STUDIES OF LEFT VENTRICULAR DYSFUNCTION

REGISTRY PROTOCOL

Revised November 1987

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I. INTRODUCTION

The patients entering the SOLVD trials are likely to represent an uncertain subset of the total population of patients with heart failure or left ventricular dysfunction at the participating clinical centers. The trial population is expected to be truncated with patients having the worst and best ventricular function excluded from the trials. Patients whose ventricular dysfunction or heart failure is related primarily to diastolic abnormalities without systolic dysfunction are excluded from the SOLVD trials, since marked systolic dysfunction is the key entry criterion. Other interesting and important subsets of patients, such as those with pulmonary edema at entry, are likely to be underrepresented in the SOLVD trials. In order to study the clinical course of a broader and more representative group of consecutively collected patients with heart failure at participating institutions and the relationship(s) of the SOLVD trial participants to this larger and less selected sample, a Registry of patients with left ventricular dysfunction will be developed. Vital status and clinical events will be determined at one year by a written questionnaire or telephone follow-up; longer term vital status will then be determined by periodic search of national death registries.

II. AIMS OF THE REGISTRY

A. Primary Objective:

The primary objective of the Registry is to study all-cause mortality at one, three and five years in a large (approximately 6,000) consecutive and relatively unselected cohort of patients with heart failure and/or with left ventricular dysfunction. The patients will be stratified according to symptoms, etiology of disease, ejection fraction and chest X-ray findings at entry into the Registry.

B. Subsidiary Objectives:

The subsidiary objectives of the Registry are:

1. To study cardiovascular mortality at one, three and five years globally and after stratification according to symptoms, etiology of disease, ejection fraction and chest X-ray findings in the above populations.

2. To study morbid events at one year in the above population.

3. To relate other baseline covariates of prognostic importance to subsequent mortality and morbidity in the above population.

4. To characterize in greater detail clinical characteristics, echocardiographic abnormalities, arrhythmia status, functional capacity and neurohumoral levels and to correlate these detailed findings with subsequent mortality and morbidity in a stratified randomly selected sample of 1000 patients from among the patients entering the Registry.

5. To compare baseline characteristics and follow-up events of this relatively unselected population with those of the SOLVD Trials.

III. PARTICIPATING CENTERS AND CAPABILITIES

All clinical centers collaborating in the SOLVD randomized trials will be invited to participate in the Registry. However, participation is not compulsory and individual centers may be free to decline. For example, if twenty centers are participating, each center will be required to enter and follow a minimum of 300 patients in the Registry. It is anticipated that at least 20% of the Registry patients at each center will also be in the SOLVD trials. Therefore, every participating center should be on target for recruitment for the SOLVD trials as a condition for participating in the Registry. In addition, each center must be willing to do high quality M-mode and 2-D echocardiograms, perform ambulatory monitoring and obtain a blood sample for renin and catecholamines in 50 patients randomly selected from their patients. Ability to do good quality echos is a condition for participation. The centers must be committed to following their patients in the Registry during the entire period of the study.

It is desirable to obtain Registry patients from one hospital site at each clinial center. Once a hospital is chosen to participate, all consecutive patients eligible for the Registry during the recruitment period of nine months must be enrolled. It is expected that around 6000 patients will be enrolled.

IV. SOURCES OF PATIENTS

Patients will enter the Registry as a result of: (1) screening consecutive exams in the laboratories of participating institutions (i.e., echocardiographic, radionuclide, and cardiac catheterization laboratories) to identify patients with an ejection fraction of 45% or less; or (2) by a survey of the consecutive hospital discharge records to identify patients with a diagnosis of congestive heart failure (CHF). In order to qualify for the Registry, patients identified from source (2) should have radiological evidence of CHF (or signs of pulmonary venus congestion) or an ejection fraction of 45% or less.

V. ENTRY AND EXCLUSION CRITERIA

Entry Criteria

Patients are eligible for the Registry if they either have an ejection fraction less than or equal to 45% or a diagnosis of congestive heart failure. The date of their logbook record or hospital admission must fall within the specified nine-month timeframe (for example, from January 1, 1988 to September 30, 1988). A diagnosis of congestive heart failure will be confirmed if the patient has radiologic evidence of CHF.

Descriptive statements consistent with heart failure which may appear in the report include:

a) Statements related to pulmonary blood flow redistribution to upper lobes.
b) Signs of pulmonary venous congestion
   - Basal or perihilar vascular blurring
   - Alveolar or pulmonary edema
   - Kerley B lines
   - Pleural effusion - judged secondary to congestive heart failure (to make this judgment may require correlation with clinical data).
c) Cardio-thoracic ratio will be included whenever possible.

In validating these heart failure criteria as positive, the interpretation on the chest X-ray report should be accepted if it is definite. Follow-up reports indicating clearing of congestive heart failure are helpful. Films should be reviewed by a physician-investigator whenever uncertainty exists.

Particular attention will be given to the subset of patients entering with the syndrome of pulmonary edema unrelated to acute myocardial infarction. Diagnosis should be (relatively) easily confirmed in this subset and the clinical history data on a large volume of patients with pulmonary edema could be a valuable contribution by this registry.

Exclusion Criteria for SOLVD Registry

1) Non-valvular congenital heart disease.
2) Any noncardiac life-threatening disease likely to significantly shorten the patient's survival, including criteria 11 (cor pulmonale), 12 (advanced pulmonary disease), 13 (major neurologic diseases), 17 (renal failure), 18 (malignancies), 21 (significant primary liver disease), and 23 (other life-threatening disease) in the SOLVD trials protocol.
3) Failure to consent to the Registry.
4) Lack of a telephone or reliable means of contact/follow-up.
5) Myocardial infarction within 7 days. This patient can be included after 6 days have passed, if there is a qualifying chest X-ray or ejection fraction measurement made 7 or more days after the MI.
6) Cardiac surgery, PTCA, or ballon valvuloplasty within 7 days. This patient can be included after 6 days have passed, if there is a qualifying chest X-ray or ejection fraction measurement made 7 or more days after the cardiac surgery or PTCA.

Thus, the following exclusion criteria from the SOLVD trials protocol are not exclusion criteria for the Registry:

1	History of intolerance to enalapril
2	Currently taking ACE inhibitor and unwilling to discontinue
4	Hemodynamically significant valvular or outflow tract obstruction
5	Constrictive pericarditis
7	Syncopal episodes presumed to be due to life-threatening arrhythmias
8	Any major cardiac surgery likely
9	Unstable angina pectoris
10	Uncontrolled hypertension
14	Cerebrovascular disease
15	Collagen vascular disease other than rheumatoid arthritis
16	Suspected significant renal artery stenosis
19	Immunosuppressive therapy
20	Active myocarditis
22	Likely to be nonadherent (alcoholism, drug addiction, lack of of a fixed address, etc.)
24	Woman likely to bear children
25	Other investigational drug protocols (except compassionate use)
26	Failure to give consent for the SOLVD trials
27	Lack of adherence or tolerance to medication
28	Lack of adherence to placebo run-in

Note also that patients scheduled for cardiac transplantation are eligible for the Registry. Given all these differences, the patient population of the Registry will thus be broader and less restrictive than those eligible for the Trials.

Additional Exclusion Criteria for SOLVD Registry Substudy

1) Inability to attend clinic for a visit (e.g., geographical difficulties)
2) Failure to consent to the Registry substudy

All patients seen at the echocardiographic, radionuclide, and cardiac catheterization laboratories or admitted with a diagnosis of congestive heart failure are to be listed in consecutive chronological order in the SOLVD Registry Log. This log will contain the following information for each patient:

Date
Patient name (or internal hospital identification number)
Source of recruitment
Suitable for Registry: Yes or No
If not suitable, why not

All patients entered in the log and considered suitable for the Registry must be contacted to obtain consent and have a Registry Baseline Form completed based on their medical records information. Those patients that refuse consent will only have the form completed through Question 5.5.

VI. STUDY SIZE

It is expected that over 6,000 patients will be recruited into the Registry during the specified nine-month time period. In order to avoid a predominance of ischemic heart disease, special attempts to include patients with other etiologies may be required. These categories include the following:

1) Valvular heart disease with EF ≤ 45%
2) Primary diagnoses of idiopathic cardiomyopathy and active myocarditis.
3) Unusual and specific causes, such as amyloidosis, hemochromatosis, hypertrophic hyperdynamic cardiomyopathy (so-called IHSS), diabetic cardiomyopathy, alcoholic cardiomyopathy, etc.

The period for collecting such unusual cases may be extended beyond the first nine months Registry collection and as long as 1991. A decision regarding that will be made after the first nine months of recruitment.

The calculations in Table 1 examine the statistical power attained for comparing the mortality rates between two subgroups from the 6000 SOLVD Registry patients, under various assumptions. Comparisons of mortality rates can be done asymptotically with the test of difference of two binomial proportions (Rosner, p. 325). A two-sided test with a 0.05 level of significance is thus considered.

The following examples aid in the interpretation of the calculations in Table 1.

Case 1 would be for testing the difference in mortality between, for example, those with EF ≤ .40 (75% of Registry) vs. those with EF > .40 (25% of Registry). Power for this case is virtually unity.

Cases 2-3 and 4-6 look at testing the different mortality rates in a very rare subgroup vs. the entire rest of the Registry, under different relative risk situations. The rarer the etiology, the higher the relative risk needs to be, but a RR of 2 or greater has sufficient power to be detected, even after only one year. The power is greatly improved after three years.

Cases 7-9 look at testing the different mortality rates between two very rare subgroups, one that is seen in 2% of the patients vs. one that is seen in 1% of the patients. Informal estimates of prevalence of different etiologies suggest that amyloidosis would be seen in 20 per 1000 patients (2%), hemochromatosis would be seen in 10 patients per 1000 (1%), diabetic cardiomyopathy in 6-8%, alcoholic cardiomyopathy in 7-10%, post-partum in 2%. These cases need three years' worth of data to be tested with reasonable power, even with a relative risk of 2.

Cases 10-11: With 6000 persons in the Registry, it is not unreasonable to expect roughly 1000 patients with idiopathic cardiomyopathies. If this group is divided by tertiles of EF into low, intermediate and high EF, one would like to compare the mortalities between the high EF group and the low EF group. Assuming a relative risk of 3 provides power close to 1, while with a relative risk of 2, the power is virtually one at the three-year comparison.

Table 1
One-year and three-year power for comparison
of mortality rate between various Registry subgroups

			One-year			Power	
Case #	n	m	p1	p2	RR	@1-year	@3-year
1	4500	1500	.12	.05	1/2.4	1.00	1.00
2	5900	100	.12	.24	2.0	.90	1.00
3	5900	100	.12	.18	1.5	.45	.77
4	5950	50	.12	.24	2.0	.69	.94
5	5950	50	.12	.30	2.5	.86	1.00
6	5950	50	.12	.36	3.0	.99	1.00
7	120	60	.20	.30	1.5	.33	.58
8	120	60	.20	.40	2.0	.81	.97
9	120	60	.12	.24	2.0	.54	.87
10	333	333	.05	.15	3.0	.99	1.00
11	333	333	.06	.12	2.0	.77	.99

Key:
n = sample size in first subgroup
m = sample size in second subgroup
p1 = 1-year mortality rate in first subgroup
p2 = 1-year mortality rate in second subgroup
RR = relative risk of second to first subgroup

Thus, it is clear from the above examples that a sample size of 6000 patients in the Registry is quite adequate for comparison of mortality rates between various subgroups, especially after three years but in several cases even after one year.

VII. DETAILED INVESTIGATIONS IN A SUBSAMPLE OF 1000 PATIENTS (REGISTRY SUBSTUDY)

Since there is no uniform requirement of investigations other than ejection fraction or chest X-ray in the Registry, it is possible that some of the data collected from the hospital records may be biased (e.g., more tests done on the "sickest" patients). In order to obtain key data on a relatively "unselected population" that differs from the Trials substudy population and to assess the biases inherent in the main body of the Registry, 1000 stratified (see appendix D) randomly chosen patients will be studied. The following procedures are to be completed:

i) M-mode and 2-D echocardiograms (to be read centrally). Doppler echocardiograms would be performed only at those centers participating in the SOLVD Echocardiography Substudy.
ii) Physical examination and history.
iii) Drawing of blood for plasma renin and catecholamines (determinations to be performed centrally).
iv) Seventy-minute ambulatory Holter monitoring (one hour at rest, during the 6-minute walking test, and for 3 minutes post walking) (to be read centrally).
v) Six-minute walking test.
vi) Chest X-ray and electrocardiogram, if not done within 90 days.

Once a patient has entered the Registry, the SOLVD microcomputer data entry system will identify whether a particular patient is to be selected for the Registry Substudy. Once such a patient is identified, he/she is invited to participate in the Registry Substudy. If he/she consents and a good quality (as defined in Appendix C) echocardiogram is obtained, all the other tests are performed. If he/she refuses or a good quality echo cannot be obtained, this patient does not enter the substudy but should still be included in the main Registry. The flowchart in appendix A2 describes the procedure for the Registry Substudy clinic visit. Preferably, the visit is to be scheduled for the day the echocardiogram can be performed. If this is not possible, the echo and the rest of the procedures must be done within two weeks of each other and any major intercurrent events occurring must be documented with a Hospitalization form. The clinic visit should take place no later than 90 days after enrollment.

A brief description of each procedure follows; for details on their protocols, see Appendix C.

a) M-mode and 2-D echocardiography: The M-mode and 2-D echocardiograms will be used to provide indices of systolic and diastolic function, chamber size (LV, RV, LA and RA) and left ventricular wall thickness. Only good quality echoes (see appendix C) will be accepted. The first 5 echoes will be submitted to the SOLVD echo core laboratory for analysis and all 5 echoes should be analyzable for all key variables. Deficiencies will be immediately notified to the participating clinics. All echocardiograms will be recorded on SOLVD Registry videotape which will be transmitted to the core laboratory for central analysis. See appendix C for further details.

b) Physical examination and history. In all patients, the clinical data on the baseline form will be collected again. This will provide a comparison of the data extracted from the patient's charts versus a direct, more standardized data collection.

c) Baseline plasma renin and cathecholamine: After the insertion of an indwelling venous cannula and with the patient resting for 30 minutes in the supine position, a 20 ml sample of blood will be drawn for plasma renin and catecholamines. The blood samples will be frozen at -70 degrees centigrade and shipped in batches to the core laboratory at the University of Texas, Galveston. See appendix C for details.

d) Seventy-minute ambulatory monitoring. All patients will receive a one-hour ten-minute ambulatory monitoring while the patient is in the outpatient clinic. The period will include the 6-minute walking test. The tape will be analyzed at a central facility. Data from BHAT (Davis et al. 1986) indicate that a one-hour ambulatory monitoring may be as predictive of mortality and sudden death as 24-hour monitoring. This seems especially likely in a group of patients with a high prevalence of arrhythmias as expected in this Registry. Coupled with the convenience and low cost, a one-hour ambulatory monitoring may be a reasonable estimate of ventricular arrhythmia. See appendix C for details.

e) Six minute walking test. The distance walked in six minutes has been shown to be a reasonable assessment of the functional capacity of patients with congestive heart failure (Guyatt et al. 1985). Previous studies have shown a good correlation between the 6-minute walking test and symptoms and objective measures of functional capacity such as VO_2max. See appendix C for procedures for conducting this test.

f) Chest X-ray and electrocardiogram. If not available from the preceding 90 days.

VIII. PERIOD OF PATIENT ACCESSION

The timetable for the SOLVD Registry is as follows:

	YEAR 1 December 1, 1987 - November 30, 1988
Dec. 1, 1987 - Dec. 31, 1987	Phase-in month. Major activities include training session for clinic personnel and quality control for substudy procedures.
Jan. 1, 1988 - Sept. 30, 1988	Nine-month recruitment period
Oct. 1, 1988 - Nov. 30, 1988	Two-month phase-down. Major activities include completing data collection of recruitment, evaluating continuation of recruitment of rare etiologies and planning for YEAR 2 follow-up activities.
	YEAR 2 December 1, 1988 - November 30, 1989
Mailing of questionnaire on vital statistics	
	YEAR 3 December 1, 1989 - November 30, 1990
Vital status ascertained by the Coordinating Center with national death registries.	
	YEAR 5 December 1, 1991 - November 30, 1992
Vital status ascertained by the Coordinating Center with national death registries.	

As shown in the timetable, patients with the more common etiologies will be enrolled during a 9-month period. Since only a few patients with the rarer etiologies (e.g., active myocarditis or specific cardiomyopathy) will be identified at each center per year, patients with these underlying diseases will be recruited until June 1991. A flow diagram for the SOLVD Registry is included in appendix A1.

IX. DATA COLLECTION

Registry data will be collected in consecutive patients screened at the participating clinical centers who meet the Registry entry criteria. These will include patients who enter the randomized trials during the accession period to the Registry. The inclusion and exclusion criteria for patients entering the Registry have been previously defined. The participating centers have been described in Section III. The period of enrollment into the SOLVD Registry has been described in Section VIII.

Each clinical center will be expected to enroll at least 300 patients into the Registry, including a subset already being enrolled in the SOLVD trials. In addition, approximately 50 stratified randomly selected patients at each center will undergo additional baseline testing, including an M-mode and two-dimensional echocardiogram, a 70-minute Holter monitoring, and a 6-minute walking exercise test. These patients, aggregated over all centers to form the substudy sample, will be stratified according to the etiology of the underlying condition, to include ischemic and/or hypertensive heart disease, patients with idiopathic cardiomyopathy, and "valvular" myopathy. Attention will be specifically directed to a subset with the entry syndrome of pulmonary edema without acute MI.

Baseline Data Collection

All patients registered in the clinical center's logbook and other sources (e.g., discharge diagnoses and outpatient files) during the period of enrollment will first be recorded in the Registry logbook and screened for inclusion or exclusion in the Registry by close scrutiny of the patient chart. Once it has been determined that the patient is eligible for participation in the Registry, he/she will be contacted by telephone to obtain verbal consent, with a written consent form sent by mail to be signed and reutrn.

The date of enrollment for qualified Registry participants is the date of the qualifying measurement (e.g., EF, chest X-ray). If more than one qualification criterion is met, the date of the earliest one is considered the date of enrollment.

The entry data will then be extracted from the patient chart by an experienced research nurse and the Registry Baseline Form (RBF) will be completed and transmitted electronically to the Coordinating Center. The RBF will record demographic data, patient eligibility status for the SOLVD Registry and the randomized trials, clinical and laboratory data. For patients selected for the Registry Substudy, the Registry Substudy Baseline (RSB) form will also be collected. This RSB form will record when the echocardiograms were done, and data from the 70-minute ambulatory Holter monitoring, the 6-minute walking test, the physical examination and clinical history. It is expected that an additional data form specific to secondary cardiomyopathies will be developed after a better estimate of such diseases that can be identified is obtained from the first few months of the SOLVD Registry. (However, such patients will be identified and their names maintained on a separate log at each center.)

All baseline forms will be promptly transmitted through the SOLVD microcomputer to the SOLVD Coordinating Center for collection, verification, storage and analysis of the Registry data. A maximum window of 90 days will be allowed between initial registration of the patient in the logbook at the clinical center and data transmission of the RBF and RSB forms to the Coordinating Center.

Follow-up Data

Two types of follow-up information will be obtained. First, a one-year follow-up questionnaire requesting information on vital status and hospitalizations will be administered by mail and followed, if necessary, by a telephone contact.

The one-year follow-up interview is to be attempted through the mailing of a letter that will be standard and ask the following questions on an attached form (SOLVD REGISTRY "FOLLOW-UP FORM"):

i) Have you been hospitalized during the period _____ to _____? If yes, please give us the name of the hospital(s), date(s) of hospitalization(s) and the reasons for the hospitalization(s). [Note that all hospitalizations are of interest. The dates to be filled in by the clinic should reflect a one-year time period from their date of enrollment into the Registry.]

ii) Are there any other matters about your health that are concerning you? [This question will not be included in the collaborative data base.]

iii) Question number 35 of the Quality of Life form (the "ladder of life").

The body of the letter will be uniform across centers, but may contain center-specific paragraphs to continue participant rapport. The participant will be asked to complete the form with the above questions and return it. Some of the data on the form will be entered on the SOLVD REGISTRY "ONE-YEAR FOLLOW-UP INTERVIEW COVER FORM."

If contact is not established through the mail, phone calls and other means of establishing contact are to be attempted. The form can be completed over the phone.

If the participant is participating in the SOLVD trials, DO NOT attempt a mail or phone contact by the Registry. Contact information is to be obtained from the closest scheduled SOLVD trial visit occurring after one year from the SOLVD REGISTRY BASELINE FORM. Since the "ladder of life" will not be available, it must be administered at a visit close to the one year time and the code entered on the SOLVD Registry "Follow-up Form."

If the participant is acknowledged to be alive and has not required any hospitalization during the preceding year, no further information will be required at this time beyond completion of the One-Year Follow-up form. If the participant has died, the research nurse will obtain reports of hospitalizations, if any have occurred, and circumstances of death as well as the death certificate, and will forward a Designation of Death form, the Death Certificate Cover Sheet form, and Hospitalization forms (as needed) promptly to the Coordinating Center. If the participant is living but has required one or more hospitalizations during the preceding year, the nurse will obtain reports of the hospitalizations, and will complete the Hospitalization form for each hospitalization. (Copies of these forms are included in appendix B.)

It should be noted that if a participant is registered in the logbook at a participating center and subsequently dies during the same hospitalization, the center is required to seek his/her eligibility for the SOLVD Registry and to complete and submit to the Coordinating Center the Main Registry Baseline form, the Designation of Death form, and the Death Certificate Cover Sheet for this participant.

There will be a time allowance of 60 days for submitting the one-year follow-up forms to the Coordinating Center, i.e., 60 days after the anniversary of enrollment.

The second type of information derived from the follow-up of the Registry participants will be a long-term ascertainment of vital status through the National Death Index (NDI) and corresponding registries in Canada and Belgium. Although several matching criteria are available for searches of the NDI, the three absolutely essential identifiers include the social security number, the date of birth and the full name of the participant. Information on vital status will be sought approximately two years and four years after enrollment of a patient in the Registry. For the United States, this will be done at the SOLVD Coordinating Center. The Canadian centers and the Belgian center will be responsible for collecting these data from their respective Bureaus of Vital Statistics and for submitting them, upon request, to the SOLVD Coordinating Center.

Endpoint Data

The follow-up endpoints will provide two sets of information. The first set will be one-year information on vital and on major *non*-fatal cardiovascular events, including recurrent and/or new complications requiring hospitalization such as worsening of functional status, myocardial infarction, stroke, pulmonary complications, severe serious arrhythmias, drug toxicity, and cardiac surgery--including cardiac transplantation.

The second set of endpoint data will provide long-term ascertainment of vital status, approximately two years and approximately four years after enrollment in the SOLVD Registry.

X. STATISTICAL ANALYSIS

The primary outcome is all-cause mortality. Thus, the main variable for analysis will be the time from entry into the Registry until death. Cardiovascular mortality as well as other causes of death will be examined from major categories of the underlying cause of death from the death certificate. The analysis of the major outcome of death will involve the use of the proportional hazards model (Cox, 1972). This analysis will allow for the adjustment of baseline covariates thought to be of prognostic importance; for example, ejection fraction, age, sex, race, etiology. Similarly, analyses will be conducted for morbid events. A careful evaluation of the suitability of the proportional hazards assumption will be conducted as part of these analyses. In addition, the relationship of the echocardiographic and Holter variables to prognosis (collected systematically on the 1000 patients) will be assessed. The data will be analyzed separately in a number of subgroups based on etiology, sex, age, functional class, etc.

References

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XI. INFORMED CONSENT

A. CONSENT TO PARTICIPATE IN THE STUDIES OF LEFT VENTRICULAR DYSFUNCTION REGISTRY

DESCRIPTION: You are being invited to participate in a Registry of patients who have congestive heart failure or left ventricular dysfunction.

The purpose of this Registry is to provide scientific information about the treatment of persons who have either congestive heart failure or left ventricular dysfunction.

This Registry is a cooperative project involving about 24 medical centers. A total of 6,000 patients, men and women, will be asked to participate in this registry. Participation means that pertinent information from your chart will be recorded. You will be contacted in about one year to provide information about your health, and your social security number will be used for research related purposes only.

BENEFITS AND RISKS: The information gathered in this registry will be very important for doctors in deciding how to treat persons who have Congestive Heart Failure and Left Ventricular Dysfunction. A possible inconvenience is the need to report your health about one year from now, although this study will not require you to visit your doctor or nurse and you can answer all the questions over the telephone or by mail in about 10 minutes.

COSTS AND PAYMENTS: There will be no payment or costs for your participation.

CONFIDENTIALITY: Information obtained about you from this research will be kept confidential. Publication of study results will not identify you. Your name will be kept separate from your medical records at the Data Center. You should be aware that certain agencies at the Department of Health and Human Services such as the Food and Drug Administration have the right to audit records for scientific or fiscal purposes.

RIGHT TO WITHDRAW: You are free to refuse to participate in this study or to withdraw at any time. Your decision will not adversely affect your present or future medical care, or cause a loss of benefits to which you might be otherwise entitled.

VOLUNTARY CONSENT: Your signature below will certify that you have read the preceding (or it has been read to you) and that you understand its contents. Any questions you have pertaining to the preceding have been and will be answered by Dr. _____ (physician), tel. _____, or Ms./Mr. _____ (data coordinator), tel. _____ or by the Study Director. Any questions you have concerning your rights as a research subject

Patient please initial here: _____

will be answered by _____. One copy of this consent form will be yours to keep. Your signature below means that you have freely agreed to participate in this study.

_____ _____

Date Patient Signature

I certify that I have explained to the above individual the nature and purpose, the potential benefits, and the possible risks associated with participating in this research study, and have answered any questions that have been raised.

_____ _____

Date Investigator's Signature

B. CONSENT TO PARTICIPATE IN STUDIES OF LEFT VENTRICULAR DYSFUNCTION REGISTRY SUBSTUDY

DESCRIPTION: You are being invited to participate in a study of patients in the SOLVD Registry.

There are two purposes for this study. One is to describe the clinical course of congestive heart failure and/or left ventricular dysfunction as it relates to certain patient characteristics. The second is to correlate the various reasons for patients getting congestive heart failure and/or left ventricular dysfunction with the clinical course.

1,000 patients from about 20 hospitals will be requested to participate in this study. Selection to participate in this study is based on the nature of your congestive heart failure and/or left ventricular dysfunction and different selection probabilities for the different types of disease. Participation means that you will come into the clinic for an echocardiogram, an electrocardiogram, an exercise test, a blood test, a history and a physical exam, all done at no cost to you.

- Echocardiogram -- An ultrasonic recording of heart action taken by a microphone device from the surface of the body will be done. There are no known risks.

- An Ambulatory Electrocardiogram (Holter Monitor) -- A tape recording of your heart rhythm using special skin contacts for 70 minutes. There are no known risks.

- A six minute exercise test -- Asked to perform natural walking activity on level ground for six minutes at your own pace. The risks are no more than those associated with your own usual activities.

- Blood drawing for neurohormones -- approximately 2 tablespoons of blood will be drawn from an arm vein to test for levels of naturally occurring substances in the body which regulate heart and blood vessel activity.

- History and physical examination. There are no known risks.

One year later you will be contacted by mail or telephone to provide information about your health. Additionally, your social security number will be used for research related purposes only.

BENEFITS AND RISKS: The information gathered in this study will be very important for doctors in deciding how to treat persons who have congestive heart failure and left ventricular dysfunction. This study will require you to visit your clinic once for the performance of the tests described above. A possible inconvenience is the need to report your health status to the study nurse or data technician one year later in response to a short half-page letter. You do not have to attend the hospital.

Patient please initial here_____

COSTS AND PAYMENTS: There will be no costs for your participation. The study will cover all expenses related to the tests.

CONFIDENTIALITY: Information obtained about you from this research will be kept confidential. Publication of study results will not identify you. You should be aware that certain agencies at the Department of Health and Human Services such as Food and Drug Administration have the right to audit records for scientific or fiscal purposes.

RIGHT TO WITHDRAW: You are free to refuse to participate in this study or to withdraw at any time. Your decision will not adversely affect your present or future medical care, or cause a loss of benefits to which you might be otherwise entitled.

VOLUNTARY CONSENT: Your signature below will certify that you have read the preceding or it has been read to you and that you understand its contents. Any questions you have pertaining to the preceding have been and will be answered by Dr. _____(physician), tel. _____ or Ms./Mr. _____(data coordinator), tel. _____ or by the Study Director. Any questions you have concerning your rights as a research subject will be answered by _____. One copy of this consent form will be yours to keep. Your signature below means that you have freely agreed to participate in this study.

_____ _____

Date Patient Signature

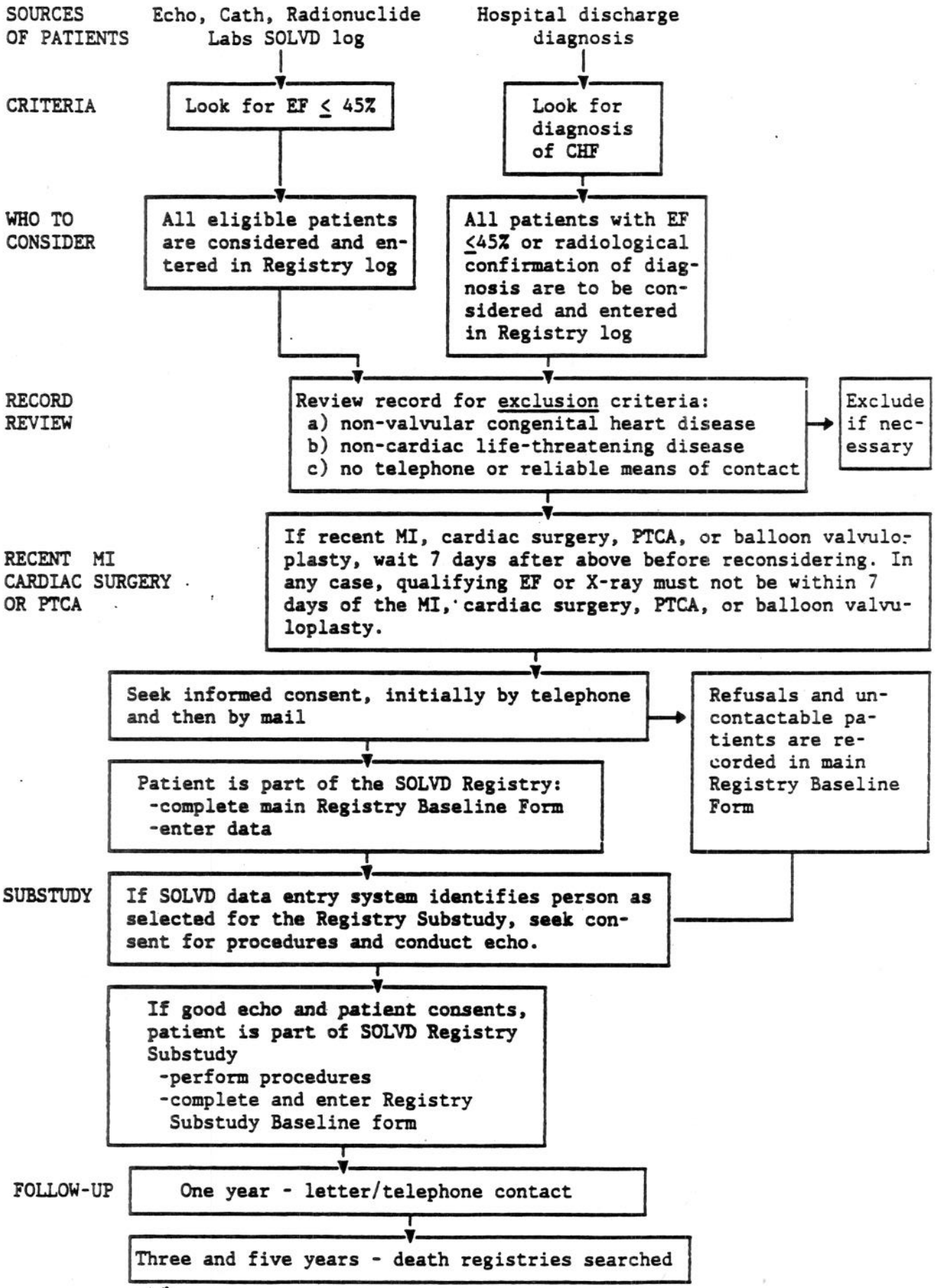
I certify that I have explained to the above individual the nature and purpose, the potential benefits, and the possible risks associated with participating in this research study, and have answered any questions that have been raised.

_____ _____

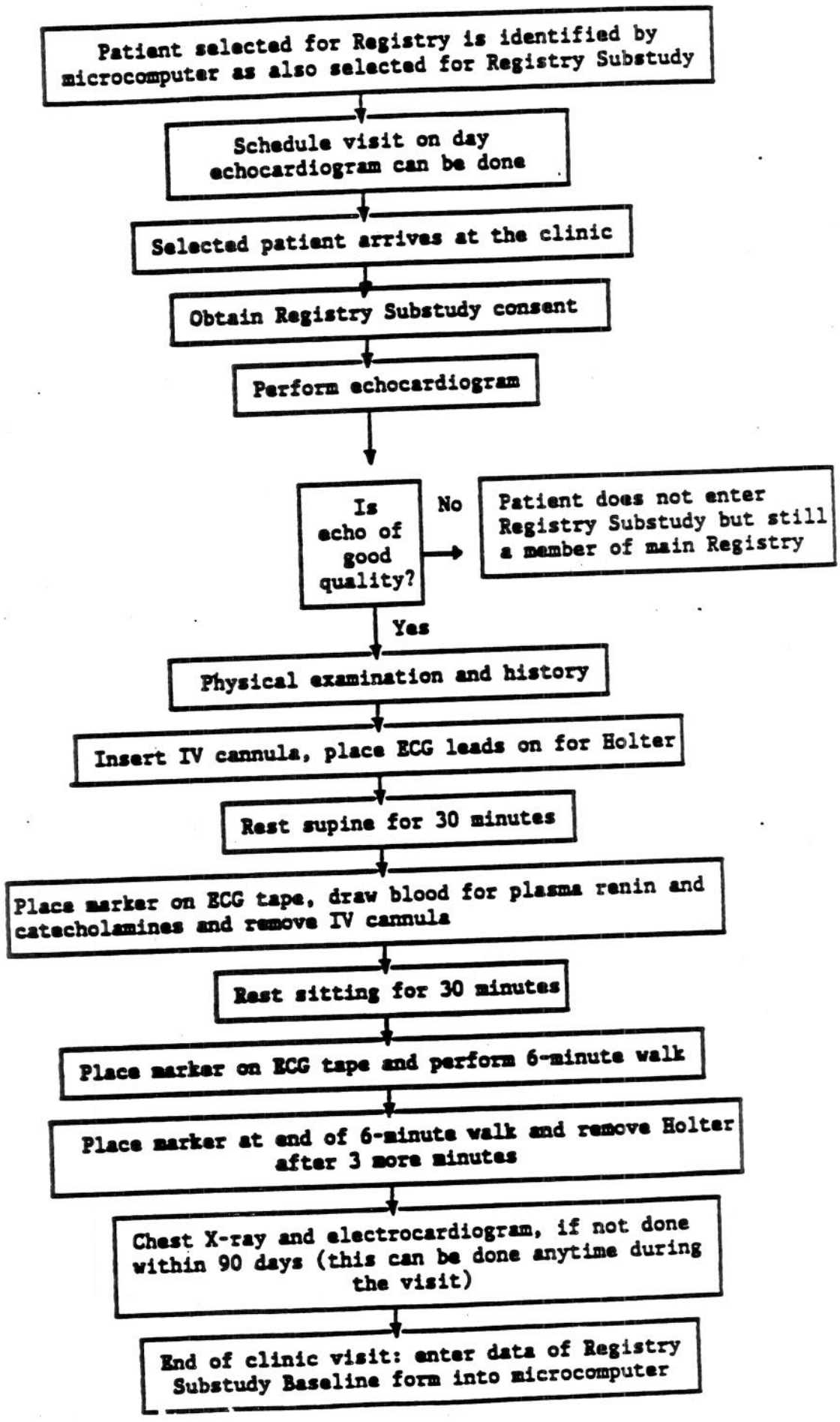
Date Investigator's Signature

Appendix A

A1: SOLVD REGISTRY FLOW DIAGRAM



A2: SOLVD REGISTRY SUBSTUDY VISIT FLOWCHART



SOLVD REGISTRY

BASELINE FORM

11/11/87

REGISTRY ID: [ ][ ][ ][ ][ ][ ][ ][ ][ ] FORM: [R][B][F] VERSION: [A] VISIT: [0]

INSTRUCTIONS: This form is to be completed on all consecutive eligible Registry subjects using only the information available from the appropriate medical records. To be eligible for the Registry, the patient must either have an EF <= 45% or have a diagnosis of congestive heart failure confirmed by radiologic evidence. Please print clearly when entering a response into the boxes. See the SOLVD General Instructions for Completing Forms for details.

SOLVD MAIN REGISTRY BASELINE FORM (screen 1 of 15) (RBF page 1 of 8)

A. IDENTIFYING INFORMATION

1.1 Today's Date: [ ][ ]/[ ][ ]/[ ][ ] (Month / Day / Year)

1.2 Initials of person completing form: [ ][ ]

2.1 Last Name: [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

2.2 First Name: [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

2.3 Middle Initial: [ ]

B. ELIGIBILITY ASSESSMENT Unrec

3. Most recently measured Ejection Fraction (should be 7 or more days after an MI, cardiac surgery, PTCA, or balloon valvuloplasty):

3.1 Percentage: [ ][ ]

3.2 Date: [ ][ ]/[ ][ ]/[ ][ ] (Month / Day / Year)

3.3 Method utilized:

Radionuclide	R
Contrast angiography	A
2-D echo	E
Not on chart	U

Yes No Unrecorded

4.1 Primary diagnosis of heart failure and chest X-ray consistent with heart failure (X-ray should be 7 or more days after an MI, cardiac surgery, PTCA, or balloon valvuloplasty) .... Y N U

4.2 Date of qualifying X-ray:

☐☐/☐☐/☐☐

Month Day Year

5. Reasons for exclusion from Registry

5.1 Presence of non-valvular congenital heart disease ..... Y N U

5.2 Presence of any non-cardiac life-threatening disease which is unlikely to allow the patient to survive one year (Includes 11, 12, 13, 17, 18, 21 and 23 of SOLVD trials) ..... Y N U

5.3 No telephone or reliable means of contact/follow up ..... Y N U

5.4 Failure to consent to Registry .... Y N U

5.5 Is patient eligible for Registry? Y N
(If NO, exit form)

C. DEMOGRAPHIC INFORMATION

6. Sex: Male M
Female F

7. Ethnic Identity

American Indian	1
Asian	2
Black	3
Caucasian	4
Hispanic	5
Other	6
Not on chart	7

8. Date of Birth:

☐☐/☐☐/☐☐

Month Day Year

9. Social Security Number (Canadian/Belgian ID):
(IMPORTANT!! MUST BE COMPLETED!!)

☐☐☐-☐☐-☐☐☐☐

10.1 Participant Street Address:

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

10.2 City:

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

10.3 State/Province: ☐☐

10.4 Country: ☐☐☐☐☐☐☐☐☐☐

10.5 Zip Code/Canadian or European Postal Code: ☐☐☐☐☐

11. Participant Telephone Number (Home):

☐☐☐-☐☐☐-☐☐☐☐

HOSPITAL INFORMATION

12.1 Hospital name:

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

12.2 Hospital street address:

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐

12.3 City:

12.4 State/Province:

12.5 Country:

12.6 Zip Code/Canadian or European Postal Code:

13. Patient hospital ID number:

PRIVATE PHYSICIAN INFORMATION

14.1 Last Name:

14.2 First Name:

15.1 Street address:

15.2 City:

15.3 State/Province:

15.4 Country:

15.5 Zip Code/Canadian or European Postal Code:

16. Telephone Number (private physician): - -

NEAREST RELATIVE OR FRIEND NOT RESIDING WITH PARTICIPANT

17.1 Last name:

17.2 First name:

18. Relationship:

19.1 Street address:

19.2 City:

(Nearest relative/friend continued)

19.3 State/Province: ☐☐

19.4 Country: ☐☐☐☐☐☐☐☐☐☐

19.5 Zip Code/Canadian or European Postal Code: ☐☐☐☐☐☐ ☐

20. Telephone number: ☐☐☐-☐☐☐-☐☐☐☐

D. X-RAY FINDINGS — Yes

21.1 Is chest X-ray available? ..... Y
(If NO, skip to section E)

21.2 Date of most recent chest X-ray (should be 7 or more days after MI, cardiac surgery, PTCA, or balloon valvuloplasty):
☐☐/☐☐/☐☐
Month Day Year

21.3 Is this X-ray the qualifying X-ray? Y

22. Pulmonary congestion:

22.1 Evidence of pulmonary congestion Y
(If NO, skip to Q. 23)

22.2 Basal or perihilar vascular blurring Y

22.3 Kerley B lines ..... Y

(continued)

	Yes	No
22.4 Alveolar or pulmonary edema	Y	N
22.5 Pleural effusion	Y	N

E. ETIOLOGY OF DISEASE

23.1 What is the primary etiology of participant's heart disease (choose only one of the following):

Ischemic heart disease (IHD)	1
Hypertensive heart disease (HHD)	2
Active myocarditis	3
Valvular heart disease - aortic	4
Valvular heart disease - mitral	5
Idiopathic cardiomyopathy ..... (specifics unknown)	6
Specific cardiomyopathy ..... (ex: viral, toxic, ETOH, postpartum, history of cocaine use) (If none, skip to Q. 24)	7

23.2 Specify: _____

	Yes	No	Unreco:
24. Indicate all of the following that occur concurrently (including etiology specified above):			
24.1 Ischemic heart disease (IHD)	Y	N	U
24.2 Hypertensive heart disease (HHD)	Y	N	U
24.3 Active myocarditis	Y	N	U
24.4 Idiopathic cardiomyopathy	Y	N	U
24.5 Specific cardiomyopathy (ex: viral, toxic, ETOH, post-partum, history of cocaine use) (If NO or UNRECORDED, skip to Q. 24.7)	Y	N	U
24.6 Specify: _____			
24.7 Valvular heart disease - aortic	Y	N	U
24.8 Valvular heart disease - mitral	Y	N	U

F. RELATIONSHIP TO SOLVD TRIALS (SKIP TO SEC G IF EF> 35%)

25.1 If participant is being considered for the SOLVD trials, copy Eligibility ID:

25.2 If participant has been randomized into the SOLVD trials, copy Randomization ID:

(If participant randomized, SKIP to Q. 27)

	Yes	No	Unrecorded
26. If participant was considered for but excluded from the SOLVD trials, please identify the reason(s) for exclusion:			
26.1 Hemodynamically significant valvular or outflow tract obstruction	Y	N	U
26.2 Constrictive pericarditis	Y	N	U
26.3 Complex congential heart disease	Y	N	U
26.4 Myocardial infarction within 30 days of expected randomization	Y	N	U
26.5 History of intolerance to enalapril	Y	N	U
26.6 Currently taking ACE inhibitor and unwilling/unable to discontinue	Y	N	U
26.7 Renal failure	Y	N	U
26.8 Uncontrolled hypertension	Y	N	U
26.9 Cor Pulmonale	Y	N	U
26.10 Advanced pulmonary disease	Y	N	U
26.11 Major neurological disease	Y	N	U
26.12 Cerebrovascular disease	Y	N	U
26.13 Collagen vascular disease	Y	N	U

SOLVD MAIN REGISTRY BASELINE FORM (screen 9 of 15) (RBF page 5 of 8)

	Yes	No	Unrecorded
26.14 Any major cardiac surgery likely	Y	N	U
26.15 Unstable angina pectoris	Y	N	U
26.16 Cancer	Y	N	U
26.17 Immunosuppressive therapy	Y	N	U
26.18 Active myocarditis	Y	N	U
26.19 Significant primary liver disease	Y	N	U
26.20 Likely to be nonadherent (alcoholism, drug addiction, lack of a fixed address, etc.)	Y	N	U
26.21 Syncopal episodes presumed to be due to life-threatening arrhythmias	Y	N	U
26.22 Other life-threatening disease or not realistically expected to be discharged alive	Y	N	U
26.23 Suspected significant renal artery stenosis	Y	N	U
26.24 Woman likely to bear children	Y	N	U
26.25 Other investigational drug protocols (except compassionate use)	Y	N	U
26.26 Failure to give consent for the SOLVD trials	Y	N	U
26.27 Lack of adherence or tolerance to medication	Y	N	U
26.28 Lack of adherence to placebo run-in	Y	N	U

27. For which trial is/was the participant being considered or is/was randomized?

Prevention	P
Treatment	T
Not considered/randomized	N

G. CLINICAL HISTORY

	Yes	No	Unrecorded
28.1 Date history taken (within 3 months of enrollment)			
Month ☐☐ / Day ☐☐ / Year ☐☐			
28.2 Diabetes mellitus	Y	N	U
28.3 Chron. obstructive pulm. dis...	Y	N	U
28.4 Cerebrovascular accident	Y	N	U
28.5 Angina pectoris	Y	N	U
28.6 Peripheral embolism	Y	N	U
28.7 Pulmonary embolism	Y	N	U
28.8 Syncope	Y	N	U
28.9 Hypertension	Y	N	U

	Yes	No	Unrecc
28.10 Peripheral vascular disease ...	Y	N	U
28.11 Edema	Y	N	U
28.12 Breathlessness on exertion	Y	N	U
28.13 Asthma ..... (If NO or UNRECORDED, skip to Q. 28.15)	Y	N	U
28.14 Approximate duration of asthma (in years): ☐☐			
28.15 Pulmonary edema	Y	N	U
29.1 Previous myocardial infarction? (If NO or UNRECORDED, skip to Q. 30)	Y	N	U
29.2 Enter date of most recent myocardial infarction			
Month ☐☐ / Year ☐☐			
29.3 Was the MI complicated by pulmonary edema, shock, or heart failure?	Y	N	U

30. Smoking history	Yes	No	Unrecorded
30.1 Has the participant ever been a smoker (tobacco)? ..... (If NO or UNRECORDED, skip to Q. 31)	Y	N	U
30.2 Does the participant currently smoke?	Y	N	U
31. Alcohol consumption history			
31.1 Has the participant ever regularly consumed alcohol? ..... (If NO, skip to Q. 32)	Y	N	U
31.2 Is there history of alcohol abuse? (See Manual of Operations for guidelines)	Y	N	U
31.3 Does the participant currently consume alcohol?	Y	N	U

	Yes	No	Unreco
32. Permanent pacemaker?	Y	N	U
33. Use of automatic implantable defibrillator?	Y	N	U
34.1 Previous cardiac surgery, PTCA, or balloon valvuloplasty? .... (If NO or UNRECORDED, skip to Q. 35)	Y	N	U
34.2 Enter date of most recent cardiac surgery, PTCA, or balloon valvuloplasty:			
Month ☐☐ / Year ☐☐			

Type of cardiac surgery:	Yes	No	Unrecorded
34.3 Coronary artery bypass graft ...	Y	N	U
34.4 Valve replacement - aortic	Y	N	U
34.5 Valve replacement - mitral	Y	N	U
34.6 Percutaneous transluminal coronary angioplasty (PTCA)	Y	N	U
34.7 Balloon valvuloplasty	Y	N	U
34.8 Other ..... (If NO or UNKNOWN, skip to Q. 35)	Y	N	U

34.9 Specify: _____

H. MEDICATIONS IN USE AT LAST HOSPITALIZATION OR OUT-PATIENT VISIT

35. Date of last hospitalization or out-patient visit:

☐☐/☐☐/☐☐
Month Day Year

	Yes	No
36.1 Potassium-losing diuretic	Y	N
36.2 Potassium-sparing diuretic	Y	N
36.3 Antiarrhythmic drug other than beta-blocker or calcium antagonist ...	Y	N
36.4 Regular use of antiplatelet	Y	N
36.5 Beta-blocker	Y	N
36.6 Long-acting oral nitrate or paste	Y	N
36.7 Hydralazine	Y	N
36.8 Open-label ACE inhibitor ..... (Select "S" if in SOLVD trial)	Y	N
36.9 Digitalis	Y	N
36.10 Calcium antagonist	Y	N
36.11 Other vasodilator	Y	N
36.12 Antihypertensive (other than above)	Y	N

(continued)

	Yes	No
36.13 Other inotropic agent	Y	N
36.14 Anticoagulant	Y	N
36.15 Insulin	Y	N
36.16 Steroids	Y	N
36.17 Beta-2 agonist inhalers	Y	N
36.18 Potassium supplements	Y	N

I. PHYSICAL EXAMINATION (At admission if hospitalized; if outpatient, last recording within 3 months)

37. Date of physical exam:

☐☐/☐☐/☐☐
Month Day Year

38. Weight (enter lbs. or kg.):

38.1 ☐☐☐ lbs.

38.2 ☐☐☐ kg.

39. Height (enter inches or cm):

39.1 ☐☐ in.

39.2 ☐☐☐ cm.

40. Heart rate: ☐☐☐ beats/min

41. Systolic blood pressure: ☐☐☐ mm Hg

42. Diastolic blood pressure: ☐☐☐ mm Hg

43. Any of the following present?	Yes	No
43.1 Rales	Y	N
43.2 Edema	Y	N
43.3 Elevated jugular venous pressure	Y	N

Any of the following present? (cont.) Yes No

43.4 S3 gallop ..... Y N

43.5 Mitral regurgitation murmur .... Y N

J. ECG FINDINGS (Latest ECG, but not within 72 hours of an MI; use only if taken within last 3 months)

44. Date of ECG: ☐☐/☐☐/☐☐ (Month / Day / Year)

Yes No

45. Atrial fibrillation/flutter ..... Y N
(If YES, skip to Q. 47)

46. P wave terminal force in V1: ☐.☐ mm

47. QRS delay <= 120 ms? ..... Y N
(If NO, skip to Section K)

48. Amplitude of R wave in V5 or V6: ☐☐.☐ mm
(whichever is larger)

49. Amplitude of R wave in AVL: ☐☐.

50. Amplitude of R wave in II, III, or AVF (whichever is larger): ☐☐.

51. Amplitude of S wave in V1: ☐☐.

52. Amplitude of S wave in V3: ☐☐.

53. ST segment depression in inferior leads of V5 or V6: ☐☐.

54. Is Q-wave MI present? ..... Y
(If NO, skip to Section K)

55. Location of MI:
Anterior
Inferior
Both
Unknown

K. LABORATORY RESULTS (Use most recent results; use only if recorded within 6 months)

56. Date of laboratory tests: ☐☐/☐☐/☐☐ (Month / Day / Year)

57. Sodium (Na): ☐☐☐ meq/l

58. Potassium (K): ☐.☐ meq/l

59. Blood urea nitrogen (BUN): ☐☐ mg/dl

60. Creatinine: ☐.☐ mg/dl

L. CORONARY ARTERIOGRAPHY (use only if taken within past 12 months)

61. Does participant have a coronary arteriogram? Yes No
(If NO, skip to Q. 64)

62. Date of coronary arteriogram: ☐☐/☐☐/☐☐ (Month / Day / Year)

63. The arteriogram shows (select ONE):

Normal coronary arteries .....
Insignificant coronary artery disease (less than 50% stenosis of at least one major artery) .....
Significant coronary artery disease (>= 50%) ....
Unknown or unrecorded .....

M. SOURCE OF REGISTRY PATIENT

64. Hospitalized (In-patient) .....

Out-patient .....

N. SELECTION FOR REGISTRY SUBSTUDY Yes

65. Data Entry System has identified this participant for the Registry Substudy ..... Y
(If NO, skip to Q. 67)

66. Participant consents to Registry Substudy Y

SOLVD REGISTRY

SUBSTUDY BASELINE FORM

11/20/87

REGISTRY ID: [ ][ ][ ][ ][ ][ ][ ][ ][ ] FORM: [R][S][B] VERSION: [A] VISIT: [0]

INSTRUCTIONS: This form is to be completed on Registry subjects selected and included in the Registry Substudy. The information is to be obtained from the subject at a clinic visit by a physician, nurse practitioner, or physician's assistant. The clinic visit should take place no later than 90 days after the Registry Baseline Form has been completed. Please print clearly. See the SOLVD General Instructions for Completing Forms for details.

A. IDENTIFYING INFORMATION

1.1 Today's date: [ ][ ] / [ ][ ] / [ ][ ]
Month Day Year

1.2 Initials of person completing form: [ ][ ]

2.1 Participant's Last Name:
[ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

2.2 Participant's First Name:
[ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

2.3 Participant's Middle Initial: ..... [ ]

B. ECHOCARDIOGRAPHY ELIGIBILITY Yes

3.1 Date 2D and M-mode echos done:
[ ][ ] / [ ][ ] / [ ][ ]
Month Day Year

3.2 Were these echocardiograms of good quality? (See protocol for criteria) (If NO, exit form) Y

3.3 Was Doppler echo done? (only for those participants in the Echo Substudy) ... (If NO, skip to Section C) Y

3.4 Date Doppler done:
[ ][.] / [ ][ ] / [ ][ ]
Month Day Year

C. ETIOLOGY OF DISEASE AND NYHA CLASS

4.1 Indicate the primary etiology of the patient's heart disease (choose only ONE of the following):

Ischemic heart disease (HD)	1
Hypertensive heart disease (HHD)	2
Active myocarditis	3
Valvular heart disease - aortic	4
Valvular heart disease - mitral	5
Idiopathic cardiomyopathy (specifics unknown)	6
Specific cardiomyopathy (ex: viral, toxic, ETOH, postpartum, history of cocaine use) (If none, skip to Q. 5)	7

4.2 Specify: _____

	Yes
5. Indicate all of the following etiologies that have occurred (including the etiology specified above):	
5.1 Ischemic heart disease (IHD)	Y
5.2 Hypertensive heart disease (HHD)	Y
5.3 Active myocarditis	Y
5.4 Valvular heart disease - aortic	Y
5.5 Valvular heart disease - mitral	Y
5.6 Idiopathic cardiomyopathy (specifics unknown)	Y
5.7 Specific cardiomyopathy (ex: viral, toxic, ETOH, postpartum, history of cocaine use) (If NO, skip to Q. 6)	Y

5.8 Specify: _____

6. New York Heart Association CHF Class: (Choose only one)

	Yes	No
D. PAST CLINICAL HISTORY (up to completion of the Registry Baseline form)		
7. Does the participant have a history of:		
7.1 Pulmonary edema	Y	N
7.2 Diabetes mellitus	Y	N
7.3 Chronic obstructive pulmonary disease	Y	N
7.4 Cerebrovascular accident	Y	N
7.5 Angina pectoris	Y	N
7.6 Peripheral embolism	Y	N
7.7 Pulmonary embolism	Y	N
7.8 Syncope	Y	N

	Yes
7.9 Hypertension	Y
7.10 Peripheral vascular disease	Y
7.11 Edema	Y
7.12 Breathlessness on exertion	Y
7.13 Asthma (If NO, skip to Q. 8)	Y
7.14 Approximate duration of asthma: ☐☐	
8. Cigarette smoking (ignore any other tobacco u	
8.1 Has the participant ever smoked cigarettes regularly? (If NO, skip to Q. 9)	Y

8.2 At what age did the participant first begin to smoke cigarettes regularly?

☐☐ years of age

8.3 For how many years in total has the participant smoked regularly?

☐☐ years

8.4 For how many of those years did the participant smoke filter-tipped cigarettes?

☐☐ years

What (approximately) was the largest number of cigarettes the participant generally used to smoke in a week? (Count 1 oz of handrolled tobacco as 28 cigarettes) -

8.5 - Before 20 years of age ☐☐☐ cigts/week

8.6 - From 20-24 years of age ☐☐☐ cigts/week

Yes

8.7 - After 24 years of age ☐☐☐ cigts/wee

8.8 - During last 6 months ☐☐☐ cigts/wee

8.9 Did the participant smoke any cigarettes in the past week? ..... Y

9. Alcohol consumption history

9.1 Has the participant ever consumed alcohol regularly? ..... Y
(If NO, skip to Q. 10.1)

9.2 Does the participant currently consume alcohol regularly? ..... Y
(If NO, skip to Q. 9.5)

9.3 Last week, how many drinks did the participant have? (1 drink = 12 oz beer = 4-5 oz wine = 1.5 oz spirits)

☐☐ drinks

9.4 Specify current drinking pattern:

Heavy	H
Regularly	R
Socially	S
Rarely	X
Unknown	U

GO TO Q.10.1

9.5 Number of days a week the participant used to drink:

☐ days

9.6 Number of drinks the participant used to consume per week (1 drink = 12 oz beer = 4-5 oz wine = 1.5 oz spirits):

☐☐ drinks/week

9.7 Specify former drinking pattern:

Heavy	H
Regularly	R
Socially	S
Rarely	X
Unknown	U

	Yes	No	Unk
10.1 Previous myocardial infarction? (If NO, skip to Q. 11)	Y	N	

10.2 Date of most recent myocardial infarction:

☐☐ / ☐☐
Month Year

10.3 Was the MI complicated by pulmonary edema, shock, or heart failure?	Y	N	
11. Permanent pacemaker?	Y	N	
12. Use of automatic implantable defibrillator?	Y	N	
13.1 Previous cardiac surgery, PTCA, or balloon valvuloplasty? ..... (If NO, skip to Section E)	Y	N	

	Yes	No	Unknown
13.2 Date of most recent cardiac surgery, PTCA, or balloon valvuloplasty:			

Month / Year

14. Type of cardiac surgery:

14.1 Coronary artery bypass graft	Y	N	U
14.2 Valve replacement - aortic	Y	N	U
14.3 Valve replacement - mitral	Y	N	U
14.4 Percutaneous transluminal coronary angioplasty (PTCA)	Y	N	U
14.5 Balloon valvuloplasty	Y	N	U
14.6 Other ..... (If NO, skip to Section E)	Y	N	

14.7 Specify: _____

E. MEDICATIONS CURRENTLY USED	Yes
15.1 Digitalis	Y
15.2 Other inotropic agent	Y
15.3 Potassium-losing diuretc	Y
15.4 Potassium-sparing diuretic	Y
15.5 Antiarrhythmic drug other than beta-blocker or calcium antagonist ..	Y
15.6 Regular use of antiplatelet	Y
15.7 Beta-blocker	Y
15.8 Long-acting oral nitrate and paste ..	Y
15.9 Hydralazine	Y
15.10 Open-label ACE inhibitor ..... (Select "S" if in SOLVD trial)	Y
15.11 Calcium antagonist	Y

(continued)

	Yes	No
15.12 Other vasodilator	Y	N
15.13 Antihypertensive (other than above)	Y	N
15.14 Anticoagulant	Y	N
15.15 Insulin	Y	N
15.16 Steroids	Y	N
15.17 Beta-2 agonist inhalers	Y	N
15.18 Potassium supplements	Y	N

F. PHYSICAL EXAMINATION

16. Weight (enter lbs or kg)

16.1 ___ lbs OR 16.2 ___ kg

17. Height (enter inches or cm)

17.1 ___ in OR 17.2 ___ cm

18. Heart rate: ___ bea

19. Systolic blood pressure: ___ mmH

20. Diastolic blood pressure: ___ mmH

21. Are any of the following present?	Yes
21.1 Rales	Y
21.2 Edema	Y
21.3 Elevated jugular venous pressure	Y
21.4 S3 gallop	Y
21.5 Mitral regurgitation murmur	Y

G. ECG FINDINGS (Should be 72 or more hours after an MI)

22. Date ECG taken: ☐☐/☐☐/☐☐ (Month / Day / Year)

23. Atrial fibrillation/flutter? ..... Yes No
(If YES, skip to Q. 25)

24. P wave terminal force in V1: ☐.☐ mm

25. QRS delay <=120 ms? ..... Yes No
(If NO, skip to Q. 32)

26. Amplitude of R wave in V5 or V6 (whichever is larger): ☐☐.

27. Amplitude of R wave in AVL: ☐☐.

28. Amplitude of R wave in II, III, or AVF (whichever is larger): ☐☐.

29. Amplitude of S wave in V1: ☐☐.

30. Amplitude of S wave in V3: ☐☐.☐ mm

31. ST segment depression in inferior leads or V5 or V6: ☐☐.☐ mm

32. Is Q-wave MI present? ..... Yes No
(If NO, skip to Section H)

33. Location of MI:

Anterior	A
Inferior	I
Both	B
Unknown	U

H. X-RAY FINDINGS (Should be 7 or more days after an MI, cardiac surgery, PTCA, or balloon valvuloplasty)

34. Date X-ray taken: ☐☐/☐☐/☐☐ (Month / Day / Year)

35. Cardiac thoracic ratio (please measure): .☐☐

	Yes
36. Serial chest X-ray available to make determinations?	Y
37. Pulmonary congestion:	
37.1 Evidence of pulmonary congestion? ..... (If NO, skip to Section I)	Y
37.2 Basal or perihilar vascular blurring? ..	Y
37.3 Karley B lines?	Y
37.4 Alveolar or pulmonary edema?	Y
37.5 Pleural effusion?	Y

I. PROCEDURES

38. Was the Holter monitoring done? ..... Y
(If NO, skip to Q. 41)

39. Date Holter performed: ☐☐/☐☐/☐☐ (Month / Day / Year)

SOLVD REGISTRY SUBSTUDY BASELINE FORM (screen 10 of 12) (RSB page 6 of 7)

Yes No

40. Neurohumoral measurements:

40.1 Was the PNE sample taken? ..... Y N

40.1 Was the PRA sample taken? ..... Y N

40.3 Date neurohumoral measurements taken:

[ ][ ] / [ ][ ] / [ ][ ]

Month Day Year

40.4 Hour neurohumoral measurements taken (01-12):

[ ][ ]

40.5 Were the neurohumoral measurements made in the morning or afternoon?

A (AM) P (PM)

40.6 Date samples sent to core laboratory:

[ ][ ] / [ ][ ] / [ ][ ]

Month Day Year

TO BE COMPLETED LATER

40.7 PNE: [ ][ ][ ][ ] pg/ml

40.8 PRA: [ ][ ][ ] . [ ][ ] ng/ml/hr

SOLVD REGISTRY SUBSTUDY BASELINE FORM (screen 11 of 12) (RSB page 6 of 7)

Yes No

41. Were the procedures done on the same day the echocardiograms were taken? ..... Y N
(If YES, skip to Section J)

42. Did any major events occur in the interim? Y N
(If YES, complete Registry Hospitalization Form)

J. SIX-MINUTE WALKING TEST

43. Did the participant finish the six-minute walking test? ..... Y N

44. Time completed: [ ] min [ ][ ] sec

45. Were there any breaks in continuity? ..... Y N

Yes

46. Indicate any of the following symptoms present:

46.1 Angina ..... Y

46.2 Dyspnea ..... Y

46.3 Fatigue ..... Y

46.4 Dizziness ..... Y

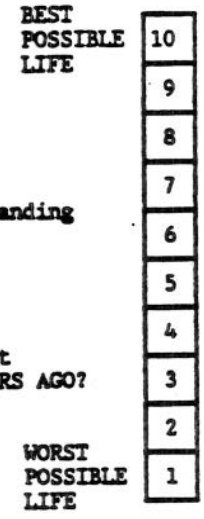
46.5 Syncope ..... Y

47. Total distance travelled (enter feet or meters)

47.1 [ ][ ][ ][ ] ft OR 47.2 [ ][ ][ ]

K. LADDER OF LIFE

Here is a ladder representing the "Ladder of Life." The top represents the best possible life for the participant; the bottom represents the worst possible life for him/her.



48. On which step of the ladder does the participant feel he/she is standing at the PRESENT time?

☐☐

49. On which step does the participant feel he/she was standing FIVE YEARS AGO?

☐☐

50. On which step does the participant feel he/she will be standing FIVE YEARS FROM NOW?

☐☐

REGISTRY

HOSPITALIZATION FORM

VERSION A / 9-1-1986

ESS ID: | | | | | | | | | | FORM: R H F VERSION: A [redacted]

SEQUENCE NUMBER: | |

INSTRUCTIONS: This form is to be used each time a [redacted] participant has been hospitalized. [redacted] The sequence number is needed to indicate the number of times this form has been used [redacted] Sequence number should start with 01 the first time the form is used for the participant [redacted]. Print clearly when entering a response in the appropriate boxes. For multiple choice questions, circle the one appropriate letter corresponding to the response chosen. Specific instructions for various questions are enclosed in boxes directly below the question. See the SOLVD General Instructions for Completing Forms for details.

HOSPITALIZATION FORM (screen 1 of 6) (HF page 1 of 4)

A. IDENTIFYING INFORMATION

1. Today's Date: | | / | | / | | (Month / Day / Year)

2.1. Last Name: | | | | | | | | | |

| | | | | | | | | |

2.2. First Name: | | | | | | | | | |

| | | | | | | | | |

2.3. Middle Name: | | | | | | | | | |

| | | | | | | | | |

3. Hospital Name: | | | | | | | | | | |

| | | | | | | | | | |

4.1. Date of Admission: | | / | | / | | (Month / Day / Year)

4.2. Date of Discharge: | | / | | / | | (Month / Day / Year)

B. PRIMARY REASON FOR HOSPITALIZATION

5. Hospitalization.....

Cardiovascular C

Noncardiovascular N

If Cardiovascular (C), go to Question 7. on page 2.

6. If Noncardiovascular (N), specify:

| | | | | | | | | | |

| | | | | | | | | | |

| | | | | | | | | | |

Go to section C. SECONDARY REASONS FOR HOSPITALIZATION, Question 11. on page 3.

6.1 NICDA coding | | | . |

7. If Cardiovascular, enter the code for PRIMARY REASON..... ☐

CODE	REASON
A	Worsening CHF
B	New CHF
C	Worsening or new angina
D	Myocardial Infarction
E	Nonfatal cardiac arrest or ventricular tachycardia that required defibrillation
F	Supraventricular tachycardia or fibrillation that required DC conversion or pacing
G	Uncertain tachycardia that required DC conversion or pacing
H	Other arrhythmias
I	Stroke
J	Cardiac surgery
K	Pulmonary embolism
L	Peripheral embolism
M	Hypotension
N	Azotemia
O	Any other major event
P	Digitoxicity

Note: If PRIMARY REASON = Myocardial infarction (D) go to Question 8.a.
If PRIMARY REASON = Cardiac surgery (J) go to Question 9.1.
If PRIMARY REASON = Any other major event (O) go to Question 10.
Otherwise, go to section C. SECONDARY REASONS FOR HOSPITALIZATION, Question 11. on page 3.

Myocardial Infarction (MI)

If Yes, indicate the following:

8.a. Date of MI: ☐☐/☐☐/☐☐ (Month / Day / Year)

8.b. Time of MI: (rounded to the nearest hour)
a) ☐☐ Hours
b) a.m. ..... A
p.m. ..... P

Indicate the presence of the following:

	Yes	No	Unk: cardiac
8.1. Pain.....	Y	N	U
8.2. Elevated enzymes.....	Y	N	U
8.3. Changes in ECG.....	Y	N	U

Go to section C. SECONDARY REASONS FOR HOSPITALIZATION, Question 11. on page 3.

Cardiac Surgery

9.1. If Yes, indicate surgery.....

Graft (CABG)	G
Valve	V
Transplantation	T
Graft & Valve	B
Other	O

If Graft (G), Valve (V), Transplantation (T) or Graft & Transplant (B), go to Question 11., page 3.

9.2. If Other (O), specify:
☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐

Go to Question 11. on page 3.

Any Other Major Event

10. If Yes, specify other major event:
☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐

HCDA coding

C. SECONDARY REASONS FOR HOSPITALIZATION

11. Hospitalization.....

Cardiovascular	C
Noncardiovascular	N
None	O

If Cardiovascular (C), go to Question 13.

If None (O), go to section D. INITIALS OF PERSON COMPLETING THIS FORM, Question 28. on page 4.

12. If Noncardiovascular (N), specify:

12. WICD4 coding

Go to section D. INITIALS OF PERSON COMPLETING THIS FORM, Question 28. on page 4.

Indicate SECONDARY REASONS:

	Yes	No
13. Worsening CHF.....	Y	N
14. New CHF.....	Y	N
15. Worsening or new angina.....	Y	N
16.1. Myocardial Infarction (MI).....	Y	N

If No (Myocardial Infarction), go to Question 17.

16.1a. Date of MI: ___/___/___ Month / Day / Year

16.1b. Time of MI: (round off to nearest hour)

a) ___ Hours

b) a.m. ..... A

p.m. ..... P

Indicate the presence of the following

	Yes	No
16.2. Pain.....	Y	N
16.3. Elevated enzymes.....	Y	N

	Yes	No
16.4. Changes in ECG.....	Y	N
17. Nonfatal cardiac arrest or ventricular tachycardia that required defibrillation...	Y	N
18. Supraventricular tachycardia or fibrillation that required DC conversion or pacing.....	Y	N
19. Uncertain tachycardia that required DC conversion or pacing.....	Y	N
20. Other arrhythmias.....	Y	N
21. Stroke.....	Y	N
22.1. Cardiac surgery.....	Y	N

If No (Cardiac surgery), go to Question 23.

22.2. If Yes (cardiac surgery), indicate the type.....

Graft	G
Valve	V
Transplantation	T
Graft & Valve	B
Other	O

If Graft (G), Valve (V), Transplantation (T) or Graft & Transplant, go to Question 23.

22.3. If Other (O), specify:

	Yes	No
23. Pulmonary embolism.....	Y	N
24. Peripheral embolism.....	Y	N
25. Hypotension.....	Y	N

	Yes	No
26. Acetesia.....	Y	N
27.1. Any other major event.....	Y	N

If No (major event), go to Question 28.

27.2. If Yes, specify other major event:

27.3 HICDA coding

D. INITIALS OF PERSON COMPLETING THIS FORM

28. Initials.....

REGISTRY

DEATH CERTIFICATE COVER SHEET

VERSION A / 3-18-86

Reg ID: | | | | | | | | | |

VISIT: | |

FORM: | R | D | C |

INSTRUCTIONS: Complete and attach this form to the participant's Death Certificate. Send both to the SOLVD Coordinating Center in Chapel Hill, NC.

DEATH CERTIFICATE COVER SHEET

A. IDENTIFYING INFORMATION

1. Today's Date: | | | / | | | / | | |
Month Day Year

2.1. Last Name: | | | | | | | | |
| | | | | | | | |

2.2. First Name: | | | | | | | | |
| | | | | | | | |

2.3. Middle Name: | | | | | | | | |
| | | | | | | | |

2. Date of Death: | | | / | | | / | | |
Month Day Year

4. Was this a hospitalized death?.....Yes Y
No N

5. Cause of Death:
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

6. Was an autopsy performed?.....Yes Y
No N

B. INITIAL OF PERSON COMPLETING THIS FORM

7. Initials..... | |

REGISTRY

DESIGNATION OF DEATH FORM

VERSION A / 9-1-1986

REG ID: | | | | | | | | | | FORM: R D D VERSION: A [redacted]

INSTRUCTIONS: This form should be completed when all clinical information has been collected following a [redacted] participant's death to determine the cause of death as cardiovascular or noncardiovascular.

[redacted]

Print clearly when entering a response in the appropriate boxes. For multiple choice questions, circle the one appropriate letter or number corresponding to the response chosen. Specific instructions for various questions are enclosed in boxes directly below the question. See the SOLVD General Instructions for Completing Forms for details.

DESIGNATION OF DEATH FORM (screen 1 of 4) (RDD page 1 of 3)

A. IDENTIFYING INFORMATION

1. Today's Date: | | / | | / | | (Month / Day / Year)

2. Date of Death: | | / | | / | | (Month / Day / Year)

2.a. Time of Death: a) | | : | | (Hours : Minutes)

b) A.M. ..... A

P.M. ..... P

3.1. Last Name: | | | | | | | | | |

| | | | | | | | | |

3.2. First Name: | | | | | | | | | |

| | | | | | | | | |

3.3. Middle Name: | | | | | | | | | |

| | | | | | | | | |

B. TYPE OF DEATH

Condition of Death:

	Yes	No
4.1. During a hospital admission.....	Y	N

If Yes, complete the REGISTRY HOSPITALIZATION FORM.

4.2. Observed.....	Y	N
4.3. Traumatic.....	Y	N
4.4. Suicide.....	Y	N

Condition of Death:	Yes	No
4.5. Within 7 days of a myocardial infarction.....	Y	N
4.6. Within 7 days of cardiac surgery.....	Y	N
4.7. Within 7 days of non-cardiac surgery.....	Y	N

C. CAUSE OF DEATH

5. Cause of Death.....Cardiovascular C

Noncardiovascular N

If Noncardiovascular (N), go to Question 7.1. on page 3.

6.1. If Cardiovascular (C), indicate one type.....

Cardiac C

Stroke S

Pulmonary embolism V

Other vascular or unknown O

If Stroke (S) or Pulmonary embolism (V) or Other vascular or unknown (O), go to section D. INITIALS OF PERSON COMPLETING THIS FORM, Question 8. on page 3.

(Cardiac Death)

6.2. Choose the one most likely terminal event.....

Circle one number.

Probable arrhythmia without preceding worsening symptoms of CHF..... 1

Probable arrhythmia with some preceding worsening symptoms of CHF..... 2

Primarily related to pump failure (even if terminal event was an arrhythmia)..... 3

Other..... 4

If the number circled was 1, 2 or 3, go to section D. INITIALS OF PERSON COMPLETING THIS FORM, Question 8. on page 3.

6.3. If Other (O), specify:

PLEASE PRINT CLEARLY.

Go to section D. INITIALS OF PERSON COMPLETING THIS FORM Question 8. on page 3.

7.1. If Noncardiovascular (N), indicate the type of death.....

Circle one number.

A secondary complication of heart failure (e.g., pneumonia, hepatic or renal dysfunction, etc.).....1

A primary event (independent of heart failure).....2

Neither 1 or 2.....3

If a secondary complication (1), go to Question 8.

If neither 1 or 2 (3), go to Question 7.4.

7.2. If a primary event, was death due to cancer?.....Yes Y

No N

If No, go to Question 8.

7.3. If Yes (cancer), specify primary site:

Go to Question 8.

7.4. If Neither 1 or 2 (3), specify:

8. INITIALS OF PERSON COMPLETING THIS FORM

8. Initials.....

Appendix C
PROTOCOLS FOR SUBSTUDY PROCEDURES

I. Collection and Shipping of Blood Samples for Catecholamine and Renin

The following tubes will be provided in dry ice by the central laboratory with each shimpent to the clinical centers. Please retain the insulated box for returning the samples in dry ice.

(a) **White top** - Collection tube for plasma catecholamines.
(b) **Lavender top** - Collection tube for renin samples.
(c) **Red top** - Storage tube for plasma catecholamines (store the separated plasma in these tubes).
(d) **Blue top** - Storage tube for renin samples.
(e) **Black top** - Quality control reference for plasma tubes for catecholamine storage. Keep this in -70°C with your samples.

(1) Collection of Blood Samples:

When the study patient is at the stage for blood drawing, a 21 gauge butterfly needle will be placed in a suitable vein and is flushed with heparinized saline. The patient now rests supine quietly for 30 minutes. Use LAVENDER TOP tubes (vacutainer B-D) for collecting samples for renin assay. Use the WHITE TOP tube for collecting the samples for catecholamine assay. Prechill these tubes in ice (4°C). Then a 20 ml sample of blood is collected into a heparinized syringe (to heparinize the syringe, aspirate some heparin [5,000 units/ml] into syringe, rinse the syringe and expell the excess liquid). Four ml of blood is placed in catecholamine collection tube (WHITE TOP) while 5 ml each is placed in 3 LAVENDER TOP tubes (do not use the vacuum--open the cap and gently expell the blood to prevent hemolysis).

Cap the tubes and gently invert them 3-4 times. Make sure that the white residue at the bottom of the catecholamine collection tube (WHITE TOP) is completely dissolved. Place all the tubes in ice (4°C). All the tubes are centrifuged within one hour of collection at 1,500 x g in a refrigerated centrifuge for 15 min at 4°C (e.g., Beckman J6B with JS 4.2 rotor at 2,000 RPM).

(a) Plasma from catecholamine collection tube is placed in catecholamine storage tube (RED TOP) (see flow chart below).

(b) Plasma from renin collection tube is placed in renin storage tube (BLUE TOP).

Transfer plasma with disposable plastic pipettes. When transferring plasma sample, do not collect the buffy coat found above the red cell layer.

All tubes are to be labelled with the following:

(a) Code number of the patient
(b) date of collection
(c) center number

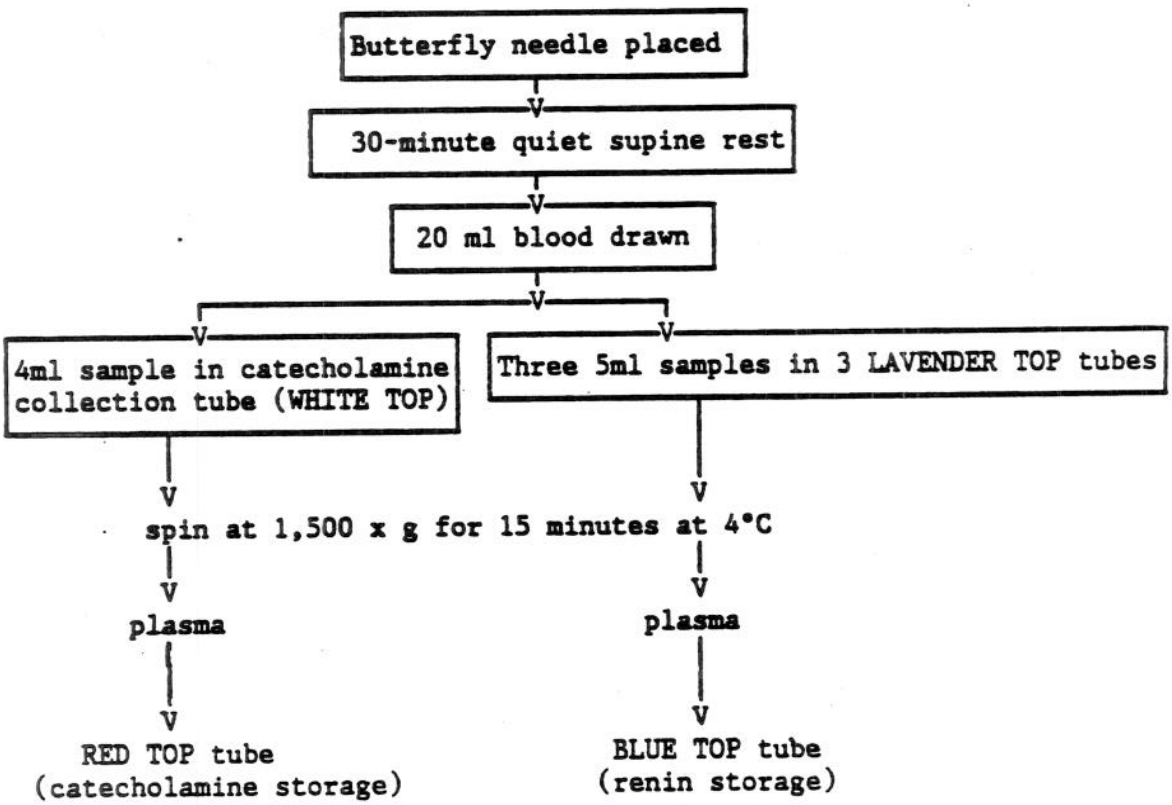
Cover the label with 3M magic tape to prevent the label from peeling or rubbing off in the freezer during storage. Store the samples in a -70°C freezer in the storage box provided. (Sample should not be stored for more than one week in a -20°C freezer.)

Central laboratory will provide, at two month intervals, a fresh lot of collection and storage tubes.

(2) Shipping of Blood Samples:

Return plasma samples every two months to the central laboratory. Return the BLACK TOP quality control tubes with them. All tubes are packed in the styrofoam shipping container provided with 5 lbs of dry ice and handed to the carrier for air delivery. (We suggest that you retain the container sent by the lab.) Avoid shipping on Friday. For shipment from Canada, use 10 lbs (4.5 kilos) of dry ice in the container and avoid shipping on Thursday or Friday. For shipment from Belgium, use 15 lbs (7 kilos) of dry ice in the container and avoid shipping on Wednesday, Thursday, or Friday. Please contact the central laboratory prior to shipping the samples. The catecholamine reference sample has been assayed by the central laboratory prior to being distributed. When returned, these samples will be reassayed to check for stability during storage of the samples at the clinical center and during transport by the carrier (quality control).

Flow Chart for Collection of Blood Samples



II. Echocardiograms

To qualify for the Registry Substudy, the echocardiogram must be of good quality. To be judged as good quality, an echocardiographic study must have the following:

(1) Adequate display of the aortic and mitral valve in the parasternal long axis view with minimal or no anterior angulation of LV apex.
(2) Adequate endocardial definition of both visualized LV walls in the parasternal long axis and apical view.
(3) Adequate endocardial definition of anterior septum and posterior wall in the short axis view with a circular appearance of the LV cavity at mid-papillary and mitral valve level.
(4) Adequate M-mode scan from LV at mid-papillary level to aortic root.

The following recording procedures will be followed.

a. Parasternal window

(1) Obtain a parasternal long axis view that shows good endocardial definition of septum and posterior walls, good visualization of mitral and aortic value as well as proximal aortic root. The view should be obtained from the intercostal space that places the LV long axis as perpendicular to the sound beam as possible. This location should be recorded for future serial studies.

(2) Obtain a parasternal short axis view at mitral valve and papillary muscles levels by rotating transducer from the long axis view. When properly angulated, the short axis view should show a circular or near circular geometry of the LV. Record an M-mode scan of the LV at papillary level gradually moving up the mitral valve and into the aortic value insuring that the M-mode cursor runs through the center of the LV cavity.

b. Apical window

(1) Obtain an apical four chamber view with the transducer as far laterally as possible to maximize size of the LV cavity and provide good visualization of mitral valve. Rotate towards the two-chamber view again insuring adequate angulation to maximize size of LV cavity.

NOTE: The following Doppler procedures are to be done only by hospitals participating in the SOLVD Echocardiography Substudy.

(2) Doppler

(a) Mitral inflow - apical four chamber view, place a 0.5-1 cm sample volume at the mitral anulus level so that during diastole it falls at the entrance at a sweep speed of 100 mm/sec.

(b) Aortic anulus (LV outflow) - apical long axis view. Place sample volume at the level of aortic anulus just proximal to aortic valve and record a minimum of 210 cardiac cycles at a sweep speed of 100 mm/sec.

(c) Direct the continuous wave (CW) beam into the ascending aorta and record 10 or more cycles after careful angulation to obtain the highest aortic peak velocity possible.

(3) Other Doppler recordings

(a) Search for mitral, aortic and tricuspid regurgitation with pulsed and CW Doppler using standard techniques. When regurgitant lesions are present, record the regurgitant jet with SW from the window providing the highest jet velocity.

(b) Ascending aorta velocity using CW Doppler from the suprasternal window.

Measurement and calculation

The original copy of the echocardiogram tapes will be sent to Dr. M.A. Quinones' laboratory in Houston for evaluation. All SOLVD patients will be studied on designated SOLVD tapes. Copies of each of the studies can be kept at the individual SOLVD center to be used locally (i.e., reports to the referring M.D.) and as backup in case the original tapes should be lost in transit.

Procedures for quality control

The quality of echocardiographic studies will be judged at the core laboratory as excellent, adequate or suboptimal for measurements. Centers with one or more suboptimal studies during the first 5 patients will be contacted directly by the director of the core laboratory to re-address the criteria to be used locally for quality judgment. The other participating centers will absorb in equal distribution the additional recruitment load.

III. Holter Monitoring

(1) Technique Procedures

Standardization of the ambulatory recording devices is mandatory. For each center, the ambulatory ECG recording devices should be able to produce a high quality ECG signal which include the following requirements:

(a) All recordings must have a standard calibration signal of 1mV (10mm) pulses over at least 8 minutes in duration for S-T analysis.

(b) A standard patient preparation utilizing a degreasing and an abrasive scrub to reduce surface impedance. (This will require an inservice with the clinic coordinators of the participating centers.)

(c) Recorders must be dual channel reel-to-reel or PR 3XST cassette recorders with frequency responses of .05-100 Hz with lead placement at CM_5 and CM_1 to allow for the detection of both ischemic events and ventricular arrhythmias. At the time of initial lead placement, alternative leads may be selected (by a predetermined algorithm) if R-wave amplitude is insufficient or evidence of MI or other factors would preclude S-T segment analysis.

(d) Test strips for signal quality will be an absolute requirement so that an adequate signal is obtained in all cases. Each center will need a test oscilloscope with a strip recorder or a single channel ECG machine for testing signal quality in each patient. Standardization pulses can be

produced either by recorders with internal calibrators or through a separate pulse generator box plugged into the recorder.

(2) Procedures for Quality Control

Quality control procedures for ambulatory electrocardiographic recordings will involve three phases. Phase I will address application techniques, Phase II ambulatory ECG equipment requirements, and Phase II ambulatory ECG tape analysis.

Phase I

This phase includes instructions to all participating centers on electrode application and skin preparation involving rigid criteria for cleaning the skin, position of electrodes at V1 and V5 positions and the application of the disposable electrodes on the skin. It is imperative that the skin be properly prepared to reduce skin impedance (3800-5000 ohms) and the site of the electrode placement be carefully chosen to eliminate the presence of artifacts and wandering baseline on the ECG recording. Electrodes should be applied on top of the bone and not on muscle or fat tissue to reduce artifacts (a detailed electrode application procedure will be included). The electrodes and lead wires should be secured with micropore tape and the use of stress loops. All ambulatory ECG recordings will be graded for tracing quality.

Phase II

All recording should be performed using AM ambulatory ECG recording devices or a comparable cardio cassette recorded with a flat frequency response of 0.05 to 100 Hz. Most manufacturers of Holter recorders would be consdered acceptable for arrhythmia documentation and S-T segment analysis except for the Oxford AM recorder which does not have an acceptable frequency response. The recording tapes should be black oxide 2.65 inches in diameter and all recorders should operate on 9V disposable batteries. The Cardio Data PR 2XST cassette recorder would be the preferred system to replace the reel-to-reel recorder since it is specifically designed to be run with the Cardio Data ST analysis software program. A standard tape calibration signal will be required for a minimum of 8 minutes on each patient. This involves a series of 1 mV calibration standards fed into the ambulatory ECG recorder for 8 minutes by an external pulse generator box or provided by recorders with internal calibrators. The Cardio Data PR 3XST cassette is equipped with an internal 8 minute calibration signal. The calibration signal would be followed by 15 seconds of ECG test strips to test for quality of the electrical signal being recorded. This requires a standard single channel 12-lead ECG machine or an oscilloscope with a strip recorder and a test cable. While obtaining the strip, the electrodes should be tapped gently to ensure the absence of artifact and baseline wander. A minimum of 5 mm amplitude at a gain of 1mV is needed on both channels. A six second segment must be sent with each tape to be scanned. (Instructions for test completion and removal of tape will be covered.)

Inservice and Training

Training sessions will be set up to cover Phases I and II for each

participating center. An instruction book with the proper steps for application of electrodes and proper ambulatory ECG recording technique will be provided. This training session should be performed at the investigators' meeting. Equipment maintenance will also be reviewed as it is important to ensure proper equipment functioning. All participating centers will be required to follow standard cleaning instructions for the external recorder surface, leadwires and the recording head. After 8 to 10 uses, each recording head should be demagnetized to ensure reliable recordings. Cables and lead wires will be checked for fraying and broken connections and discarded if warranted.

Supplies

All participating centers will be supplied with recording kits from the Core Lab consisting of 5 electrodes, 1 9V battery, gauze sponges, razor and reel-to-reel tape (or cassette tape) mailing labels. Additional supplies would be sent in bulk, such as preparation solution (Freon), prep pens for skin abrasion, micropore adhesive tape and cleaning solution for the ambulatory ECG recording head.

Phase III - Ambulatory ECG Analysis

Ambulatory ECG analysis will be performed on the Cardio Data MK4 Scanning System with an S-T analysis software program. After each tape is received it will be scanned and the results transmitted to the Coordinating Center. Quality control of the scanning system to test the reproducibility and accuracy of the MK4 will be carried out monthly and whenever the research scanner detects a malfunction of the system. This involves running a tape with known quantity of arrhythmia. Quality control of the research scanner will be performed on 2% of all recordings submitted in a random fashion from the Coordinating Center. The selected tape will be read by the quality control coordinator. If a discrepancy of greater than 10% occurs, the quality control coordinator will determine the cause and reduce the variability appropriately. Analysis of QC will be stored at the Coordinating Center. A hand count comparison will be performed on 1% of all submitted recordings. All reports will be reviewed by the staff cardiologist or his designee to confirm the ECG interpretation. Ten percent of these reports will be read blindly be a second cardiologist to quality control the interpretations. Since the appropriate quality control of tapes for silent S-T shifts is not well defined, the ambulatory monitoring laboratory at the University of Florida (Gainesville) under the supervision of Dr. Hill will randomly re-read 5% of the tapes for S-T segment quantitation.

S-T Segment Analysis

All S-T segment analysis will be performed utilizing the MK4 S-T analysis software program. To perform S-T segment analysis, eight minutes of 1mV calibration signals must be present on the analog or cassette tape to be scanned. The technician sets two S-T markers; one at the isoelectric baseline and one at the J point. A third measurement is made at .06 seconds to the right of the J point. Once set, a minute-by-minute trend will be compiled for

all minutes containing valid measurements. For the data to be used, there must be at least sixteen beats retained in every minute.

Mailing and Storage of Tapes

All participating substudy centers will be required to label and mail all accumulated tapes to the Core Lab on a weekly basis. The scanning center will be responsible to log all tapes received per center, including patient name (study initials and ID), date of ambulatory ECG recording, and date of birth. The ambulatory ECG recorder and cable number will be included on the mailing sticker so a technical difficulty can be quickly identified. All tapes will be stored in an environment with low humidity and protected from ultraviolet light.

IV. Six-minute Walking Test

The patient is to take nothing by mouth except for clear liquids for at least four hours prior to the test. Daily cardiovascular medications may be given four hours prior to the test or held until after the test. Patients should be advised not to smoke for at least two hours prior to exercise. The walking test is to be conducted in an enclosed corridor on a course 100 feet (approx. 30.5 meters) long. The corridor should not be heavily transited and should be free of obstacles and distractions. It should be divided into taped five-foot sections to allow easy measurement of the distance walked. Chairs are to be placed at either end of the course so that patients may rest when needed.

Patients are to be instructed to walk from end to end for six minutes, covering as much distance as possible. During the six minutes they may rest whenever necessary. However, patients should be encouraged to exercise to the point of exhaustion and should only terminate the walk prior to six minutes if severe shortness of breath, muscular pain, dizziness or anginal symptoms should develop. In order to standardize the test, encouragement is offered during the walk. Every thirty seconds while facing the participant, one of the following two phrases is delivered: "You're doing well" or "Keep up the good work." Instructions are given to the patient as outlined below and immediately prior to the start of exercise a marker is placed on the Holter tape. At the end of six minutes, the patient is directed to stop, a marker is placed on the Holter tape and the distance walked to the nearest foot (or meter) is recorded.

The following instructions are to be read verbatim to the patient:

> The purpose of this test is to determine how far you can walk in six minutes. You will start here and go to the chair at the end of the hall, turn around, and walk back. After arriving back at the starting point, you will go back and forth again. Go back and forth as many times as you can in the six-minute period. If necessary, stop and rest and stay there until you can start again. However, the most important thing about the test is that you cover as much distance as possible during the six-minute period.
>
> I will let you know when the six minutes are up. When I say STOP, please stand right where you are.

Do you have any questions about the test?

Please explain to me what you are going to do.

Are you ready?

Start when I say "GO."

Appendix D
STRATIFICATION FOR SUBSTUDY PARTICIPANTS

It is expected that the vast majority of the participants eligible for the SOLVD Registry will have ischemic or hypertensive heart disease, and that about 5-10% would have cardiomyopathies or other "rare" etiologies. Thus, of the 6000 expected participants for the Registry, approximately 300-600 participants would be of the "rare" etiologies, and 5400-5700 would be of the more common etiologies.

The Registry has the potential to provide valuable clinical history information on the so-called "rare birds" of congestive heart failure. Given the interest in obtaining complete and detailed baseline information on these patients, the computer program for identifying those patients to be included in the Registry Substudy will essentially sample the Registry participants with two different sampling proportions: 100% of the rare etiologies would be included in the Substudy, and somewhere around 7-13% (approximately 400-700 participants) of the ischemic heart disease participants would be included in the Substudy, to roughly complete the 1000 patient desired.

Essentially, the Substudy subsample is a stratified random sample of the Registry sample, with two strata (ischemic heart disease, other) with different sampling proportions (.07-.13, 1.00, respectively).