MANUAL OF OPERATIONS

TABLE OF CONTENTS — PAGE NUMBER

STUDIES OF LEFT VENTRICULAR DYSFUNCTION

Study Phase	Visit Number	Time From Randomization
Recruitment Logbook Begins February 1986	---	Screening
Eligibility Visit Begins June 1986	1	16-24 days Pre-randomization (Withdraw non-study vasodilator, if possible)
Medication Tolerance Visit Begins June 1986	2	14-17 days Pre-randomization (Withdraw non-study vasodilator, if possible)
Baseline Visit June 1986-June 1989	3	RANDOMIZATION
FOLLOWUP VISITS July 1986-July 1991		
Followup Visit	4	2 Weeks Post-Randomization
Followup Visit	5	6 Weeks Post-Randomizatiion
Followup Visit	6	4 Months Post-Randomization
Followup Visit	7	8 Months Post-Randomization
Followup Visit (every 4 months)	8	Annual Visit, 12 Months Post-Randomization
Closure Visit June 1991	X	Varies- 3 to 5 Years Post-Randomization

1.2 INITIAL SCREENING AND PATIENT RECRUITMENT

1.2.1 Screening Logbook

The recruitment log should serve as a means to screen potential participants for SOLVD. Copies of it should be sent to the study nurse at each hospital affiliated with this Clinical Center. MAKE ENOUGH PHOTOCOPIES OF THE LOG SO THAT YOU HAVE AT LEAST ONE EXTRA BLANK COPY. When the study nurse has finished with pages of the log, she or he should send them to the Clinical Center to be kept on file. The recruitment log should not be sent to the Coordinating Center.

The purpose of the recruitment log is to help you develop a list of potential participants in screening for eligibility for SOLVD. This should include all patients who have an ejection fraction less than or equal to 40% or who have been hospitalized for congestive heart failure. When you begin a new recruitment log page, write the name of your Center and the name of the hospital at which it is filled out. In the left column enter the date of each day that you add entries to the log.

When you are checking various sources for potential participants, fill in whatever available information that has been recorded. For instance, if you are looking at the record book in a catheterization lab, the patients' names, ages, ejection fractions and the dates on which they were done, hospitalization diagnoses and hospital ID number may be noted, while the physician name and phone number might not be there. If you are looking at ward records, the available information may be slightly different.

As you fill out the form, you will notice that there will be patients who are obviously unsuitable for SOLVD (e.g., too old, patient has cancer, is pregnant, or alcoholic, or who have ejection fractions greater than 40%. Do not list these patients on your log sheet). There will also be patientss who have just had a myocardial infarction, who might otherwise be a potential participant for SOLVD. In a month's time you will want to review the status of that patient and then perhaps add him/her to the list of potential participants to be screened. You will also want to note those patients whose ejection fraction is greater than 35 but less than or equal to 40. These patients, whom you will want to flag, may be prospective participants.

After you have checked your sources of participants, you will see some of them will require further checking in hospital records to see if they are still eligible for SOLVD. Once you have checked for other reasons for exclusions, then you should contact the prospective participant to arrange a mutually convenient time for an Eligibility Visit. You should enter the date and the time of this visit when contacting the prospective participant. You may have to explain the nature of this visit and what will be done.

SOLVD

RECRUITMENT LOG

CLINIC _____ HOSPITAL NAME _____

DATE of Logbook Entry	PATIENT'S NAME Last, First	HOSPITAL ID NUMBER	PATIENT'S PHYSICIAN's NAME	PHYSICIAN'S PHONE NUMBER	Source of Potential Patient (Check One)				PATIENT'S AGE at Date of Logbook Entry	EF	DATE of EF	Physician's Assessment of Eligibility	
					Radio-nuclide	Cath.	Echo	Other				NO Reason for Ineligibility	YES Screening Visit Scheduled (Date)

1.2.2 Logbook Summary Form

INSTRUCTIONS FOR COMPLETING THE MONTHLY RECRUITMENT LOG REPORT

1. A reporting period extends from the first day of the month to the last day of the month. There are 12 report periods each year.

2. Collect all recruitment log sheets from all hospitals for the latest reporting period.

3. Write your assigned 2 letter characters in the boxes marked "Clinical Center."

4. Fill in the reporting period beginning and ending dates in the designated boxes.

5. On line 1, fill in the boxes with the date on which this form is being completed.

6. Count the total number of potential participants from the log sheets that were recorded during the latest reporting period. This number should include participants from log sheets from all of the hospitals affiliated with your center. Enter this number in the boxes in line 2.1.

5. Count the number of potential participants whose ejection fractions were equal to or less than 35 % during this report period. Write this number in the boxes in line 2.2.

6. Count the number of participants during this report period whose ejection fractions were greater than 35% but less than or equal to 40%. Write this number in the boxes in line 2.3.

7. Count the number of participants during this report period who were found to be ineligible for SOLVD. Write this number in the boxes in line 2.4.

8. Count the number of participants who were invited to an eligibility visit during this report period and write the number in the boxes in line 2.5.

9. The person completing this form should fill his or her initials in the boxes in line 3.

10. Mail this report to Ken Kral at the Coordinating Center right now. If you have any questions, call Ken at 919-962-3227.

SOLVD

MONTHLY RECRUITMENT LOGBOOK REPORT

CLINICAL CENTER: [ ][ ]

Reporting Period: (Beginning and Ending Dates)

[ ][ ] / [ ][ ] / [ ][ ] to [ ][ ] / [ ][ ] / [ ][ ]

Month Day Year Month Day Year

1. Date report completed: [ ][ ] / [ ][ ] / [ ][ ]

Month Day Year

2.1. Total number of potential participants recorded in clinic logbook during this reporting period..... [ ][ ][ ]
(Only participants with known EF ≤ 40%)

2.2. Number of participants **(from 2.1.)** with ejection fraction ≤ 35%..... [ ][ ][ ]

2.3. Number of participants **(from 2.1.)** with ejection fraction > 35% but ≤ 40%..... [ ][ ][ ]

2.4. Number of participants with an EF ≤ 35% **(from 2.2.)** who were ineligible (not invited to the Eligibility Visit)..... [ ][ ][ ]

2.5. Number of participants with an EF ≤ 35% **(from 2.2.)** who were eligible and invited to the Eligibility Visit..... [ ][ ][ ]

3. Initials of person completing this form..... [ ][ ]

1.3 VISIT 1: THE ELIGIBILITY VISIT

1.3.1 General Description

The Eligibility Visit is the first visit of potential participants for SOLVD. The following are to be completed at this visit:

i. Explain the purpose of the Study and obtain informed consent.
ii. Participant receives an temporary ID number.
iii. Pertinent identifying information is obtained.
iv. The qualifying ejection fraction, its date and method of measurement are recorded.
v. Each of 26 exclusion criteria are checked. Note that this includes obtaining informed consent.
vi. For participants still suitable for the study, supine and sitting blood pressure and heart rate are to be obtained.
vii. For participants still suitable for the Study, the standard battery of laboratory determinations are to be performed.
viii. For participants still suitable for the Study blood is to be drawn for measurements and storage at a central laboratory.
ix. For participants still suitable for the Study, their next visit should be scheduled within a 2-7 day period.
x. For participants still suitable for the Study, the 2-7 day medication for the tolerance period should be dispensed.
xi. For participants still suitable for the Study who are NYHA Class IV, taking a vasodilator other than isosorbide and have hyponatremia, they must be hospitalized for 24 hours for the start of the tolerance period and have the Medication Monitoring Form completed as well.
xii. The Eligibility Visit form is completed.
xiii. For potential participants who are on a vasodilator, physicians should consider the discontinuation of these drugs if the indication for their use is not clear-cut. If a non-ACE vasodilator needs to be reinstituted, this should be documented and the participant can be randomized. In particular, try to withdraw Hydralazine, Prazosin, Minoxidil and Calcium antagonists. It is recognized that a significant proportion of patients will need Isosorbide. While vasodilators are not prohibited, the general aim is to minimize the use of non-study vasodilators. It is hoped that only about 35% of patients in the Treatment Trial will be on a vasodilator at baseline. This number will be reviewed monthly.

The order in which the above are performed is not crucial except in the obvious requirement that items i.-v. be obtained prior to items vi.-xi. At the end of the visit, prospective participants who are still eligible for the Study will leave with their medication for the tolerance period and verbal instructions on when to take it unless they satisfy item xi. The sections below provide details of the above procedures.

NOTE: Prospective participants for the SOLVD Study should not be started through the prerandomization visits at a hospital prior to the NIH receiving the Institutional Review Board approval letter from that hospital. The clinic must receive a written response of approval from NIH before any participants are randomized.

1.3.2 Eligibility and Exclusion Criteria

The eligibility criteria for potential participants in SOLVD are detailed in Section A of Chapter V of the Protocol. The age of the participant on the day of randomization must be between 21 and 80 years, inclusive; and the participant must have a qualifying ejection fraction (see page V-1 of the Protocol).

The exclusion criteria for potential participants in SOLVD are listed in Section B of Chapter V of the Protocol (see page V-1 to V-3 of the Protocol). The intent of the criteria is to exclude only those prospective participants with non-cardiac conditions or diseases likely to independently limit their long-term survival. Certain cardiac conditions are included in the list in an attempt to study myocardial disease (pump dysfunction) as opposed to other cardiac diseases. Deliberately, exact guidelines have not been specified. All twenty-six (26) criteria are to be checked NO for a prospective participant to be eligible for the trials. If one of the criteria is answered YES, the participant is no longer eligible for the study.

1.3.3 Informed Consent

Informed consent can be obtained at any point during the Eligibility Visit. However, failure to provide informed consent is one of the twenty-six (26) exclusion criteria for the study. The visit can be considered over as soon as the participant denies informed consent. Guidelines for obtaining informed consent are given in Appendix C of the Protocol.

1.3.4 Drawing Blood

For prospective participants that are still eligible for the Study, a 20 ml blood sample is to be drawn. Details for this procedure are presented in Appendix A of the protocol and Appendix B of the Manual of Operations.

1.3.5 Laboratory Measurements

For prospective participants who are still eligible for the Study, the following standard battery of laboratory determinations are to be performed:

1. Blood
   a. Percent hematocrit
   b. Total white blood cell count
   c. Percent neutrophils
   d. Percent lymphocytes
   e. Sodium in meq/l
   f. Potassium in meq/l
   g. Blood urea nitrogen(BUN) in mg/100ml
2. Urine
   a. Creatinine in mg/100ml
   b. Number of positives on dipstick examination for proteinuria

These are to be performed at the local hospital or Clinical Center laboratory. Guidelines for these procedures are not specified in the Manual of Operations since they are standard laboratory measurements.

1.3.6 Physical Examination

For prospective participants still eligible for the study, heart rate and systolic and diastolic blood pressures are to be obtained. These will be obtained both in a supine and a sitting position at this visit only. See Appendix C of the Manual of Operations for details on these procedures.

1.3.7 Dispensing of Medication

Prospective study participants who are still eligible for the SOLVD Study will be given active medication and scheduled for their next visit in order to assess short term tolerance to active treatment (Medication Tolerance Visit or Visit 2). See section 1.3.10 for exceptions. Visit 2 is to be scheduled within 2 to 7 days from the date of Visit 1. The amount of medication dispensed should be enough for the period until Visit 2 plus one extra day in case of an unforeseen delay in the visit. The amount of medication dispensed can be noted as part of the optional data for clinic use only in order to be able to assess adherence to the prescribed medication at Visit 2. The medication being prescribed is 2.5 mg bid of enalapril, but the prospective participant is not to be told that the medication is the active drug.

1.3.8 Instruction to Participants

Each Clinical Center should provide participants with a 24 hour telephone number at the center. Participants should be alerted to report severe dizziness and symptoms of angioneurotic edema. Although the common manifestations of

angioneurotic edema are redness and swelling of the skin, facial lip and eye swelling, there have been some very rare reports of laryngeal edema and stridor. Therefore, if a participant should have any difficulty breathing, he or she should be instructed to seek immediate emergency care.

1.3.9 Participant Safety in Medication Tolerance

Each participant should be called 24 hours after study drug is started to check that no major adverse symptoms have occurred (e.g., syncope, angioneurotic edema, etc.). Although the first post-randomization dose is 5 mg BID or equivalent placebo, the investigator may wish to start at 2.5 mg or equivalent in certain high risk groups to avoid hypotension. The dose can then be titrated to 5 mg BID or equivalent within a few days and 2 weeks later increased to 10 mg BID or placebo as per the protocol. Such deviations are permitted at the individual physician's discretion.

1.3.10 Hospitalization of Participants at High Risk of Hypotension

On rare occasions initiation of treatment with an ACE inhibitor may result in symptomatic hypotension which may persist for several hours. This generally occurs in participants with hyponatremia, hypovolemia, or low arterial pressure, and may also be more common when congestive failure is advanced, i.e., Class IV. The frequency of this problem may be minimized if diuretic dose is reduced prior to treatment and/or a lower dose of ACE inhibitor is used. There is only minimal experience, however, with the use of ACE inhibitor in patients who are already taking other potent vasodilators (e.g., prazosin, hydralazine, nifedipine, etc.) other than long-acting nitroglycerin; and it is not known whether these potential participants will also have an excessive tendency to develop significant hypotension. This problem should be minimized if not obviated by gradually and carefully initiating active drug therapy at a low dose and progressing to the higher maintenance dose, while reducing the dose of the non-ACE vasodilator or stopping it altogether if hypotension develops.

Potential participants with class IV CHF, hyponatremia and those on other vasodilators other than isosorbide are to be hospitalized for about 24 hours to assess the hypotensive response to the first and possibly the second 2.5 mg dose of enalapril. (The data from the first 100 such patients will be reviewed and a decision whether or not to continue to hospitalize these prospective study participants will then be made.) The Medication Monitoring form is to be completed for these prospective study participants (see section 1.5.12 for detailed instructions). In high risk participants, the investigator may wish to start at 2.5 mg BID or equivalent placebo post-randomization to minimize the potential of first dose hypotension and increasing the dose to 5 mg BID or equivalent placebo in a few days.

1.3.11 Withdrawing Use of Non ACE Inhibitor Vasodilator During the Pre-Randomization Period

In those potential participants currently on any non ACE inhibitor vasodilators, physicians are encouraged to attempt the discontinuation of these drugs during the pre-randomization period. If the participant is clinically stable after withdrawal of the drug, he or she can be randomized and question 26.1 should be answered "Yes." If the participant needs a non ACE inhibitor vasodilator, the drug can be reinstituted before randomization. Documentation for continued use of the drug must be provided on the appropriate forms(s).

1.3.12 Instructions to Complete the Eligibility Visit (Visit 1) Form

The Eligibility Visit form is used for all prospective participants attending Visit 1. The form is not designed to be self-administered. General guidelines and instructions for completing all paper forms are presented in Appendix G. The specific instructions for each item on the Visit 1 form are as follows.

TEMPORARY IDENTIFICATION (ID). Each prospective participant for the SOLVD Study will have a unique ID for use on all three prerandomization visit forms. Even if a prospective participant is found to be ineligible during any point of the prerandomization period, the ID Number must not be reused. The identification number will consist of the following 9-digit number:

(i) the capital letter E (1st digit);
(ii) the capital letters denoting the code for the Clinical Center (2nd and 3rd digit);
(iii) the capital letter denoting the code for the hospital within the specified Clinical Center (A,B,C, etc., (4th digit);
(iv) a 5-digit number to be assigned sequentially:
00001 to 01000 at hospital A
01001 to 02000 at hospital B
02001 to 03000 at hospital C
etc.

If a given hospital screens more than one thousand potential participants, contact the Coordinating Center for a new sequence starting point.

A. IDENTIFYING INFORMATION

1. Today's Date. Self-explanatory.
2. Participant's Name. Self-explanatory.
3. Participant's Mailing Address. Self-explanatory.
4. Participant's Home Telephone Number. Self-explanatory. Note to record the area code with the telephone number.

5. Hospital Name, Address and Patient's Hospital Identification Number. Self-explanatory. The identification number is the hospital records number for the participant.
6. Private Physician. This is the name, address and telephone number of the participant's private physician.
7. Nearest Relative or Friend Not Residing With Participant. Record name, relationship, address and telephone number.
8. Participant's Employer. Record name of employer or other employment status, the participant's job title and the address and telephone number of the employer. as the participant's job title.
9. Sex. Self-explanatory.
10. Ethnic Identity. Self-explanatory.
11. Birthdate. Self-explanatory.
12. Social Security Number. Self-explanatory. Canadian and Belgian Clinical Centers may leave this blank.

B. ENTRY CRITERION

13.1. Qualifying Ejection Fraction Percentage. Record only two significant digits. The EF must have been performed within three (3) months of the date of this visit. The EF may not be performed within seven (7) days of an acute myocardial infarction, reperfusion therapy or cardiac surgery. If more than one method has been performed to determine an EF, or if an EF has been performed several times within the previous three (3) months, the most recent EF should be chosen, or if using a previous EF, the subsequent ones must be less than 40%. (See Questions 13.4 to 14.3.)

13.2. Date of Measurement. Self-explanatory.

13.3. Method Utilized. Check only one of the three methods. The qualifying EF must be assessed by one of the following techniques: Radionuclide left ventricular angiography (MUGA or first pass), Left ventricular contrast angiography (RAO or biplane) or 2-D echocardiogram (either by area-length method or by modified Simpson's rule).*

13.4. Is the Qualifying Ejection Fraction the Most Recent? Self-explanatory. If YES, proceed with question 15.1. If NO, proceed with question 14.1.

14.1. Most Recent Ejection Fraction Percentage. Record only the significant digits. The EF must have been performed within three (3) months of the date of this visit. The EF must have been performed within three (3) months of

the date of this visit. The EF may not be performed within seven (7) days of an acute myocardial infarction, reperfusion therapy or cardiac surgery. This value must be less than 40 for the participant to remain eligible.

14.2. Date of Most Recent Ejection Fraction Measurement. Self-explanatory.

14.3. Method Utilized for the Most Recent Ejection Fraction Measurements. Check only one of the three methods. The qualifying EF must be assessed by one of the following techniques: Radionuclide left ventricular angiography (MUGA or first pass), left ventricular contrast angiography (RAD or biplane) or 2-D echocardiogram (either by area-length method or by modified Simpson's rule).*

C. EXCLUSION CRITERIA

A response must be checked for each of the twenty-six criteria. If a potential study participant's answer is YES, he is no longer eligible for the SOLVD Study. It is not necessary to complete the rest of the form after section D. However, it is of scientific interest to complete answers to the remaining questions of section C. The initials of the person completing the form as well as section D must always be recorded regardless of the participant's eligibility.

15.1-15.25. Details of the exclusion criteria are presented in section B of chapter V of the Protocol (see pages V-1 to V-3 of the Protocol).

15.26. Failure to Give Consent. Informed consent must be obtained from all prospective participants according to the guidelines in Appendix C of the Protocol before answering this question. (See also Appendix A, Manual of Operations.)

D. INITIALS OF PERSON COMPLETING THIS FORM.

16. Each person that completes forms at the Clinical Center or its hospitals shall have a unique code based on two initials. These codes need not be unique among Clinical Centers.

E. STUDY SUITABILITY.

17. This decision is to be based primarily on the questions of section C. However, it may also be answered after the information from sections E and F is available. Participants

---

*NOTE: Detailed information on the measurement of ejection fraction should be maintained until after the randomization visit. A random sample of participants will be selected and the EF measurement reviewed by the Coordinating Center (see section 6.1.4).

suitable to continue are to have blood drawn (see section 1.3.4 and Appendix B of the Manual of Operations), have their next visit scheduled, have their tolerance period medication dispensed and the rest of the form completed.

F. PHYSICAL EXAMINATION

18. Supine Blood Pressures. At this visit, both sitting and supine blood pressure readings are to be obtained. Details on the procedures are presented in Appendix D, section D-3 of the Manual of Operations.

19. Sitting Blood Pressures. At this visit, both sitting and supine blood pressure readings are to be obtained. Details on the procedures are presented in Appendix D, section D-3 of the Manual of Operations.

20. Heart Rate. At this visit, both sitting and supine heart rate readings are to be obtained. Details on the procedures are presented in Appendix D, section D-2 of the Manual of Operations.

G. LABORATORY DATA

21-27. The standard battery of laboratory determinations described in section 1.3.5 of the Manual of Operations is to be performed locally. No specific guidelines on procedures are outlined by this Manual of Operations.

H. MEDICATION TOLERANCE MONITORING

28. Participant Taking Isosorbide Medication? If YES, enter the daily dose being taken in question 28.2. If NO, proceed with question 29.1.

29. Participant Taking any Vasolidator Medication other than Isosorbide Medication? If YES, check Yes or No for each of question 29.2 to 29.4, as well as total daily dose, if applicable. If NO, proceed with question 30.

30.1. If a participant is on a non ACE inhibitor vasodilator, consider discontinuing the use of the drug. Check appropriate response. If YES, go to question 31.

30.2. Provide documentation for continued use of vasodilator.

31. New York Heart Association CHF Classification. Self-explanatory.

32. Participant's Known Sodium (Na) Value Less than 130 meq/l? Self-explanatory. Based on questions 28 to 31, if the participant is taking a vasodilator other than isosorbide, is NYHA Class IV or has known sodium (Na) less than 130 meq/l, then the participant is to be hospitalized for 24 hours for medication

monitoring and the SOLVD Medication Monitoring Form (see section 1.3.12 of the Manual of Operations) is to be completed.

33.1. Participant Not Taking Hydralazine or Isosorbide Medication? If YES, proceed with question 32.2. If NO, end of form.

33.2. If Participant not Taking Hydralazine or Isosorbide, What Is the Likelihood that these Drugs Would Be Used if the Participant's Condition worsens? Self-explanatory.

1.3.13 Instructions for Completing the Medication Monitoring Form

A. IDENTIFYING INFORMATION

1. Today's date. Same as the Visit 1 date.
2. Name of Participant. Self-explanatory.
3. Hospital Name, Address and Patient Hospital ID Number. Self-explanatory.

B. INITIALS OF PERSON COMPLETING THIS FORM. Self-explanatory.

C. MEDICATIONS CURRENTLY USED

5. Is the Participant Currently Taking Diuretics? If NO, proceed with question 6.1. If YES, indicate name and daily dose (in milligrams) of each diuretic in 5.2 to 5.4.
6. Is the Participant Currently Taking Digoxin? If NO, proceed with question 7.1. If YES, indicate name and daily dose (in milligrams) of each digoxin in 6.2 to 6.4.
7. Is the Participant Currently Taking any B-Blocker Medication? If NO, proceed with question 8. If YES, indicate name and daily dose (in milligrams) of each B-Blocker in 7.2 to 7.4.

D. BLOOD PRESSURE MONITORING

8. Supine and sitting blood pressures and a record of either dizziness or syncope are to be taken before the first dose of medication (2.5 mg) is administered (question 8.1). Instructions for obtaining supine and sitting blood pressures are given in Appendix C of the Manual of Operations. The blood pressures and recording of side effects is to be repeated every hour up to 8 hours (questions 8.2 to 8.9). At 12 hours after the first dose, blood pressures are taken again and side effects recorded, and a second dose of medication (2.5 mg) is administered (question 8.10). Blood pressures and recording of side effects are repeated every 2 hours until about 24 hours have passed since the first dose was administered (questions 8.11 to 8.16).

1.4 VISIT 2: THE MEDICATION TOLERANCE VISIT

1.4.1 General Description

The Medication Tolerance Visit is the second visit for prospective participants for SOLVD. It should occur two to seven days after the Eligibility Visit. The following are to be completed at this visit:

i. The participant's blood pressure and heart rate are recorded.
ii. Adherence to the prescribed medication is assessed.
iii. Tolerance to the prescribed medication is assessed.
iv. For potential participants still suitable for the Study, the standard battery of laboratory determinations are to be performed.
v. For participants still suitable for the Study, their next visit should be scheduled within a 14-17 day period.
vi. For participants still suitable for the study, the 14-17 day medication (placebo) for the run-in period should be dispensed.

The order in which the above are performed is important since items i.-iii. are necessary to determine continued eligibility of the participant. Item iv. may also be needed to evaluate the continued eligibility of the participant. At the end of the visit, prospective participants that are still eligible for the Study will leave with their medication for the run-in period and verbal instructions on when to take it. The sections below provide details of the above procedures.

1.4.2 Adherence Criteria

Based on the amount of medication prescribed at the Eligibility Visit(anywhere from 4 to 14 pills plus an extra two in case of a missed visit), the percent compliance is to be calculated as follows:

$$\%\text{Adherence} = \frac{\text{\# of pills dispensed} - \text{\# of pills returned today}}{2 \times \text{\# days since last visit}} \times 100.$$

If the %Adherence is less than 75% or if the participant has not taken any medication in the two days prior to this visit, the participant is to be considered as a nonadherer for this period. Nonadherers may be given a second chance by having another Visit 2 scheduled within a 2-7 day period, and being prescribed a second batch of the medication for the tolerance period. The second chance is the final opportunity for the participant to adhere to the tolerance period medication. The Medication Tolerance Visit form should not be administered to a nonadherer who is given a second chance. Nonadherers not given another chance are to be considered as having completed the visit and must have a Medication Tolerance Visit form. However, they are no longer eligible to participate in the Study.

If the %Adherence is 75% or more and the participant has taken at least some medication in the two days prior to this visit, the participant is to be considered as an adherer for this period and the run-in period continues.

1.4.3 Tolerance Criteria

For participants that adhered to the medication during the test period, tolerance to the test medication is to be assessed using clinical judgment. Specific symptoms of relevance are symptomatic hypotension, angioneurotic edema, altered taste* and skin rash.* Based on the physician's judgment, the participants are to be classified as tolerant or nontolerant. In addition, if azotemia, hyperkalemia or severe proteinuria develop, the patient should be considered intolerant.

Participants who do not tolerate the active agent may be completely excluded or may be rescreened after modification of appropriate ancillary drug therapy. If excluded, the visit is ended and the Medication Tolerance Visit form is to be completed. If the participant is to be rescreened, the participant is to be given a second batch of the 2-7 day test medication(after modification of appropriate ancillary drug therapy), and scheduled for this visit. The Medication Tolerance Visit form is not to be administered to rescreened participants. The process of modifying ancillary drug therapy and rescreening nontolerant participants may be done twice in total.

Participants who tolerate the active agent must have the rest of the visit completed and the Medication Tolerance Visit form completed.

---

*Skin rash or altered taste do not necessarily exclude patients, particularly if these have been mild.

1.4.4 Laboratory Measurements

For prospective participants that are still eligible for the Study, the following standard battery of laboratory determinations are to be performed on blood and urine samples:

1. Blood
   a. Percent hematocrit
   b. Total white blood cell count
   c. Percent neutrophils
   d. Percent lymphocytes
   e. Sodium in meq/l
   f. Potassium in meq/l
   g. Blood urea nitrogen(BUN) in mg/100ml
2. Urine
   a. Creatinine in mg/100ml
   b. Number of positives on dipstick assessment of proteinuria

These are to be performed at the local hospital or Clinical center laboratory. Guidelines for these procedures are not specified in the Manual of Operations since they are standard laboratory measurements.

1.4.5 Physical Examination

At this visit, sitting diastolic and systolic blood pressure and sitting heart rate are to be obtained.

1.4.6 Dispensing of Medication

Once prospective participants who are still eligible for the SOLVD Study have been scheduled for the Baseline or Randomization Visit (Visit 3), their medication for the period is to be dispensed. Visit 3 is to be scheduled within 14 to 17 days from the date of Visit 2. The amount of medication dispensed should be enough for the period until Visit 3 plus one extra day in case of an unforeseen delay in the visit. The amount of medication dispensed can be noted on the Medication Tolerance Visit form as part of optional data for local clinic use only in order to be to be able to assess adherence to the prescribed medication at Visit 3. The medication being prescribed is placebo, but the prospective participant is not to be told what the medication is.

1.4.7 The Medication Tolerance Visit (Visit 2) Form

The Medication Tolerance Visit form is to be administered to prospective participants completing Visit 2. Participants being rescreened or being given a second chance to adhere to the test medication should not have a form completed until their rescheduled Visit 2. The form is not

designed to be self-administered. The specific instructions for each item on the form are as follows.

TEMPORARY IDENTIFICATION (ID). This is the same ID Number on the Visit 1 form.

A. IDENTIFYING INFORMATION

1. Today's Date. Self-explanatory.
2. Participant's Name. Self-explanatory.

B. PHYSICAL EXAMINATION

3. Blood pressure. These are from a sitting position for the participant.
4. Heart Rate. This is from a sitting position for the participant.

C. EXCLUSION CRITERIA

5. Medication Adherence. The %Adherence with the test period medication is to be calculated according to the following formula:

$$\%\text{Adherence} = \frac{\text{\# of pills dispensed} - \text{\# of pills returned today}}{2 \times \text{\# days since last visit}} \times 100$$

If the %Adherence is 75% or more and the participant has taken at least some of the medication in the last two days, the answer to the question is YES. Otherwise, the answer to the question is NO. Note that the extra pills dispensed in case of a delay in the visit should not be included in the calculation above unless it was necessary to have taken them. Refer to section 1.4.2 of the Manual of Operations for determining continued eligibility of the participant based on this adherence measure. If the visit is terminated here and the participant is not being rescheduled for other Visit 2, the answer NO is to be marked and the rest of the form up to section E is to be completed. If the visit is terminated here and the participant is being rescheduled for another Visit 2, the form should not be filled out. If the visit is not terminated, the answer YES is to be marked; proceed with the rest of the form.

6.1. If a participant is on a non ACE inhibitor vasodilator, consider discontinuing the use of the drug. Check appropriate response. If YES go to question 7.

6.2. Provide documentation for continued use of vasodilators.

7. Medication Tolerance.
For participants that adhered to the medication during the test period, tolerance to the test medication is to be assessed using clinical judgment. Specific problems of relevance are symptomatic hypotension, azotemia, hyperkalemia, and in the rare patient angioneurotic edema, altered taste and skin rash based on the examiner's judgment, the participants are to be classified as tolerants or nontolerants. If tolerant, proceed with the rest of the form. If not tolerant, the reason(s) are to be specified. Mark an answer for each of the specified reasons as they apply. (Questions 6.2 to 6.6) and record the willingness of the participant to continue on medication despite the presence of side effects (question 6.7).

D. INITIALS OF PERSON COMPLETING THIS FORM.

8. This should always be filled out for all completed visits. If a visit is rescheduled, this form is discarded and a new form is filled out at the rescheduled visit.

E. TRIAL SUITABILITY.

9. Based on the answers to questions 5 and 6, the continued eligibility of the participant is assessed. If YES, continue with question 9. If NO, end the visit.

F. LABORATORY DATA

10-16. The standard battery of laboratory determinations described in section 1.4.4 of the Manual of Operations is to be performed locally. No specific guidelines on procedures are outlined by this Manual of Operations.

G. PARTICIPANT SUITABILITY

17.1. Based on clinical judgment about the laboratory results, the continued eligibility of the participant is to be recorded. If the answer is NO, the reason must be specified in question 17.2. If the answer is YES, continue with question 17.3 on this form.

17.2. Specify reason.

17.3. If the participant is still eligible to continue, the participant is to be scheduled for the next visit, which is to take place 14 to 17 days from Visit 2. The date of the scheduled Visit 3 is to be recorded. The medication for the run-in period is to be dispensed(see section 1.4.6 of the Manual of Operations) before the participant leaves.

1.5 VISIT 3: THE BASELINE (RANDOMIZATION) VISIT

1.5.1 General Description

The Baseline visit is the last of the three prerandomization visits and it is at this visit that eligible participants are randomized into the study. The following are to be completed at this visit:

i. Adherence to the prescribed medication during the run-in period is recorded. Participants who qualify will complete a Baseline Visit Form.
ii. Eligibility of the participant is assessed.
iii. Participants suitable for randomization will have a clinical history taken, the medications they are currently taking listed, information from a recent electrocardiogram and a chest X-ray recorded, a physical examination performed, and their primary cause of congestive heart failure and New York Heart Association classification assessed.
iv. Participants suitable for randomization will be classified into either the Prevention Trial or the Treatment Trial.
v. Participants suitable for randomization will have a Randomization Form completed and be randomized.
vi. Participants suitable for randomization will complete the self-administered Quality of Life form.
vii. Participants randomized will be scheduled for their next visit, to take place 2 weeks after randomization.
viii. Participants scheduled for their next visit will have their postrandomization medication dispensed.

The order in which the above is to take place is quite important and must not be altered. NOTE that once item v. is performed, the participant is to be considered as part of the trial study into which (s)he has been randomized. In addition, the Quality of Life form could be completed at any time during the visit. The sections below provide details of the above procedures.

1.5.2 Adherence and Eligibility Criteria

Based on the amount of medication prescribed at the Medication Tolerance Visit (anywhere from 28 to 34 pills plus an extra two in case of a missed visit), the percent

compliance is to be calculated as follows:

$$\text{Adherence\%} = \frac{\left[\begin{array}{c}\text{\# of pills}\\ \text{dispensed}\end{array}\right] - \left[\begin{array}{c}\text{\# of pills}\\ \text{returned}\\ \text{today}\end{array}\right]}{2 \times \text{\# of days since Visit 2}} \times 100.$$

If the Adherence% is less than 80%, the participant is to be considered as a nonadherer for this period. Participants who are nonadherers may be given a second chance by having another Visit 3 scheduled within a 14-17 day period, and being prescribed a second batch of the medication for the run-in period. The second chance is the final opportunity for the participant to adhere to the run-in medication. The Baseline Visit form and the Randomization form should not be administered to a nonadherer that is being given a second chance. Nonadherers not being given a second chance are to be considered as having completed the visit and must have a Baseline Visit form.

If the Adherence% is 80% or more, the participant is to be considered as an adherer for this period and the visit continue. The participant's health must be considered stable and the 26 exclusion criteria assessed at Visit 1 (see section 1.3.2 of the Manual of Operations) must all still be negative for the participant to remain eligible for the trials. Once these conditions are satisfied, the participant is eligible for randomization and MUST be randomized regardless of the outcome of the rest of the visit. The rest of the Baseline Visit form elicits information to assist the physician in deciding the trial to which the participant is to be randomized.

1.5.3 Stratification Criteria

See section D of Chapter V of the Protocol (page V-5) for details of the stratification criteria for eligible participants.

1.5.4 Randomization Procedures

Once a participant has been found to satisfy all eligibility criteria (section B of the Baseline Visit form), the participant can be randomized into one of the SOLVD trials. The remaining sections of the Baseline Visit form may aid in deciding the trial to which the participant will be randomized. At the point of randomization, the Randomization Form MUST be completed. This is the only way a participant can be randomized into the Study.

The randomization procedure is described with the following example. Assume Clinical Center XX has several hospitals from which they recruit participants for SOLVD. Assume that Hospital A from Clinical Center XX has a participant in for Visit 3 and the participant is eligible for randomization after successfully completing section B of the Baseline Visit form and question 38 of the Baseline Visit Forms is answered. While the participant is still at Hospital A, the following steps are to be done:

i. Staff member from Hospital A completes part of the paper Randomization Form for the participant. This form verifies the calculation of Adherence% and the other eligibility criteria.

ii. Staff member from Hospital A telephones a staff member at Clinical Center XX who is seated by the microcomputer.

iii. Staff member from Hospital A reads over the phone to staff member at Clinical Center XX the participant's name, Temporary ID, date of Visit 2, # of pills given at Visit 2, # of pills returned today, today's date, whether the participant still meets the eligibility criteria and for which trial the participant is being considered. See section 1.5.8 of the Manual of Operations for a description of the Randomization Form.

iv. The Staff member at Clinical Center XX enters the information into the microcomputer, and verbally verifies the participant's name and Temporary ID with the staff member from Hospital A.

v. The microcomputer will automatically compute the Adherence% once the date of Visit 2, the # of pills given at Visit 2, the # of pills returned today, and today's date are entered. If Adherence% is 80% or greater, the computer will allow the process to continue. When a computer message appears indicating adherence is less than 80%, the participant will not be eligible to continue. Return to question 39 on the Baseline Visit form after completion of the Randomization form.

vi. The staff member from Clinical Center XX enters the information on eligibility criteria and the trial for which the participant is being considered.

vii. The microcomputer will ask to verify the accuracy of all the entered information. The staff member at Clinical Center XX must read back the entered information to the staff member at Hospital A.

viii. Once all entered information is verified, the microcomputer will automatically provide a randomization ID number for the participant.

ix. The staff member at Hospital A should enter the randomization ID number on the paper Randomization Form and reconfirm on the telephone the participant's name, Temporary ID and randomization number. A further check of accuracy of 5 digit ID number should be made by clinic staff.

x. Return to question 39 on the Baseline Visit form after completion of the Randomization form.

xi. The randomized participant is to be given the medication matching the randomization ID number for the next period (see section 1.5.7 of the Manual of Operations) and scheduled for the next visit.

1.5.5 Backup Randomization Procedure

Since the SOLVD randomization procedure requires the randomization information to be entered on the Clinical Center microcomputer in order to obtain the appropriate drug supply number (and corresponding post-randomization ID number), a backup procedure is necessary for cases in which the Clinical Center PC is unusable (due to power failure, equipment malfunction, etc.). The following procedure should be used in such cases.

After completing the usual randomization summary form, call the SOLVD Coordinating Center (919/962-6971) and ask to speak to a SOLVD Research Assistant. If they are unavailable, ask for the Coordinating Center Director of Data Management, the Coordinating Center Director, or the Acting Coordinating Center Director (in that order). Note that the Coordinating Center is normally staffed from 8 AM to 5 PM EST, Monday through Friday.

The randomization procedure will then proceed as usual. As soon as the Clinical Center microcomputer becomes operational, repeat the randomization procedure with your system. It will not be possible to randomize any further participants from your hospital until this is done. If the drug supply number does not match that provided by the Coordinating Center, inform the Coordinating Center immediately. Do not attempt to randomize any other participants until the problem has been resolved.

In rare cases, the Coordinating Center may not have been informed of the last drug supply number used in your hospital. For that reason it will be helpful if, when you call, you know the last drug supply number assigned by your hospital in this Trial. When you are given the drug supply number, please check immediately to assure

that that number has not already been assigned. If it has, retrieve the randomization summary form for that participant. You will have to provide that information to the Coordinating Center staff before the next drug supply number can be assigned.

1.5.6 Quality of Life Form

All participants completing the Baseline Visit should complete the self-administered Quality of Life Form. See Appendix D for details on this procedure.

1.5.7 Laboratory Measurements

There are no laboratory measurements scheduled to take place at this visit.

1.5.8 Dispensing of Medication

Each randomized participant will have a unique randomization ID number that matches the identification number on a set of medication. The set of medication will consist of various dosages of either the active drug or placebo. At this visit, the participant will be given 5 mg BID of medication (Dose 2) for two weeks, until Visit 4. The participant is to be instructed to take the first pill today. 24 hours later a telephone call from clinical staff to the participant must be made to assess any symptoms. The participant will also be given a reserve amount of 2.5 mg BID and 10 mg BID medication as well. See Section 2 of the Manual of Operations for details on the medication protocol.

1.5.9 Randomization Form

The Randomization form is to be completed for participants at Visit 3 that are to be randomized to one of the SOLVD trials. Completion of this form requires interaction with the microcomputer at the Clinical Center. The specific instructions for each item on the form are as follows.

TEMPORARY IDENTIFICATION (ID). This is the same ID the participant has for the pre-randomization visits.

A. IDENTIFYING INFORMATION
   1. Today's Date. Self-explanatory.
   2. Date of Last SOLVD Visit. This is the date the participant completed Visit 2.
   3. Participant's Name. Self-explanatory.

4. Initials of Person Completing this Paper Form. These are the initials of the person seeing the participant and completing the forms. The initials of the person at the microcomputer are NOT the initials to be entered until the participant is at the Clinical Center.
5. Trial for which the Participant Is Being Considered? Either the Prevention Trial OR the Treatment Trial must be denoted. See section V.-D. of the Protocol for a description of the stratification criteria for the Study.

B. ADHERENCE

6.1. Number of Pills Dispensed at Visit 2. This total should only include the latest batch of run-in period medication if the participant had been given a second chance.

6.2. Number of Pills Returned Today. Self-explanatory.

6.3. Number of Days Since Visit 2. This should be the number of days since the uncompleted Visit 3 for those participants being given a second chance on the run-in period medication. The microcomputer will be able to calculate this number for participants not requiring a second chance using questions 1 and 2 above.

6.4. Using the information from questions B.1 to 6.3, the microcomputer will calculate the Adherence%, which if less than 80%, will not allow the participant to be randomized.

7. Does the Participant Still Meet the Entrance Criteria? This is the final check that all 26 exclusion criteria are still negative, that the participant is still willing to participate and that the health of the participant is stable.
8. Are You Sure That All of the Above Information is Correct? The staff member at the microcomputer should verify all entered information with the hospital staff member on the telephone since after this question is answered YES, there will be no way to change the information on this form. If the question is answered NO, there will be a chance to modify some of the information.

Once all the information has been entered on the microcomputer and been verified, the participant's

randomization ID number will be automatically assigned by the microcomputer. If the microcomputer (based on the compliance calculation) does not allow the participant to be randomized, no randomization ID will be assigned. In this case, question 39 on the Baseline Visit Form should be marked NO. If the participant is allowed to be randomized, the participant's TempID (the prerandomization ID), name and randomization ID will appear on the screen and should be entered on the Randomization form. If the staff member completing the form is not at the microcomputer, these three items should be verbally confirmed over the telephone. Return to question 39 on the Baseline Visit form and mark it YES.

1.5.10 Instructions to Complete the Baseline Visit

The Baseline (Randomization) Visit Form is to be administered to prospective participants completing Visit 3. Participants being given a second chance to adhere to the run-in period medication should not have a form completed until their rescheduled Visit 3. The form is not designed to be self-administered. The specific instructions for each item on the form are as follows.

TEMPORARY IDENTIFICATION (ID). This is the same ID number used at all prerandomization visits.

A. IDENTIFYING INFORMATION

1. Today's Date. Self-explanatory.
2. Participant's Name. Self-explanatory.

B. EVALUATION OF ELIGIBILITY

3.1. Did the Participant Take 80% or More Tablets in the Run-in Period? The clinic staff must compute Adherence% (see section 1.5.2 of the Manual of Operations) in order to answer this question. If the answer is NO, the participant may be given a second chance at the run-in period at the discretion of the clinic staff. If given a second chance, do not administer the form. If not given a second chance, the visit is ended and the participant is not eligible for the Study; the form is considered completed after the initials are recorded (question 4). If the answer is YES, continue with the form.

3.2. Is the Participant's Condition Stable? The answer is based on physician's or clinical judgment. If the answer is NO, the participant is not eligible for the Study and the visit is ended; the form is considered completed after the initials are recorded (question 4). If the answer is YES, continue with the form.

3.3. Does this Participant Still Meet the Inclusion Criteria? The answer is based upon verifying that the 26 exclusion criteria assessed at Visit 1 are still negative and that the participant is still willing to participate. If the answer is NO, the participant is not eligible for the Study and the visit is ended; the form is considered completed after the initials are recorded (question 4). If the answer is YES, continue with the form.

C. INITIALS OF PERSON COMPLETING THE FORM.

4. Initials. Self-explanatory. This should always be filled out for completed visits.

D. TRIAL SUITABILITY.

5. Is the Participant Still Suitable for Randomization? At this stage, if the answers to questions 3.1 to 3.3 are all YES, the participant is eligible for randomization. Although NOT encouraged, the staff may elect to complete the Randomization Form at this stage or wait until some of the rest of the Baseline Visit Form is obtained in order to decide to which trial to assign the participant. Before the Randomization Form is completed, Question 38 in section M. of the Baseline Visit Form must have been completed. After the Randomization Form has been completed, the rest of section M. and section N. of the Baseline Visit Form must be completed and any remaining incomplete sections (E. through L.) of the Baseline Visit Form must be completed. If the participant is not suitable for randomization, the visit ends.

E. CLINICAL HISTORY

6. Does the Participant Have Angina? Self-explanatory.
7. Has the Participant had Dizzy Spells? Self-explanatory.
8. Has the Participant Fainted (Syncope)? Self-explanatory.
9. Smoking History

9.1. Has the Participant Ever Smoked Cigarettes? Self-explanatory. If the answer is NO, go to question 10. If the answer is YES, continue with question 9.2.

9.2. Does the Participant Currently Smoke? Self-explanatory. If the answer is YES, go to question 10. If the answer is NO, continue with question 9.3.

9.3. Number of Months Ago When Participant Stopped Smoking. Self-explanatory.

10. Average Number of Alcoholic Drinks Consumed per Week in the Past Two Years. Include beer, wine and liquor. Roughly, 12 oz. beer = 1 glass wine = 1.5 oz. liquor = 1 Alcoholic Drink.
11. Previous Myocardial Infarction? Self-explanatory.
If the answer is YES, provide the date of the most recent MI (question 11.2). If the answer is NO, proceed with the next question.
12. Permanent Pacemaker? Self-explanatory.
13. Previous Cardiac Surgery? Self-explanatory.
If the answer is YES, provide the date of the most recent cardiac surgery (question 13.2) and circle the type of cardiac surgery (question 13.3). If the answer is NO, proceed with the next question.
14. History of several conditions. Check YES or NO for each condition listed in questions 14.1 to 14.8.

F. NON-STUDY MEDICATIONS CURRENTLY USED

15-25. Non-study Medications. Check YES or NO for each of the medications listed. The data on name of medication, dosage and frequency is optional and for clinic use only.

G. QUALIFYING EJECTION FRACTION RECORDED AT ELIGIBILITY VISIT 1 (SEF FORM)

26.1. EF Percentage. Self-explanatory. This figure must be less than or equal to 35% and must agree with the EF recorded on question 13.1. of the Eligibility Visit Form.
26.2. Date Obtained. Self-explanatory. This must agree with the date recorded on question 13.2. of the Eligibility Visit Form.

H. ELECTROCARDIOGRAM

27. Normal? Check YES or NO.
28. Atrial Fibrillation or Atrial Flutter? Check YES or NO.
29. QRS Delay >= 120 ms? Check YES or NO.
30. Left Ventricular Hypertrophy? Check YES or NO. If No, go to question 31.1. If YES, check YES or NO for each of questions 30.2 to 30.4.

I. CHEST X-RAY

31.1. Cardiac-thoracic Ratio. Recorded as a decimal with two significant digits.
31.2. Are there any Signs of Pulmonary Venous Hypertension? Check YES or NO.

J. PHYSICAL EXAMINATION

32. Weight. Record weight in either pounds or kilograms (but not both) without shoes or outdoor garments.
33. Heart Rate (sitting, in beats per minute). Self-explanatory.

34. Blood pressure (sitting, systolic and diastolic). Self-explanatory.

35.1. Rales? Check YES or NO for presence.

35.2. Edema? Check YES or NO for presence.

35.3. Elevated Jugular Venous Pressure? Check YES or NO for presence.

35.4. S3 Gallop? Check YES or NO for presence.

K. PHYSICIAN'S JUDGMENT OF PRIMARY CAUSE OF CONGESTIVE HEART FAILURE.

36. Primary Cause of CHF. Check only one of the three choices. If "Other," please specify the cause in question 36.2.

L. NEW YORK HEART ASSOCIATION CLASSIFICATION CHF.

37. Check only one of the possible four choices.

M. RANDOMIZATION INFORMATION.

38. For Which Trial is This Participant Being Considered? Check EITHER the Prevention Trial OR the Treatment Trial. This question MUST be answered prior to attempting to obtain a randomization number for the participant.

39. Was the Participant Eligible for Randomization? The answer to this question will be obtained from the microcomputer as you attempt to randomize the participant. If NO, end the visit. In this case, it is still of scientific Interest to have any incomplete sections of the Baseline Visit Form completed. If YES, proceed with question 40 and it is then mandatory to complete any incomplete sections of the Baseline Visit Form.

40. RANDOMIZATION NUMBER. Record here the randomization number after double checking it with the staff member at the microcomputer and before dispensing any medication to the participant.

N. MEDICATION DISPENSING/VISIT SCHEDULING

41. Pills Dispensed. Record the number of pills dispensed of each of the three possible dosages as well as whether they are to be taken QD or BID.

42. Date of Next Scheduled Visit. Self-explanatory. Visit 4 is to take place 2 weeks after Visit 3.

1.6 POST-RANDOMIZATION VISITS

1.6.1 General Description

The post-randomization visits are to occur at 2 weeks (Visit 4) and 6 weeks (Visit 5) post-randomization and then at 4 months (Visit 6), 8 months (Visit 7) and 12 months (Visit 8) post-randomization. Thereafter, clinic visits will be required at 4 month intervals to the end of the study. The procedures at the different follow-up visits are not always the same. However, after Visits 4 and 5, they will be the same except for the annual visits (Visits 8, 11, 14, etc.). The following procedures occur at the regular follow-up visits:

i. The current address and telephone number of the participant, the participant's private physician and the participant's employer are verified.
ii. Interim symptoms and side effects are recorded.
iii. Possible interim hospitalizations will be assessed.
iv. Non-study medications being used are recorded.
v. The dosage of the study medication is recorded and the adherence pill count is assessed.
vi. A brief physical examination is conducted.
vii. The New York Heart Association classification is assessed.
viii. Evidence of developed or worsening CHF is assessed.
ix. The standard battery of laboratory determinations is performed on certain visits.
x. The next visit is scheduled. After Visits 4 and 5, there is a "time window" of +/- 3 weeks.
xi. Medication is dispensed for the period until the next scheduled clinic visit.
xii. The patient is called 24 hours after the visit to assess any problems with the study medication.
xiii. The Follow-up Visit Form is completed. Other forms may need to be completed as well (see sections 5.3 and Appendix D of the Manual of Operations).

The order in which the above are performed is not crucial, except in the obvious timing of procedures. The sections below provide details of the above procedures and the follow-up visits at which they occur.

1.6.2 Visit 4, Visit 5 and Subsequent Follow-up Visits

VISIT 4: The first visit post-randomization will differ from the other regular SOLVD follow-up visits in the following procedures:

i. Visit 4 occurs 2 weeks after the day of randomization.

ii. Participants are to be titrated upwards to the maintenance dosage (Dose 3) of the study medication.
iii. The clinic visit is optional but the laboratory determinations are mandatory. Clinic staff are responsible for retrieving all such data from outside laboratories and entering the data on the appropriate forms. The Follow-up Form must be completed in all cases.

VISIT 5: The second visit post-randomization will differ from the other regular SOLVD follow-up visits in the following procedures:

i. The Quality of Life Form is administered.
ii. The standard battery of laboratory determinations are to be performed.

VISITS 6 and 7: These visits are regular SOLVD follow-up visits.

VISIT 8: The first post-randomization annual visit will differ from the other regular SOLVD follow-up visits in the following procedures:

i. The Quality of Life Form is administered.
ii. Since it is an annual visit, the standard battery of laboratory determinations are performed.

VISITS 9-10, 12-13, etc.: These visits are regular SOLVD follow-up visits.

VISITS 11, 14, etc.: These are regular SOLVD annual visits and they differ from the other regular SOLVD follow-up visits in that the standard battery of laboratory determinations are performed.

CLOSURE VISIT: This visit will differ from the regular SOLVD follow-up visits in several ways:

i. The Quality of Life Form will be administered
ii. Other specific close-out procedures will be developed by the Steering Committee. See section XIII of the Protocol for details.

1.6.3 Instructions for Completing the Follow-up Interview/Examination Form

The Follow-up Interview/Exam Form is to be administered at all visits after Visit 3. Optional data that are to be collected at the discretion of the clinic can be recorded on the paper version of the form, on the right hand side provided and labelled OPTIONAL DATA FOR LOCAL CLINIC USE ONLY. The optional data will not be entered into the microcomputer. Guidelines and specific instructions for the optional data beyond those provided on the paper version of the form are not given in this Manual of Operations.

RAND ID: This is the participant's ID obtained once randomized into the Study.

A. IDENTIFYING INFORMATION

1. Date of this interview/exam. Self-explanatory.
2. Date of last SOLVD interview/exam. Self-explanatory.
3. Name of Participant. This must correspond with the Randomization ID at the top of the form.
4. Participant's address and telephone number. If the address or telephone number has changed since the previous visit, the current ones must be recorded on questions 4.2 to 4.7. If there is no change, proceed with question 5.
5. Participant's private physician. If there is a change in the participant's private physician or the physician's address or telephone number, the current ones must be recorded in questions 5.2 to 5.9. If there is no change, proceed with question 6.
6. Participant's employment. If there is a change in the participant's employer, employment status, title on the job, employer's address or telephone number, the current ones must be recorded in questions 6.2 to 6.9. If there is no change, proceed with section B.

B. INTERIM SYMPTOMS AND SIDE EFFECTS

7. Angina. If the participant had angina since the last visit, record the average number of attacks per week in question 7.2.

8.1. Dizzy spells (since the last visit). Self-explanatory.

8.2. Syncope (faintness) (since the last visit). Self-explanatory.

9. Hospitalizations. If the participant was hospitalized since the last visit, the SOLVD Hospitalization Form must be completed. See section 5.3.2 of the Manual of Operations.
10. Illness without hospitalization. Record the occurrence of illness requiring a visit to a physician but not hospitalization since the last SOLVD visit.

C. NON-STUDY MEDICATIONS CURRENTLY USED

Record whether a particular medication was used or not for each one of the listed medications in questions 11 through 21. The instructions are self-explanatory. Name, dosage and frequency can be recorded as Optional Data for Local Clinic Use Only in the right-hand side of the paper form.

D. STUDY MEDICATION

22. Pills dispensed at previous visit and pills returned. For each pill type dispensed at the last SOLVD visit or last use of this form, enter the number of pills dispensed, dose (whether QD or BID) the number of pills returned and the number of days since the last visit or use of this form.
23. Symptoms present since the last visit. Check YES or NO for each one of the symptoms listed in 23.1 to 23.8. If "Other," please specify.

E. PHYSICAL EXAMINATION

24. Weight. See Appendix C of the Manual of Operations.
25. Heart rate, sitting. See Appendix C of the Manual of Operations.
26. Blood pressure, sitting. See Appendix C of the Manual of Operations.

F. PHYSICIAN'S ASSESSMENT

27. New York Heart Association CHF Classification. Self-explanatory.
28. Previously symptomatic participant? Participants in the Prevention Trial who had never previously developed symptoms of CHF are called "Previously asymptomatic." All participants in the Treatment Trial and those participants in the Prevention Trial who were found to be symptomatic at a previous visit are called "Previously symptomatic." If "Previously symptomatic," skip to question 31.
29. For "Previously asymptomatic" participants, record if there is evidence that CHF has developed since the previous visit. If NO, proceed to section G. If YES, check whether each of the listed symptoms was present or not (questions 29.2 to 29.5), and answer question 30.
30. For "Previously asymptomatic" participants (see question 28 above) that answered YES to question 29.1, record whether each of the listed signs of CHF was present or not (questions 30.1 to 30.5). Question 31 is not to be answered. Proceed to section G.
31. For "Previously symptomatic" participants (see question 28 above), record the change in the participant's CHF severity since the last visit.

G. LABORATORY DATA

The standard battery of laboratory determinations is to be performed at Visit 4, Visit 5 and at the annual follow-up visits only. These include:

i. Hematocrit
ii. Total White Blood Count
iii. Percent Neutrophils
iv. Percent Lymphocytes
v. Sodium (meq/l)
vi. Potassium (meq/l)
vii. Blood Urea Nitrogen (mg/dl)
viii. Creatinine (mg/dl)
ix. Number of Positives on dipstick test for Proteinuria

Specific instructions for these laboratory determinations are not provided in this Manual of Operations. Record results in questions 32 to 38.

H. STUDY MEDICATION DISPENSING INFORMATION

39. Record the number of pills dispensed at this visit for each of the three pill types. Also indicate whether they are to be taken QD or BID.
40. Has the Dosage of Study Drug Been Changed since the Last SOLVD Visit or Use of a SOLVD Alteration in Study Drug Dosage Form? If NO, go to section L, question 52. If YES, proceed with Section I, question 41.

I. STUDY DRUG DOSAGE CHANGE

41. Type of Change in Dosage. Record whether the change in study drug dosage is an increase or a decrease. If INCREASE, go to section J, question 42. If DECREASE, go to section K, question 43.

J. REASON FOR INCREASING DOSE

42. Check YES or NO for each of the possible reasons given in questions 42.1 to 42.3. Proceed with section L, question 52.

K. REASON FOR DECREASING DOSE

43. Check YES or NO if the reason for decreasing dose was the presence of side effects. If NO, go to question 44. If YES, check YES or NO for presence of each of the side effects listed in questions 43.2 to 43.6.
44. Check YES or NO if the reason for decreasing dose was a myocardial infarction.
45. Check YES or NO if the reason for decreasing dose was cardiac surgery (other than transplant). If YES, specify the type of cardiac surgery in question 45.2.

46. Check YES or NO if the reason for decreasing dose was cardiac transplant.
47. Check YES or NO if the reason for decreasing dose was noncardiac surgery.
48. Check YES or NO if the reason for decreasing dose was worsening CHF with need for treatment with "open label" medication identical or similar to the study drug.
49. Check YES or NO if the reason for decreasing dose was a request by the referring physician.
50. Check YES or NO if the reason for decreasing dose was a request by the participant.
51. Check YES or NO if the reason for decreasing dose was another reason than ones listed in questions 43 to 50. If YES, specify reason.

L. SCHEDULING INFORMATION

52. Date of Next Visit. Self-explanatory.

M. ORIGIN OF FORM

53. This form can be completed at the clinic or by telephone. Preferably, the form is to be completed at a clinic visit. However, Visit 4 is an optional clinic visit, with mandatory laboratory data. The laboratory results and other available information can be obtained over the telephone if the patient has been seen at a distant location by a collaborative physician. In addition, in extraordinary circumstances, if the participant cannot be seen in the time window of a visit, sections A, B and C of the Follow-up Interview/Exam Form can be completed by telephone.

N. INITIALS OF PERSON COMPLETING THIS FORM

54. Initials. Self-explanatory.

2. MEDICATION PROTOCOL

2.1 General Description

After participants are identified as being potentially eligible for the SOLVD Study by having an ejection fraction $\leq$ 35%, they will be screened for exclusions. At Visit 1, the Eligibility Visit, eligibility will be ascertained, written consent will be obtained, key clinical data will be recorded and 2-7 days of 2.5 mg. BID enalapril will be dispensed. Participants are not to be told that they are receiving active medication (the study is single blind at this stage). Blood will be obtained for both storage and measurements to be done centrally and for the standard battery of laboratory determinations (see section V.C.2.in the Protocol) to be measured locally. The participant will be instructed to take the study drug (single-blind) for 2-7 days and the next visit appointment will be made.

At Visit 2, the Medication Tolerance Visit, an assessment of whether or not the participant has suffered adverse reactions will be done. Additionally, blood will be drawn for the standard battery of laboratory determinations. If the participant is not suffering any adverse symptoms, he/she will be started on 14-17 days placebo (single blind) to assess adherence. The participants are not to be told they are receiving placebo. The laboratory results should usually be available the next day, and will alert the physician to possible pre-renal azotemia or changes in blood counts. The participant will be excluded from the Study if he/she had a significant hypotensive bout secondary to the active agent that cannot be controlled with measures other than stopping the drug, or if major changes in renal function are detected.

If the participant was only moderately or mildly symptomatic, several treatment options could be considered. These might include decreasing concomitant diuretics or other vasodilators, or liberalizing the intake of sodium if the participant was on a restricted diet. If the participant is felt to be a reasonable candidate for the Study Trial, a new medication tolerance period could be tried after modifying his/her ancillary drug regimen. If no adverse reactions to the medication tolerance period occur and adherence to the test dose is at least 75% during the 2-7 day medication tolerance period (with at least some drug taken in the last 2 days of the test period), then the participant will be started on placebo BID to assess adherence. There is only one recycling procedure allowed for each prospective participant for the medication tolerance or the placebo run-in periods.

At Visit 3, the Randomization Visit, adherence to the placebo run-in period will be assessed. If the participant's health is stable and he/she meets the inclusion criteria, the adherence during the placebo run-in

period is at least 80%, then a clinical history will be taken, medications currently used will be assessed and a physical examination will be performed. Blood will be drawn for the standard battery of laboratory tests.

2.2 Alterations in Other Drugs at Onset of Active Drug Treatment

At the physician's discretion, participants may need some modification of their usual medication. For example, those participants who recently had an increase in diuretic dosage, or are dehydrated or hyponatremic, could have their diuretics discontinued for a period of about 1 or 2 days.

Likewise, it may seem prudent to temporarily withhold other vasodilators during the initiation of therapy NYHA Class IV patients. Because of the low initial dose of the active agent, however, the frequency of hypotension at the onset of therapy is likely to be very low and for this reason, individual physicians may or may not wish to reduce the dose of the other vasodilators.

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

2.3 Titration to Maintenance Dose

At this time the participant will be randomized and given enalapril 5 mg. BID or placebo (Dose 2). At this stage the study becomes double blind for its duration. The participant will be instructed to take his/her medication on the day of the clinic visit and 24 hours later a phone call will be made to assess any symptoms. If the participant has dizziness or fainting, modification of other treatments as detailed above could be made. If the participant tolerates that dose, he/she will then continue on (Dose 2) for 2 weeks, until Visit 4. In high risk participants, the investigator may wish to start at 2.5 mg BID or equivalent placebo post-randomization to minimize the potential of first dose hypotension and increasing the dose to first dose hypotension and increasing the dose to 5 mg BID or equivalent placebo in a few days.

Visit 4 will occur 2 weeks after randomization (Visit 3). A history will be taken and physical examination performed with attention paid to symptoms of orthostatic hypotension, syncope and the presence of angina. Blood for the standard battery of laboratory tests will be drawn and clinical data will be obtained. This optional visit may occur at the clinic or the participant's private physician's office but laboratory data are required for this visit and must be obtained and recorded at the Clinical Center. If the participant is not tolerating medication, further

modification of nonstudy drugs may have to be made. At Visit 4 the physician has the option to increase, decrease or maintain the dose of the study medication. If the participant tolerates Dose 2, enalapril or placebo will be increased to 10 mg BID (Dose 3) and again a phone call 24 hours later will be made to review the results of laboratory tests done on the preceding day and to determine if the participant has had any new symptoms. If the participant tolerates Dose 3, this will be continued for a 4-week period and thereafter throughout the study.

Dosage options will include Doses 1, 2 or 3 and, if necessary, any of the doses 2.5 mg, 5 mg or 10 mg) may be used. The dose of the study medication may be increased or decreased at the discretion of the investigator, but whenever possible investigators are encouraged to maintain participants on 10 mg. BID or the highest possible dose tolerated. Should a participant develop azotemia, hyperkalemia, mild proteinuria, or symptoms of orthostatic hypotension, investigators are encouraged initially to modify the dose of any nonstudy drugs such as diuretics, vasodilators or potassium supplements rather than modifying the study drug as outlined below:

(a) Hypotension

Symptomatic hypotension may occasionally complicate treatment with any angiotensin converting enzyme inhibitor. This may be during acute treatment (a response to the first few doses) or during more prolonged treatment. Previous studies have suggested that about one to five percent of heart failure patients may develop symptomatic hypotension during treatment with ACE inhibitors. Patients with more severe heart failure (e.g., Class IV), especially of unstable (pulmonary edema) or if hyponatremic, are at greater risk of marked symptomatic hypotension. There is only limited experience of the added use of ACE inhibitors in patients receiving other vasodilators for heart failure. It may, therefore, be prudent to take careful precautions in Class IV hyponatremic patients or those receiving other vasodilators while initiating therapy (see below). It is recommended that such patients be hospitalized so as to assess the hypotensive response to the first 2 doses until more information is available. The data from the first 100 patients in this category will be reviewed by the Data and Safety Monitoring Committee who will then recommend whether such (or some of these) patients should continue to be hospitalized to initiate treatment.

The onset of first dose symptomatic hypotension occurs usually between 4 and 8 hours after enalapril administration. The duration of hypotension is usually shorter at the lower doses and more prolonged at the higher doses (the exact duration can vary considerably from patient to patient). If a patient develops hypotension after randomization, previous experience suggests that the drug

can often be safely reinstituted at a lower dose (e.g., use 2.5 mg if 5 mg is not tolerated). If diuretics or other vasodilators (including calcium channel blockers) are being used, they should be decreased or stopped. In patients prone to symptomatic hypotension, it may be wise to decrease/stop the dose of diuretics or other vasodilators a few days prior to starting enalapril.

When the participant is sent home, he/she should be provided with a telephone number for emergency contact and instructions of how to cope if severe dizziness or fainting occurs (telling the participant to lie down with feet elevated, and that until given further instructions, he/she should not take the next set of study medications). If a participant develops symptomatic hypotension that is prolonged and that does not respond to simple postural changes, then expanding the plasma volume with i.v. fluids may be required. If these steps are not adequate, then using vasopressors such as dopamine or nor-epinephrine may have to be used. If the hypotensive episode is associated with a relative bradycardia, atropine may be useful as a vasovagal component to the hypotension secondary to enalapril has been described.

All severe episodes of hypotension should be immediately notified to the Coordinating Center, who in turn will keep the Executive Committee informed.

(b) Azotemia.

A small percentage of patients, especially those on high doses of diuretics or in Class IV CHF may develop azotemia which is usually reversible. If a patient's serum creatinine rises to 4 mg% or more, the physician should decrease the dose of the diuretic or study drug or both. If this does not result in a return of the serum creatinine to 2 mg% or lower, the study drug should be stopped. If renal artery stenosis is suspected, then the study drug should be discontinued indefinitely. In other patients, especially if they are on high doses of diuretics, the drug may usually be reinstituted at low doses after reducing the diuretics.

(c) Hyperkalemia.

Since ACE inhibitors decrease the production of aldosterone, patients receiving these agents are prone to develop hyperkalemia, especially if they are concomitantly receiving potassium sparing diuretics. It may therefore be prudent to decrease the dose of any potassium sparing diuretic and stopping potassium supplements while instituting the study drug. If hyperkalemia (potassium > 5.5 meq/l) develops or persists despite these measures, the study drug should be stopped. If the hyperkalemia is more extreme and is potentially life-threatening, a number of additional steps such as i.v. glucose-insulin, i.v. calcium gluconate, potassium binding resins or, if necessary, dialysis may be needed. However, no occurrence of such extreme and life-threatening hyperlakemia has been reported with the use of the ACE inhibitors.

(d) Angioneurotic edema

A very small proportion of patients have been reported as developing angioneurotic edema following the first dose of enalapril. This is manifested by orbital, facial and buccal swelling and breathing difficulties. Such patients should be urgently hospitalized and treated appropriately (i.v. hydrocortisone, adrenaline subcutaneously, respiratory support, etc.

2.4 Management of Study Drug During an Intercurrent Event

It is anticipated that intercurrent events may necessitate either no change in study drug administration, transient stopping of the study drug or, in some cases, irreversible termination of the study drug. It is recommended that unless clear contraindications arise, the study drug should be continued at the same or lower dose or only briefly interrupted for the duration of the intercurrent event and then reinstituted as soon as possible. Some typical situations are outlined below:

1) Worsening congestive heart failure: Study drug can usually be continued although it may be stopped or continued at the discretion of the attending physician. The participant's heart failure should be treated utilizing conventional pharmacologic measures (other than an "open-label" ACE inhibitor) and, once the participant is stable, the participant should be continued on the same dose of the study drug (and additional pharmacologic therapy, if needed).

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

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

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

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

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

3) Suspected adverse drug reaction: If a severe adverse reaction thought to be related to the study drug occurs, the dose of the study medication may be reduced. If this is not adequate, then it may be discontinued temporarily, and if medically feasible, reinstituted.

4) Need for ACE-inhibitor therapy: While management or exacerbation of symptomatic CHF with non ACE-inhibitor therapy is strongly encouraged, it is recognized that the referring physician may insist on the use of an open-label ACE inhibitor. The study drug should then be terminated. Individual Clinical Center Principal Investigators should share in the decision for starting patients on open-label ACE inhibitor therapy, whenever possible. Institution of open-label ACE-inhibitor therapy should only commence after all other pharmacologic means of controlling heart failure have failed (e.g. increasing diuretics, adjustment of digoxin dosage, use of other vasodilators, etc.).

2.5 Adverse Reactions and Discontinuation of Study Drug

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

2.6 Unblinding Study Medication

Under unusual circumstances chiefly relating to participant safety, unblinding may be necessary. This should usually be done after consultation with the Principal Investigator of the Clinical Center involved, the Chairman of the Steering Committee and the Project Officer.

In extreme emergencies (i.e., accidental overdosage, etc.) the hospital pharmacy of the Clinical Center will be able to identify treatment assignments. This will be handled in the following manner:

1. At the beginning of the study, and possibly at subsequent intervals during the study, the Coordinating Center will mail to the Clinical Center Director of Pharmacy sealed envelopes with randomization numbers and the treatment assignment for both the Prevention and Treatment Trials. The following will also be printed on the outside of each envelope:

TO BE OPENED ONLY IN EXTREME EMERGENCY.
ONCE THIS ENVELOPE IS OPENED, IMMEDIATELY RETURN IT AND ITS CONTENTS TO:

Dr. C. E. Davis
Principal Investigator
SOLVD Coordinating Center
Suite 400, NCNB Plaza
137 East Franklin Street
Chapel Hill, N.C. 27514

2. Should unblinding be required, after confirming with the clinic Principal Investigator, the Chairman of the Steering Committee, and the Project Officer, a phone call would be made to the clinic center's hospital pharmacy and the appropriate envelope would be opened. Once opened, it should be immediately returned to the Coordinating Center.

3. At the termination of the Study, all envelopes should be returned from the Clinical Center's hospital pharmacy directly to the Coordinating Center.

2.7 Deviations from Protocol Therapy

At any time during the Study, study medication may be increased, decreased, or discontinued. Discontinuation or use of open-label ACE therapy should be used only when necessary for patient safety; and should involve the clinic Principal Investigator, and when possible the Chairman of the Steering Committee, and the Project Officer.

2.8 Alteration in Study Drug Dosage

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

3. ASSESSMENT AND MANAGEMENT OF SIDE EFFECTS (See also Section 2.3 a to d)

3.1 Local Laboratory Analyses

The following standard battery of laboratory determinations are to be performed:

a. Percent hematocrit
b. Total white blood cell count
c. Percent neutrophils
d. Percent lymphocytes
e. Sodium in mEq/l
f. Potassium in mEq/l
g. Blood urea nitrogen(BUN) in mg/dl
h. Creatinine in mg/dl
i. Number of positives on proteinuria

These are to be performed at the local hospital's or Clinical Center's laboratory. Guidelines for these procedures are not specified in the Manual of Operations since they are standard laboratory measurements. Any other laboratory tests which would be done for patient safety are to be done at the individual physician's discretion.

3.2 Assessment of Symptoms

Minor side effects can be defined as effects that may be unpleasant or distressing to the participant, but that do not require reducing the dose or discontinuing the drug; minor side effects are not harmful to the participant. Major side effects, on the other hand, are effects that are of sufficient severity to warrant reducing or discontinuing the drug, either because they are intolerable or because they are judged to be potentially harmful to the participant.

Management of side effects is based on the philosophy of primarily protecting the safety of the participant while at the same time making every effort to adhere to the treatment protocol. Suggested approaches to some of the more notable potential problems are specified in some detail. Other, less common problems are not described, reflecting the philosophy that each clinic physician will need the flexibility to use his or her own judgment for handling the wide variety of situations that may develop, in a fashion that will maintain both the safety of the participant and the integrity of the Study. In difficult situations, participant safety is of paramount importance, even if this violates any aspect of the protocol.

It is important to obtain reliable information on all side effects, and a placebo-controlled double-blind trial offers the opportunity to do so. A suggested approach to differentiate between side effects that are volunteered by the participant and those that are elicited as a result of specific questions, and, thus, suggested to the participant would be to use open-ended questions where possible.

3.3 Management of Side Effects (See also Section 2.3 a to d.)

3.3.1 General Precepts

Every effort should be made to prevent interruptions of treatment except for bona fide, major side effects. When drug therapy is initiated, the participant is briefed on the possibility of side effects from the study drugs and is reassured that these side effects are not harmful. If there are side effects that are judged to be minor or not drug-related, the clinician should use all of his or her skills to reassure the participant and maintain effective dosage. The clinician should emphasize that the side effects are not usual and that they are likely to become less bothersome with time, and that every effort should be made to tolerate them.

If major side effects that may be drug-related occur, the study physician may at his/her discretion, reduce or stop administration of the study drug. In those instances where dosage is reduced, every attempt should be made to lower it as little as is necessary and for as short a time as possible. The participant should be told that a temporary lowering of the dosage may be sufficient to eliminate the side effect, and that a later restoration of the full dosage may be tolerable. The clinician should ascertain and record the effect of the dosage change upon the undesirable side effects. Whenever possible, full dosage may be subsequently restored. A review by the Clinical Center staff of the status of participants who are on reduced medication could conducted at some regular interval, such as monthly.

3.3.2 Specific Conditions

3.3.2.1 Hypotension

Patients who are volume depleted (e.g. high doses of diuretics, salt restriction) are more likely to develop hypotension. Patients who are treated with betablockers are also more prone to hypotension in that treatment with an ACE inhibitor such as enalapril leads to a decreased sympathetic nerve activity and enhanced vagal activity. Normally, a patient can tolerate the lower blood pressure induced by enalapril. However, at a certain pressure level, which is individual for each patient, cerebral symptoms may occur. The most common symptom is dizziness but many other signs can occur as the result of the underperfusion of the brain. The symptoms can be confusion, irritability, depression and memory dysfunction. In the case of a severe drop in blood pressure, which is most likely to occur as a first dose response, syncope can occur. In the case of symptomatic hypotension, diuretics should be withheld for 1-2 days and

then be restarted at a lower dose level. Concurrent medication with another vasodilator should be stopped and the need for continuation with that drug be reevaluated. If the symptoms do not disappear, the dose of the study drug should be decreased. In the case of severe hypotension, an i.v. infusion of saline or angiotensin II amide may be needed in addition to the actions described earlier.

3.3.2.2 Azotemia

In spite of the increase in renal blood flow induced by enalapril, the glomerular filtration rate decreases due to the loss of a beneficial direct intrarenal action of angiotensin II. This decrease in glomerular filtration gives an increase in serum creatinine and urea of about 10-20 %. In most participants, this slight increase in creatinine will not be clinically significant. However, in a subgroup of participants, specifically those with initially severely impaired kidney function and those with renal artery stenosis, an ACE inhibitor can push the participant into overt renal failure. In those cases, the treatment need to be temporarily stopped and readministred gradually at a lower dose.

3.3.2.3 Skin Rash and Taste Disturbances

Skin rashes and taste disturbances are relatively rare (0.5-1.5% reported for enalapril) and are usually mild and at the most, annoying. They appear to be more common in patients with depressed renal function and therefore achieving higher plasma levels of the drug. These symptoms may be resolved with continued therapy, although a slight dose reduction may be needed in some cases.

3.3.2.4 Cough

A dry cough experienced by a small group of patients treated with enalapril (about 1.5%) is not due to any change in lung function and the pathogenesis in unknown. It is seldom a reason to discontinue the therapy and often disappears after several weeks treatment.

3.3.2.5 Hyperkalemia

The fall in plasma levels of aldosterone induced by enalapril will give a slight rise in serum potassium of about 10 %. This is normally clinically insignificant; however, it will reduce the need of potassium supplementation and potassium sparing diuretics should be avoided.

3.3.2.6 Angioneurotic Edema

A very small proportion of patients have been reported as developing angioneurotic edema following the first dose of enalapril. This is manifested by orbital, facial and buccal swelling and breathing difficulties. Such patients should be urgently hospitalized and treated appropriately (i.v. hydrocortisone, adrenaline subcutaneously, respiratory support, etc.).

4. ASSESSING ADHERENCE

4.1 Medication Adherence by Pill Count

The measurement of adherence will be based on pill count. Adherence will be determined by comparing the number of pills actually taken since a previous visit to the number returned to the current visit and dividing this difference by twice the number of days elapsed between the two visits. The adherence percentage will be this result multiplied by 100. The adherence percentage will be determined from the dose that the participant currently is prescribed.

4.1.1 Visit 2 Adherence

At Visit 1, the Eligibility Visit, all participants will be given 2 to 7 days of enalapril, 2.5 mg BID. At Visit 2, the Medication Tolerance Visit, a pill count of the drug returned will be taken. If 75% or more of the drug dispensed at Visit 1 had been taken before Visit 2, with at least some drug taken during the 2 days prior to Visit 2, then the participant is eligible to continue in the pre-randomization phase of the study, with the condition that the drug was tolerated during this period. If less than 75% of the drug was taken, then the participant may be re-issued a second 2 to 7 days of enalapril, 2.5 mg BID if no side effects were indicated and the participant is willing to test the drug for tolerance again. In this case, the SOLVD Medication Tolerance Visit Form should be completed only at the second attempt of Visit 2. Only one SOLVD Medication Tolerance Visit Form will be accepted. A participant will only have 2 attempts at medication tolerance.

4.1.2 Visit 3 Adherence

At Visit 2, the Medication Tolerance Visit, all participants eligible to continue in SOLVD will be given 14 to 17 days of placebo. At Visit 3, the Baseline Visit, a pill count of the medication returned will be taken. If 80% or more of the placebo pills dispensed at Visit 2 had been taken before Visit 3, then the participant is eligible to continue at Visit 3 and potentially be randomized. As at Visit 2, if less than 80% of the placebo pills were taken, then the participant may be re-issued a second 14 to 17 days of placebo. The SOLVD Baseline Visit Form should be completed only at the second attempt of Visit 3. Only one SOLVD Baseline Visit Form will be accepted. A participant will only have 2 attempts at the placebo run-in.

4.1.3 Follow-up Visits

At each follow-up visit, the number of pills dispensed and the current dosage will be indicated on the SOLVD Follow-up Interview/Exam Form. If a dosage change (SOLVD Alteration in Study Drug Dosage Form) has not occurred before the subsequent follow-up visit, the adherence percentage will be determined by comparing the next follow-up visit date and returned number of pills with the previous follow-up visit date and dispensed number of pills. In the event of a dosage change occurring between follow-up visits, the number of pills taken during each dosage period will be added to indicate the total number of pills taken during 2 follow-up visits. At each visit, the adherence rate will be determined by computer calculation.

4.2 Adherence to Visit Schedule

Each visit is scheduled with a certain time window and all attempts should be made to complete a visit within the window, otherwise the visit is missed. Visit 2 is to occur after 2 to 7 days of drug has been taken. Visit 3 is to occur after 14 to 17 days of placebo has been taken. Visit 4 is optional (except for laboratory data) and should take place 2 weeks after randomization (Visit 2). Visit 5 is 4 weeks after Visit 4. Visit 6 is 2-1/2 months after Visit 5. All visits after Visit 6 will occur at 4 month intervals. The time window to complete a follow-up (for visits after Visit 5) visit is $\pm$ 3 weeks of the projected visit date calculated from the date of randomization.

4.3 Promotion and Maintenance of Adherence

All attempts should be made to promote and maintain adherence standards to the maintenance dose of 10 mg BID. Participants will be provided with information on congestive heart failure and treatment effects, expectations, motivation for adherence with treatment regimens and research protocols, and previous experience with medical treatment for chronic diseases.

4.4 Management of Poor Adherence

The adherence goal for each participant is to always achieve 100% adherence at each visit. Coordinators should be alerted to possibilities of poor adherence in association with dosage increases, change in regimen, toxic side effects, multiple drug regimens and hospitalizations affecting medication usage. When participants do drop out of the study or adherence is poor, special efforts such as personal contact should be made to retrieve participants to clinic visits and, if possible, reinstitute medication.

Whenever adherence falls below approximately 80%, the clinic physician should also be involved in measures to increase adherence. However, even at higher levels of adherence (say 85% or 90%), every effort should be made to improve upon them. The use of calendar packs will enable coordinators to assess the pattern of adherence. Where participants do not take a whole day's medication or several consecutive days' medication, efforts must be made to get participants to take at least one tablet a day (enalapril supposedly has some effect even 20 to 24 hours after a single dose especially at the higher doses. In participants with hypertension, some investigators have found it to be useful even when used once daily. Therefore, if side effects develop, one strategy may be to prescribe the drug once daily).

5. MAIN OUTCOMES OF INTEREST

In both the Prevention and Treatment Trials the primary outcome is mortality due to any cause. Secondary outcomes for both trials include nonfatal cardiac arrest, myocardial infarction, stroke, hospitalization for cardiac failure and need for for cardiac transplant. In the Prevention Trial onset of congestive heart failure is an additional outcome.

Because of the high probability of death or complications in the Treatment Trial, participants should be contacted by telephone at least once between visits to determine if any study outcome has occurred. Likewise, participants in the Prevention Trial who become symptomatic should also be contacted by telephone between visits. Any participant in either the Prevention Trial or the Treatment Trial who misses a study visit should be contacted by telephone as soon as possible to determine if there has been a change in morbidity or mortality status. If the participant has died or has been hospitalized since the last visit, the appropriate forms should be completed.

5.1 Outcome Forms

First Notification of Death Form

Immediately after the discovery of the death of a study participant, the First Notification of Death Form should be completed. The nurse coordinator also should call the clinic monitor at the Coordinating Center immediately to report the death of a participant. Both the phone call and the form completion should be done quickly even if information about the death is incomplete.

Final Designation of Death Form

The nurse coordinator should collect all available clinical information about the death for review by a study physician. Once the cause of death is diagnosed, the study physician completes the Final Designation of Death Form. On the basis of all available clinical information, each death should be classified as cardiovascular or non-cardiovascular. If cardiovascular, the study physician, using whatever information is available, should indicate on the form whether the death was cardiac, stroke or other or if the death was cardiovascular, whether the death was sudden or not. (See General and Specific Instructions for Completing Forms, Appendix E.) Complete documentation of the death and data entry of the information onto the Final Designation of Death Form should be done within 30 days of the discovery of the death.

If the participant died in a hospital, the study physician should review the hospital record and complete the Hospitalization Form. AS PART OF THE DOCUMENTATION FOR A DEATH, THE OFFICIAL DEATH CERTIFICATE SHOULD BE OBTAINED, PHOTOCOPIED AND SENT TO THE COORDINATING CENTER. A copy of the death certificate should be kept for the Clinical Center files.

Hospitalization Form

A Hospitalization Form should be completed for each hospitalization since the last visit. The study nurse should request hospital records for each hospitalization, which should be given to the study physician for review. The study physician will complete the Hospitalization Form for each hospitalization. (See General and Specifics Instructions for Completing Forms, Appendix E.) Hospitalizations should be documented and the information on the Hospitalization Form entered into the data entry system within 30 days after detection of the event.

5.2 Onset of Congestive Heart Failure in the Prevention Trial

The onset of congestive heart failure in a participant in the Prevention Trial is a secondary outcome and will be defined by the onset of symptoms and/or signs of congestive heart failure which, in the opinion of the study physician, are sufficiently severe to warrant pharmacologic treatment. This definition is the same as that used to stratify participants at baseline to the Prevention or Treatment Trials. (See in the SOLVD protocol, section V5, Stratification Criteria.) For those participants in the Prevention Trial in whom pharmacologic treatment, consistent with treatment for CHF has been instituted in the interval since the last visit by a non-study physician, the study physician will be responsible for ascertaining the reason for initiation of therapy. If there is documented clinical or radiographic evidence of peripheral or pulmonary congestion, this should be recorded on the Followup Interview/Exam Form if the participant were not hospitalized. A Hospitalization Form should be filled out by the study physician if the participant were hospitalized.

5.3 Changes in the Severity of Symptoms of Congestive Heart Failure

In participants of the Treatment Trial and participants of the Prevention Trial who have developed congestive heart failure, the study physician should document changes in the presence or severity of symptoms on the Followup Interview/Exam Form if the participant has not been hospitalized since the last visit. If the participant has been hospitalized since the last visit, the study physician should complete the Hospitalization Form after reviewing the hospital records.

6. QUALITY CONTROL

6.1 Ongoing Quality Control Efforts

6.1.1 Clinical Center Activities

The integrity and ultimate credibility of the Study depends on such factors as maintenance of the double blind, adherence to the protocol, attempting to obtain complete follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards of data quality.

Specific guidelines for quality control at the Clinical Centers are not delineated since quality control of the physical examinations, the laboratory measurements, the taking of clinical histories and the conduct of participant interviews are assumed to be standard practices in the SOLVD clinics.

Each Clinical Center will have a nurse coordinator trained by the Coordinating Center on the protocol and operations of the SOLVD studies. New or replacement personnel at the Clinical Center or its hospitals are to be trained by the existing nurse coordinator or by Coordinating Center staff if needed. The nurse coordinator will have primary responsibility for the conduct of the study, including the quality of the data collected on paper forms and the data entered on the personal computer.

Since the entry criteria and possible endpoints are crucial to the study, the Principal Investigator will meet with the staffs of the participating hospitals on a regular basis to review the entry criteria (particularly the validity of the ejection fraction measurements) for all potential participants entered and to review the mortality information on any participant who dies.

In order to maintain the double blind, clinical chemistry results which might indicate the treatment assignment should not be routinely reported to Clinical Center staff with direct contact with the participants unless the particular result might require clinical action to protect the participant's safety.

In order to ensure complete follow-up information on all patients enrolled, procedures for missed visits and rescheduled visits must be developed by each clinic. Procedures may be needed for collecting basic data on patients who are willing to continue participating in the study but are not willing or able to return to the clinic. A few participants are likely to refuse to continue in the study after randomization. Telephone contact should be maintained with such participants; at a minimum, information on hospitalizations, morbidity and mortality must be sought. It is crucial and extremely important that each participant be contacted at the end of the study to obtain mortality status. Extraordinary

efforts in contacting a participant lost-to-followup are warranted.

6.1.2 Central Laboratory Activities

At the Eligibility Visit (Visit 1), a blood sample is to be drawn after the participant has rested supine at least 30 minutes (see Appendix B of the Manual of Operations). The blood will be analyzed and stored at central laboratories and appropriate quality control procedures must be specified for the analyses and the storage procedures.

6.1.3 Coordinating Center Activities

The Coordinating Center is responsible for the quality of the data utilized for Steering Committee reports, Data and Safety Monitoring Board reports, Project Office reports and all scientific and other publications of the collaborative data of the SOLVD studies. The specific activities of the Coordinating Center for ensuring the quality of the data include:

a. Standardized training and certification of the Clinical Center staff members who conduct study procedures.

b. Maintenance of open lines of communication among the Coordinating Center, the Clinical Centers, and other program agencies.

c. Monitoring clinic performance in recruitment, timeliness of form completion, adherence of their participants, and adherence of the clinic staff to the protocol.

d. Monitoring the quality of the data collected and its processing by periodic analyses. These analyses will be presented in reports to the Steering Committee and/or the Data and Safety Monitoring Board.

e. The Coordinating Center will identify a 5% random sample of participants entered. The Clinical staff will ensure that the ejection fraction measurement data are copied and made available for re-reading by the Coordinating Center cardiologist (see section 6.1.4). If there are questions concerning the eligibility of the ejection fraction, a cardiologist from one of the other centers will be asked to provide a third reading. The analyses of this random 5% check will be made available to the Data and Safety Monitoring Board and Executive Committee annually.

f. Maintaining the study data management system.

g. Maintaining the quality of the collaborative data base. The data files received from the Clinical Centers will be used to update the collaborative study data base, adding, deleting, or modifying records as specified. The primary editing will be performed at the Clinical Centers on the microcomputers. The Coordinating Center will

verify those edits and perform additional editing such as comparing data across field centers. In any case, modifications to existing data by Coordinating Center staff will only be made with written authorization from the personnel responsible for collecting the data. The quality of the data entry, editing and correcting will be monitored on an ongoing basis. A complete audit trail of all entries, corrections and changes will be maintained and used to monitor the entry/editing process. In addition, an external quality control system will be implemented. Quality control data will be periodically submitted for routine processing by the system. These records will be indistinguishable from the study data at the time of processing. After processing, the results will be compared to the reference standards and the quality of processing will be reported on a regular basis.

h. Maintaining the quality of the collaborative data analyses. Prior to creating data files for analyses, the data base will be "closed." Closure will ensure that all expected data have been received, that all data received have been completely processed, that all suspicious values identified have been resolved, that the final data inventory at the Coordinating Center matches Clinical Center records, and that a stratified sample of clinic data entry records match the corresponding collaborative data base records. Standard statistical software will be used for the data analysis and proper documentation of programs will provide sufficient information to allow verification or replication of any processing or analysis performed during the study.

6.1.4 Quality Control of Left Ventricular Ejection Fraction Data

The following procedures will be used for quality control of the left ventricular ejection fraction data obtained in the SOLVD study population. Data from the representative sample of randomized patients obtained by the Coordinating Center for general verification, will be used to check the measurement of left ventricular ejection fraction. All data relevant to this measurement should be forwarded on request to the Coordinating Center where analysis will be performed by independent cardiologists. The method of validation used will vary according to the technique employed to make the functional measurement until an independent figure is calculated.

In the case of cardiac catheterization data, the Clinical Center from which the data were obtained will provide cineangiograms and data sheets with the specific formulas used to make the ejection fraction calculation. The cineangiograms must be supplied in a format that can be displayed on a standard Vanguard projection device.

These angiograms will be assessed visually in a blinded fashion and an independent left ventricular edge at end diastole and end systole will be drawn. It is assumed that either grids will be provided on the cine film to allow calculation of a magnification factor for the study or that a magnification factor will be provided in the data submitted. This factor and the planimetered area of the left ventricle either in single or biplane format will be used with the appropriate formulas after the area length methods of Dodge and associates to calculate an ejection fraction.

In the case of the nuclear cardiology data it will not be possible to recalculate the study ejection fraction beginning with raw data. The processed data, represented by ventriculograms in all projections available, functional images, and a time activity curve of the MLAO study will be evaluated in detail as follows. First, a cine of the radionuclide data obtained on the individual study participant will be provided. This cine should be furnished on 3/4 inch video tape which can be replayed on a standard 3/4 inch videocassette recorded. A blinded visual estimation of the ejection fraction of the participant will be made from these data and any functional images available. After this evaluation, the time activity curve of the study taken from the MLAO projection and any other derived data such as left ventricular volume or ejection and filling rates will be examined for technical accuracy and confirmation of visual estimation of the ejection fraction.

The echocardiographic image data should be submitted on 1/2 inch videotape for playback in an appropriate standard cassette player. From playback of this raw data, a visual assessment of the level of left ventricular ejection fraction will be made. In addition, a two chamber long axis image should be provided as part of the image data to allow computation of ejection fraction based on an area length determination of end diastolic and systolic volume. The echo data will be digitized and computations will be performed with an Irex Cardio 80 computer system. Investigators using echocardiographic data for determination of ejection fraction should provide correlative catheterization or radionuclide data which validates this measurement in their institution.

These quality control procedures may detect absolute errors in ejection fraction measurement that may or may not result in randomization of a patient with an inappropriately high level of left ventricular function. Since intraobserver differences of 5% would be expected, the Clinical Center and Coordinating Center ejection fractions would have to differ by more than this amount for the possibility of a significant error to exist. The data associated with those cases where a question arose about the measurement would be forwarded to the Data and

Safety and Monitoring Board for evaluation and arbitration.

6.1.5 Project Office/Steering Committee Activities

The Project Office and the Steering Committee will oversee all aspects of the conduct of the studies. The Steering Committee is discussed in section III-A of the Protocol.

6.1.6 Data and Safety Monitoring Board Activities

The Data and Safety Monitoring Board(DSMB) is discussed in section III of the Protocol.

6.2 Clinic Monitoring and Visits

The following approaches will be used for clinic monitoring:

a. Maintenance of open lines of communication among the Coordinating Center and the Clinical Centers.
b. Direct observation of clinic activities to assess adherence to the protocol.

In order to implement the above, the Coordinating Center will assign a clinic monitor to each Clinical Center. Note that the responsibility for hospital monitoring at each Clinical Center will be with the Clinical Center's nurse coordinator. The nurse coordinator is also responsible for the data flow to the Coordinating Center and is the liaison with the clinic monitor.

The main interaction between the Clinical Centers and the Coordinating Center will be through weekly telephone calls during the recruitment phase and biweekly thereafter. In these calls, the Coordinating Center clinic monitor will obtain current information on equipment problems, supplies of forms and medication, and other information about the status of the study. Weekly recruitment status reports may be transmitted electronically over telephone lines. The clinic monitor will answer questions concerning the protocol, forms completion, and the operation of the data management system.

It will be important for the Coordinating Center clinic monitors to visit each Clinical Center annually or on an ad hoc basis to help resolve certain types of problems. It is important to observe the Clinical Center staff and participants during clinic visits to assess recruiting difficulties and participant interviewing techniques, and to verify adherence to protocol when such adherence is in question. In addition, there will be times when a Clinical Center needs assistance in following the protocol or operating the data management system.

At the time of the visit, the Coordinating Center staff will bring a copy of the computer files of a sample of participants which will be compared with the clinic paper files. This will detect any unexplained discrepancies on the files.

7. CLINICAL CENTER DATA MANAGEMENT

This section describes the procedures that should be used in managing paper forms within the participating hospitals in each SOLVD Clinical Center, and procedures for transferring forms from the hospitals to the Clinical Center. Entry of forms using the SOLVD Data Entry System (DES), and transfer of data to the Coordinating Center are covered in the SOLVD DES Training Manual.

7.1 Handling Forms within a Participating Hospital

7.1.1 Reviewing Forms During the Visit

At the end of each visit, before the participant leaves the hospital, the forms collected should be reviewed for completeness and legibility. All SOLVD forms are printed as two part No Carbon Required (NCR) sets, consisting of a (white) copy and a hospital (blue) copy. Make sure that the entries on the bottom (blue) copy of each page are readable.

7.1.2 Disposition of Copies

Forms which have more than one page are bound as booklets with a stiff manila cover. After a form has been completed, the Clinical Center (white) copies of each page should be removed from the booklet and stapled together. The hospital (blue) copy of each page remains in the booklet. For single page forms, the Clinical Center and hospital copies are simply glued together along the top edge and should be separated after completion of the form.

The Clinical Center (white) copies of each form collected during the week should be filed together, to be sent to the Clinical Center at the end of the week. The hospital (blue) copies should be kept on file at the participating hospital for the duration of the SOLVD Study. During the closure phase of the study, a decision will be made about the ultimate disposition of these copies.

7.1.3 Sending Completed Forms to the Clinical Center

Forms should be sent from each participating hospital to the Clinical Center on the same day of each week. Therefore a shipment ("batch") will consist of all forms collected in one hospital during the previous week. The scheduled day and method of shipment will be defined by each Clinical Center for their participating hospitals.

The hospital should complete an Inventory List 1) for each batch shipped. This is also a two-part NCR form. The (white) copy should be included in the batch, and the blue copy filed at the hospital.

7.2 Correcting Errors on Forms Already Shipped

If an error is detected by hospital staff before the form is sent to the Clinical Center, it can be corrected as described in General Instructions for Completing Forms (Appendix E). Make sure to correct both the Clinical Center (white) and hospital (blue) copies of the form.

If a correction is necessary for a form already sent to the Clinical Center, a Correction Form must be used. The hospital copy of the original form should also be corrected for future reference.

7.2.1 Correcting Errors Detected by the Hospital

When the hospital staff discovers an error in a form already transmitted to the Coordinating Center, a Data Correction Form should be completed. This form is then treated like any other; the Clinical Center (white) copy is filed to be sent to the Clinical Center at the end of the week along with data forms, and the hospital (blue) copy is filed at the participating hospital for the duration of the Study.

7.2.2 Responding to Queries from the Clinical Center

When the Clinical Center staff discovers a questionable value, either manually or through a computer edit, they will request clarification from the staff of the participating hospital. This request may be either verbal or written, but the response must always be in the form of a completed Data Correction form shipped from the hospital to the Center. Note that the Data Correction Form allows the questionable item to be corrected, confirmed as already correct, or declared to be unresolvable.

A value should only be confirmed if the hospital staff are certain that it is correct. A value should not be confirmed simply because it is what is written on the form.

If it is not possible to confirm that a suspicious value is, in fact, correct, or to determine a corrected value, the value should be declared to be unresolvable.

Whenever a value is confirmed or defined to be unresolvable, any explanatory information should be written in the comment field. Comments are allowed, but ordinarily are not necessary when a corrected value is provided.

7.3 Handling Forms within a Clinical Center

7.3.1 Receiving Forms from Participating Hospitals

For each participating hospital, a day should be selected on which all forms collected during the previous week (a "batch") will be sent to the Clinical Center. If a batch is not received on a given week, the Clinical Center staff should contact the hospital staff to resolve the problem.

Each shipment should include a completed Inventory List (see Figure 1), and the Clinical Center (white) copy of each form specified on the list. Upon receipt of a batch, the Center staff should immediately check the contents against the enclosed Inventory List. If any discrepancies are discovered, the hospital staff should be contacted to resolve the problem.

If one or more pages or forms are lost, the hospital should not send its copy of the missing pages to the Clinical Center. If the quality of the hospital copy is adequate, a photocopy should be made and sent to the Clinical Center. If photocopying is not possible, hospital staff should transcribe the information from their copy onto a blank form. Each page of this second form should have the word "TRANSCRIBED" written prominently across the top. Send the white copy to the Clinical Center; the two blue copies should be filed together at the hospital for future reference.

7.3.2 Investigating Suspicious Data Values

Whenever Clinical Center staff discover a suspicious data value, the staff of the hospital at which the data item was collected must be contacted to determine what should be done. These inquiries may be verbal or written, at the option of the Clinical Center.

When the suspicious value is detected by an edit in the Data Entry System, a Questionable Log (Figure 3) will automatically be printed. If a suspicious value is detected by Clinical Center staff in some other way, a Questionable Value Form (Figure 4) should be completed. In either case, the written form should be added to a file of "pending data queries" for that hospital.

Clinical Center staff must never change the data written on a form without written authorization from the staff of the hospital at which the data were collected. Written authorization should be in the form of a Data Correction Form completed by a hospital staff member. A verbal response by hospital staff is not sufficient authorization for a change to a value written on a form.

When a Data Correction Form has been received and the corresponding action entered into the database, the original Questionable Log or Form should be stapled to the Data Correction form and filed with the data collection form to which the query applied.

7.3.3 Storage of Forms

All forms received from participating hospitals should be filed and kept for the duration of SOLVD. During the closure of the Study, a decision will be made concerning the further disposition of the paper forms.

8. SOLVD MEDICATION DISTRIBUTION

8.1 Pre-randomization Drug Supply

Two samples of drugs will be needed during the pre-randomization phase of SOLVD: a 2-7 day supply of active drug for the tolerance phase and a 14-17 day supply of placebo for the adherence phase. These supplies do not need individual participant identifier, since they will be identical for all people screened. The drugs for the tolerance and adherence periods will be packaged separately, using the same packaging technique that will be used for the drug after randomization.

Merck, Sharp, and Dohme (MSD) will supply each Clinical Center with a supply of these packages at the beginning of each year of recruitment, and additional supplies if requested. The initial shipment to each Clinical Center will consist of 100 one-week folders of the active drug for use in the tolerance phase, 300 one-week folders of placebo for use in the adherence phase, and 20 packages of active drug for the Treatment Trial pilot study. In order to facilitate distribution of this supply to the hospitals within a Clinical Center, these drugs will be supplied in cartons of a convenient size, perhaps 10 folders per carton.

It is the responsibility of the staff at each Clinical Center to distribute these supplies to their participating hospitals and to insure that the supplies are replenished as needed. When the Clinical Center has a two-month supply of one of these packages remaining, additional supplies should be ordered by completing a SOLVD Medication Ordering Form and mailing it to the Coordinating Center. Clinical Centers cannot order supplies of medication directly from MSD. The number of folders or packets that represents a two-month supply is obviously dependent on the Clinical Center's screening rate, but a reasonable initial guess might be 40 folders for the tolerance phase and 120 folders for the adherence phase (assuming a randomization rate of 10 participants per month for the two trials combined and an average of two participants enrolled for each participant randomized).

8.2 Identification of Drug Supplies for Randomized Participants

The post-randomization drug supplies will be individually labeled for each randomized participant. The drug supply number will be the five digits of the participant's permanent ID number, assigned by the SOLVD Data Entry System during the randomization procedure.

8.3 Initial Post-randomization Drug Supply

MSD will ship the drug supplies for use on newly randomized participants in lots of 16. This initial supply will include a four-month supply of drug, at all three possible dosage levels for each supply number. Thus, the Clinical Center will have all three dosages on hand during the titration period. The two strengths not used by each participant should be stored in the hospital for use in case a dosage change is necessary during the course of the trial.

Initially MSD will ship each Clinical Center one block of 16 post-randomization supplies per trial per participating hospital. The Clinical Centers will be responsible for distributing the blocks to their participating hospitals. The Clinical Center is responsible for ordering additional lots of post-randomization supplies from the Coordinating Center (using the Medication Ordering Form) whenever a hospital is down to a two-month supply. Assuming a randomization rate of one participant per hospital per trial per month, reordering when twelve of the sixteen supplies have been used is a reasonable starting point. The Coordinating Center will order the additional lots from MSD. MSD will ship them directly to the Clinical Centers and the Clinical Centers will send the blocks to their hospitals.

As soon as the treating physician believes the participant's dosage to be stabilized, an additional supply of the appropriate dose should be ordered using the Medication Ordering Form. If the participant is still not stabilized by the end of the second month after randomization, a second supply of all three dosage levels can be ordered. For participants whose dosage is stable, MSD will ship a 12 month supply at the appropriate dose. For unstable participants, an additional four-month supply of all three doses will be shipped.

8.4 Reorders of Post-randomization Drug Supplies.

For the remainder of the study the Coordinating Center will be responsible, on a regular schedule, for reordering drugs for randomized participants. Drugs will be shipped by MSD to the Clinical Center, and from there distributed to the appropriate hospital.

The Clinical Center is responsible for the immediate notification of the Coordinating Center if a participant's dosage must be changed, so that the new dosage can be ordered from MSD. This will ordinarily be accomplished by entering and transmitting the Alteration in Study Drug Dosage form. However, remember that approximately two months is needed from the time the Coordinating Center is notified until the new supply can be expected to arrive. If

the participant does not have a two-month supply of the new dosage remaining at the hospital, contact the Coordinating Center at once to arrange for an emergency shipment.

8.5 Disposal of Excess Drug

The Steering Committee will develop a proposal for discarding unused drug supplies (from participants who die or drop out, etc.) that is acceptable to NIH, MSD, and the Clinical Centers. Until that proposal is developed, all unused drug supplies should be retained at the hospitals to which they were originally sent. Medication should not be returned to MSD.