Safety Monitoring Board to the NHLBI. The statistical tests will be only one of many considerations in making these decisions. At each of the analyses where appropriate for each outcome, separate analyses in each trial and a combined analysis of the two trials will be performed. The boundaries for the combined analyses will be more conservative than the boundaries for individual trials.

3. Final Analysis

The primary outcome is all cause mortality for each trial considered individually. An additional analysis of critical and fundamental importance will be the combined mortality from both trials. Thus, the main variable for analysis will be the time from randomization to death. The generally accepted statistical method for analyzing this type of data is the logrank statistic (Peto et al.,1977). The logrank statistic has the advantage of requiring no assumptions other than the random assignment of the treatments. Since the allocation of treatment will be done within clinic, the Coordinating Center will compute a

stratified logrank statistic using clinical center as the stratifying variable. This analysis will be the primary measure of the success or failure of treatment.

A subsidiary analysis of the major outcome of death will involve the use of the proportional hazards model (Cox, 1972). This analysis will allow for the adjustment of important baseline covariates of prognostic importance; for example, ejection fraction, history of myocardial infarction, age, clinical chemistry measurements, smoking history, etc. A careful evaluation of the suitability of the proportional hazards assumption will be conducted as part of these analyses.

The possible adverse effects of chronic therapy will be explored using simple comparative methods. Time-dependent proportional hazards models can be used to assess the cumulative effect of the drug for the development of any side effects (Kalbfleisch and Prentice, 1980).

4. Subgroup Hypotheses

A test of treatment by subgroup interaction will be carried out via the proportional hazards model. If this interaction is not statistically significant, no subgroup results will be claimed. If this test of interaction is statistically significant, treatment comparisons will be made within subgroups adjusting for the multiple comparison problem by using Bonferroni's inequality. Point and interval estimates of treatment effects in subgroups will be computed using empirical Bayes methods (Morris, 1983).

The clinical course of the control groups will be described using both simple descriptive statistical methods along with multivariable modeling techniques to assess the interrelationships within groups of variables.

5. Substudy analyses

The analysis of substudies will be carried out as appropriate and their progress will be monitored throughout the course of the trial to ensure that the substudies have no impact on recruitment, adherence, or the blinding of participants.

6. References

Chatterjee SK and PK Sen. Nonparametric testing under progressive censoring. Calcutta Statistical Association Bulletin 22:13-50, 1973.

Cox, DR. Regression models and life tables (with discussion). J Royal Statistical Society, Series B, 34:187-220, 1972.

Davis, CE. A two sample Wilcoxon test for progressively censored data. Communications in Statistics--Theory and Methods A7(4):389-398, 1978.

Halperin M, Lan KKG, Ware JH et al. An aid to data monitoring in long term clinical trials. Controlled Clinical Trials 3(4):311-324, 1982.

Halperin M, and Ware JH. Early decision in a censored Wilcoxon two sample test for accumulating universal data. J Amer Stat Assoc 69:414-422, 1974.

Kalbfleisch JD and Prentice RL. The Statistical Analysis of Failure Time Data, John Wiley and Sons, 1980.

Morris CN. Parametric empirical Bayes inference: Theory and applications. J Amer Stat Assoc 78:47-65, 1983.

O'Brien PC, and Fleming TR. A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979.

Peto R, MC Pike, P Armitage et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part 2. Analysis and examples. Br. J. Cancer, 35: 1-39, 1977.

Tsiatis, AA. The asymptotic joint distribution of efficient scores test for the proportional hazards model over time," Biometrika, 68: 311-315, 1981.

XII. PUBLICATION POLICY

The Publication and Substudies subcommittee will review all publications following the guidelines given below and report its recommendations to the Steering Committee.

A. Data Analysis and Release of Results

The scientific integrity of the project requires that the data from all SOLVD sites be analyzed study-wide and reported as such. Thus, an individual center is not expected to report the data collected from its center alone. The development of reports of data from individual sites for the determination of institutional variability is the prerogative of the Steering Committee in consultation with the Project Office. Additionally, all presentations and publications are expected to protect the integrity of the major objective(s) of the study; data breaking the blind will not be presented prior to the release of mainline results. Recommendations as to the timing of presentation of such endpoint data and the meetings at which they might be presented will be given by the Steering Committee.

B. Review Process

Each paper or abstract, as described below, must be submitted to the appropriate Subcommittee for review of its appropriateness and scientific merit prior to submission. The Subcommittee may recommend changes to the authors and will finally submit its recommendations to the Steering Committee for approval.

C. Primary Outcome Papers

The primary outcome papers of SOLVD are papers that present outcome data (such as mortality or the efficacy of the SOLVD agent in reducing heart failure) on the SOLVD participant group. The determination of whether or not a particular analysis represents a primary outcome will be made by the Steering Committee on the recommendation of the Publications and Substudy Subcommittee.

Primary outcome manuscripts will not have named individual authors but will be published under the byline of the SOLVD Investigators. For such manuscripts, there will be an appendix containing the names of the sites, their Principal Investigators and Co-Investigators. Sites will include the Clinical Centers, the Coordinating Center, the Program Office and the Central Laboratory. The Data and Safety Monitoring Board and The Writing Group for the manuscript will also be listed under those designations in the appendix.

D. Other Study Papers, Abstracts and Presentations

All studies other than those designated as "Primary Outcome" fall within this category. Papers or abstracts resulting from these studies will have named authorship of individuals involved, ending with the phrase "for the SOLVD

Investigators." In addition, papers will have an appendix containing the names of the sites, their Principal Investigators and Co-Investigators and other individuals participating in the study. Sites will include the Clinical Centers, the Coordinating Center, Central Laboratory and the Project Office. All papers and abstracts must be approved by the Publications and Substudies Committee before they are resubmitted.

It is possible that in certain instances SOLVD may be asked to contribute papers to workshops, symposia, volumes, etc. The individuals to work on such requests should be appointed by the Executive Committee, but where time permits, a proposal will be circulated soliciting other participants as in the case of other study papers as described in the Application Review Process.

XIII. CLOSE-OUT PROCEDURES

A. Statement of Objectives

The SOLVD Prevention and Treatment Trials may terminate at the planned target of minimum two years follow-up of the last participant randomized, or at an earlier or later date if the circumstances warrant. Plans for close-out must be made in the absence of any knowledge as to these circumstances and must therefore be fairly flexible, yet specific enough to be useful.

Regardless of the circumstances for termination of the Trials, our objectives in closing out the study are as follows:

1. To evaluate as fully and accurately as the data permit the effect of enalapril on all-cause mortality, and to make these results public as expeditiously as possible.
2. To fulfill our ethical and humane obligations to those who have participated in the Trials.
3. To exploit the scientific value of study data as fully as possible.

Close-Out procedures will be developed by the Steering Committee. Regardless of the timing and circumstances of the end of the study, close-out will proceed in four stages:

1. Closure of data collection.
2. Interim period for analysis and documentation of study results.
3. Debriefing of participants and dissemination of study results.
4. Follow-up.

B. Closure

No Closure Visit (CV) shall be scheduled before the completion of 2 years minimum of follow-up of the last randomized participant unless exceptional circumstances (documented by the clinic) make this impossible. This visit will be the last "on study" data collection for the participant and marks the official end of each participant's follow-up in the Trial.

All dropouts should be contacted during the Closure period. Those who come to clinic should be treated as if the visit were the last annual visit. A form should be submitted for participants who refuse to come in; it should indicate the date of final contact and that no visit was made.

C. Interim

Every attempt will be made to reduce to an absolute minimum the interval between the completion of first close-out visit and the release of the study results. We expect to take about 2 to 3 months to compile the final results paper for an appropriate journal.

D. Reporting of Study Results

The study results will be released to the participating physicians, referring physicians, patients and the general medical community.

E. Follow-up

Long term follow-up studies on SOLVD participants (e.g., periodic ascertainment of vital status) may be useful and can be performed through the national death records.