BETA-BLOCKER EVALUATION OF SURVIVAL TRIAL (BEST)

PROTOCOL

Updated First Edition: June 22, 1999

Sponsored by the National Heart, Lung and Blood Institute and
the Department of Veterans Affairs Cooperative Studies Program

Preface

The protocol for the Beta-Blocker Evaluation of Survival Trial (BEST) describes the background, design and organization of the clinical trial. All changes to the study protocol during the trial require approval of the Steering Committee, the Data and Safety Monitoring Board, the VA and NHLBI. The protocol will be maintained by the BEST Study Coordinating Center over the course of the trial through new releases of the entire protocol, or issuance of updates either in the form of revisions of complete chapters or pages thereof or in the form of supplemental protocol memoranda. This preface summarizes the major changes to the protocol during the trial.

Releases of the Protocol

Edition	Date Released
First	September, 1994
Updated	March 20, 1995
Updated	September 20, 1996
Updated	June 22, 1999

First Edition: September, 1994

The protocol was developed and edited by the BEST Planning and Steering Committees. The first edition of the protocol was distributed in September of 1994 to clinical centers participating in BEST in preparation for the initiation of recruitment.

Updated: March 20, 1995

Several updates and clarifications were incorporated in this edition of the protocol. This edition was distributed in April of 1995 to participating clinical centers. The following clarifications are reflected in the updated edition:

1) The stratifying criteria for randomization were clarified (pp.6-7, 28)
2) The weight categories for determining the target dose were clarified (pp.7, 29)
3) The protocol references were updated (p.8, Appendix K)
4) The number of participating sites was updated (p.15, and Appendices A and E)
5) The Study Schedule presented in Table 1 was revised (p.25)
6) The study flow chart was revised (p.26)
7) The baseline data collection was clarified (p.27)

Updated: September 20, 1996

This edition contains modifications with regard to baseline co-therapy, discontinuation of

study medication for clinical reasons, and to the guidelines for reinstitution of study medication. A DNA bank has been added and an addendum developed to the informed consent form for the DNA bank. Other minor clarifications were made to include updating the list of blood laboratory work and specifying the patient's weight used for determining the target dose of study medication. These are summarized as follows:

1) The weight used for determining the study medication target dose has been clarified (p.7)
2) Digitalis has been changed from required to optional baseline co-therapy (p.21)
3) The blood laboratory work has been updated to make it inclusive of all required tests (p.27)
4) The addition of a DNA bank (p.27)
5) An addendum has been added to the informed consent form for the DNA bank (Appendix C)
6) The section on discontinuation of study medication for clinical reasons has been revised (pp.31-32)
7) The guidelines for reinstitution of study medication has been updated (pp.32-33, Appendix B)

This updated first edition was distributed to participating centers in October of 1996.

Updated: June 22, 1999

This edition contains an extension to the three year patient accrual period and subsequent duration of study follow-up, and an addition to the specified treatment effect modifiers. Other minor revisions were made to include updating the list of participating sites, committee memberships and conflict of interest statement.

These are summarized as follows:

1) The three year patient accrual period and corresponding study follow-up has been extended by 7 months (p.7)
2) Baseline creatinine and changes in creatinine level and BUN/creatinine ratio from baseline to 3 months of study follow-up has been added to the list of treatment interactions or effect modifiers (pp.18-19)
3) The list of participating clinical sites has been updated (Appendix E)
4) Committee memberships have been updated (Appendices G, H and I)
5) Addition of Endpoints, Recruitment, Monitoring, Closeout, and Publications Committees (Appendices J, K, L, M and N)
6) The conflict of interest statement has been updated (Appendix O)

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I. Introduction and Background

Hypothesis

The Beta-Blocker Evaluation of Survival Trial (BEST) will test the hypothesis that the addition of a beta-adrenergic blocking agent to standard therapy will reduce mortality in patients with moderate to severe chronic heart failure.

Adverse effects of neurohormonal activation

Congestive heart failure (CHF) is a major public health problem in the United States. At a time when mortality from coronary artery disease is in decline, the incidence and prevalence of congestive heart failure are increasing[1]. This syndrome affects about 1% of the United States population and the prevalence is 10% in patients older than 75 years[1]. Treatment remains unsatisfactory. Heart transplantation is severely limited by the number of donors[2] and major advances in immunology will be needed to make xenografting (which would permit an unlimited supply of donor organs) feasible. A practical mechanical replacement seems unlikely in the immediate future. For these reasons, pharmacologic therapy will continue, for the present, to be the mainstay of therapy for most patients.

Much of the contemporary therapy of heart failure is based upon a paradigm that postulates that compensatory mechanisms that initially maintain cardiac output and systemic blood pressure ultimately contribute to deterioration of ventricular function and to mortality[3,4]. These compensatory mechanisms include activation of the renin-angiotensin system, the sympathetic nervous system and the arginine vasopressin system[1,3,4]. Support for the validity of this paradigm can be found in the results of clinical trials that demonstrate a reduction in mortality in CHF patients treated with angiotensin converting enzyme inhibitors[5-8]. The combination of hydralazine and isosorbide dinitrate also reduces mortality in CHF patients but to a lesser degree than the angiotensin converting enzyme inhibitors[8]. This suggests that factors in addition to relief of wall stress, such as inhibition of neurohumoral activation, are operative[3,4]. Though real, the reduction in mortality afforded by the angiotensin converting enzyme inhibitors is small and further advance in pharmacologic therapy is needed.

Evidence exists that increased adrenergic activity may produce reductions in left ventricular function. Myocardial lesions have been produced in the rat heart using isoproterenol[10]. In humans, elevated catecholamine levels have been associated with myofibrillar degeneration[11] and with cardiomyopathy[12]. Furthermore, the degree of adrenergic activation in patients with CHF is a prognostic marker[13]. While angiotensin converting enzyme inhibitors delay the progressive increase in sympathetic activation, they do not inactivate this potentially deleterious system[14].

Increased adrenergic activity also has a dramatic effect on the myocardial beta adrenergic receptors. Beta 1 receptors are down regulated, meaning that their number is reduced[15-20]. Also, there is alteration in the G protein complex that is important in coupling the beta receptors to adenylate cyclase with a resultant decrease in its functional effect on the heart[15-17]. These effects probably account for the reduced response to beta agonists in patients with CHF[16,17,19,20]

Effect of beta-blockers on ventricular function

That these mechanisms are indeed operative in the cardiomyopathic heart is supported by a substantial number of small clinical studies which demonstrated a salutory effect of beta-adrenergic blockade on ventricular function and clinical course. The first report of the use of beta-blockers in CHF was by Waagstein et al in 1975[21]. They reported seven patients with advanced congestive heart failure who were treated with beta-blockers, either alprenolol or practolol. All of the patients were felt to be in a steady state or deteriorating. In all of these patients, their clinical condition and left ventricular function improved. Despite being suggestive, given the small number of patients and the variable history (six of these patients were said to have had a virus infection before the onset of CHF), these findings could be explained by mechanisms other than beta-blockade. Swedberg et al from the same group reported regression of clinical improvement when patients treated with beta-blockers for CHF were subsequently withdrawn from these agents [22]. These data further suggested a beneficial effect of beta-blockers.

In 1985 Engelmeier et al reported 25 patients randomized to metoprolol or placebo[23]. In the metoprolol patients but not in the placebo group there was a significant improvement in exercise capacity, functional class, and ejection fraction. Two patients who were initially randomized and treated with metoprolol had the drug withdrawn. As in the trial by Swedberg, these two patients

initially improved on drug and then deteriorated after beta-blocker withdrawal. Only one patient was intolerant of metoprolol suggesting that this drug can be used relatively safely in this setting.

Heilbrunn et al studied 14 patients with dilated cardiomyopathy who were given metoprolol[24]. An increase in beta-receptor density and a heightened ventricular function response to beta agonist was documented. These data suggested a mechanism (i.e., beta-receptor up regulation) by which metoprolol could improve exercise tolerance as seen in the Engelmeier study. Stroke work index and ejection fraction as well as the response of peak left ventricular dp/dt all improved with metoprolol treatment.

In 1989, Waagstein reported on 33 patients who were treated with metoprolol, with marked hemodynamic improvement in most[25]. Subsequent withdrawal of metoprolol led to hemodynamic deterioration as previously reported by Swedberg and Engelmeier.

Gilbert et al reported a double blind study of 24 patients randomized to placebo or to bucindolol[26]. The bucindolol treated group experienced a significant improvement in ejection fraction and a decrease in pulmonary capillary wedge pressure and heart rate. The placebo group did not experience this improvement.

Eichhorn et al studied 15 patients treated with bucindolol[27] and found a hemodynamic improvement in the patients treated. They also studied end-systolic elastance and the dP/dtmax-end diastolic volume relation, two relatively load independent measures of contractility. Both were improved by bucindolol treatment suggesting that increases in ejection fraction seen with beta-blockade are indeed due to increased contractility rather than to alterations in loading conditions. Eichhorn and colleagues subsequently documented this same effect with metoprolol in a double-blind placebo controlled trial of 24 patients[28]. In addition, they found improvement in myocardial stroke work and minute work while myocardial oxygen consumption fell. Thus, myocardial efficiency improved[28]. In the two studies by Eichhorn, despite the presence of patients with left ventricular ejection fractions <0.15, there were no patients who were intolerant of beta-blockade.

Pollock et al[29] also reported a controlled trial of bucindolol versus placebo. Bucindolol was found to improve both hemodynamic parameters and quality of life. The dose ranging study of Bristow and colleagues suggests that the effects of bucindolol are dose related[30] with the greatest effect on LVEF found at the highest doses of drug (200 mg daily).

What is the effect of CHF etiology on the effectiveness of beta-blockers? Woodley et al performed a double-blind, placebo controlled evaluation of bucindolol in patients with ischemic cardiomyopathy and in a second group with idiopathic dilated cardiomyopathy[31]. The patients treated with bucindolol had a significant improvement in ejection fraction compared to the placebo group which did not experience an improvement. Interestingly, however, the bucindolol treated patients with an ischemic etiology experienced no improvement in ejection fraction. However, a more recent study by Bristow[30] suggests that patients with ischemic etiology do improve with therapy at higher beta-blocker dosages but do not respond as well at lower dosages. These data suggest that the etiology of the CHF may be important in predicting hemodynamic response to beta-blockade.

Preliminary data on the effect of beta-blockers on survival

The Cardiac Arrhythmia Suppression Trial (CAST) compared the effect of certain antiarrhythmic drugs on mortality after myocardial infarction[32,33]. When patients with an ejection fraction less than .40 were studied retrospectively, survival to death or cardiac arrest was significantly better in patients receiving beta-blockers[33]. Survival from arrhythmic death or cardiac arrest was also significantly better in patients receiving beta-blockers. Chadda et al reported reduced cardiovascular mortality and sudden death in a subgroup of patients with heart failure who were treated with propranolol following myocardial infarction[34].

In the recently reported Metoprolol in Dilated Cardiomyopathy trial, 383 patients were randomized to metoprolol or placebo[35]. Patients were followed for an average of 18 months. There was a 34% reduction in a combined morbidity and mortality endpoint ($p= 0.06$) in the metoprolol treated group. There was also a reduction in the hospitalization/emergency room visits for decompensation in the metoprolol treated group and, as observed in the Englemeier trial[23], a significant improvement in exercise tolerance. This trial did not demonstrate a significant reduction in mortality in the metoprolol group, perhaps because of a much greater rate of heart transplantation in the placebo group. Furthermore, there was no reduction in sudden cardiac death in the metoprolol group. The lack of an effect of metoprolol on sudden death in this trial may be related to metoprolol's intrinsic properties such as its inability to block the beta-2 receptor combined with its inability to reduce plasma norepinephrine [36-38], a prognostic marker of survival in heart failure[4,13]. Bucindolol has, on the other hand, been shown to reduce plasma norepinephrine[26,31] and blocks both the beta-1

and beta-2 receptors. These data suggest that more complete beta-blockade may result in more protection than selective beta-blockade.

So, despite data suggesting that beta-blockers improve ejection fraction and exercise tolerance and reduce emergency room visits/hospitalizations as well as the need for transplantation, there is no demonstration in the literature that they improve survival in CHF patients. Only with a definitive study of this question will the role of this family of drugs in CHF be fully understood. A randomized, controlled trial of sufficient size and with adequate follow-up is needed to make a determination about the ability of beta-blockers to prolong life.

II. Overview of Study Design

A. Program objectives

1. Primary objective

The primary objective of the BEST trial is to determine whether the addition of beta-blockers to standard therapy reduces the total mortality of patients with moderate to severe chronic congestive heart failure.

2. Secondary objectives

The secondary objectives are to evaluate the effects of beta-adrenergic blockade on:

a. Cardiovascular mortality
   total
   due to worsening heart failure
   due to sudden death
b. Quality of life
c. Hospitalizations and costs
d. Left ventricular ejection fraction at 3 and 12 months of therapy
e. The incidence of myocardial infarction
f. Combined transplant/mortality endpoint
g. Changes in the need for co-therapy

In addition, it is planned to assess the impact of etiology, race, ejection fraction and gender on the effect of treatment on primary and secondary outcomes.

B. Patient eligibility

All study participants will be adults with ejection fraction 0.35 or less and will be in New York Heart Association (NYHA) functional class III or IV. Patients with definite indications or contraindications to beta-blocker therapy will be excluded.

C. Treatment

Patients will be randomized to treatment with either bucindolol or placebo in a double blind design that will be stratified based upon etiology of heart failure, gender, ejection fraction, race and the hospital at which they are treated. Etiology of congestive heart failure will be divided into presence or absence of coronary artery disease (CAD). For the purpose of the study, coronary artery disease will be defined as either: (1) a history of previous myocardial infarction (MI), diagnosed by ECG (Q-waves) or enzymes, (2) evidence of significant obstruction, greater than 70% diameter luminal narrowing of at least one major epicardial artery with corresponding regional wall motion abnormality, (3) an unequivocally positive stress perfusion study demonstrating coronary artery disease, (4) an exercise stress test in a patient with an interpretable ECG (i.e. no BBB, LVH, or ST-T changes at baseline, and not on digitalis), who demonstrates provokable ischemia (i.e. 2 mm or more of flat or down sloping ST - depression at 80 msec after the J-point). In the case of positive ETT and normal angiography, the patient will be classified as non-CAD. While coronary angiography or stress perfusion is not mandated for entry, the investigator is expected to determine the etiology of ventricular dysfunction as part of the patient's routine care. Following randomization, patients will be started on a twice daily treatment regimen consisting of either bucindolol 3.0 mg, or placebo. Doses of drug will be titrated over a 5-9 week period as tolerated with the ultimate goal of reaching a dose of bucindolol of 200 mg PO daily (100 mg PO twice daily) for patients weighing greater than or equal to 75 kg at randomization, and 100 mg daily (50 mg PO twice daily) for patients weighing less than 75 kg at randomization.

D. Study size and duration

The recruitment will extend for 3 years and there will be a minimum follow-up of 1.5 years (*note: patient accrual was extended by 7 months*). The study will have a 85% power to detect a 25% mortality reduction. Based on these considerations, a target sample size of 2800 randomized patients with equal numbers assigned to each treatment group is needed (see Appendix A for sample size calculation).

E. Drug Rationale

Rationale for drug selection

Three beta-adrenergic blocking agents have been used extensively for the treatment of congestive heart failure: metoprolol, bucindolol, and carvedilol.[3] The latter two have mixed actions with primarily beta-blocking effects and some vasodilator effects. Neither of these agents (bucindolol and carvedilol) are Food and Drug Administration approved for any indications and are thus investigational agents.

Metoprolol

Metoprolol is a beta-1 selective antagonist without vasodilator or agonist action. It has been widely studied with over 500 heart failure patients in ten published studies placed on this agent [3,23-25,35,36,39-42]. Previous heart failure trials with metoprolol have used the following initial and target doses:

Investigator	Initial Dose	Target Dose	Entry NYHA	Patient Tolerance
Anderson[39]	12.5 mg BID	50 mg BID	II-IV	22/25 (88%)
Engelmeier[23]	6.25 mg daily	100 mg daily	I-IV	20/21 (95%)
Heilbrunn[24]	6.25 mg BID	150 mg daily	I-III	14/14 (100%)
Waagstein[25]	5 mg BID	150 mg daily	-----	26/33 (79%)
Currie[40]	25 mg BID	100 mg BID	III	10/10 (100%)
Andersson[36]	5 mg BID	50 mg TID	II-IV	21/21 (100%)
Fisher[41]	6.25 mg BID	50 mg BID	-----	17/17 (100%)
Sachdev[42]	12.5 mg daily	100 mg BID	II-IV	12/12 (100%)
MDC Trial[35]	5.0 mg BID+	I50 mg TID	I-IV	400/417 (96%)
Eichhorn[28]	6.25 mg BID	50 mg BID	I-IV	15/15 (100%)
Totals				557/585 (95%)

These data demonstrate that metoprolol is well tolerated, even in severe heart failure. In addition, much of the intolerance seen in the study by Anderson and colleagues [39] was due to a high initial

dosage of 12.5 mg BID. In general, patient intolerance to beta-blocker therapy appears most prominently at low dose initiation of therapy, and is seen less frequently as the patient is titrated to target dose.[30] Thus, the initiating dosage is more critical than the target dosage.

Bucindolol

Bucindolol hydrochloride is a phenoxypropanolamine with potent non-selective beta-antagonist and mild vasodilatory properties.[43,44] Bucindolol has equipotent beta-1 and beta-2 antagonist actions and has beta-blocking properties equivalent to those of propranolol.[43,44] Although mild intrinsic beta-sympathomimetic activity has been demonstrated in rats and dogs, [45-47] and while escalating doses of bucindolol (0.003-3 mg/kg) have been shown to increase heart rate and right ventricular contractile force in reserpinized vagotomized dogs (an effect blocked by prior beta-blockade with propranolol)[45], no intrinsic sympathomimetic activity has been found in human ventricular myocardium.[44] While bucindolol (and carvedilol) exhibit an "agonist" binding site modulated by guanine nucleotides in human myocardium, this does not confer agonist (adenylate cyclase) activity.[48] In addition, bucindolol possesses weak alpha-1-antagonist (affinity for alpha-1 receptors is 30 fold lower than for beta-receptors in humans),[43,44,49,50] weak serotonin antagonist (in animals)[50], and mild vasodilator action.[44,45,50,51] As compared to labetolol, the vasodilator action is not modulated by its weak alpha-1 antagonist action.[49-53]

The pharmacokinetics of bucindolol and its major metabolites 5-hydroxy-bucindolol and 6-hydroxy-indolyl-bucindolol have been studied.[43,52,54] Gastrointestinal absorption is complete with a mean absolute bioavailability of 30%. The low systemic availability is due to presystemic metabolism. Orally administered bucindolol is rapidly and extensively metabolized by the liver with a first pass effect. While there are some interindividual differences in the metabolism of bucindolol,[54] in general the onset of action after oral dosing is 30 minutes with peak plasma levels at 0.5 - 2 hours, and bioavailability up to 24 hours. In one clinical study in normal human volunteers, bucindolol reached a maximal plasma concentration (T_{max}) at 1.6±0.20 hours, and had a plasma elimination half-life ($T_{1/2}$) following acute oral dosing of 3.6 ± 0.3 hours (while elimination of 5-hydroxy-bucindolol is 0.15±0.13 hours).

Bucindolol is an effective agent for treating patients with angina. Bucindolol promotes systemic vasodilation without a reflex tachycardia and it attenuates the increase in coronary vascular tone

during a cold pressor test.[55] In addition, bucindolol has been shown to protect rat hearts better than propranolol against depletion of high energy phosphates found during experimentally induced ischemia.[56] Bucindolol has been shown to decrease the incidence of inducible ventricular fibrillation in ischemic pig hearts more than propranolol or sotolol, an effect that may be due to better blood flow in ischemic regions of the heart.[57]

There is a large experience with bucindolol with over 225 patients in six reported studies placed on this agent.[3]

Investigator	Initial Dose	Target Dose	Entry NYHA	Patient Tolerance
Eichhorn[27]	12.5 mg BID	100 mg BID	I-IV	15/15 (100%)
Gilbert[26]	12.5 mg BID	100 mg BID	II-III	23/24 (96%)
Pollock[29]	12.5 mg BID	100 mg BID	I-III	14/14 (100%)
Bristow[30]	12.5 mg BID	12.5, 25, 200 mg daily	I-IV	139/141 (98%)
Woodley[31]	12.5 mg BID	100 mg BID	II-III	50/51 (98%) *
Anderson[58]	12.5 mg BID	100 mg BID	II-III	20/20 (100%)†
Totals				261/265(98%)‡

*These numbers include 13 patients who were previously treated with bucindolol from the study of Gilbert et al.[26]

† These numbers include 13 patients who were previously treated with bucindolol and 7 patients who had previously tolerated a test dose of bucindolol from the study of Gilbert et al.[26]

‡ These numbers reflect only the new patients who have received bucindolol. Patients in more than one study are counted only once.

As is evident, bucindolol is very well tolerated, even in very sick patients.[3] To date, no patient has died on optimal bucindolol therapy (100 mg or more daily) during a trial period.

In humans with congestive heart failure, bucindolol is extremely well tolerated and produces improvements in left ventricular systolic (ejection fraction, systolic elastance, cardiac index, and stroke work) and diastolic (isovolumic relaxation) performance while reducing pulmonary artery pressures and heart rate.[27] These improvements occur without an increase in myocardial oxygen

extraction or oxygen consumption.[27] In addition, functional class improves with this agent although exercise tolerance and maximal oxygen uptake (VO_2) does not change, an effect which is not unexpected with a beta-adrenergic antagonist.[26,30]

Carvedilol

Compared to bucindolol, there is a much smaller published experience with carvedilol.[59] Carvedilol is a less selective beta-blocker than metoprolol, but is more selective for beta-1 receptors than bucindolol (i.e. carvedilol has less beta-2 antagonism than bucindolol but more than metoprolol). This is shown in the table below where selectivity ratios of various beta-blocking agents are shown (data based on ^{125}[I] ICYP cold ligand competition curves in presence of 30 μM Gpp(NH)p: [48]

Agent	**K_H (beta-1) (nm)**	**K_L (beta-2) (nm)**	**Selectivity beta-1:beta-2**
Metoprolol	45.6±31.0	3345±1789	73
Carvedilol	3.37±0.75	105±6.0	31
Bucindolol	3.83±1.14	3.83±1.14	1
Propranolol	4.42±1.53	4.42±1.53	1

In addition, carvedilol has moderate vasodilator activity (as compared to bucindolol's mild vasodilator activity).

Reasons for choice of agent

There are several reasons why bucindolol was chosen for this trial over metoprolol, propranolol and carvedilol:

1. Carvedilol was eliminated as it has moderate vasodilator activity, a property which may have independent effects on mortality.[9] While bucindolol also has some vasodilator action, it is so mild that systemic vascular resistance does not change significantly.[27] Carvedilol was also eliminated due to a very small published experience with this agent.
2. Hemodynamic improvement may be better with bucindolol than with metoprolol. Increases in systolic elastance (and other relatively load independent indices of contractility) have been demonstrated with bucindolol.[27] However, increases in systolic elastance have not been clearly demonstrated with metoprolol.[28,42]
3. Previous studies of heart failure have shown "downregulation" of the beta-1-adrenergic

receptors on the myocardial cell surface while beta-2 receptors are relatively preserved.[15-19] In the failing ventricle, the ratio of beta-1 to beta-2 receptors is approximately 60:40 (instead of the 80:20 ratio seen in patients without heart failure).[16,17] Thus, in congestive heart failure, the beta-2 receptor assumes a more important role in the regulation of contractility, heart rate, and relaxation. These responses to a beta-2 agonist are modulated by increased cAMP, the intracellular second messenger. When the beta-2 receptor is unblocked, cAMP levels within the myocyte may increase in the presence of post-synaptic norepinephrine, even when the beta-1 receptor is blocked. Long-term increases in intracellular cAMP in patients with heart failure has been shown to be disadvantageous as it may result in increased arrhythmias and sudden death.[3,60-64] Thus, blockade of the beta-2 receptor (with bucindolol) may provide more protection from sudden death than a beta-1 selective agent (metoprolol).

4. Metoprolol does not reduce plasma norepinephrine (and may increase it in some cases)[36-38] while bucindolol has been shown to decrease systemic norepinephrine.[26,31] These data suggest more complete deactivation of cardiac adrenergic drive with bucindolol. This is especially cogent in the face of an unblocked beta-2 receptor in patients taking metoprolol[48] and reduced clearance of norepinephrine with metoprolol.[38]
5. While the Metoprolol in Dilated Cardiomyopathy (MDC) trial did show a favorable mortality and morbidity combined effect, the absolute mortality and incidence of sudden death with metoprolol was not different from placebo. In this trial, metoprolol appeared to have a favorable effect on progression of heart failure as a disproportionate number of patients in the placebo group needed transplantation. However, the lack of an effect on sudden death with a beta-1 selective agent as seen in the MDC trial and the more number of transplantations in the placebo group and while this study was never designed recent CIBIS trial[65], is troublesome. While this may be an artifact of a disproportionate to be a mortality study, the lack of even a small effect on sudden death suggests that blocking the beta-2 receptor (as well as the beta-1 receptor) may be important for reducing mortality. The reduction in sudden death in heart failure patients seen in an earlier trial[34] was on propranolol, an agent which is a non-selective beta-blocker.
6. While one could argue to use a more "pure" non-selective beta-blocker such as

propranolol, no substantial experience with this agent exists. In addition, anecdotal experience with this agent has shown high degrees of intolerance during titration[66,67]. As shown above, bucindolol is as efficacious at blocking the beta-1 and beta-2 receptors as propranolol and blocks exercise heart rate as well as propranolol.[44,48] Since bucindolol is such a mild vasodilator, it can be considered to be primarily a beta-blocker.[27, 43] While a head-to-head comparison has not been made, the changes in systemic vascular resistance with bucindolol are similar to those seen with metoprolol at 3 months of therapy (unpublished data). Thus, this agent is primarily a beta-blocker.

A dose ranging study has been performed for bucindolol[30], but not for metoprolol.

III. Study Organization

A. Steering Committee

The voting members of the Steering Committee (SC) will include the Principal Investigator of the Coordinating Center, the Chief of the Clinical Trials Branch (NHLBI) and Study Co-Chairman, the Department of Veterans Affairs (VA) Study Co-Chairman, and appropriate investigators as agreed upon by the National Heart, Lung, and Blood Institute (NHLBI) and the VA (Appendix G). The SC oversees all aspects of the study. This includes design of the protocol and the manual of operations, monitoring the progress of the trial and analysis and publication of trial results. The SC will also consider and act upon any special issues related to the study that may arise. The SC will establish committees to develop procedures and report their recommendations to the full SC for approval. An Executive Committee, a subset of the SC will be composed of the PI of the Coordinating Center, the VA Co-Chairman, two or more Clinical Site PIs and the NHLBI Co-Chairman. The Executive Committee will develop the agenda and make recommendations for consideration by the SC. The Executive Committee will provide study direction between meetings of the SC.

The SC will meet at least once each year to monitor the progress of the study and to review non-endpoint data. The SC will not have access to endpoint data until the trial is completed. The committees will include (1) Ancillary and Substudies Committee (2) Endpoints Committee, and (3) Publications Committee. *Additional Committees added during the course of the trial are: (4) Recruitment Committee, (5) Monitoring Committee, and (6) Closeout Committee. Memberships for these Committees are given in Appendices F-N.* Chairmen and Co-Chairmen of the committees will be appointed by the SC subject to the approval of the NHLBI and the VA. In any votes by the Steering Committee, each member shall have a single vote, and no center shall have more than one vote.

B. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) has been appointed by the NHLBI and the VA (Appendix H) and will review the protocols of the main study and substudies during the planning phase. Thereafter it will periodically monitor the progress, data, outcomes, toxicity, safety and other confidential data. The DSMB will recommend to the NHLBI and the VA changes to be made in the conduct of the study. The DSMB is comprised of experts in relevant biomedical fields including cardiology, biostatistics and bioethics. The members will have no direct relationship to the study.

Outcome data will be privileged and shared only with the DSMB. The DSMB will meet at least once a year during the study and reports will be sent to the DSMB every six months. The DSMB will make its recommendations concerning study conduct, the feasibility of substudies and ancillary studies including premature ending of the studies, directly to the NHLBI and the VA.

C. Clinical Sites

Ninety clinical centers will be selected for study participation. Approximately two-thirds of the clinical sites will be non-VA medical institutions and the remainder will be composed of VA sites. A listing of participating clinical sites is provided in Appendix E.

IV. Objectives of the Study

A. Primary endpoint

The principal objective of the trial is to evaluate the effect of adding beta-adrenergic blockade to standard medical therapy, on all cause mortality in patients with moderate to severe chronic heart failure.

B. Secondary endpoints

The secondary objectives are to evaluate the effect(s) of a beta-adrenergic blocking agent on:

a. Cardiovascular mortality
   - total
   - due to worsening heart failure
   - due to sudden death

b. Quality of life

c. Hospitalizations and costs

d. Left ventricular ejection fraction at 3 and 12 months of therapy

e. The incidence of myocardial infarction

f. Combined transplant/mortality endpoint

g. Changes in the need for co-therapy

In addition, it is planned to assess the impact of etiology, race, ejection fraction and gender on the effect of treatment on primary and secondary outcomes.

C. Justification of secondary objectives

In previous studies of congestive heart failure, the majority of all cause mortality has been due to cardiovascular death.[5-9,34,63] Among heart failure patients taking angiotensin converting enzyme inhibitors, sudden death accounts for 26-51% of cardiovascular deaths while progressive heart failure accounts for 45-52% of cardiovascular deaths.[5-9,63] Non-selective beta-blockers may have an effect on cardiovascular mortality by reducing progressive left ventricular dysfunction[3,27,28,30] and by reducing sudden death.[33,34] Beta-adrenergic blocking agents have been shown to improve ventricular function and symptom scores in patients with heart failure who are taking angiotensin converting enzyme

inhibitors[3]. In fact, compared to every other agent, beta-blockers provide the most dramatic improvement in ejection fraction,[3,8] which has been proposed as a surrogate marker of mortality outcome[68]. The addition of a beta-blocking agent may reduce death due to progressive heart failure. This has yet to be proven conclusively and will be prospectively evaluated in this trial.

There are several reasons for including an evaluation of quality of life as a major secondary endpoint in a mortality study. One aim is to discover if the treatment prolongs life but at low quality of life. Another aim is to investigate whether bucindolol actually increases the quality of life in survivors. Since beta-blocker studies of more than one month duration have demonstrated improvement in symptom score[3], we would not anticipate an adverse effect on quality of life in these patients. However, a large systematic prospective evaluation of quality of life in these patients has not been published and smaller trials of shorter duration have shown variable quality of life outcomes[3].

Hospitalization for congestive heart failure reduces the patient's quality of life and represents a large monetary investment on the part of society. While improvement in ventricular function and symptom score would be expected to translate into shorter length of stay, an increase in frequency or duration of hospitalization during the period of drug titration might counteract a beneficial long term effect of this therapy. Thus frequency, duration, and cost of hospitalization as well as quality of life are important issues to examine.

We will examine prospectively whether left ventricular ejection fraction improves by 3 months and whether left ventricular function continues to improve between 3 and 12 months or deteriorates in the interim. Prior smaller trials have shown continued improvement between 3 and 6 months.[28,35,58] We will also test the hypothesis that patients who respond to beta-blocker therapy (i.e. have an improvement in left ventricular ejection fraction) live longer. Precedent for such an examination comes from the results of the V-HeFT trial.[68] We will examine whether beta-adrenergic blocking agents reduce the incidence of myocardial infarction in patients with congestive heart failure as they have been shown to do in one study of post myocardial infarction secondary prevention (from 20.1% to 14.4%)[69]. We will analyze the combined endpoint of transplant/mortality. In addition, we will compare the groups with respect to the need for changes in co-therapy.

D. Treatment interactions or effect modifiers

Analysis of all cause mortality will take into account the following variables that may modify

the association between treatment and mortality:

1. Presence or absence of coronary artery disease
2. Gender
3. Race
4. Age
5. Baseline left ventricular ejection fraction
6. Baseline serum sodium concentration
7. Baseline NYHA functional class
8. Baseline plasma norepinephrine
9. Baseline creatinine
10. Baseline heart rate
11. Baseline heart rhythm (sinus rhythm vs. atrial fibrillation)
12. Baseline systolic blood pressure
13. Improvement in left ventricular ejection fraction from baseline to 3 months
14. Change in creatinine and change in BUN/creatinine ratio from baseline to 3 months
15. VA versus non-VA site, after adjusting as far as possible for clinical prognosis

E. Justification of examining treatment interactions or effect modifiers

It is important to identify which patients will receive the most survival benefit from beta-adrenergic blocking agents. There is a reasonable possibility that the treatment effect of beta-blockers in patients with heart failure may be different in patients with and without coronary artery disease. For the purposes of this study, coronary artery disease will be defined as a history of previous myocardial infarction and/or evidence of significant obstruction (>70% diameter luminal narrowing) of at least 1 major epicardial artery. Two previous ventricular function studies of beta-blocker therapy comparing its effect on patients with ischemic versus non-ischemic etiology demonstrated some differential effects on these two groups of patients.[30,31] In these studies, the patients with idiopathic dilated cardiomyopathy had a more dramatic improvement in ventricular function and size than patients with ischemic heart disease when treated with beta-adrenergic blocking agent for 3 months. However, both groups of patients received benefit in reduction of ventricular size and improvement in ejection fraction at maximal dosages. In addition, patients with idiopathic dilated

cardiomyopathy have been shown to have a greater degree of beta-receptor downregulation than patients with heart failure due to ischemic heart disease.[70] On the other hand, patients with heart failure due to ischemic heart disease have a greater degree of functional uncoupling of the beta-receptors to both adenylate cyclase activation and the mechanical response to beta-agonist stimulation.[70] Thus, there is a reasonable chance that beta-adrenergic blockade will have a differential effect on mortality in patients with and without coronary artery disease. This study will examine whether the presence of coronary artery disease will have an impact on all cause mortality changes due to beta-blockade.

Previous studies have demonstrated that left ventricular ejection fraction, [71,72] serum sodium concentration,[4] New York Heart Association (NYHA) functional class, [71] and plasma norepinephrine[4,13] are all independent prognostic indicators of mortality in congestive heart failure. However, it is not known if they modify the effects of beta-blockade in all cause mortality.

This study will examine whether the degree of initial sympathetic activation, as reflected by baseline heart rate, modifies the effect of beta-adrenergic blockade on survival. This hypothesis is motivated by the fact that beta-adrenergic blockade impedes the effect of the sympathetic nervous system on the heart,[3,66] and heart rate reflects sympathetic activation.[73] Two previous hemodynamic studies suggested that patients with the highest baseline heart rate received the most hemodynamic benefit.[74,75]

Data from the SOLVD Prevention and Treatment Trials show that renal dysfunction in patients with heart failure is strongly associated with mortality.[83] Creatinine levels and the BUN/creatinine ratio will be prospectively examined to determine if these measures of renal function are indicative of outcome in patients treated with beta-blockade. A rising BUN/creatinine ratio may reflect renal perfusion and stroke volume, which would likely represent deterioration of ventricular function on active therapy.

It has been previously documented that the presence of atrial fibrillation predisposes patients with heart failure to adverse events such as cerebral embolic phenomena and may have an adverse effect on survival.[76] Thus, the study will prospectively examine whether rhythm at baseline (atrial fibrillation versus sinus rhythm) modifies the survival benefit of beta-adrenergic blockade.

A recent hemodynamic study has demonstrated that systolic blood pressure is the best predictor of response (defined as an improvement in left ventricular ejection fraction) to chronic

beta-adrenergic blockade.[77] This study demonstrated a linear relation between baseline systolic blood pressure and change in left ventricular ejection fraction. Thus, it is unclear if baseline systolic blood pressure will modify an effect on survival. This issue will be prospectively examined in BEST.

In previous studies of congestive heart failure, left ventricular ejection fraction has proven to be an independent prognosticator of survival.[71,72] Additionally, the Veterans Affairs Cooperative Studies of heart failure (V-HeFT I and II) have recently demonstrated that the greater the increase in ejection fraction from baseline, the greater the survival benefit, independent of therapy randomization.[68] Thus, it is reasonable to hypothesize that the greater the improvement in left ventricular ejection fraction, the better the survival. This hypothesis will be tested by assessing the relationship among change in ejection fraction (from baseline to 3 months of therapy), treatment, and improvement in survival.

Finally, differences in beta-1 receptor density has been noted in females and with advancing age.[78] With advancing age, progressive beta-1 down regulation occurs which is more marked in females as compared to males. Thus, differences in survival benefit may exist between young and old patients, males versus females and in racial groups. For this reason, the study will examine age, race and gender differences.

V. Patient Selection

The patient population will consist of eligible patients based on the following inclusion and exclusion criteria:

A. Inclusion criteria

1. Patients must be age 18 or over and may be of either gender and of any race.
2. Women of child bearing potential who are not surgically sterile must have a negative pregnancy test and be using a reliable method of contraception.
3. Patients must be on optimal conventional therapy, including an angiotensin converting enzyme inhibitor (ACEI) for at least 30 days prior to randomization, or patients must have had a trial of ACEI and have been proven to be intolerant. Optimal conventional therapy frequently includes digitalis, diuretics or other vasodilators. While diuretics and digitalis are encouraged for appropriate patients, they are not mandated for randomization. However, should the investigator choose to place a patient on one or more of these medications, the patient must be taking them for at least 30 days prior to randomization.
4. At time of randomization, patients must be NYHA functional class III or IV.
5. Patients must be competent to give informed written consent.
6. Patients must have a left ventricular ejection fraction by radionuclide determination of ≤ 0.35.

B. Exclusion criteria

1. Patients must not have heart failure due to or associated with uncorrected primary valvular disease, uncorrected thyroid disease, obstructive/hypertrophic cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, or malfunctioning artificial heart valve.
2. Heart transplant candidates (actively on a list or anticipated to be on a list within 6 months of randomization) are excluded.
3. Patients must not have had an acute myocardial infarction within the past six

months.

4. Patients must not have had coronary bypass surgery, percutaneous transluminal coronary angioplasty (PTCA), or other cardiac surgery within the 60 days prior to randomization. In addition, patients in whom PTCA or cardiac surgery is contemplated are excluded.
5. Patients with severe or unstable angina will be excluded. Angina pectoris frequent enough to require more than 6 sublingual NTG tablets per week will be excluded from randomization.
6. The following patients are excluded because of current medications they are receiving: Patients receiving calcium channel blocking agents, theophylline, tricyclic antidepressants, MAO inhibitors, or beta-agonists who cannot be safely withdrawn from such. Patient must be off these medications for at least 1 week prior to baseline evaluation. Patients taking oral beta-adrenergic blocking agents within 30 days of baseline evaluation. Beta-adrenergic blocking agents should not be withdrawn in order to be randomized into this trial. Patients on investigational cardiovascular medications or involved in another investigational trial. Patients taking flecainide, encainide, propafenone, sotalol, or disopyramide within 2 weeks of randomization or amiodarone within 8 weeks. Patients on an intravenous or oral inotrope (other than digitalis) within 2 weeks of entry.
7. The following patients are excluded for medical reasons: Patients with a contraindication to beta-adrenergic blockade. Patients with other life threatening disease with a life expectancy of < 3 years due to other illness. Patients with active liver (T. Bili ≥ 3.0 mg%), renal (creatinine ≥ 3.0 mg%), hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease which in the opinion of the investigator may adversely affect the safety and efficacy of the study drug or the life span of the patient. Patients who have unstable decompensated heart failure (i.e. evidence of hypoperfusion, acute pulmonary edema, or hypotension with BP < 80 systolic). Patients actively abusing ethanol (> 100 gm ethanol per day) or illicit drugs

within the past 3 months. Patients with an AICD that has fired within 3 months of randomization. Asymptomatic waking, resting heart rate <50, or symptomatic bradycardia with heart rate <60. Uncontrolled insulin-dependent diabetes mellitus with a history of hypoglycemia episodes. High degree atrioventricular block (Mobitz II or complete heart block).

8. Demonstrated non-compliance with previous medical regimens.

C. Recruitment of Women and Minorities

The enrollment of patients from historically under-represented groups especially women and minorities is strongly encouraged. To ensure that sufficient women are enrolled, the study has set a target of 50% female enrollment in the non-VA sites which will be 2/3 of the sites; for an overall study-wide proportion of 33% women. If the study has not reached this target after the first 300 patients are randomized, the DSMB will recommend that non-VA sites that are not meeting the above criteria will recruit women only until they have reached the target. This policy will continue until the DSMB concludes that all reasonable efforts have been made.

VI. Informed Consent Procedure

A new patient in whom history, physical, and laboratory findings are compatible with participation in the study will be interviewed by the principal investigator or designated physician. The purpose of the study and the long-term follow-up required will be discussed. In addition, the possible side effects of the medication will be discussed with the patient. The patient will be given the consent form to read and the investigator or team member will remain available to answer any questions regarding the protocol. If the patient agrees to participate, he/she will be asked to sign the consent form with the understanding that he/she is free to withdraw at any later date. If possible, a family member will also be advised about the study. See Appendix C for a copy of the consent form.

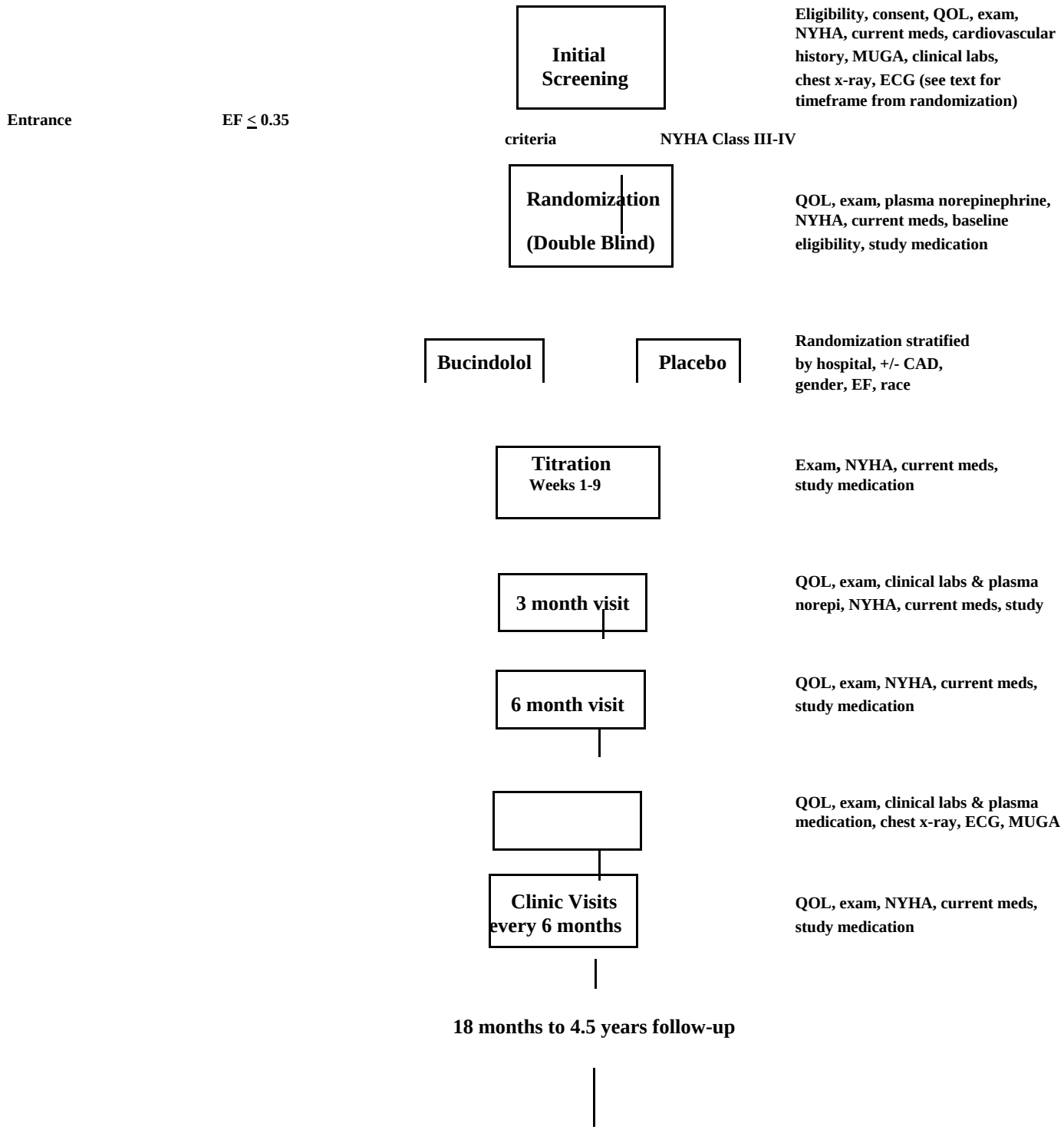
VII. Screening Clinic Visit and Schedule of Tests

A. Table 1 "Study Schedule"

TABLE 1. Study Schedule

			Months from Randomization				
	Initial Screening	Randomization	1 - 2	3	6	12	q6
Number of Visits	1	1	5 - 9	1	1	1	1+
Eligibility Criteria	X	X					
Informed Consent	X						
Cardio-vascular History	X						
Physical Examination	X	X	X X	X	X	X	X
Body Weight	X	X	X X	X	X	X	X
Vital Signs	X	X	X X	X	X	X	X
NYHA Class	X	X	X X	X	X	X	X
Quality of Life	X	X		X	X	X	X
MUGA	X			X		X	
Clinical Laboratory	X			X		X	
Chest X-ray	X			X		X	
ECG	X			X		X	
Plasma Norepi-nephrine		X		X		X	
Current Medications	X	X	X	X	X	X	X
Study Medication		X	X	X	X	X	X

Flowchart of Study



B. Initial screening visit

Screened patients will be seen as in-patients or out-patients, and a complete history and physical examination will be performed including body weight and vital signs. Current drug therapy will be examined and all inclusion and exclusion criteria should be met. If the patient is deemed a suitable candidate for entry into the study, the informed consent process should be initiated. A signed consent form for participation in the study will be required prior to randomization. If the patient has not had an assessment of left ventricular ejection fraction by MUGA at a BEST site within 60 days before randomization, a MUGA scan should be performed prior to consideration for randomization. The MUGA scan should contain an assessment of both left and right ventricular ejection fraction. In addition, a chest x-ray, electrocardiogram, and clinical laboratory will be performed within 14 days prior to randomization. Clinical laboratory will include complete blood count (CBC), platelet count, INR, PTT, electrolytes, BUN, creatinine, liver function tests, calcium, phosphorous, total protein, albumin, lipids, cholesterol, triglycerides, uric acid and serum magnesium.

DNA will be banked from patients enrolled in the trial for further elucidation of genetic etiologies and risk factors that contribute to the development of heart muscle disease in heart failure. Remarkable progress is being made in the molecular genetics of cardiovascular disease, including cardiomyopathy. At the present time there are two families with familial dilated cardiomyopathy whose chromosomal locus has been identified by linkage analysis, and it is anticipated that before BEST is completed the gene responsible for these or other inherited cardiomyopathies will be determined. Management of the central DNA bank will be determined by the Steering Committee. All subsequent uses of DNA from this bank will require approval and genetic testing will be limited to the study of genes that may be associated with cardiovascular disease. All samples will be destroyed at the termination of the genetic studies.

A one time blood specimen for DNA banking will be taken from BEST participants at screening (or during a follow-up visit). Separate consent must be obtained from the patient prior to collecting blood for DNA banking. DNA blood specimens will be coded separately to ensure patient confidentiality and mailed to a central DNA laboratory for extraction.

C. Baseline visit and randomization

1. Baseline data collection

The baseline visit must be at least 7 days after the screening visit to ensure the clinical baseline stability of the patient. If after review of the inclusion and exclusion criteria, clinical laboratory and MUGA the results do not exclude the patient from participation in the trial, the patient may be randomized. The patient must be NYHA functional class III or IV at the time of the baseline visit in order to be randomized. If at this time, the patient in the opinion of the investigator is clinically unstable, his/her therapy may be changed, and randomization cannot occur until the patient is deemed stable. The patient may be randomized at any time point after all baseline data collection has occurred as long as the Quality of Life questionnaires, clinical laboratory, chest x-ray, and electrocardiogram have been performed within 14 days of randomization. The MUGA must have been performed within 60 days of randomization. Plasma norepinephrine will be collected at the randomization visit before study medication is dispensed.

2. Randomization to drug

Patients will be randomized to coded study drug by the Cooperative Studies Program Coordinating Center in response to a phone call at the baseline visit. The site coordinator will fax the randomization form to the center. An adaptive allocation procedure will be used to randomize patients within a hospital site, balancing treatment groups with respect to presence/absence of coronary artery disease, ejection fraction, race and gender. Every effort should be made by the investigator to determine the etiology of ventricular dysfunction. However, cardiac catheterization is not mandated for entry.

D. Drug Administration

1. Initial drug administration

After randomization, patients will be immediately started on study medication (bucindolol or placebo) 3.0 mg capsule orally twice daily. The first dose will be administered either in the hospital or under close supervision as an outpatient. Vital signs including blood pressure, pulse, and symptoms will be monitored every hour for the first two hours. If the entering subject is an outpatient, he/she will be encouraged to weigh himself/herself daily and to call or return promptly should symptoms occur (i.e. not wait until the next scheduled visit). Worsening heart failure (i.e. an increase in weight, shortness of breath, rales, edema, etc.) should not be taken as a drug failure unless adjustment of diuretics (including if necessary IV diuretics) fails to provide reinstitution of a

compensated state. If at any point in the study the patient requires hospitalization or IV inotropic therapy, the study medication may be discontinued, but only if absolutely necessary. Every effort should be made to restart the study medication after such a discontinuation. The study chair must be notified within 72 hours of the start of any discontinuation of study medication. It should be emphasized that some patients who undergo drug titration with beta-adrenergic blocking agents have a 4-6 week period of feeling mildly worse and a few will have frank decompensation. Clinical improvement may not be noted until the second to third month of therapy (i.e. it is not unusual for the patients to worsen somewhat prior to seeing symptomatic improvement). Thus, persistence with therapy is encouraged unless frank decompensation occurs.

2. Follow-up visits and dose titration

Months 1 - 2 -- Dose Titration

Each week a brief history and physical examination will be performed by the investigator to assess the impact of progressive dose titration. The dose of study medication will be increased at weekly intervals to the appropriate target dose based on the patient's weight on the day of randomization: patients < 75 kg receiving a target dose of 50 mg BID (100 mg daily) and patients $\geq$75 kg receiving 100 mg BID (200 mg daily). The patient will receive 3.0 mg BID for the first week after randomization and then will be titrated according to the following schedule:

week 2.....	12.5 mg daily (all patients) (6.25 mg BID)
week 3.....	25 mg daily (all patients) (12.5 mg BID)
week 4.....	50 mg daily (all patients) (25 mg BID)
week 5.....	100 mg daily (all patients) (50 mg BID)
week 6.....	200 mg daily (patients ≥ 75 kg at randomization) (100 mg BID);
	100 mg daily (patients <75 kg at randomization) (50 mg BID)
week 7.....	1 week follow-up
	(No visit for patients <75 kg)
	(Dose titration may require more than 7 weeks)

Should decompensation or adverse effects occur during this dose titration period, the investigator is encouraged to increase the dose of diuretic and continue the drug if at all possible. However, if the patient has an increase in his/her heart failure symptoms, the investigator may slow drug titration by:

1. Deciding to delay the increase in the study medication dose for 1-2 weeks, or
2. Deciding to reduce the dose (i.e. go back to the previous dose) temporarily and defer further titration for 1-3 weeks.

However, the investigator is encouraged to resume upward titration as soon as the patient is clinically stable. As previous studies have demonstrated more benefit of beta-blockers at higher doses, all investigators are encouraged to titrate patients to full target dosage if at all possible.

Should other side effects of study medication occur, such as impotence, dizziness, lightheadedness, nightmares, etc., the investigator may choose to decrease the dosage of study drug. However, the investigator is encouraged to maintain the highest possible effective dose without side effects. For example, while a patient may not tolerate 100 mg daily, he/she may tolerate a dose of 50 mg daily. In addition, the patient may at some later time period tolerate retitration to the higher dosage. See Appendix B, Section 9 for the drug handling procedures and Operations Manual for detailed clinical guidance for slow, gradual reduction of the drug dosage and re-challenge.

3 Month Follow-Up Visit

All patients will return for a follow-up visit at 3 months after the date of randomization at which time a physical examination including body weight and vital signs will be performed. A repeat assessment of NYHA functional class and Quality of Life questionnaires will be done. Repeat MUGA for left and right ventricular ejection fractions, clinical laboratory, chest x-ray and electrocardiogram will be performed. Additionally, a repeat plasma norepinephrine will be performed at this visit.

6 Month Follow-Up Visit

All patients will return for a follow-up visit at 6 months after the date of randomization at which time a physical examination including body weight and vital signs will be performed. A repeat assessment of NYHA functional class and Quality of Life questionnaires will be done.

12 Month Follow-Up Visit

All patients will return for a follow-up visit at 12 months after the date of randomization at which time a physical examination including body weight and vital signs will be performed. A repeat assessment of NYHA functional class and Quality of Life questionnaires will be done. Repeat

MUGA for left and right ventricular ejection fractions, clinical laboratory, chest x-ray and electrocardiogram will be performed. Additionally, a repeat plasma norepinephrine will be performed at this visit.

Subsequent Visits -- Every 6 months

All patients will return for follow-up every 6 months (or more frequently as clinically indicated) after 1 year at which time a physical examination including body weight and vital signs will be performed. A repeat assessment of NYHA functional class and Quality of Life questionnaires will be done. Other laboratory tests may be performed as clinically indicated.

3. Discontinuation of study medication for clinical reasons

Patients who develop worsening congestive heart failure while on study medication may be treated according to the severity of their decompensation. There are essentially three levels of decompensation:

a) Fluid retention which responds to increased diuretic or ACE inhibitor administration

b) Frequent recurrent fluid retention unresponsive to diuretic dosage increase

c) Incipient cardiogenic shock

The treatment of these conditions differs substantially:

a) Fluid retention which responds to increased diuretic or ACE inhibitor administration may be handled as an outpatient and should not routinely require discontinuation of study medication. In rare instances, study medication may have to be temporarily or permanently decreased.

b) If a patient is not in incipient cardiogenic shock but has frequent recurrent fluid retention unresponsive to diuretic dosage increase or an increase in ACE inhibitor therapy, an investigator may choose to give intermittent low dose inotropic therapy. In this situation, it is preferable to administer a short 12-24 hour course of intravenous inotropic (preferably milrinone because its mechanism of action is not dependent on the beta-receptor) or vasodilator (nitroprusside, nitroglycerin) therapy during concomitant study drug therapy to reach compensation rather than discontinue drug altogether. Despite these efforts, should the patient not be able to be maintained on study drug therapy, the study drug dosage may be slowly, gradually reduced or discontinued. As acute withdrawal of beta-adrenergic blockade has been associated with cardiovascular events, it is recommended that drug dosage be slowly, gradually reduced rather than stopped acutely. **Should a patient not tolerate**

study medication and the investigator wish to discontinue it, the Study Co-Chairman must be called prior to study drug reduction and the case discussed. When the patient is again compensated, the investigator and patient may choose to reinstitute the study medication and are encouraged to do so if at all possible. Re-titration starting at 3 mg orally twice daily should be performed as previously described, with weekly or biweekly up-titration.

c) In the face of incipient cardiogenic shock (fluid retention, hypotension, end organ hypo-perfusion), the study drug should be immediately discontinued to administer inotropic therapy. When the patient is again compensated, the investigator and patient may choose to reinstitute the study medication. Re-titration starting at 3 mg orally twice daily should be performed as previously described, with weekly or biweekly up-titration.

4. Reinstitution of study medication

Reinstitution of study medication for patients who are again well compensated should be performed carefully using the following suggested guidelines:

a) For patients who have been off study medication less than 72 hours and who have not been in incipient cardiogenic shock, restart the study medication at the dose he/she was taking just prior to discontinuation.

b) For patients who have been off study medication greater than 72 hours but less than 7 days and who have not been in incipient cardiogenic shock, restart the study medication at half the dose he/she was taking just prior to discontinuation.

c) For patients who have been off study medication greater than or equal to 7 days or have recently been in incipient cardiogenic shock, restart the study medication at 3 mg orally twice daily.

Other causes for discontinuation of study medication may include: a) intolerable side effects unresponsive to reduction in study drug dosage, b) performance of a cardiac or non-cardiac surgical procedure, or c) other acute medical illness which require cessation of drug therapy. For emergency surgery, study drug may be discontinued for 72 hours. For elective surgery where the patient will be unable to take medications for a prolonged period of time, slow, gradual reduction of the study drug dosage (cutting the dosage in half every 3 days) is recommended. In all cases, every effort should be made by the investigator to maintain or reinstitute the study drug.

5. Breaking the study medication code

The investigator should manage the patient by assuming he/she is on an active drug. In extraordinary, life-threatening circumstances, there may be a necessity to break the study code. In such circumstances, the investigator should attempt to reach a Study Co-Chairman, the Clinical Research Pharmacist or Biostatistician for instructions prior to breaking the code. In all other circumstances, temporary discontinuation of study medication should be handled without breaking the code, as described in Section D.1. on pages 28-29.

VIII. Statistical Analyses

A. Monitoring 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 trial.

1. Executive Committee

The recruitment progress of each center and of the whole trial will be updated weekly for the Executive Committee.

2. 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 **a)** patient recruitment, **b)** patient adherence, **c)** "effective adherent patient years," **d)** quality control, and **e)** clinical performance data at each center. Special attention will be paid to the recruitment of participants (especially women) during that phase of the study and maintaining high adherence. These quarterly reports will include summaries of the Clinical Center progress on patient screening as well as relevant statistics from the screening and randomization visits. If required, the data can be transmitted via telephone lines. No endpoint or side effect data will be included in the Steering Committee Reports.

3. 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 six major sections: **a)** General Progress of Study and Recruitment, **b)** Endpoints, **c)** Possible Toxicity and Side Effects, **d)** Adherence, **e)** Data Quality, and **f)** Substudies. The General Section will outline participant recruitment and effective patient-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.

One to two months prior to the scheduled reporting date to 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 data forms 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, as well as within site variability of measures. 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 within 7 days preceding the meeting so that the committee will have the most up-to-date data possible at the time of the meeting.

4. Quality Control of MUGA

The first two intake MUGA's at each site will be sent to a Core laboratory for re-reading. Thereafter, 5% of intake MUGA's will be sampled at random for rereading. Additional quality control procedures will be performed as indicated by the results of these re-readings.

B. Final Analysis

1. Baseline comparability

Because of the size of this study, it is expected that the randomization process will balance baseline characteristics and produce comparable groups of patients. Baseline comparability between treatment groups will be evaluated with respect to entry criteria, as well as demographic, physical and laboratory characteristics. Summary statistics and graphical techniques, such as boxplots, will be used to compare the baseline characteristics of treatment groups.

2. Primary Objective

The primary objective of this study is to determine whether treatment with beta-adrenergic blockade compared to placebo reduces all cause mortality in patients with moderate to severe congestive heart failure who are concurrently receiving optimal medical therapy. The null hypothesis to be tested is that there is no difference in survival time between active and placebo arms.

Two-tailed treatment comparisons will be made by the nonparametric logrank statistic with the exact variance calculation stratified by site, presence/absence of CAD and gender. This statistic is the optimal nonparametric test when censoring is equal in the treatment groups under proportional hazards. The analysis will include all survival times for all randomized patients in the treatment group to which the patient had originally been assigned (intention-to-treat principle). Significance levels will be set in accordance with the plan for monitoring the study.

Cumulative survival curves will be constructed by Kaplan-Meier methods.[79] The Cox life table regression method[80] will also be used to calculate estimates of relative risk, provided the model fits the data.

3. Secondary Objectives

Treatment differences will be evaluated in cause-specific cardiovascular mortality: total cardiovascular mortality, sudden death, worsening congestive heart failure, and ischemic cardiac events. These outcomes will be classified by the Mortality Committee which will remain blinded to treatment assignment. Cause-specific mortality will be further examined to estimate if treatment effect is similar for the different causes of death. Also, the cost of the two therapies will be examined.

The frequency of adverse effects in each treatment group will be analyzed using the chi-square statistic.

4. Subgroup analyses

All prior subgroup hypotheses related to treatment effect modification will be examined with tests to detect significant interactions. Our clinical interest focuses on qualitative interactions. We will use appropriate methods such as Cox regression[80] and stratified Kaplan-Meier curves.[79] However, the power to detect differences in treatment effects among subgroups will generally be lower than the power to detect an overall treatment effect. If tests of interaction are significant, then estimates of treatment effect will be derived within each subgroup. All reports of differences based on data-derived subgroups will be identified as such.

The following subgroups will be included in analyses to evaluate the effect of beta-adrenergic blocking agents on all cause mortality

1. Presence or absence of coronary artery disease.
2. Gender
3. Race
4. Age
5. Baseline left ventricular ejection fraction.
6. Baseline serum sodium concentration.
7. Baseline NYHA functional class.
8. Baseline plasma norepinephrine.
9. Baseline heart rate.
10. Baseline heart rhythm (sinus rhythm versus atrial fibrillation).
11. Baseline systolic blood pressure.
12. Improvement in left ventricular ejection fraction from baseline to 3 months of therapy.
13. VA versus non-VA site, after adjusting as far as possible for clinical prognosis.

5. Other analyses

Additional analyses for treatment group effects will include as outcome variables:

a. Hospitalizations per month of life
b. Quality of life indicators

c. Incidence of myocardial infarction

d. Left ventricular ejection fraction at 3 and 12 months of therapy.

As beta-adrenergic blockade has been shown to improve ventricular function in patients with congestive heart failure, examination of changes in left ventricular ejection fraction in the bucindolol group will be compared to the placebo group. Analyses will include examination of the response of patients (i.e. change in left ventricular ejection fraction) with regard to baseline norepinephrine levels, baseline heart rate, baseline ejection fraction, baseline systolic pressure and presence or absence of coronary artery disease, to determine which group will have the most favorable hemodynamic response to beta-adrenergic blockade.

C. Interim analysis

Interim monitoring will focus on patient intake (overall and within hospital), hospital adherence to protocol, adverse reactions, baseline comparability of treatment groups and effect of treatment on the primary study outcome.

Due to ethical considerations, the study will be reviewed by the DSMB which may recommend early termination of the trial based on interim analyses. The DSMB will use a Lan-DeMets upper boundary with an intermediate spending function, and stochastic curtailment for the lower boundary.

IX. Data Collection and Management

After the study is approved, data forms will be field tested. An Operations Manual will be provided to the investigators as a guide to the operation and management of the study as well as a technical reference manual. A training session is planned prior to the initiation of patient intake for all study participants in order to assure uniformity in the protocol implementation--specifically patient management and data collection procedures, and to train the participants in study procedures (e.g. randomization, titration).

The study coordinator at each medical center will assemble the completed case report forms at least weekly. Originals of the forms will be kept at the participating investigator's office and faxed to the Coordinating Center where the fax is received by a computer.

All forms received at the Coordinating Center are reviewed manually, after the computer has assembled a database from optical character recognition of the fax image, which is also stored. Several independent sequential checks on the data are performed by the center's statistical assistants. Computer data files containing the accumulated patient information are updated at regular, frequent intervals with appropriate backups. New information is screened by a computer program to check for missing and out-of range values. This program generates notices to be mailed to the participating investigators requesting completion, correction or verification of specific data items. Simultaneously, a file is created containing the questionable data and the type of data error. This file is used to edit the necessary data when the requested information is returned. Data found to be irretrievable will be assigned a code to distinguish the value from pending data. A computerized record will be kept of types of errors to ensure a high level of data integrity.

Other quality control measures include periodic reports containing patient recruitment information and relevant medical data for checking. Each site will be visited by study monitors to ensure adherence to the rules for informed consent and criteria for inclusion and exclusion.

X. Monitoring the Study

A. Monitoring Patient Compliance

Several concurrent mechanisms will be used in an attempt to enhance and monitor patient compliance with the medication dosing regimen. These mechanisms include use of an individualized drug therapy kit, capsule counts, patient counselling, and titration monitoring.

At each clinic visit the patient will be reminded of the importance of taking the study medication exactly as prescribed. The study drug will be supplied in prescription vials or bottles containing adequate study medication to last until the next scheduled clinic visit. Patients will be instructed to return each vial or bottle at the next clinic visit. Capsule counts will be made, with or without the patient's knowledge (at discretion of study personnel), as a means of assessing patient compliance. Patients taking 90-110% of the capsules prescribed will be considered compliant. Patients will also be questioned about any non-study medications that have been taken since the previous visit and will be reminded of any drugs that should be avoided.

Tolerance to the study medication during the titration period will be monitored by the co-chairman. Periodic calls will be made to each center to evaluate their titration efforts and to counsel centers with problems.

B. Monitoring Adverse Treatment Effects

1. Adverse Experiences

This study will be conducted under an IND (Investigational New Drug Application) sponsored by the VA Cooperative Studies Program. Monitoring and reporting adverse experiences will comply with FDA requirements. Patients will be closely monitored at each visit for adverse experiences possibly due to study participation. An adverse experience is defined as any adverse change from the patient's baseline condition, including any clinical or laboratory test value abnormality that occurs during the course of the study, regardless of its association with the study medication. All unexpected events or adverse experiences that occur during the study period, regardless of their association with the study medication, will be reported on the "Adverse Events" form. An assessment of medication relatedness will be required for each event reported.

2. Immediately Reportable Adverse Experiences

ANY ADVERSE EXPERIENCE CONSIDERED TO BE SERIOUS OR UNEXPECTED (PREVIOUSLY UNREPORTED) AND POSSIBLY OR PROBABLY RELATED TO THE STUDY MEDICATION REQUIRES PROMPT NOTIFICATION OF THE STUDY CO-CHAIRMEN AND CLINICAL RESEARCH PHARMACIST. A supplementary adverse experience report (using FDA Form 3500, MedWatch) will be submitted as soon as possible following any adverse experience meeting the above criteria. Completed FDA Forms 3500 will be mailed to the Clinical Research Pharmacist (Albuquerque CSPCRPCC) with a copy to each of the Study Co-Chairmen's offices.

If an adverse experience is fatal or life-threatening, an immediate telephone report is required and a written report (using FDA Form 3500) must follow within 72 hours. All such reports (written and telephone) will be submitted to both the Clinical Research Pharmacist and the Study Co-Chairmen.

Reports of alarming adverse experiences will be screened by the Clinical Research Pharmacist and Study Co-Chairmen. All investigators will be notified of any report suggesting new hazards. The Clinical Research Pharmacist will provide periodic summaries of all alarming adverse experiences to the Palo Alto CSPCC, the Data Safety and Monitoring Board and if applicable, the FDA.

A serious adverse experience is defined as any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experiences, this includes any experience that 1) is fatal or life-threatening, 2) is permanently or substantially disabling, 3) requires hospitalization, 4) prolongs an existing hospitalization; or is 5) a congenital anomaly; 6) cancer; or 7) the result of an overdose.

An unexpected adverse experience is defined as any experience not identified in the Investigator's Brochure or elsewhere in the protocol, is thought by the reporter to be unanticipated in nature, intensity or frequency, or to have potential relevance to the overall safety of the study medication.

XI. Substudies and Ancillary Studies

A. Introduction

There are two types of substudies: ancillary studies and databank studies. Databank studies are based on data collected in the course of the main study while ancillary studies consist of additional data collected beyond that in the primary protocol. It is the express intent of the Steering Committee and the sponsoring federal agencies to derive the maximum amount of scientific information from the BEST database via primary endpoint analyses and to encourage the development of Ancillary Studies, Databank and Substudies. An equal opportunity will exist among the BEST 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 BEST sites, the Coordinating Center, the Central Clinical Office 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 BEST participants in an investigation which is not described in the BEST protocol and involves data which is not collected as part of the routine BEST data set. Such studies may be carried out independently by the applicant investigators or in conjunction with other BEST investigators or units, and require independent (non BEST) funding.

Ancillary studies must be approved by the Steering Committee on the recommendation of 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 BEST. They should be implemented only after recruitment and performance in the main study are satisfactory at the relevant clinical centers. Studies may not begin until approval is transmitted from the Coordinating Center.

C. Databank studies

A databank study utilizes data which has been routinely collected as part of the main BEST 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 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 BEST.

D. Other ("Non-BEST") projects

Simultaneous participation of the BEST participants in an unrelated study is strongly discouraged since this may result in interference with BEST objectives or place demands on the participant that may diminish his/her availability, cooperation or willingness to participate in additional BEST-related studies. In certain circumstances, it may be desirable, for clinical reasons, to enter a BEST 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 Site 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 BEST participant in a non-BEST prospective investigation requires the prior approval of the Executive Committee.

E. Data storage and analysis

Data forms will be stored at the Coordinating Center and data will be entered into the computer system. Data will be analyzed at the Coordinating Center unless other arrangements have been approved by the Substudies Committee.

F. Application Review Process

The Substudies committee will review proposals at each of the semi-annual meetings as well as between meetings as necessary. If several applications for similar substudies (Ancillary or Databank) are received, the Substudies committee 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 Substudies committee will individually grade the applications by scientific merit and feasibility. It is implicit that performance of additional studies must not undermine the major objectives of BEST at any site.

In order to assure that all sites have an equal opportunity to develop and participate in the analyses, proposals will then be circulated through the Chairman of the Substudies Committee 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 Steering Committee. Once the concept of a substudy has been approved, the protocol will be developed by the particular investigator(s). 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-BEST investigators or institutions are welcomed but will be accorded secondary status should a similar application be received from a qualified BEST investigator.

XII. Publication Policy

The Publications 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 BEST 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. Additionally, all presentations and publications are expected to protect the integrity of the major objective(s) of the study; data that break 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 BEST are papers that present outcome data (such as mortality or the efficacy of the BEST agent in reducing heart failure) for the BEST 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 Subcommittee.

Authorship on primary outcome manuscripts will be "The BEST Investigators". For such manuscripts, there will be an appendix containing the names of the organizational units, their Principal Investigators and Co-Investigators. Organizational units will include the Clinical Sites, the Central Research Pharmacy, the Coordinating Center, Central Laboratory, the Central Clinical Office and the Project Office. The Data and Safety Monitoring Board 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 BEST Investigators." In addition, papers will have an appendix containing the names of the organizational units, their Principal Investigators and Co-Investigators and other individuals participating in the study. Units will include the Clinical Sites, the Central Research Pharmacy, the Coordinating Center, Central Laboratory, the Central Clinical Office and the Project Office. All papers and abstracts must be approved by the Publications Committee before they are submitted.

It is possible that in certain instances BEST 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

BEST may terminate at the planned target of 1.5 years after the last participant has been 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 trial, our objectives in closing out the study are as follows:

- To evaluate as fully and accurately as the data permit the effect of the beta-blocker on all-cause mortality and to make these results public as expeditiously as possible.
- To fulfill our ethical and humane obligations to the BEST study participants.
- To promote the scientific value of study data as fully as possible.

Close-out procedures including recommendations for further patient care will be developed by the Steering Committee. Regardless of the timing and circumstances of the end of the study, close-out will proceed in two stages:

- Interim period for analysis and documentation of study results.
- Debriefing of participants and dissemination of study results.

A. Interim

Every attempt will be made to reduce to an absolute minimum the interval between the completion of data collection and the release of the study results. We expect to take about 3 to 4 months to compile the final results paper for an appropriate journal.

B. Reporting of study results

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

APPENDIX A - SAMPLE SIZE AND RATIONALE

A. Overview

The primary objective of this study is to evaluate the effectiveness of beta-blocker therapy in reducing all cause mortality in patients with moderate to severe congestive heart failure who are receiving concomitant optimal medical therapy. The study is planned as a double-blind, two-arm clinical trial of NYHA class III-IV patients with ejection fraction ≤ 0.35 randomized to either the placebo or beta-blocker (bucindolol) groups. The primary endpoint is time to death. We estimate that 2800 patients will be required to detect with 85% power a 25% annual mortality reduction with bucindolol therapy, taking into account several factors that tend to reduce power. Our approach to sample size was a) to calculate the required number of patients for a range of reasonable design assumptions; b) decide on a sample size; and c) carry out a sensitivity analysis for the fixed sample size in order to evaluate the impact of misspecification of assumptions on the power of the trial.

While there are many approaches to calculating sample size for time-to-event data, the method of Lakatos[81, 82] was used because it provides estimates of sample size for tests based on the logrank statistic after adjusting for complex trial characteristics such as staggered accrual, time-varying hazard ratios, a lag in treatment effect, losses to followup, noncompliance, and heart transplantation. The adjustment is accomplished by assuming a placebo death rate and percent mortality reduction with treatment (or equivalently a hazard reduction) in a "perfect" trial and then adjusting the rates based on a schedule over time of losses, noncompliance, etc. The observed mortality reduction after adjustment will be lower than before adjustment.

Although randomization will be stratified by hospital site, presence/absence of coronary artery disease, ejection fraction, race and gender, we did not incorporate stratification in the sample size calculations and instead assumed average rates across strata.

B. Assumptions

The target sample size of 2800 patients (1400 per group) was based on the following assumptions (annual rates for mortality, losses to follow-up, noncompliance, and heart transplantation refer to patient years on study, not calendar time):

1. **Significance level** (Type I error) of 5%, two-sided
2. **Power** (sensitivity) of 85%
3. **Patient accrual** assumed to be uniform over a 3 year intake period, 18 month minimum followup, 3 year average followup, total study length of 4.5 years.
4. **Annual mortality rate** of 15% in the placebo group (prior to adjusting for noncompliance, losses etc.) which is conservative based on similar previous studies of heart failure[5,6,8,9,63]. These studies are summarized in the table below, with our proposed study BEST as the last entry.

Study	Severity of Heart Failure	Mortality Rate
VA V-HeFT II[8] enalapril group	NYHA class II & III with <1% class IV	16.5% annually
SOLVD[6] enalapril group	mild to moderate	12% year 1 10% year 2 13% year 3 7% year 4
CONSENSUS[5] enalapril group	severe, NYHA class IV	36% year 1
PROMISE[63]	moderate to severe (all patients) NYHA class III NYHA class IV	32% year 1 27% year 1 40% year 1
BEST (proposal)	moderate to severe EF ≤ 35, NYHA class III-IV	15% annually

(The rates shown for SOLVD are approximations estimated from the cumulative rates extrapolated from Kaplan-Meier curves).

Patients in PROMISE had a high mortality rate despite angiotensin converting enzyme inhibitors. However, PROMISE randomized patients to inotropic therapy and therefore only the sickest patients were entered. Due to some investigator bias against randomizing the sickest patients to a beta-adrenergic blocking agent, a conservative annual placebo group mortality of 15% is assumed in the proposed study.

5. **Mortality reduction** The study target is set for detecting a reduction in annual mortality of 25%, i.e. from 15% to 11.25% before adjusting for losses, noncompliance, etc. The design implications of these factors are discussed below. The planning committee decided that a 25% reduction in annual mortality under ideal experimental conditions was the smallest effect size of clinical interest upon which they were willing to base the trial. It is estimated below that the adjusted cumulative 4.5 year mortality rates would be 35% and 30% in the placebo and beta-blocker groups, respectively, which results in an adjusted cumulative 4.5 year mortality reduction of 15%. The need for adjustment is due to the following complicating assumptions.

6. **Lag** An initial 3 month lag in treatment benefit is assumed (i.e., death rates in the two groups were assumed to be equal during the initial 3 months of patient follow-up) since 5-9 weeks are needed to titrate patients onto bucindolol.

7. **Loss-to-followup** An annual rate of ~1% or cumulative rate of 5% in each treatment group. A loss is defined to be a patient who at some point during the study can no longer be observed for the occurrence of death. Survival status in the VA can be ascertained with almost 100% accuracy through the VA Beneficiary Identification and Record Locator Subsystem (BIRLS).

8. **Noncompliance** The projected annual rate of noncompliance (i.e. permanent discontinuation) in the bucindolol group of 10% in year 1 and 2% per year for the next 3.5 years. This is approximately a 16% cumulative rate, which is conservative based on the experience with the drug [3,26,27,30,31,43] but reasonable in a large multi-center clinical trial. The assumed rates are 'front-loaded' to reflect higher anticipated rates of noncompliance and intolerance early in patient followup. In accordance with the

intention-to-treat principle, outcomes of noncompliant patients are counted in the treatment group, to which they were randomized. Noncompliance is expected to diminish the mortality reduction achieved with therapy because patients will be off drug. (When noncompliers go off therapy they are assigned placebo death rates in sample size calculations.)

9. **Drop-in rate** (i.e. patients assigned to placebo but taking bucindolol) was assumed to be 0% since it is rare for heart failure patients to be placed on beta-blocker therapy.

10. **Heart transplantation rates** of 1.85% per year in the placebo group and .37% in the bucindolol group, beginning in year 2 of patient followup. This is based on a projected study population composed of the following proportions of patients: 50:50 VA:NIH, 40:60 women:men, 1% per year transplant rate in NIH women (older population not transplant eligible), 3% per year transplant rate in NIH men, and 1.5% per year transplant rate in VA men. The differential group transplantation rates reflect those in the MDC trial[35], 9% cumulative rate in the placebo group and 1% cumulative rate in the beta-blocker (metoprolol) group. Because the rate of transplantation in women and in the VA system is far less than that in the MDC participating centers, we expect lower rates during this trial. Transplants are assumed to occur after year 1 because patients on a transplant list or anticipated to be on a list within the 6 months following randomization are excluded from entering the study and are unlikely to have a transplant during year 1 of followup. Although we discourage patients who will be considered for transplant from being randomized, we cannot ethically exclude these patients from transplant after they have entered the trial. Because transplantation may not be random, censoring patients at time of transplantation could introduce a bias. Rather than censoring at transplant, we decided that post-transplant survival should accrue to the randomized treatment (intention-to-treat principle). We adjusted mortality rates in sample size calculations making the assumption that 80% of patients receiving transplants would have died within a year if they not received their transplants. This lowered the expected mortality rate preferentially in the placebo group and had the net effect of diminishing the observed mortality reduction.

11. **AICD** The sample size was not adjusted for the use of automatic implantable defibrillators (AICD). These devices are permitted by protocol but currently about 1% of heart failure patients receive these devices annually. We also do not have evidence for a differential implantation rate between treatment groups. Under the assumption that half of the deaths will be due to progressive heart failure and half to sudden death and that use of AICD will not diminish death due to progressive heart failure, then at most 0.5% of each group may have prolonged survival. This would lower the mortality rate in the two groups, but by an equal and negligible amount.

Table 1. Sample Size for Joint VA-NHLBI Trial

Power	Noncompliance	# deaths	Sample Size
80%	10% yr 1, 2% per yr 2+ ~ 16% cum	799	2433
	15% yr 1, 4% per yr 2+ ~ 25% cum	908	2754
85%	10% yr 1, 2% per yr 2+ ~ 16% cum	916	2790
	15% yr 1, 4% per yr 2+ ~ 25% cum	1041	3157
90%	10% yr 1, 2% per yr 2+ ~ 16% cum	1068	3254
	15% yr 1, 4% per yr 2+ ~ 25% cum	1215	3683

Assumptions: two-sided .05 level, uniform entry, 15% per year placebo event rate, 11.25% per year bucindolol event rate, 25% unadjusted annual mortality reduction,
3 month lag in treatment effect, 1% per year loss to followup, front-loaded noncompliance, 0% drop-ins, 3 year intake, 4.5 year trial, intention to treat;

Heart transplantation rates for joint trial are 1.85% in the placebo group and .37% in the bucindolol group. These rates assume -- 50:50 VA:NIH, 40:60 women:men, 1% per year transplants in NIH women (older population not transplant eligible), 3% per year heart transplants in NIH men, 1.5% per year transplants in VA men. (Lakatos method).

All annual rates given in terms of patient follow-up time not calendar time.
Sample size of 2790 patients for the trial (shaded cell) is rounded up to 2800.

C. Sensitivity Analysis

Table 3.1 shows the pattern of sample sizes as power and noncompliance rates vary. Approximately, a 5% increment in power results in a 15% larger sample (350-450 patients). Also, there is approximately an increase of 13% (325-425 patients) as the cumulative noncompliance increases from 16% to 25%. The shaded cell in the table shows the projected sample size of about 2800 for this trial.

Using the method of Lakatos,[81, 82] Figures 3.1-3.4 were constructed to show trends in the sensitivity of the trial as we fix the sample size at the targeted 2800 patients, make the design assumptions described above, and then vary these assumptions.

Figure 3.1 shows an acceptable loss in power (85% to 81%) if beta-blocker noncompliance is twice as high as projected (~16% vs 25% cumulative).

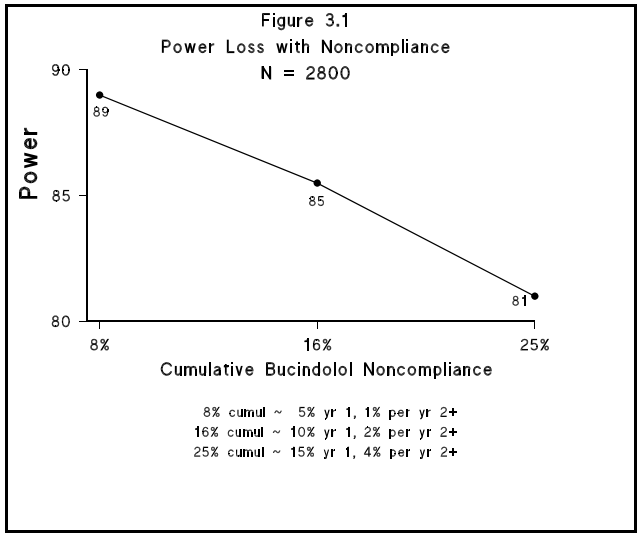


Figure 3.2 illustrates the loss in power with a lag in the treatment effect. This loss is expected since the sample size is driven by the number of deaths observed, which will be reduced by about 1/12 with a 3 month lag. The trial was sized for a 3 month lag based on the conservative assumption that patients will not obtain any benefit of therapy for three months because of the initial 5-9 week titration period. If the lag is 6 months instead of 3 months then power is reduced from 85% to 72%. The study investigators against using the more conservative 6 month lag in designing the trial since such a long delay in therapeutic benefit is not anticipated.

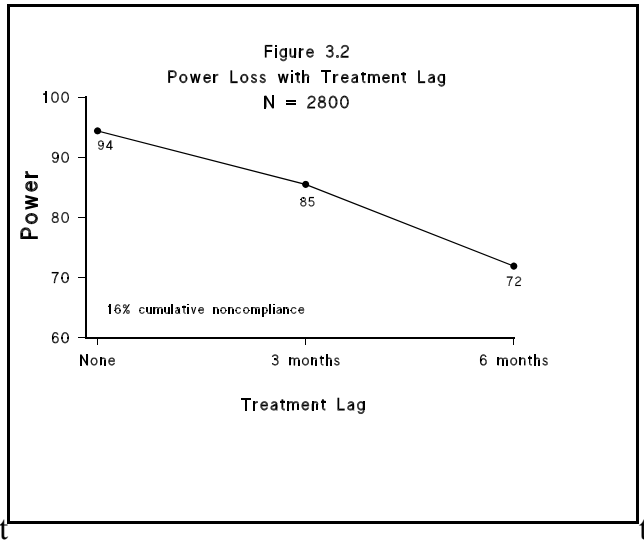
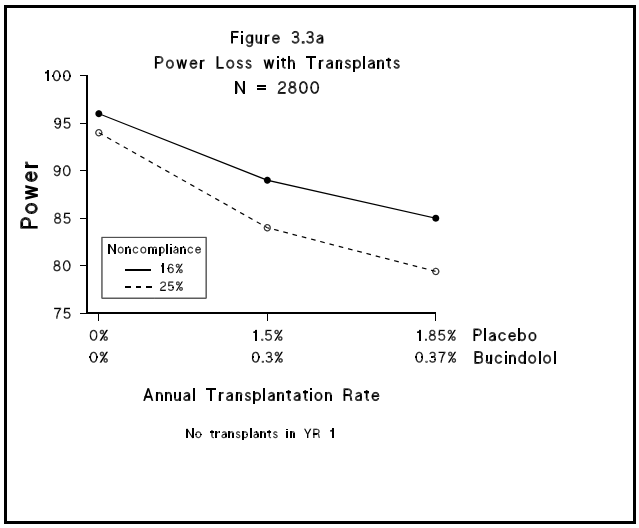


Figure 3.3a shows that transplantation rates in the range of interest effect the power of the trial. The study investigators assumed the higher placebo transplant rate of 1.85% and bucindolol transplant rate of .37% per year after year 1 in calculating our target sample size (see Table 1 in this section). Power is reduced from 96% to 85% as transplantation rates range from 0% to 1.85% per year in the placebo group when the cumulative noncompliance is 16%. We also assumed that 80% of patients receiving transplants would have died within a year if the transplantations had not been performed. If we increment this death rate among transplant patients from 50 to 80 to 100% the power decreases about 5% or less with each increment, as shown in Figure 3.3b. Sensitivity differences were about 5% or less as the level of noncompliance increased in Figures 3.3a and 3.3b.



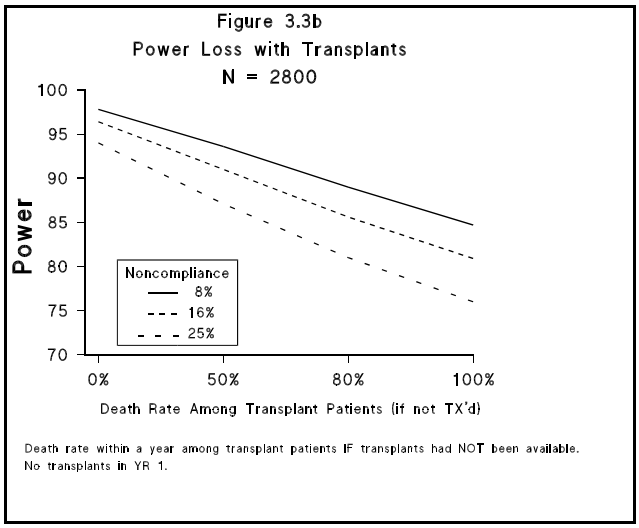
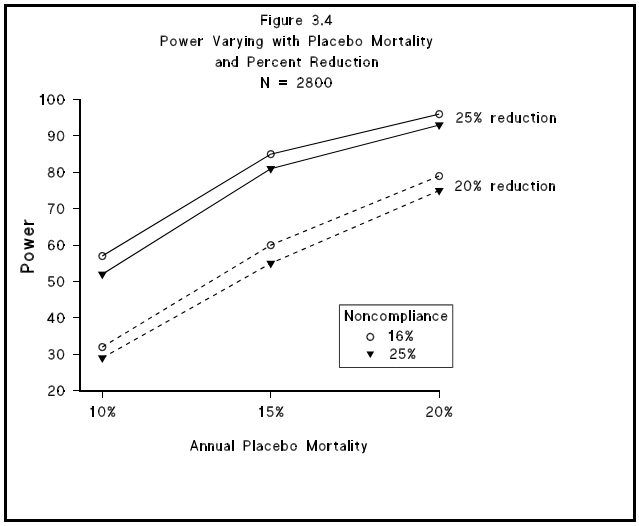


Figure 3.4 is included to show that placebo mortality rates and percent mortality reduction have pronounced effects on the sensitivity of the trial. By comparison, misspecification of the noncompliance rate has a much smaller effect. If the noncompliance rate is 16% and percent reduction with treatment is 25% as assumed for this trial, and if the unadjusted placebo rate is an unexpectedly low 10%, then power is reduced to 57%. Because the projected placebo mortality rate of 15% is considered conservative in a population of moderate to severe heart failure patients, we show that a higher mortality rate of 20%, which may be obtained, offers some protection against misspecification of other assumptions. If the mortality reduction is 20% versus the desired 25% and the noncompliance is 16% with a placebo mortality rate of 15% then the power of the trial is reduced to 60%. The study investigators chose 25% to be the effect size of clinical interest in designing this trial.



D. Study Duration

This study is planned for a total duration of 4.5 years in 90 medical centers. Three years will be needed to recruit 2800 patients at an average rate of approximately 1 patient per month per center. A minimum followup of 18 months was considered necessary to observe the effects of bucindolol. Other smaller studies previously discussed have shown therapeutic benefit within this period of time. Other combinations of intake period and study duration were considered such as a shorter trial with more centers and a longer trial with fewer centers, but the advantages did not appear to outweigh the disadvantages in terms of complexity and cost.

E. Contingency Plans

If the cumulative mortality rate in the control group is substantially lower than expected by the end of the second year of the study, the sample size may have to be increased and/or follow-up extended to observe a sufficient number of deaths, or the need for a study reevaluated in the light of the low control mortality.

APPENDIX B - DRUG PROTOCOL

The following appendix contains two editions of the Drug Treatment and Handling Procedures, a VA Edition and a Non-VA Edition. Please refer to the appropriate document based on your site.

DRUG TREATMENT AND HANDLING PROCEDURES

for

"Beta-Blocker Evaluation in Survival Trial (BEST)"

Prepared by:

VA COOPERATIVE STUDIES PROGRAM CLINICAL RESEARCH PHARMACY COORDINATING CENTER (151-I)

Department of Veterans Affairs Medical Center
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Albuquerque, NM 87108

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Attachment

DHP-1 Study Personnel Directory

1. INTRODUCTION

This Drug Treatment and Handling Procedures (DTHP) describes the procedures used by the local Pharmacy and study clinic personnel in handling the study drug involved in this trial at both VA sites and non-VA sites. Drug accountability forms are used to maintain a record of all study drug received, dispensed, and returned by the participating medical center. **A complete and accurate accounting for all investigational drugs is the responsibility of both the participating investigator and Pharmacy.** Drug records are maintained by Pharmacy to meet the accountability requirements of the FDA (Food and Drug Administration), VA CSP (Department of Veterans Affairs Cooperative Studies Program), NHLBI (National Heart, Lung and Blood Institute), and the pharmaceutical industry.

2. RESPONSIBILITIES OF PHARMACY

Pharmacy is responsible for:

a. Providing secure storage for the study drug in the pharmacy or elsewhere in the medical center.

b. Maintaining complete and accurate records of all study drug received, dispensed and returned to CSPCRPCC (Cooperative Studies Program Clinical Research Pharmacy Coordinating Center).

c. Verifying that informed consent has been obtained from each patient before any study drug is dispensed.

d. Dispensing the study drug only upon the written order (e.g., outpatient prescription blank or inpatient doctor's order form) of a physician authorized to prescribe the study drug.

e. **VA SITES ONLY** - Providing the nursing unit with a copy of the Investigational Drug Information Record (VA Form 10-9012) for inclusion in the medical record of each patient randomized.

To coordinate pharmacy activities, CSPCRPCC recommends that a liaison pharmacist be designated for this study. The liaison pharmacist should: 1) meet with participating study clinic personnel before the study begins and 2) consult with the Clinical Research Pharmacist at CSPCRPCC when necessary. The Study Personnel Directory (DHP-1) lists the names, addresses and telephone numbers of other key personnel involved in the study. The liaison pharmacist should keep this list updated and retain copies of all correspondence received from CSPCRPCC regarding CSP #395.

3. RESPONSIBILITIES OF THE PARTICIPATING INVESTIGATOR

The participating investigator is responsible for providing their local Pharmacy with:

a. A copy of the signed informed consent form for each patient to whom the study drug will be dispensed and administered.

b. Prescriptions or inpatient doctor's order forms signed by the investigator or one of the other authorized physicians.

c. The names of physicians currently authorized to prescribe the study drug at the participating medical center.

4. AUTHORIZED INVESTIGATORS

4.01 Participating Investigator

The study drug may be dispensed and administered only to patients who are under the supervision of the participating investigator and only for the purposes of this study. The participating investigator (henceforth referred to as the "Investigator") is the primary physician authorized by the FDA, VA CSP, NHLBI, and the local VA Research and Development Committee or Institutional Review Board to prescribe the study drug at the medical center. The investigator's name will appear on Form FDA 1572, "Statement of Investigator" [and on the Investigational Drug Information Record (Form DHP-2, VA Form 10-9012, Item 2 - VA SITES ONLY)].

4.02 Other Authorized Physicians

To authorize other physicians to prescribe the study drug, the investigator must include their names on Form FDA 1572, "Statement of Investigator" [and on the Investigational Drug Information Record (Item 19) - VA SITES ONLY]. CSPCRPCC will send the appropriate form(s) to the investigator prior to activating the study.

4.03 Authorizing New Physicians Throughout the Study

Additional physicians may be authorized to prescribe the study drug at any time by either completing an Addendum to FDA Form 1572 (Form DHP-3) or by submitting a memorandum to Pharmacy with the name(s) of additional physicians.

Blank Addendum to FDA Form 1572 forms will be available in Vol. II of the Operations Manual and from CSPCRPCC. The investigator (or his designee) should send the original of this form to CSPCRPCC, route the YELLOW copy to Pharmacy and retain the PINK copy for his files.

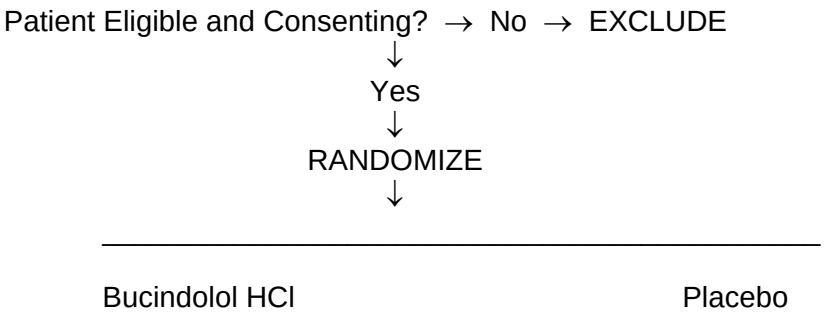
If the memorandum method is used, investigators (or his designee) should send the original to Pharmacy, a copy to CSPCRPCC and retain a copy for their files.

5. DESCRIPTION OF TREATMENT GROUPS

5.01 Outline of Study Design

The primary objective of this prospective, randomized, double-blind study is to evaluate the effect of β-adrenergic blockade on all cause mortality in patients with moderate to severe chronic heart failure in spite of conventional medical therapy. The basic study design is outlined in Figure 1.

[FIGURE 1]



Patients screened by study personnel and found to be eligible for participation in the study will be stratified according to (1) the hospital site and (2) the presence or absence of coronary artery disease. Patients will be treated and followed serially until death, refusal to continue study follow-up or termination of the study. Approximately 2,800 patients will enter the study during the three year enrollment period. The study will have a total duration of 4.5 years.

5.02 Treatment Groups

Patients will be assigned to one of two possible treatment groups:

a. Bucindolol HCl **(Code Named: B-395)**

b. Placebo

6. DESCRIPTION OF DRUG TREATMENT PHASES

6.01 Start-Up Treatment Phase

The start-up treatment phase begins the day the patient is randomized (Visit 2) and will end the day of Visit 10 (6-month visit). This phase consists of two parts: Part I (Titration) - a three month period during which B-395 is titrated to a target dose of either 50 mg BID for patients weighing ≤ 75 Kg (165 lb), if tolerated or 100 mg BID for patients weighing > 75 Kg (165 lb), if tolerated; and Part II (Transition) - a three month period during which the highest possible dose without side effects is administered until the day of Visit 10 (6-month visit).

6.01 (a) Part I - Titration Period

The titration period begins the day the patient is randomized (Visit 2) and ends the day of Visit 9 (3-month visit). All study drug needed during the titration period can be obtained from the patient's B-395 Titration Kit.

During the titration period, the study drug will be increased at weekly intervals according to the following schedule:

TITRATION

Visit 1 (Week 00*):Initial screening - NO DRUG THERAPY

Visit 2 (Week 01): Randomization - Begin 3.0 mg BID x 7 days

Visit 3 (Week 02): Begin 6.25 mg BID x 7 days

Visit 4 (Week 03): Begin 12.5 mg BID x 7 days

Visit 5 (Week 04): Begin 25 mg BID x 7 days

Visit 6 (Week 05): Begin 50 mg BID x 7 days **(target dose if patient weighs ≤ 75 kg)**

Visit 7 (Week 06): Begin 75 mg BID x 7 days
(50 mg BID x 7 days if patient tolerates dose and weighs ≤ 75 Kg)

Visit 8 (Week 07): Begin 100 mg BID x 7 days **(target dose if patient weighs > 75 Kg)**
(50 mg BID x 7 days if patient tolerates dose and weighs ≤ 75 Kg)

Week 08: Continue follow-up at target dose, if tolerated**

Week 09: Continue follow-up at target dose, if tolerated**

Week 10: Continue follow-up at target dose, if tolerated**

Week 11: Continue follow-up at target dose, if tolerated**

Week 12: Continue follow-up at target dose, if tolerated**

(* Refers to week in titration period, e.g., Week 03 means third week of titration period)

(** Beginning with Week 08 and continuing to the day of Visit 9 (3-month follow-up visit), the dose of B-395 administered should continue to be the highest possible tolerated dose without side effects.)

During the titration period, any one of the following dosing regimens can be prescribed:

DOSING REGIMENS PERMITTED

Dose	Dispense Capsules From:	SIG
3 mg BID	B-395 3 mg bottle (1)[1]	Take 1 capsule BID
6.25 mg BID	B-395 6.25 mg bottle (1)	Take 1 capsule BID
12.5 mg BID	B-395 12.5 mg bottle (1)	Take 1 capsule BID
25 mg BID	B-395 25 mg bottle (1)	Take 1 capsule BID
37.5 mg BID	B-395 25 mg bottle	Take 1 capsule TID[2]
50 mg BID	B-395 50 mg bottle (1)	Take 1 capsule BID
75 mg BID	B-395 50 mg bottle	Take 1 capsule TID[3]
100 mg BID	B-395 100 mg bottle (1)	Take 1 capsule BID

[1] Number in parentheses refers to number of bottles in Titration Kit.

[2] For a 37.5 mg BID "interim" dose, change prescription directions to read "Take one capsule (25 mg) TID. **This dosing regimen will be allowed only during the titration period.**

[3] For a 75 mg BID "interim" dose, change prescription directions to read "Take one capsule (50 mg) TID. **This dosing regimen will be allowed only during the titration period.**

(Note: Each B-395 dosage form will have a matching placebo.)

Should decompensation or adverse effects occur during the titration period, the investigator is encouraged to increase the patient's dose of diuretic and continue the study drug if at all possible. However, if the patient has an increase in heart failure symptoms, the investigator may slow drug titration by any of the following methods:

a. choosing to delay the increase in the dose of study drug for 1-2 weeks,
b. choosing not to further titrate the dose of study drug, or
c. choosing to reduce the dose of study drug (i.e., go back to the previous dose) temporarily and defer further titration for at least 1-3 weeks.

Should other side effects of B-395 occur (e.g., impotence, dizziness, lightheadedness, nightmares, etc.), the dose of study drug may be decreased. Investigators are encouraged, however, to titrate patients to the full target dose (i.e., 50 mg BID for patients weighing $\leq$ 75 Kg or 100 mg BID

for patients weighing > 75 Kg), if at all possible.

6.01(b) Part II - Transition Period

Part II of the start-up treatment phase, the transition period, begins the day of Visit 9 (3-month visit) and ends the day of Visit 10 (6-month visit). Prior to each patient's Visit 9 (preferably) or the day of Visit 9, study personnel must contact CSPCRPCC for a "Transition" bottle assignment.

Each "Transition" bottle contains a 3-month (98 days) supply of study drug. A number of these bottles, not predesignated for any particular patient, will be available at each participating medical center. The bottles will be individually numbered. **SINCE THESE BOTTLES MAY CONTAIN EITHER ACTIVE OR PLACEBO STUDY DRUG, STUDY CLINIC PERSONNEL MUST CALL CSPCRPCC [FTS 572-2580 (VA SITES ONLY) OR 505-265-1711, Ext. 2580] FOR ALL "TRANSITION" BOTTLE ASSIGNMENTS.**

Depending on the patient's highest tolerated dose during the titration period, study personnel should request one of the following types of "Transition" bottles indicated below:

TRANSITION BOTTLES

If the patient's highest tolerated dose during the titration period was:[1]	Request a Transition bottle containing:
3 mg BID	B-395 3 mg capsules
6.25 mg BID	B-395 6.25 mg capsules
12.5 mg BID	B-395 12.5 mg capsules
25 mg BID	B-395 25 mg capsules
50 mg BID	B-395 50 mg capsules
100 mg BID	B-395 100 mg capsules

([1] NOTE: THESE ARE THE ONLY DOSING REGIMENS ALLOWED DURING THE TRANSITION PERIOD. If the patient's highest tolerated dose during the titration period was 37.5 mg BID, the dose will have to be either decreased to 25 mg BID or increased to 50 mg BID. If the highest tolerated dose during the titration period was 75 mg BID, the dose will have to be either decreased to 50 mg BID or increased to 100 mg BID.)

6.02 Maintenance Treatment Phase

Beginning the day of Visit 10 (6-month visit), patients will enter a maintenance treatment period for the duration of the study. During this period, patients return to the study clinic for Visit 10 (6-

month visit), Visit 11 (12-month visit) and then subsequent follow-up visits every six-months thereafter. *[NOTE: It can be anticipated that some patients will need to return to the study clinic more frequently (e.g., every 4-8 weeks) due to the severity of their illness.]*

At Visit 10 (6 month visit) and all subsequent follow-up visits thereafter, the study drug should be prescribed at the highest tolerated dose without side effects. For example, if the highest tolerated dose administered to a patient during Part II of the start-up phase was 25 mg BID, then the dose prescribed at Visit 10 should be 25 mg BID; if the highest tolerated dose administered to a patient weighing > 75 Kg during Part II of the start-up phase was 100 mg BID, then the dose prescribed at Visit 10 should be 100 mg BID. *(NOTE: A dose as low as 3 mg BID will be allowed.)*

During the maintenance treatment phase, if intolerable side effects occur with B-395 (any dose), the dose of study drug may be reduced temporarily or permanently, if necessary (see Section 10, Discontinuation of Study Drug for Clinical Reasons). The patient may at some later time tolerate re-titration to a higher dose.

7. DESCRIPTION OF STUDY DRUG

7.01 Study Drug

Patients randomized to treatment receive the study drug, either Bucindolol HCl or a placebo. Bucindolol HCl is a non-selective, beta-adrenergic blocking agent. It is currently an investigational drug. The study drug and matching placebo are made by Bristol Myers Squibb and donated by Cardiovascular Pharmacology and Engineering Consultants, Inc. (CPEC). The Albuquerque CSPCRPCC will distribute the study drug to each participating medical center for the duration of the study. Patients will be treated with the study drug for three years, on average.

7.02 Patient Kit Designs

7.02 (a) B-395 Titration Kits

These are the only kits that CSPCRPCC will ship to each participating medical center prior to activating the study. All Titration Kit assignments will be made by the Palo Alto Cooperative Studies Program Coordinating Center (CSPCC). *(NOTE: Titration Kits may or may not be assigned in numerical order.)* Titration Kits contain B-395, either active or placebo. Each kit has six bottles of study drug. The study drug will be available in six clearly marked dosage forms: 3 mg, 6.25 mg, 12.5 mg, 25 mg, 50 mg, and 100 mg capsules.

Each Titration Kit contains a three month (98 days) supply of study drug and the bottles within each kit will contain varying quantities of drug:

Drug	# Bts/Kit	Dosage Form	# Caps/bt
B-395 3 mg	1	3 mg capsules	196s
B-395 6.25 mg	1	6.25 mg capsules	182s
B-395 12.5 mg	1	12.5 mg capsules	168s
B-395 25 mg	1	25 mg capsules	210s
B-395 50 mg	1	50 mg capsules	189s
B-395 100 mg	1	100 mg capsules	126s

Each Titration Kit is identified with a specific kit number. Upon randomization, the Palo Alto CSPCC will assign each patient his own Titration Kit.

7.02(b) B-395 Maintenance Kits

Each B-395 Maintenance Kit will be identified with the same number as on the patient's Titration Kit. *[NOTE: Drug assignment (active or placebo) also will be the same as in the patient's Titration Kit.]* Each kit contains a 12-month supply of medication and each bottle has enough medication to treat the patient for three months (98 days). Subsequent Maintenance Kits will be prepared by CSPCRPCC and automatically shipped to each participating medical center.

POSSIBLE CONTENTS OF B-395 MAINTENANCE KITS

CODE NAME	STUDY DRUG	QUANTITY
B-395 3 mg	Bucindolol HCl or placebo	4 bottles (196)*
	OR	
B-395 6.25 mg	Bucindolol HCl or placebo	4 bottles (196)
	OR	
B-395 12.5 mg	Bucindolol HCl or placebo	4 bottles (196)
	OR	
B-395 25 mg	Bucindolol HCl or placebo	4 bottles (196)
	OR	
B-395 50 mg	Bucindolol HCl or placebo	4 bottles (196)
	OR	

B-395 100 mg	Bucindolol HCl or placebo	4 bottles (196)

(* number in parenthesis is the number of capsules in each bottle)

7.03 Transition Bottles

Also available at each participating center are unassigned bottles of B-395, called "Transition Bottles." Each of these bottles contains a 3-month (98 days) supply of the study drug. Both active and placebo Transition Bottles are available.

POSSIBLE TRANSITION BOTTLE ASSIGNMENTS

CODE NAME	STUDY DRUG	DAYS SUPPLY
B-395 3 mg	Bucindolol HCl or placebo	98 (196)*
B-395 6.25 mg	Bucindolol HCl or placebo	98 (196)
B-395 12.5 mg	Bucindolol HCl or placebo	98 (196)
B-395 25 mg	Bucindolol HCl or placebo	98 (196)
B-395 50 mg	Bucindolol HCl or placebo	98 (196)
B-395 100 mg	Bucindolol HCl or placebo	98 (196)

(* number in parenthesis is the number of capsules in each bottle)

One of these bottles will be dispensed to each patient at Visit 9 (3-month visit). These bottles can also be used for any dosing regimen changes that occur during the transition period or maintenance phase. One or more of these bottles can be obtained by calling the Albuquerque CSPCRPCC [VA SITES ONLY: FTS 700-572-2580; ALL OTHERS: 505-265-1711, Ext. 2580]. *(NOTE: Either the pharmacist or one of the study personnel must call the Albuquerque CSPCRPCC for all Transition Bottle assignments.)*

Also available at each participating center are unassigned bottles of B-395, called "X-Bottles." Each bottle contains a two week (14 days) supply of the study drug. Both active and placebo X-Bottles will be available.

POSSIBLE X-BOTTLE ASSIGNMENTS

CODE NAME	STUDY DRUG	DAYS SUPPLY
B-395 3 mg	Bucindolol HCl or placebo	14 (28)*
B-395 6.25 mg	Bucindolol HCl or placebo	14 (28)
B-395 12.5 mg	Bucindolol HCl or placebo	14 (28)*
B-395 25 mg	Bucindolol HCl or placebo	14 (28)
B-395 50 mg	Bucindolol HCl or placebo	14 (28)
B-395 100 mg	Bucindolol HCl or placebo	14 (28)

(* number in parenthesis is the number of capsules in each bottle)

If the patient is ever hospitalized without his bottle of study drug, one or more X-Bottles can be obtained by calling the Albuquerque CSPCRPCC [VA SITES ONLY: FTS 700-572-2580; ALL OTHERS: 505-265-1711, Ext. 2580]. *(NOTE: Either the pharmacist or one of the study personnel must call the Albuquerque CSPCRPCC for all X-Bottle assignments.)*

7.05 De-Titration Cards

Three types of unassigned blistercards containing B-395, called "De-Titration Cards," are available at each participating medical center. Both active and placebo De-Titration Cards will be available.

POSSIBLE DE-TITRATION CARD ASSIGNMENTS

DRUG	DAYS SUPPLY	CODE NAME	STUDY
B-395 Card A	Bucindolol HCl or placebo	9 days (18)*	
B-395 Card B	Bucindolol HCl or placebo	6 days (12)	
B-395 Card C	Bucindolol HCl or placebo	3 days (6)	

(* number in parenthesis is the number of capsules on the card)

Whenever patients are on a daily dose of either **200 mg/day**, **150 mg/day (during titration period only)**, **100 mg/day**, or **50 mg/day** and need to have their study drug discontinued (temporarily or permanently), a De-Titration Card must be obtained by calling the Albuquerque CSPCRPCC [VA SITES ONLY: FTS 700-572-2580; ALL OTHERS: 505-265-1711, Ext. 2580). *(NOTE: Either the pharmacist or one of the study personnel must call the Albuquerque CSPCRPCC for all De-Titration Card assignments.)* See Section 9.03 for prescribing de-titration doses.

8. ORDERING AND STORING STUDY DRUG

8.01 Initial Order

To start the study, CSPCRPCC will send each participating medical center's pharmacy the following study drug supplies:

a. B-395 Titration Kits (8 boxes)
b. B-395 Transition Bottles (8 boxes)
c. B-395 X- Bottles (6 boxes)
d. B-395 De-Titration Cards (3 boxes)

Provisions must be made available by Pharmacy for adequate storage space (secured storage

required; refrigeration not required).

8.02 Additional Supplies

Inventory levels of Titration Kits, Transition Bottles, X-Bottles, and De-Titration Cards will be closely monitored by CSPCRPCC. Additional supplies will be sent automatically from CSPCRPCC to the medical center's Pharmacy.

9. DISPENSING STUDY DRUG

9.01 Dispensing Schedule

9.01 (a) B-395 Titration Kit Bottles

Beginning on the day of randomization (Visit 2) and continuing throughout the titration period, patients will be dispensed a weekly supply of study drug from one of the B-395 bottles in their Titration Kit. These six bottles are "bulk dispensing" bottles, so multiple dispensings can be made from each bottle, if necessary. **AT NO TIME, HOWEVER, SHOULD THE PHARMACIST DISPENSE A WHOLE B-395 TITRATION BOTTLE (ANY STRENGTH) TO A PATIENT!** The study drug should be dispensed as in the following examples:

a. if a study prescription calls for 3 mg BID for seven days, the pharmacist will dispense 14 capsules from the patient's bottle of B-395 3 mg capsules in his Titration Kit, with directions to "Take one capsule by mouth twice a day;"

b. if a study prescription calls for 6.25 mg BID for seven days, the pharmacist will dispense 14 capsules from the patient's bottle of B-395 6.25 mg capsules in his Titration Kit, and change the directions to read "Take one capsule by mouth twice a day;"

c. if a study prescription calls for 12.5 mg BID for seven days, the pharmacist will dispense 14 capsules from the patient's bottle of B-395 12.5 mg capsules in his Titration Kit, and change the directions to read "Take one capsule by mouth twice a day;"

d. if a study prescription calls for 37.5 mg BID for seven days, the pharmacist will dispense 21 capsules from the patient's bottle of B-395 25 mg capsules in his Titration Kit, and change the directions to read "Take one capsule by mouth THREE times a day;"

e. if a study prescription calls for 50 mg BID for 14 days, the pharmacist will dispense 28 capsules from the patient's bottle of B-395 50 mg capsules in his Titration Kit, with directions to "Take one capsule by mouth twice a day;"

f. if a study prescription calls for 75 mg BID for seven days, the pharmacist will dispense 21 capsules from the patient's bottle of B-395 50 mg capsules in his Titration Kit, and change the directions to read "Take one capsule by mouth THREE times a day;"

g. and if a study prescription calls for 100 mg BID for six weeks (42 days), the pharmacist

will dispense 84 capsules from the patient's bottle of B-395 100 mg capsules in his Titration Kit, with directions to read "Take one capsule twice a day."

(NOTE: Pharmacy personnel will need to dispense all titration period study drug in their own prescription vials.)

9.01(b) B-395 Transition Bottles

On the day of Visit 9 (3-month visit), the patient must be prescribed ONE of the six types of Transition Bottles available in Pharmacy. The type of bottle prescribed for this visit will likely depend on the highest dose tolerated by the patient during the titration period. Each Transition Bottle contains a 3-month supply (98 days) of study drug. *(NOTE: Transition Bottles are not patient-specific until assigned by the Albuquerque CSPCRPCC. Remember...study personnel must call the CSPCRPCC for all Transition Bottle assignments.)*

9.01(c) B-395 Maintenance Kit Bottles

On the day of Visit 10 (six-month visit) and at each of the follow-up visits outlined below, the patient will be prescribed TWO bottles of study drug. The type of Maintenance Kit bottles automatically shipped by CSPCRPCC for each patient will be based on either (1) the type of Transition Bottle assigned to the patient at Visit 9 or (2) the last type of Transition Bottle assigned to the patient at any other time during the transition period (i.e., other than at Visit 9). Each bottle in the patient's Maintenance Kit will be numbered consecutively. The bottles should be dispensed in numerical order to facilitate recordkeeping.

MAINTENANCE PHASE DISPENSING SCHEDULE

Follow-Up Visit:	Number of B-395 Bottles To Dispense:
10 (6-month)	2 bts (196)*
11 (12-month)	2 bts (196)
12 (18-month)	2 bts (196)
13 (24-month)	2 bts (196)
14 (30-month)	2 bts (196)
15 (36-month)	2 bts (196)
16 (42-month)	2 bts (196)
17 (48-month)	2 bts (196)
18 (54-month)	NO MEDICATION DISPENSED

(* the number in parenthesis is the number of capsules in each bottle)

9.02 Prescribing Reduced-Dose Regimens

When patients experience intolerable side effects (e.g., impotence, dizziness, lightheadedness, nightmares, etc.), the investigator may choose to decrease the dose of B-395. Patient doses will be reduced according to the following procedure:

a. Reduce patient's current dose by one-half and continue for one week.
b. If symptoms persist, reduce patient's dose again by one-half and continue for one week.
c. Continue reducing the patient's dose at weekly intervals until symptoms subside.

(NOTE: The investigator is encouraged to maintain the patient on the highest tolerated dose without side effects.)

For example, a patient is on a dose of 100 mg BID and experiences nightmares. The investigator prescribes a dose of 50 mg BID for one week, then see the patient again. If the patient's symptoms continue to persist, the investigator should prescribe a dose of 25 mg BID for one week, then see the patient again. This procedure should continue until the patient's symptoms subside.

Dosage reductions will always involve switching the patient from one B-395 dosage form to another (i.e., 100 mg capsules to 50 mg capsules; 50 mg capsules to 25 mg capsules, etc.). This will make it necessary for the patient to return to the study clinic anytime a dosage reduction is needed.

a. Dosage reductions during the titration period: if a dosage reduction is needed at any time during this period, a lower dose of B-395 can be obtained from the patient's B-395 Titration Kit.

b. Dosage reductions during the transition period or maintenance phase: if a dosage reduction is needed anytime during these times, study personnel must contact the Albuquerque CSPCRPCC and request an X-Bottle assignment for each dosage reduction. Study personnel must contact CSPCPRCC personnel and provide them with the following information for each patient needing a dosage reduction:

1. patient's B-395 Titration Kit number
2. dosage form of B-395 needed (e.g., 3 mg, 6.25 mg, 12.5 mg, 25 mg, 50 mg, or 100 mg capsules)
3. is the request for this dosage form temporary or permanent?
4. date of patient's next scheduled follow-up visit (if known)

(NOTE: CSPCRPCC will automatically ship all remaining Maintenance Kits with the last dose of B-395 requested unless otherwise directed. If the patient's dose is ever increased or decreased again, the Albuquerque CSPCRPCC must be notified immediately.)

9.03 Prescribing De-Titration Doses

Acute withdrawal of beta-adrenergic blockade has been associated with cardiovascular events.

Therefore, it is recommended that all doses of the study drug that are 25 mg BID or higher be de-titrated over several days rather than stopped abruptly. The following de-titration schedules are recommended:

DRUG	IF PATIENT'S DOSE IS:	USE FOLLOWING DE-TITRATION SCHEDULE:
B-395	100 mg BID	Prescribe a B-395 **Type A** De-Titration Card. This card reduces the patient's dose as follows: 50 mg BID x 3 days, then 25 mg BID x 3 days, then 12.5 mg BID x 3 days, then discontinue.
B-395	75 mg BID	Prescribe a B-395 **Type A** De-Titration Card. This card reduces the patient's dose as follows: 50 mg BID x 3 days, then 25 mg BID x 3 days, then 12.5 mg BID x 3 days, then discontinue.
B-395	50 mg BID	Prescribe a B-395 **Type B** De-Titration Card. This card reduces the patient's dose as follows: 25 mg BID x 3 days, then 12.5 mg BID x 3 days, then discontinue.
B-395	25 mg BID	Prescribe a B-395 **Type C** De-Titration Card. This card reduces the patient's dose as follows: 12.5 mg BID for 3 days, then discontinue.
B-395	12.5 mg BID	No further de-titration is necessary.
B-395	6.5 mg BID	No further de-titration is necessary.
B-395	3.0 mg BID	No further de-titration is necessary.

9.04 Prescriptions for Study Drug

The study drug can be ordered on either a standard prescription blank or a doctor's order sheet (in-patient only). Each time the study drug is prescribed, however, an order must be signed by the investigator or one of the other authorized physicians. Each prescription or doctor's order sheet must provide the following information:

a. Patient's name, social security number (VA SITES ONLY) and current address
b. Study identification: CSP #395
c. Patient's B-395 Titration Kit number
d. Drug code name and dose: B-395 3 mg, B-395 6.25 mg, B-395 12.5 mg, B-395 25 mg, B-395 50 mg, or B-395 100 mg capsules
e. Amount to be dispensed (refer to Dispensing Schedule, Section 9)
f. Directions

g. Signature of investigator or other authorized physician
h. Date prescription is written
i. Refills (local policy permitting)

9.05 Pharmacy Prescription Labels

The pharmacist (or their designee) must label each container of study drug dispensed with the following information (being careful not to cover any part of the CSPCRPCC label, including any barcodes, when applicable):

a. Medical center's name, address and telephone number
b. Prescription number and date prescription was written
c. Patient's name and B-395 Titration Kit number
d. Drug code name, quantity and directions for use
e. Prescribing physician's name
f. Auxiliary label: "RETURN REMAINING MEDICATION AT NEXT CLINIC APPOINTMENT"

The following table provides specific directions for labeling the various dosing regimens of B-395. The quantity dispensed will vary depending on the type of follow-up visit and dose.

DOSE	DISPENSE:	DIRECTIONS SHOULD READ:
3.0 mg BID (6 mg/d)	B-395 3 mg capsules	Take 1 capsule two times a day.
6.25 mg BID (12.5 mg/d)	B-395 6.25 mg capsules	Take 1 capsule two times a day.
12.5 mg BID (25 mg/d)	B-395 12.5 mg capsules	Take 1 capsule two times a day.
25.0 mg BID (50 mg/d)	B-395 25 mg capsules	Take 1 capsule two times a day.
37.5 mg BID (75 mg/d)	B-395 25 mg capsules	Take 1 capsule THREE times a day.*
50 mg BID (100 mg/d)	B-395 50 mg capsules	Take 1 capsule two times a day.
75 mg BID (150 mg/d)	B-395 50 mg capsules	Take 1 capsule THREE times a day.*
100 mg BID (200 mg/d)	B-395 100 mg capsules	Take 1 capsule two times a day.

(* these are considered "interim" doses and may only be prescribed during the titration period.)

9.06 CSPCRPCC Drug Accountability Form

Only one drug accountability form will be provided by CSPCRPCC - *"Returned Drug Inventory"* (Form DHP-4). One of these forms will be included in each patient kit shipped by CSPCRPCC. Returned Drug Inventory forms are used to inventory bottles of study drug returned by Pharmacy to

CSPCRPCC (see Section 13.02, Pharmacy Returns to CSPCRPCC).

9.07 Additional Items Provided by CSPCRPCC

Wallet identification cards (DHP-5) and chart alert stickers (DHP-6) will be provided directly to study personnel by CSPCRPCC. A wallet ID card should be filled out and given to randomized patients, with instructions to present the card to any non-study related physician or dentist they may see for treatment during the course of the study. Chart alert stickers should be placed on the front cover of a patient's medical chart(s), local hospital policy permitting. Pharmacy will be provided with the auxiliary label noted in Section 9.05. The above items will be sent with the initial drug shipment; additional supplies will be provided upon request of study personnel or the research pharmacist. Study personnel are responsible for ensuring adequate supplies of all study drug supplies and related items.

10. DISCONTINUATION OF STUDY DRUG FOR CLINICAL REASONS

If a patient develops progressive worsening of his heart failure that does not respond to oral or intravenous diuretics and/or a reduction in the dose of study drug, the study drug may be discontinued. *[NOTE: It is recommended that B-395 be de-titrated (see Section 9.03, Prescribing De-titration Doses) rather than abruptly withdrawn.]* It is preferable to administer a 24-48 hour course of inotropic therapy (e.g., amrinone, dopamine or dobutamine) during concomitant beta-blocker therapy to reach compensation rather than discontinue the study drug altogether. Despite these efforts, if the patient is not able to be maintained on beta-blocker therapy, the study drug may be de-titrated or discontinued (depending on the dose).

If a patient does not tolerate the study drug and the investigator wishes to withdraw the patient, the Study Chairman or a physician member of the Steering Committee must be contacted prior to withdrawal and the case discussed.

11. RETURNING MEDICATION

11.01 Patient Returns/Capsule Counts

Study personnel will instruct each patient to return all unused study drug in its original prescription container at the next follow-up visit. The patient will also be instructed to return all empty containers. *(NOTE: Any X-Bottle that may have been dispensed to the patient when he was hospitalized without his bottle of study drug, should be returned to either study personnel or the Pharmacy as soon as the patient is discharged.)* Study drug returned by the patient will be counted by study personnel in the presence of the patient as a measure of compliance at each follow-up visit. After recording the remaining number of capsules on the patient's clinic visit form and writing the remaining count on the container's prescription label, the container should be returned to Pharmacy on a regular basis by study personnel. The pharmacist will record the remaining number of capsules on the appropriate Returned Drug Inventory (Form DHP-5). Any container returned to Pharmacy should be placed in the appropriate patient kit box from which it was dispensed. *[EXCEPTIONS: (1) Do not return any previously assigned X-Bottles or Transition Bottles to their original boxes (return to CSPCRPCC individually); and (2) return any titration period prescription vials containing study medication to CSPCRPCC individually.]*

11.02 Pharmacy Returns to CSPCRPCC

All containers of study drug returned to Pharmacy by study personnel must be returned to the Albuquerque CSPCRPCC. Only when all the bottles in a particular patient kit box have been dispensed and the unused capsules returned by the patient, should Pharmacy return the entire box to CSPCRPCC. This same procedure should be followed if a patient's dose of B-395 is permanently discontinued. The prompt return of B-395 Titration Kits once the patient is dispensed a Transition Bottle for Visit 9 (3-month visit) will help reduce the storage space required for this study, as well as eliminate a potential source for dispensing errors.

When the study is completed (or terminated early), CSPCRPCC will request that all remaining study drugs (both used and unused) be inventoried on the appropriate Returned Drug Inventory forms and shipped to Albuquerque, via certified mail. Unless specifically requested, no other pharmacy records need to be returned to CSPCRPCC.

12. BREAKING THE STUDY BLIND IN EMERGENCIES

12.01 Drug Code Envelopes

Participating pharmacies will receive sealed Drug Code Envelopes (DHP-8) for each Titration Kit shipped. *(NOTE: All Drug Code Envelopes for a given study site will be sent with the initial drug shipment.)* Each envelope is numbered with a B-395 Titration Kit number and contains a brief description of the study drug (bucindolol or placebo) in the corresponding Titration Kit box. These envelopes should be stored in a secure area of the pharmacy and are to be accounted for and returned to CSPCRPCC upon completion (or early termination) of the study.

12.02 Authorization to Break the Blind

The ultimate responsibility for decisions affecting patient care will lie with the investigator. The treatment assignment code will be broken only if knowledge of the specific study drug is essential to the medical management of the patient. In the event of a medical emergency, the investigator is to call the Study Chairman for consultation or, if the Study Chairman is not available, the CSPCRPCC Clinical Research Pharmacist or the Palo Alto CSPCC Biostatistician. *(NOTE: A Drug Code Envelope should be opened only if the investigator is unable to reach one of the above parties or has been directed to do so by one of them.)*

If Pharmacy receives a request for code break information from anyone other than study personnel, the call should be referred to study personnel or, in their absence, to any one of the parties listed above. Telephone numbers are provided in the Study Personnel Directory (DHP-1). Pharmacy must notify the CSPCRPCC Clinical Research Pharmacist by telephone as soon as possible that a drug code has been broken and must return the envelope and its contents to CSPCRPCC within 72 hours of a code break.

13. DISTRIBUTION AND USE OF CSPCRPCC STUDY DOCUMENTS

Instructions for the use and routing of forms, documents and items provided by CSPCRPCC:

ITEM #	NAME	MAINTAINED OR USED BY	ORIGINAL	YELLOW COPY	PINK COPY
DHP-1	Study Personnel Directory	Pharmacy and Study Personnel	-	-	-
Form DHP-2*	Investigational Drug Information Record VAF 10-9012 (VA SITES ONLY)	Study personnel	Route to Pharmacy	Make copy and retain in study files	-
Form DHP-3*	Addendum to Form FDA 1572	Study personnel	Mail to CSPCRPCC	Route to Pharmacy	Retained by study personnel
Form DHP-4*	Returned Drug Inventory	Pharmacy	Enclose in shipments to CSPCRPCC	Retained by Pharmacy	-
DHP-5*	Patient Wallet Identification Card	Study personnel	Give to patient	-	-
DHP-6*	Patient Chart Alert Sticker	Study personnel	Place on cover of patient chart(s)	-	-
DHP-7*	Adverse Reaction Report Form FDA 1639	Study personnel	Mail original to CSPCRPCC. Mail copy to Chairman's office.	Make copy and retain in patient's study file.	-
DHP-8*	Drug Code Envelope	Pharmacy and Study Personnel	If opened, mail to CSPCRPCC within 72 hours of code break	-	-

*These items are not illustrated in the following section (Attachments).

ATTACHMENTS

CSPCRPCC STUDY FORMS

STUDY PERSONNEL DIRECTORY
Department of Veterans Affairs Cooperative Studies Program

TITLE: CSP #395, "Beta-Blocker Evaluation in Survival Trial (BEST)"

VA CO-CHAIRMAN: Eric Eichhorn, M.D., FACC

ADDRESS: Director, Cardiac Catheterization Lab (111A2), VA Medical Center, 4500 South Lancaster Road, Dallas, TX 75216

FTS #: 700-749-7904
PAGER#: 214-322-5714
COMMERCIAL #: (214) 372-7904
COMMERCIAL FAX #: (214) 302-7437

NHLBI CO-CHAIR: Michael Domanski, M.D.

ADDRESS: NHLBI, Room 5-C10, 7550 Wisconsin Avenue, Bethesda, MD 20892

COMMERCIAL #: 301-496-4323
COMMERCIAL FAX #: 301-402-0517

STUDY COORDINATOR: Lucille Marcoux, R.N.

ADDRESS: Cardiac Catheterization Lab (111A2), VA Medical Center, 4500 South Lancaster Road, Dallas, TX 75216

FTS #: 700-749-7904
COMMERCIAL #: (214) 372-7904
COMMERCIAL FAX #: (214) 302-7437

VA CSP CLINICAL RESEARCH PHARMACIST: Cindy L. Colling, R.Ph., M.S.

ADDRESS: VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
VA Medical Center, 2100 Ridgecrest Drive S.E., Albuquerque, NM 87108

FTS #: 700-572-2580
FTS FAX #: 700-572-2878
COMMERCIAL #: (505) 265-1711, Ext. 2580
COMMERCIAL FAX #: (505) 256-2878

VA CSPCC CHIEF: Philip Lavori, Ph.D.

ADDRESS: VA Cooperative Studies Program Coordinating Center (151-K)
VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94394

FTS #: 700-463-2181
FTS FAX #: 700-463-2605
COMMERCIAL #: (415) 617-2720
COMMERCIAL FAX #: (415) 617-2605

VA CSP BIOSTATISTICIAN: Heidi Krause-Steinrauf, M.S.

ADDRESS: VA Cooperative Studies Program Coordinating Center (151-K)
VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94394

FTS #: 700-463-2181
FTS FAX #: 700-463-2605
COMMERCIAL #: (415) 617-2720
COMMERCIAL FAX #: (415) 617-2605

APPENDIX C - INFORMED CONSENT FORM

APPENDIX D - DATA FORMS

APPENDIX E - CLINICAL SITES

200	Baptist Memorial Hospital	Memphis, TN
201	Minneapolis Heart Institute	Minneapolis, MN
202	Heart Care Midwest	Peoria, IL
203	Albany Medical Center	Albany, NY
205	Washington University School of Medicine	St. Louis, MO
212	Cardiology of Tulsa	Tulsa, OK
213	Cedars-Sinai Medical Center	Los Angeles, CA
214	Cleveland Clinic Foundation	Cleveland, OH
216	Cook County Hospital	Chicago, IL
220	Duke University Medical Center	Durham, NC
224	Albert Einstein College of Medicine	Bronx, NY
225	Elmhurst Hospital	Elmhurst, NY
230	George Washington University	Washington, DC
235	Georgetown University Hospital	Washington, DC
236	Emory Univ./Grady Memorial Hospital	Atlanta, GA
237	MCP Hahnemann University	Philadelphia, PA
238	Hospital of the University of Pennsylvania	Philadelphia, PA
240	Medical College of Wisconsin	Milwaukee, WI
241	John Hopkins Hospital	Baltimore, MD
242	University of Florida Health Science Center	Jacksonville, FL
245	LDS Hospital	Salt Lake City, UT
250	Louisiana State University	Shreveport, LA
255	Loyola University Medical Center	Maywood, IL
256	Dartmouth Hitchcock Medical Center	Lebanon, NH
257	Maricopa Medical Research Foundation	Phoenix, AZ
258	Mayo Clinic, Scottsdale	Scottsdale, AZ
259	New England Medical Center	Boston, MA
260	The Methodist Hospital	Houston, TX
261	Montreal Heart Institute	Montreal, Canada
262	Medical College of Virginia	Richmond, VA
265	Morristown Memorial Hospital	Morristown, NJ
266	New Mexico Heart Institute	Albuquerque, NM
275	National Naval Medical Center	Bethesda, MD
276	Nebraska Heart Institute	Lincoln, NE
277	Oklahoma Foundation for Cardiovascular Research	Oklahoma City, OK
280	Oregon Health Sciences University	Portland, OR
285	Parkland Memorial Hospital	Dallas, TX
290	Penn State University Hospital	Hershey, PA
295	Robert Wood Johnson Univ. Hospital	New Brunswick, NJ
296	Shands Hospital, University of Florida	Gainesville, FL
297	St. John's Mercy Medical Center	St. Louis, MO
300	St. Mary's Hospital, Mayo Clinic	Rochester, MN
309	University of Arizona/Arizona Heart Institute	Tucson, AZ
310	University of Alabama Medical Center	Birmingham, AL
311	University of Conn. Health Center	Farmington, CT
314	University of California, San Diego Medical Center	San Diego, CA
316	University of Cincinnati	Cincinnati, OH
317	University of Iowa Hospital	Iowa City, IA

320	University of Minnesota Hospital	Minneapolis, MN
325	University of Rochester Medical Center	Rochester, NY
335	University of Colorado Health Sciences Center	Denver, CO
340	University of Maryland	Baltimore, MD
345	University of Mississippi Medical Center	Jackson, MS
346	University of Montreal	Montreal, Canada
350	University of North Carolina	Chapel Hill, NC
355	University of Pittsburgh Medical Center	Pittsburgh, PA
356	University of Wisconsin Hospital and Clinics	Madison, WI
360	Medical University of South Carolina	Charleston, SC
365	University of Utah Health Sciences Center	Salt Lake City, UT
368	Watson Clinic	Lakeland, FL
370	Yale-New Haven Hospital	New Haven, CT
512	Baltimore VA Medical Center	Baltimore, MD
523	Boston VA Medical Center	Boston, MA
526	Bronx VA Medical Center	Bronx, NY
534	Charleston VA Medical Center	Charleston, SC
549	Dallas VA Medical Center	Dallas, TX
554	Denver VA Medical Center	Denver, CO
558	Durham VA Medical Center	Durham, NC
570	Fresno VA Medical Center	Fresno, CA
578	Hines VA Medical Center	Hines, IL
580	Houston VA Medical Center	Houston, TX
586	Jackson VA Medical Center	Jackson, MS
596	Lexington VA Medical Center	Lexington, KY
598	Little Rock VA Medical Center	Little Rock, AR
600	Long Beach VA Medical Center	Long Beach, CA
607	Madison VA Medical Center	Madison, WI
614	Memphis VA Medical Center	Memphis, TN
618	Minneapolis VA Medical Center	Minneapolis, MN
627	Newington VA Medical Center	Newington, CT
648	Portland VA Medical Center	Portland, OR
652	Richmond VA Medical Center	Richmond, VA
657	St. Louis VA Medical Center	St. Louis, MO
658	Salem VA Medical Center	Salem, VA
662	San Francisco VA Medical Center	San Francisco, CA
664	San Diego VA Medical Center	San Diego, CA
665	Sepulveda VA Medical Center	Sepulveda, CA
671	San Antonio VA Medical Center	San Antonio, TX
673	Tampa VA Medical Center	Tampa, FL
678	Tucson VA Medical Center	Tucson, AZ
688	Washington VA Medical Center	Washington, DC

DROPPED SITES

239	Henry Ford Hospital	Detroit, MI

270	Mount Sinai Hospital	New York, NY
305	Stanford University Hospital	Stanford, PA
306	Temple University	Philadelphia, PA
315	University of California, San Francisco Medical Center	San Francisco, CA
330	University of California, Davis Medical Center	Davis, CA
366	Vancouver Hospital	Vancouver, Canada
689	West Haven VA Medical Center	West Haven, CT
691	West Los Angeles VA Medical Center	Los Angeles, CA
642	Philadelphia VA Medical Center	Philadelphia, PA

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** Cindy Colling, R.Ph., M.S., CSPCRPCC (1994 - Dec. 1998)

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Hershey, PA

APPENDIX O - STATEMENT REGARDING CONFLICT OF INTEREST

STATEMENT FOR THOSE SERVING IN AN AD HOC REVIEW OR ADVISORY CAPACITY AND MEMBERS OF THE STEERING COMMITTEE

Except as noted below, I am not an employee (part or full-time, paid or unpaid) of any organization(s) either involved in the study(s) under review or whose products or services would be clearly and directly affected in a major way by the outcome of the study(s), nor am I an officer, member, owner, trustee, director, expert, advisor or consultant of such an organization. It is important to recognize that conflict of interest applies if these interests or relationships exist or give the appearance of existing.

Except as noted below, I do not have any financial interest in any organization meeting the above criteria, nor does my spouse, minor child, nor an organization with which I am connected. (State "None" or identify any exceptions)

I will notify the chief of the Palo Alto CSPCC promptly (a) if a change occurs in any of the above during the tenure of my responsibilities or (b) if I discover that an organization with which I have a relationship meets the criteria.

I am aware of my responsibilities for the maintenance of confidentiality of any non-public information that I receive or become aware of through this activity and for the avoidance of using such information for my personal benefit or for the benefit of my associates or of organization with which I am connected or with which I have a financial involvement.

Signature

Date

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Steering Committee
for the Beta-Blocker Evaluation of Survival Trial (BEST)

The BEST Steering Committee guides the conduct of the BEST study through its decision-making and policy-setting processes. The BEST study directly involves drugs owned or marketed by Astra Merck/Astra Pharmaceuticals, LP; Bristol-Myers Squibb; CPEC; Intercardia; Interneuron; or Knoll AG/BASF Pharma. Research with data collected by the study may have implications for other commercial enterprises.

It is important that members of the BEST Steering Committee avoid taking part in decisions that would significantly

STATEMENT FOR THOSE SERVING ON THE BEST STEERING COMMITTEE

affect their own financial interests and even the appearance of such a conflict of interest. Assets owned by or held in trust for a committee member, the member's spouse, or the member's minor children, must be considered, as must relationships by those same persons to affected companies and institutions. Additionally, a member's knowledge that a parent, sibling, or adult child has a financial interest or relationship to affected companies and institutions may also appear as a conflict of interest. Many organizations could be affected to some extent by research results. For example, if the BEST study and/or its ancillary research results in a change in health care costs, this could affect employers that contribute to employee health care costs, as well as organizations that provide health care services. Concern over conflicting interests arises when an organization might be significantly and unusually affected by the research results.

A significant financial interest for the purposes of this form includes any gifts, gratuities, royalties, stock or other ownership interests, options, bonds or other debt interests, or any contracts or leases in or with an organization that might be significantly or unusually affected by the research results. Generally an equity interest is not considered a significant financial interest if it meets both of the following tests: 1) does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and 2) does not represent more than a 5% ownership interest in any single entity. Significant financial interests do not include securities held as part of mutual funds where you either are unaware of the specific holding or where the security does not constitute a substantial part of the fund's holdings. The relationships that are relevant for the purposes of this form include any current or past relationship as an officer, director, trustee, employee, consultant, or independent contractor for such an organization.

Please list below the nature of any significant financial interests or relationships, as defined above, that you, your spouse, your children, your parents, or your siblings have or have had with the organizations listed above or with any other organization that you believe might be significantly and unusually affected by the research results. Please note that listing a possible conflict does not necessarily disqualify a member from serving on the Committee or from participating in any particular Committee decision. Such a list merely enables the Committee to inquire further about possible conflicts.

1. Consulting relationships, or salary for an executive position or other employee position

_____

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2. Stock, stock options, partnership share, or other ownership interest.

_____

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3. Gifts or gratuities

STATEMENT FOR THOSE SERVING ON THE BEST STEERING COMMITTEE

The organizations significantly and unusually affected by the results of the BEST study or the ancillary studies considered by the Committee may change over time, as may the financial interests and relationships of committee members, their spouses, children, parents, and siblings. Although this form will be renewed annually, please inform the Director of the Palo Alto CSPCC (Cooperative Studies Program Coordinating Center) promptly if a) a change occurs in any of the above during the tenure of your responsibilities or (b) if you discover that an organization with which you have a relationship meets the criteria.

You are responsible for maintaining the confidentiality of any non-public information that you receive or become aware of through the Committee. You recognize that you must avoid using such information for your personal benefit, whether financial or professional, or for the benefit of your associates or of any organization in which you have a financial interest or a relationship as defined above.

I understand and concur with the above:

_____
Print Name

_____
Signature

_____
Date

Data and Safety Monitoring Board (DSMB)
for the Beta-Blocker Evaluation of Survival Trial (BEST)

The BEST DSMB exercises oversight of the BEST study and influences the course of the trial through its decision-making process. The BEST study directly involves drugs owned or marketed by Astra Merck/Astra Pharmaceuticals,

STATEMENT FOR THOSE SERVING ON THE BEST DSMB

LP; Bristol-Myers Squibb; CPEC,;Intercardia; Interneuron; or Knoll AG/BASF Pharma. Research with data collected by the study may have implications for other commercial enterprises.

It is important that members of the BEST DSMB avoid taking part in decisions that would significantly affect their own financial interests and even the appearance of such a conflict of interest. Assets owned by or held in trust for a committee member, the member's spouse, or the member's minor children, must be considered, as must relationships by those same persons to affected companies and institutions. Additionally, a member's knowledge that a parent, sibling, or adult child has a financial interest or relationship to affected companies and institutions may also appear as a conflict of interest. Many organizations could be affected to some extent by research results. For example, if the BEST study and/or its ancillary research results in a change in health care costs, this could affect employers that contribute to employee health care costs, as well as organizations that provide health care services. Concern over conflicting interests arises when an organization might be significantly and unusually affected by the research results.

A significant financial interest for the purposes of this form includes any gifts, gratuities, royalties, stock or other ownership interests, options, bonds or other debt interests, or any contracts or leases in or with an organization that might be significantly or unusually affected by the research results. Generally an equity interest is not considered a significant financial interest if it meets both of the following tests: 1) does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and 2) does not represent more than a 5% ownership interest in any single entity. Significant financial interests do not include securities held as part of mutual funds where you either are unaware of the specific holding or where the security does not constitute a substantial part of the fund's holdings. The relationships that are relevant for the purposes of this form include any current or past relationship as an officer, director, trustee, employee, consultant, or independent contractor for such an organization.

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1.Consulting relationships, or salary for an executive position or other employee position

_____

_____

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2.Stock, stock options, partnership share, or other ownership interest.

_____

STATEMENT FOR THOSE SERVING ON THE BEST DSMB

_____

_____

3.Gifts or gratuities

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_____

The organizations significantly and unusually affected by the results of the BEST study or the ancillary studies considered by the Committee may change over time, as may the financial interests and relationships of committee members, their spouses, children, parents, and siblings. Although this form will be renewed annually, please inform the Director of the Palo Alto CSPCC (Cooperative Studies Program Coordinating Center) promptly if a) a change occurs in any of the above during the tenure of your responsibilities or (b) if you discover that an organization with which you have a relationship meets the criteria.

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I understand and concur with the above:

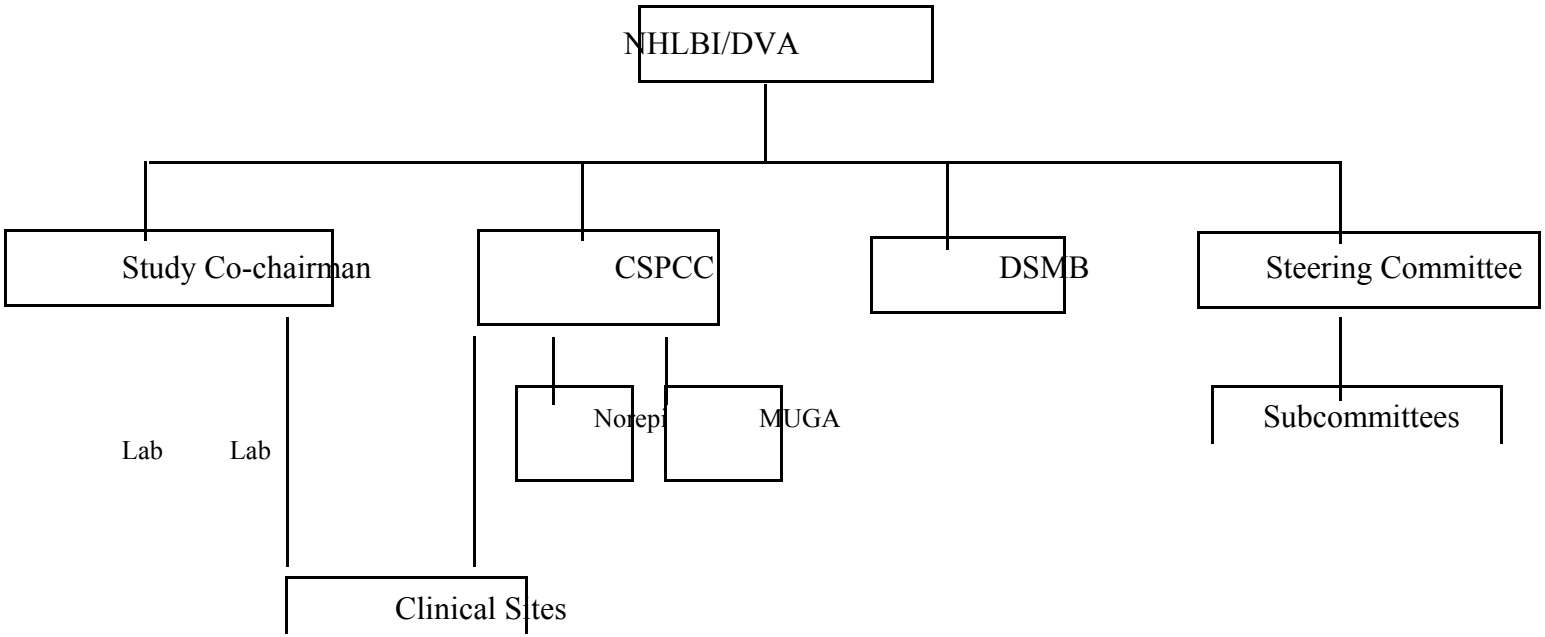
_____
Print Name

_____
Signature

_____
Date

APPENDIX P - TABLE OF ORGANIZATION

BEST ORGANIZATIONAL TABLE



APPENDIX Q - REFERENCES

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