PROTOCOL

TRIAL TO EVALUATE THE EFFECT OF DIGITALIS ON MORTALITY IN HEART FAILURE

Digitalis Investigation Group [DIG]

FINAL PROTOCOL

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ABSTRACT

National statistics from the U.S. and several other western countries indicate that the incidence and prevalence of heart failure have been increasing in recent years. With increases in the average age of the population in many countries, the prevalence of heart failure is expected to continue to rise. The number of deaths in which heart failure was considered to be the underlying or contributing cause increased from 51,000 in 1955 to 246,000 by 1982 in the U.S. Even taking into account the growth in population, a two-fold increase in death due to heart failure was observed.

Digitalis is one of the drugs most commonly prescribed for heart failure and has been used for over 200 years. In 1986, it was one of the most commonly prescribed drugs in the U.S., accounting for over 12 million prescriptions. Despite the widespread use of digitalis, considerable controversy surrounds the appropriateness of its role and value in treating heart failure patients who are in sinus rhythm. This is reflected in markedly different rates of prescribing digitalis in various countries. Also, a number of recent small uncontrolled studies have come to apparently contradictory conclusions about the effects of digitalis on mortality in post-MI patients.

This study is sponsored by the U.S. National Heart, Lung and Blood Institute (NHLBI) and the Department of Veterans Affairs Cooperative Studies Program. This document outlines the protocol of a collaborative, international, double-blind, randomized, controlled clinical trial of patients with heart failure to assess the effect of digoxin on mortality, morbidity, and quality of life. Seven thousand patients with heart failure and an ejection fraction ≤ 0.45 will be randomized to receive either digoxin or placebo in the main trial. Heart failure patients with an ejection fraction > 0.45 will also be entered into an ancillary study. Patients will be enrolled over three years and followed for a minimum of two further years or until the end of the study.

A. BACKGROUND

1) The Medical Problem

Despite major advances in the prevention and treatment of cardiovascular diseases as evidenced by a substantial decline in the mortality rates due to acute myocardial infarction and strokes in the U.S. and several other Western countries, national statistics from some of these countries indicate that the incidence and prevalence of congestive heart failure (CHF) have been increasing in recent years. About 2.5 million individuals are currently estimated to have CHF in the U.S. CHF was responsible for about 0.5 million hospitalizations in 1985, and is the leading diagnostic-related group in the U.S. among hospital& patients over the age of 65 years. With the continuing increase in the age of the population in many countries, the prevalence of CHF is expected to continue to rise. The number of deaths in which C'HF was considered to be the underlying or contributing cause increased from 51,000 in 1955 to 246,000 by 1982 in the U.S. (1). Even accounting for the growth in the population this represents a two-fold increase. The mortality rate in CHF patients is about 50% at five years following the diagnosis, and the age-adjusted death rate showed a 21% increase, during the decade from -1968 to 1978. Additionally, about 30 to 40% of patients with CHF are hospitalized every year. Similar data are available from only a few other countries; these limited data indicate that CHF is likely to be a major clinical and public health problem in most western countries.

Digitalis is one of the drugs most commonly prescribed for CHF and has been used for over 200 years. In 1986 it was also one of the most commonly prescribed drugs in the U.S., accounting for over 12 million prescriptions. Furthermore, there has been little decline in the drug's use over the last 5 years indicating that newer treatments for CHF have not replaced the widespread use of digitalis (2). For example, 60% of patients with CHF in the Treatment Trial of the Studies of Left Ventricular Dysfunction (an ongoing large study in 100 hospitals in the U.S., Canada and Belgium) were receiving digitalis at entry into the study. Moreover, data from Worcester, Massachusetts (3) on the use of various drugs in patients with acute myocardial infarction indicate that about 40% of patients who were discharged continued to take digitalis; this proportion has remained unchanged during the last 10 years.

Despite the current widespread use of digitalis and its availability for nearly two centuries, considerable controversy surrounds the appropriateness of its role and value in treating CHF patients. A recently published survey of over 2700 physicians conducted by the American Heart Association reported a wide spectrum of opinions on the use of digitalis (4). About 2/3 of physicians considered it to be effective in improving exercise tolerance but fewer than 1/3 believed that it prolonged life. Furthermore, only about 1/3 of physicians reported that they would use digitalis as the initial drug in treating patients with CHF who were in sinus rhythm. These divergent views are reflected in markedly different rates of prescribing digitalis in various countries (e.g., relatively low frequency of use in the UK compared to much higher usage in Scandinavia and probably intermediate levels of use in the U.S.) and also within a country (e.g., a two-fold variation in use in different parts of Sweden).

In the last few years a number of investigators have studied the effects of digitalis on mortality (when used for an average of 2 years) in post-MI patients. However, all these studies, which came to apparently contradictory conclusions, were based, not on data from randomized trials, but on retrospective analyses of data bases collected primarily for other purposes. Because such methods have at least moderate inherent biases, they are generally not capable of distinguishing reliably between no

effect, moderate reductions, and modest excesses in mortality. Even a moderate effect on mortality would have substantial public health and medical importance. For example, a trial that showed a reduction in mortality of perhaps 10% or 20% would appropriately encourage the widespread use of digitalis. If, however, the trial showed that treatment had no detectable effect on mortality or major morbidity, the numbers of patients receiving the drug would decline. If digitalis was shown to increase the risk of death by only about 10% or 15%, it might prove to be responsible for about 10,000 - 20,000 deaths annually in the U.S. and many more world wide. A trial which clearly demonstrated such an adverse effect would lead to a major re-evaluation of the role of digitalis. Therefore, a large randomized trial to evaluate reliably the effect of digitalis on mortality is urgently needed.

2) Design Considerations

The effect of digoxin on mortality (positive or negative) is likely to be only moderate rather than large. Detection of such moderate effects necessitates that a randomized trial designed to study the effects on mortality be large (a study with about 2000 to 2500 end points). Such a large study can be practicable at a reasonable cost within a short time only if a large number of physicians collaborate. Fortunately, once the patients have been carefully characterized at baseline, a trial that primarily aims to study the effects of digoxin on mortality (an endpoint that can be ascertained easily without bias) or major morbidity, such as hospitalization for CHF, can be conducted reliably without extensive follow-up data collection other than the information that is routinely collected in clinical practice. A fundamental principle that underlies the design of this trial is a focus on those data or procedures that are essential to the main question (e.g., unbiased treatment allocation, important baseline patient descriptors, assessment of compliance, elicitation of major and troublesome side effects, use of relevant concomitant drugs, and unbiased and complete evaluation of major clinical outcome measures during follow-up)

3) Patient Selection and Subgroup Issues

Congestive heart failure is a syndrome that is the end result of a number of different diseases that all ultimately lead to myocardial damage and dysfunction. Patients with CHF have varying degrees of systolic or diastolic dysfunction of either or both ventricles and exhibit a variety of different compensatory responses. It is possible that once CHF develops secondary to left ventricular dysfunction, the etiology of the underlying myocardial dysfunction may not matter. On the other hand, associated pathology or compensatory mechanisms may modify the degree to which digitalis affects survival. Some small studies have suggested, but not proven that the response to digitalis might depend upon etiology (existence of ischemic heart disease), the clinical severity (NYHA class), whether or not the heart is dilated and degree of systolic dysfunction as opposed to diastolic dysfunction, i.e., that the salutary effects are primarily those on the myocardium as opposed to those on the autonomic nervous system. In addition, there is general consensus that digitalis treatment is indicated in patients with atria1 fibrillation chiefly to slow down ventricular response.

In this study we propose to primarily study a group of patients diagnosed with CHF who are in sinus rhythm and have moderate or severe impairment of left ventricular systolic function (EF $\leq$ 0.45). An ancillary study will include patients with an EF $>$ 0.45. The effects in a number of important prespecified subgroups will also be examined. It should, however, be noted that the power to examine the effects of treatment in subgroups will generally be lower than the power to detect an overall effect

(unless all the benefit is confined to one group) and that "slicing" the data many ways will increase the likelihood of observing spurious results by chance alone. We, therefore, propose that the number of subgroup hypotheses be limited to those few that have a compelling prior rationale and in which the subgroups are expected to be of reasonable size (see section El).

4) Previous Randomized Trials of Digitalis

Only 11 randomized trials (5-16) have been identified (Table 1). The first two included patients without clear evidence of CHF (5-6) and the third included patients with atria1 fibrillation (7). Five small trials (8-12) of CHF evaluated patients using a crossover design with treatment periods of 2-3 months each. Almost all patients were withdrawn from previous chronic use of digitalis and were randomized to placebo or digoxin. Lee et al. (8) found a significant improvement in heart failure score (based upon clinical and radiographic changes) in the digoxin treated patients, although similar numbers of patients deteriorated clinically during the. control and active phases. Retrospective analyses suggested that presence of a third heart sound, enlarged heart, and low ejection fraction correlated with benefit among responders. No improvement in EF with digoxin was found. Fleg et al. (9) reported no difference in exercise capacity, physical findings, or symptoms between digoxin and placebo in a study of 40 patients. Taggart et al. (10) found no clear evidence of benefit in 22 patients (4 patients developed worsening CHF while on placebo compared to 2 on digoxin). Guyatt et al. (11) screened 380 patients, included 30 patients and reported the results in the 20 who completed the study. A beneficial effect with respect to symptoms, clinical assessment of CHF, walking capacity, and EF was found during the digoxin period compared to placebo. The large proportion of patients excluded or with missing end point data makes interpretation of the results difficult.

Pugh et al. (12) studied 44 patients in a double-blind crossover study and observed that 11 (25%) of patients deteriorated clinically while on placebo compared to only 5 (11 %) while on digoxin. However, most patients who deteriorated could be stabilized by increasing the dose of diuretics. Only two patients required reintroduction of digoxin. Benefit from digoxin could not be predicted on the basis of the third heart sound, hemodynamic criteria, echocardiographic measures or heart size.

Three larger trials have compared digoxin with placebo and a second active drug. In the captopril-digoxin trial (13) 196 patients were randomized to digoxin or placebo. All patients had an EF < 40% and 85% of the patients were in NYHA class I-XI. After six months there was no difference in exercise time while EF increased by 4.1% in the digoxin group, compared to 1.3 % in the placebo group ($p < 0.05$). The number of hospitalizations due to CHF was eight in the digoxin and 19 in the placebo group. Seven deaths occurred in the digitalis group and six in the placebo group. In the xamoteroldigoxin trial (14), 204 patients were randomized to digoxin or placebo; 80% were in NYHA class I-II. A fixed dose of 0.25 mg digoxin/day was administered. In those who completed the three-month double-blind phase there was no difference in exercise duration between the digitalis and the placebo groups. There was no difference in symptoms, although a decrease in the number of patients with peripheral edema and rales was found among digitalis treated patients. No deaths occurred in the digitalis group compared to one in the placebo group. In the milrinone/digoxin trial (15), 111 patients were randomized to digitalis or placebo. After three months, EF increased by 1.7% in the dlgoxin group compared to a decrease of 2% in the placebo group-@ < 0,01). Exercise tolerance @creased by

TABLE I RANDOMIZED, CONTROLLED TRIALS OF DIGITALIS IN CHF

Trial	Design	No Patients	Digoxin dose (mean)	Dosing by Serum level	Mean Plasma Concentration	Treatment Duration	Withdrawal rate Digoxin	Withdrawal rate Placebo	Endpoint	Comments
1. Starr 1969	Withdrawal crossover	12	digitoxin 0.1 mg/d	no		4 weeks			Clinical Status	probably not CHF
2. Kirsten 1973	"	22	?	no		6 months				probablynot CHF
3. Dobbs 197'7	"	46	0.125.0.5	yes	1.4 ng/ml	6 weeks			Clinical Status	13 patients with atria1 fibrillation
4. Lee 1982	"	35	0.125-1.0	yes	> 1.2 ng/ml	2.5 months	29%		CHF score	NYHA I-III
5. Fleg 1982	"	40	0.125-0.5 (0.24)	yes	1.4 ng/mls	3 months	25%		Exercise tolerance, echo	NYHA I-III
6. Taggart 1983	"	22	?	no	1.2 ng/ml	3 months			Clinical Status	21/22 patients in NYHA I-II
7. Guyatt 1988	17/30 withdrawal crossover	30	0.125-0.937 (0.39)	yes	1.75 nmo/1	7 weeks	33%		6 min walk echo	380 patients screened
8. Captopril-Digoxin 1988	65 % withdrawal parallel	196	0.125-0.37s	yes	0.7-2.5 ng/ml	6 months	4.2%	15%	Exercise	85% NYHA I-II
9. Xamoterol-Digoxin 1988	50% withdrawal parallel	213	0.25	no	0.87 ng/ml	3 months	15.8%	16.7%	Exercise	87% NYHA I-II tolerance
10. Milrinone Digoxin 1987	Withdrawal parallel	110	0.125-0.5	yes (0.21)	1.2 ng/ml	3 months	4%		Exercise	NYHA II-IV tolerance
11. Pugh 1989	Withdrawal crossover	44	0.25/d	no	?	8 weeks	5%	5%	Hemodyn, symptoms	NYHA II-III

14% ($p < 0.05$) compared to placebo. There were three deaths in the digoxin group compared to four in the placebo group. None of the above trials reported preferential benefit in any particular subgroup.

The effect of digitalis on survival among patients following myocardial infarction has been examined by several investigators using analyses of existing databases (16-21). Two studies (16-17) suggested that digitalis might be harmful because in these studies, digitalis use was associated with a higher risk of death compared to those not using digitalis, after adjustment for differences in risk factors. However, four other studies (18-21) suggested that the higher mortality seen among digitalis treated patients was entirely accounted for by a higher incidence of adverse risk factors. A critical review of the studies indicates that the effect of digitalis on survival cannot be addressed by retrospective analyses of data bases, but requires large randomized controlled trials (22). In this context, it is worth noting that an overview of all randomized trials with inotropic agents other than digitalis indicates excess mortality with each class of agent, and overall, a two-fold excess death rate in the treated patients ($p < 0.001$) (23).

5) Withdrawal From Digoxin

In any large trial evaluating the role of digoxin in CHF, it is important to enroll a reasonable proportion of patients who had been on digoxin prior to entry into the study, as well as those who had not previously been on the drug. Such a study would provide an answer applicable to a broader group of patients and would also be more feasible.

One potential problem with enrolling patients previously on digoxin is that those "requiring" the drug who are randomized to placebo might have worsening of their heart failure. Thus, they might be prescribed open-label digoxin thereby decreasing the contrast between the two randomized groups. On the other hand, excluding such patients from the trials will bias the study against digoxin. A review of all published studies suggests that worsening of heart failure may occur in less than 5% of patients following the withdrawal of digoxin. This proportion is likely to be smaller if ACE-inhibitors are used commonly. Therefore, the approach used in the protocol tries to maximize randomization of patients who might potentially be "responders" and minimize deterioration by using ACE-inhibitors in all patients prior to randomization.

6) Standard Therapy

In any trial, imbalances in concomitant treatments could potentially confound the interpretation or detection of a difference between the active and control groups. In order to minimize this, it is important that patients be on a stable dose of diuretic at entry into the trial. For patients who are not an ACE-inhibitors, it is strongly recommended that these patients receive this class of agents (enalapril, captopril , or lisinopril) unless they are known to be intolerant or their ejection fraction is > 0.45. This recommendation is based on the currently available data suggesting improvement in symptoms, exercise tolerance, and ejection fraction in patients with mild or moderate heart failure. Although improvement in survival has been demonstrated with NYHA class IV patients, similar data are not available in patients with NYHA classes I to III. The available data on the effects of ACE-inhibitors in patients with an EF > 0.45 are limited. Therefore, the choice of co-therapy in such patients is left to the judgment of the treating physician.

The Studies of Left Ventricular Dysfunction (SOLVD) will report in early 1991, coinciding with the start of recruitment into the digitalis trial. If SOLVD demonstrates clear reduction in mortality or morbidity, the currently proposed policy would be appropriate and the use of ACE-inhibitors will be required. If SOLVD does not provide evidence of benefit with ACE-inhibitors, this therapy will not be mandated. Instead, specific guidelines will be developed and the trial will be analyzed by strata based upon use of ACE-inhibitors at baseline.

B. STUDY DESIGN

1) Objectives

Main Objective: The main objective is to determine whether digitalis has beneficial, harmful or no effect on total mortality inpatients with clinical heart failure and an ejection fraction ≤ 0.45.

Subsidiary Objectives: The most important subsidiary objective is to determine whether digitalis treatment reduces hospitalization for worsening heart failure. Other subsidiary objectives include assessing the effect of treatment on:

a) cardiovascular mortality;
b) death due to progressive heart failure;
c) deaths and hospitalization for CHF in the group of patients with an EF > 0.45 (ancillary study);
d) hospitalizations for all other causes, including digitalis toxicity; and
e) quality of life.

Subgroups: The effects of treatment on mortality will be assessed separately in the following subgroups:

a) In patients according to EF. It is postulated that any beneficial effect of digitalis would be larger in patients with low EF.
b) In patients according to heart size on chest x-ray. It is postulated that the effect of digitalis would be larger or confined to the group of patients with dilated hearts.

The effects of digoxin will also be evaluated based upon etiology, previous use of digoxin, and among those with different baseline NYHA classes. The effect of digoxin on mortality is expected to be more marked in the first two years from the time of randomization. Therefore, mortality and hospitalizations for CHF that occur within the first two years will be analyzed separately.

2) Patient Eligibility

Patients with clinical heart failure (NYHA Class I-IV) with an ejection fraction ≤ 0.45 are eligible for the main study. The diagnosis of clinical heart failure is based on current or past evidence of low output (such as limitation of activity) or congestion (edema, elevated JVP, or rales or radiologic evidence of pulmonary congestion). Patients with an EF > 0.45 will be entered into a-parallel, but separate, ancillary study.

The digitalis study will attempt to enroll as representative a sample of both women and minorities as possible, consistent with the prevalence of heart failure among these groups, but taking into consideration the location and kinds of participating centers. Because a number of VA hospitals will be participating, it is expected that the percent of women will be somewhat smaller than might otherwise be the case. Similarly, because a number of hospitals from Canada are participating, the percents of Blacks and Hispanics will likely be smaller than would otherwise be the case.

3) Exclusion Criteria

- Age <21 years
- Baseline left ventricular EF not available
- Myocardial infarction, cardiac surgery, or PTCA within four weeks
- Unstable or refractory angina ≤ 1 month
- II° - III° AV-block without a pacemaker
- Atria1 fibrillation (with or without pacemaker) or atria1 flutter
- Cor pulmonale
- Constrictive pericarditis (such patients are eligible after surgery)
- Acute myocarditis
- Hypertrophic cardiomyopathy
- Amyloid cardiomyopathy
- Complex congenital heart disease
- Pre-excitation syndromes
- Current treatment with intravenous inotropic agents
- Potassium below 3.2 mmol /l or above 5.5 mmol /l
- Need for cardiac surgery (e.g., severe valvular disease, planned CABG surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA.) Patients on heart transplant list are not eligible.
- Sick sinus syndrome without pacemaker.
- Recognizable noncardiac causes of CHF
- Significant renal insufficiency (creatinine > 3.0 mg/dl) or severe liver disease
- Any noncardiac disease which shortens life expectancy to less than three years (e.g., most cancers)
- Patient is unlikely to comply with the protocol requirements for follow-up and drug adherence (e.g., chronic alcoholism, no fixed address)

4) Informed Consent

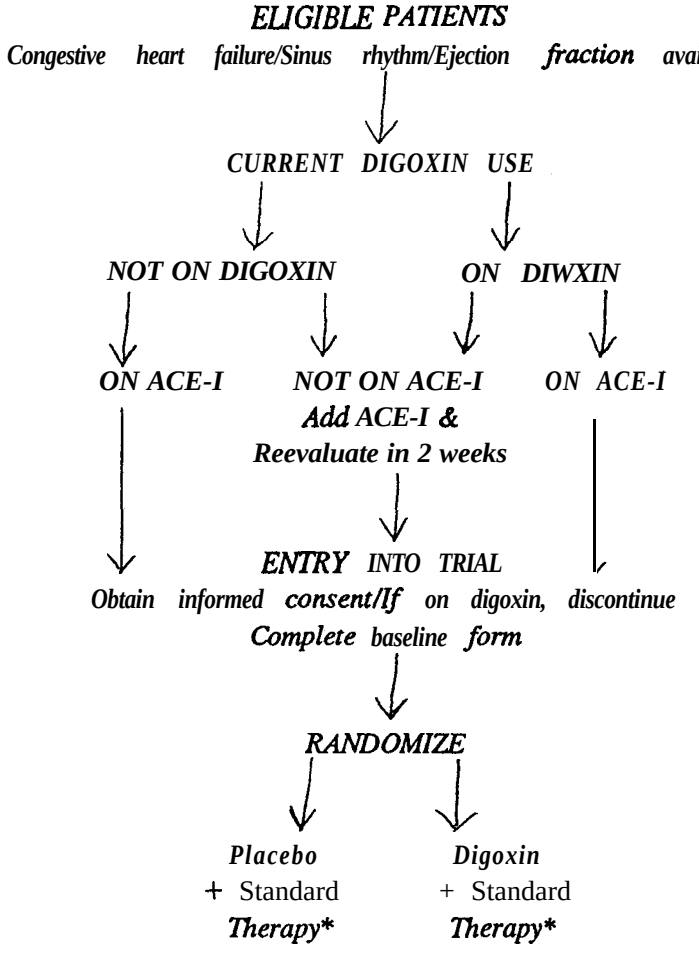
Standard forms meeting regulatory requirements in each participating country will be developed. However, all consent forms will at a minimum, meet U.S. Federal Government requirements (see Appendix I).

5) Stabilization Phase

Prior to randomization, all patients should have been clinically stable for at least two weeks. In patients not receiving ACE-inhibitors, this should be prescribed unless there are known contraindications or the Patient is known to have developed side effects to one of these agents. Other aspects such as low salt diet, physical activity and diuretics shill also be optimized. Such patients should be reassessed after a two-week period on ACE-inhibitors prior to randomization.

6) Patients Receiving Previous Digoxin Therapy

It is desirable to maximize the randomization of patients who might be responsive to digoxin. Patients who have previously been receiving an ACE-inhibitor and have been stable for at least two weeks can be randomized, as soon as eligibility is determined, to continuation of digoxin therapy or replacement with digoxin placebo (i.e., open-label digoxin is stopped and the trial medication is substituted). Patients on digitalis, but not receiving an ACE-inhibitor, should be prescribed an ACE-inhibitor and seen two weeks later. If they have been clinically stable, use of open-label digoxin is stopped and the patient is randomized as above. This will minimize the number of patients who will require open-label digoxin reinstated after randomization (see Figure 1).



*It is strongly recommended that standard therapy include ACE-inhibitors in patients with EF ≤ 0.45 unless specifically contraindicated.

FIGURE 1. Randomization Scheme

(This page revised 10/91)

7) Baseline Data Collection

Eligible patients who have been clinically stable (with no change in medication and stable symptoms) for a minimum of two weeks will be enrolled. At this time the baseline data will be collected (Appendix IIA).

Ejection fraction measurements and chest X-rays within six months of randomization will be accepted if they fulfill the criteria of the study, if no major cardiac event (e.g., MI, heart surgery) that is likely to have altered cardiac function has occurred between the investigation and randomization, and the patient has remained clinically stable.

The EF must be assessed by one of the following techniques:

a) Radionuclide left ventricular angiography (MUGA or first pass).
b) Left ventricular contrast angiography (RAO or biplane).
c) 2-D echocardiogram (by a computer program, area-length method, or by modified Simpsons' rule).

If an EF has been performed several times within the previous six months, the investigator should choose the most recent EF. If more than one technique to determine EF has been used within a relatively short period and during which the patient's clinical condition has remained unchanged, then angiographic or radionuclide techniques are preferable to echocardiograms. The EF to be considered for eligibility may not be performed within seven days of an acute myocardial infarction, percutaneous transluminal angioplasty, or cardiac surgery (i.e., CABG or valve replacement). While the use of different methods for EF measurements makes it more difficult to define a precise level of ventricular function, it will, however, be possible to reliably discriminate between low, intermediate and good LV function. Excellent correlations between EF calculated from 2-D echocardiograms (using the above methods described) and other techniques have been demonstrated in numerous studies. Moreover, the use of different techniques to evaluate LV function reflects varying clinical practice and will maximize patient recruitment. Such a strategy has been used successfully by previous large trials and has been validated (Appendix III).

Some of the key data collected at baseline will be immediately transmitted over the telephone prior to issuing the randomization number. This procedure ensures that only eligible patients are randomized and that certain key baseline data are complete in all patients. In addition, an appropriate dose of digoxin is recommended. The rest of the baseline data will be collected on a form which is mailed in a pre-addressed stamped envelope to the Data Coordinating Center (Appendix IIA); one copy of the form is kept with the patient's records.

8) Telephone Randomization

The randomization information in Figure 2 is to be provided to the Data Coordinating Center over the telephone. After receipt of complete and appropriate baseline data over the telephone, the patient is randomized and assigned a DIG starter kit that bears the randomization number assigned by the Data Coordinating Center. This kit contains the study medication (digoxin/placebo) (see Section 10). This number should be written in the box at the top right-hand corner and on line 11 of the Baseline Form

BASELINE FORM

Randomization Number
691/- - - -

Local Center Name VAMC, West Los Angeles, CA

PRINT Patient Name _____
Last First M.I.

Date of Randomization Mo __ __ Day __ __ Yr __ __

Items 1 through 9 must be transmitted over the telephone at the time of randomization.

1. SOCIAL SECURITY NUMBER ..... - - - - - - - - -
2. DATE OF BIRTH ..... Mo __ __ Day __ __ Yr - -
3. EJECTION FRACTION (percent) ..... - -
   METHOD (1=Radionuclide, 2 =Angiography, 3=2-D Echo) .....
4. SEX (1=Male, 2=Female) .....
5. RACE (1=White, 2=Black, 3=Other) .....
6. CHEST X-RAY (CT-ratio) ..... .0- -
7. WEIGHT ..... Kg OR __ __ __ lbs.
8. HEIGHT ..... - - - cms OR - - - inches
9. SERUM CREATININE LEVEL ..... mg/dl OR - - - μ mol/l
9A SERUM POTASSIUM LEVEL ..... __.__mEq/l OR __.__mmol/l
10. PLEASE RECORD RECOMMENDED DIGOXIN DOSE ..... 0.___
11. PLEASE RECORD RANDOMIZATION NUMBER ..... 6 9 1 /- - - -

FIGURE 2. Information to be transmitted over the telephone prior to randomization.

(see Figure 2). The patient is dispensed one bottle of the study medication from the kit and a date for the first follow-up visit (4 weeks ± 1 week) is set. At this visit, each patient should be provided with a patient identification card which indicates the date of the next visit, a brief description of the study, contact telephone numbers in case of questions or emergency, and his or her physician's name. DIG pill dispenser and medication calendar will also be provided. At all subsequent visits, one or two bottles of the study medication will be dispensed depending upon the dose prescribed and the interval between visits. Patients prescribed 0.125 (one tablet) or 0.25 mg (two tablets) per day will be given one bottle of study medication while patients prescribed 0.375 (three tablets) or 0.50 mg (four tablets) per day will be given two bottles.

(This page revised 7/92)

9) Follow-Up Visits

Schedule: The first follow-up visit will be scheduled at four weeks (± 1 week) after randomization. At this visit, in addition to filling out the Follow-Up Form (see Appendix IIB), a blood sample to determine the digoxin level will be drawn in the first 500 patients entering the study. Patients from whom blood should be drawn for digoxin measures will be identified at the time of randomization by the Data Coordinating Center. On the day of each scheduled visit, patients are instructed to withhold their dose of study medication until after the visit is completed A Digoxin Blood Level Form is completed and mailed to the Central Laboratory (Appendix IID). After this visit the patients will be seen at four-month (± 4 weeks) intervals until the end of the study. Any participant who misses a study visit should be contacted as soon as possible to reschedule the regular follow-up visit before the participant runs out of tablets.

Data Collection* The current address and telephone number of the participant should be verified at each visit. At each visit an identical Follow-Up Form will be filled out and mailed to the Data Coordinating Center (Appendix IIB). If the participant has died, a Follow-Up Form (as a means of immediate notification) should immediately be mailed to the Data Coordinating Center, even-if the exact cause of death is not yet known. Once the cause of death is ascertained by review of hospital charts or death certificates, another Follow-Up Form with this information should be completed and mailed. On the basis of all available clinical information, each death should be classified as cardiovascular or noncardiovascular. If cardiovascular, the study physician using all available information, should state if the death was presumed to be primarily arrhythmic or primarily due to progressive heart failure. If the patient had been hospitalized prior to a visit or has suffered from suspected digoxin toxicity, a separate Event Form (Appendix IIC) should be filled out for each hospitalization or episode of digoxin toxicity. Information regarding hospitalizations should be based on review of hospital records. The main diagnoses for each hospitaliition should be recorded.

10) Drug Administration

Four different doses of digoxin or matching placebo can be used (0.125 mg/day, 0.25 mg/day, 0.375 mg/day, and 0.50 mg/day). Drugs will be provided in only one strength (0.125 mg). Therefore, patients should be instructed to take one, two, three, or four tablets as appropriate. The initial dose will be recommended by the Data Coordinating Center based upon the patient's age, sex,' weight, and serum creatinine level (Appendix IV). It will be calculated automatically at the Data Coordinating Center by entering these data into a computer at the time of randomization. The dose recommended is aimed at achieving digoxin blood levels in the therapeutic range. Other factors, such as concomitant medications, clinical conditions, or previous stable dose of digoxin that the patient tolerated may occasionally prompt the physician to use an initial dose that is lower or higher than the one recommended. Patients on current digoxin therapy known to be within the therapeutic range (by prior measurement of plasma concentration) should be given the same dose of trial medication. The final choice of dose of digoxin (or placebo) is made by the treating physician. During the course of the trial, dose adjustments are allowed at the discretion of the treating physician if the clinical condition or other factors change. In order to minimize use of open-label digoxin, avoid imbalance in use of other vasodilators, and for unbiased assessment of secondary end points, every effort must be taken to avoid unblinding. Therefore, investigators are discouraged from obtaining digoxin blood levels except in life-threatening emergencies (see sections B 13-B16).

11) Concomitant Medication

It is important to consider possible interactions with other drugs when determining the individual dose. It is recommended that the dose of trial medication be halved in patients concurrently treated with amiodarone, verapamil, or quinidine. If a specific patient is known to have safely tolerated a higher dose along with one of these drugs, then the physician can choose to use this dose. In order to minimize the potential for imbalance of other drugs used to treat CHF, it is important that patients are stabilized on a regimen that includes an ACE-inhibitor (except if a patient is known to be intolerant or in patient'; with an EF > 0.45) before randomization. In addition, patients should be on a stable dose of diuretics at entry into the trial. The use of such drugs during the trial will be recorded at each follow-up visit.

12) Adherence

It is important to keep as many patients as possible on assigned therapy. Monitoring adherence will be based on tablet count at each scheduled visit. A calibrated, graduated cylinder, provided by the study. can be used to count the approximate number of tablets that are returned. An accompanying chart will indicate the level of patient adherence. If adherence is less than 80% the participant should be encouraged to take a higher proportion of tablets, unless specific side effects have occurred. It is preferable in cases of side effects that the patients continue on a lower dose of the study drug rather than completely stopping it. Patients who have been unblinded due to serious toxicity or other reasons should, ii possible, continue on the assigned therapy after appropriate dose reductions. This preserves the statistical power of the trial and reinforces to the patients that they are still part of the study. All patients will remain in the group they were originally allocated to for all analyses.

13) Management During Intercurrent Events

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 intercurrent events (serum digoxin levels should not be obtained locally except when absolutely essential for the immediate management of the patient). Some common situations and suggestions for patient management are outlined below:

a) Worsening Congestive Heart Failure: Study drug can usually be continued. The patient's heart failure should be treated by conventional measures (other than open-label digoxin). For example, the dose of diuretics or ACE-inhibitors could be increased or other vasodilators (e.g., nitrates or hydralazine) could be added. Patients who are thought to be clinically in need of digoxin, after the above measures have been tried, can have the study drug discontinued and be started on open-label digoxin. The patients will remain in the originally allocated groups, for the outcome analyses.

b) Acute Myocardial Infarction: At the discretion of the treating physician, the study drug may be stopped during the early phase following myocardial infarction, but should be restarted as soon as possible.

c) Supraventricular Arrhythmias: If toxicity is suspected, the study drug should be stopped or the dose decreased, without unblinding the treatment. If a patient develops atrial fibrillation or flutter the study drug may be stopped and open-label digoxin may be prescribed to control rapid ventricular rate. Other symptomatic supraventricular arrhythmias should, if possible, be treated with calcium channel blockers, intravenous adenosine, or other antiarrhythmic drugs. Note that most patients who develop a supraventricular arrhythmia while receiving digoxin do not have digoxin toxicity.

d) Ventricular Arrhythmias: If toxicity is suspected, the study drug should be temporarily stopped or the dose decreased. Other symptomatic ventricular arrhythmias may be treated with appropriate antiarrhythmic agents at the discretion of the treating physician. Note that most patients with heart failure have asymptomatic ventricular arrhythmia. These arrhythmias are rarely due to digoxin toxicity.

If any of the above events is associated with a hospitalization, an Event Form (Appendix IIC) should be completed and mailed to the Data Coordinating Center.

e) Suspected Digitalis Toxicity: Management of the individual patient depends upon the physician's judgment. However, all such events should be recorded on the Event Form (Appendix IIC) and mailed to the Data Coordinating Center. Three categories for severity of symptoms are identified below:

i) The patient has symptoms or signs that are nonspecific but might indicate toxicity. In such cases the dose of the study drug may be decreased or temporarily discontinued but should be reinstituted later. No blood is drawn for determining a digoxin concentration.

ii) The patient has symptoms or signs that make drug toxicity highly likelv. The study drug should be discontinued or the dose decreased. An Event Form (Appendix IIC) is completed and mailed to the Data Coordinating Center. A blood sample for determination of serum digoxin concentration is drawn and sent to the Central Laboratory by express mail in tubes provided by the study along with a Digoxin Blood Level Form (Appendix IID). It is expected that approximately three to four working days will be needed until a report (as to whether or not the digoxin blood level is consistent with toxicity) is returned to the clinic.

iii) Serious toxicity is suspected. If knowledge of the treatment allocation is judged to be essential for the immediate management of the patient, an emergency unblinding by telephone is possible 24 hours a day (Pharmacy Coordinating Center, Albuquerque, New Mexico). Local analysis of the serum concentration of digoxin in these cases is allowed. An Event Form (Appendix IIC) is completed and mailed to the Data Coordinating Center. Other situations, such as accidental or intentional overdose, may also prompt unblinding and local analysis of digoxin concentrations. The Pharmacy Coordinating Center must immediately be informed of all cases of unblinding or if blood is analyzed locally for digoxin blood levels.

14) Routine Blood Digoxin Levels

Blood samples will be obtained from the first 500 patients (i.e., 250 patients receiving digoxin) enrolled in the study at the one-month and one-year follow-up examinations in order to assess whether:

a) most patients are in the therapeutic range
b) further dose-titration is necessary in the trial
c) routine monitoring of digoxin blood levels is useful in predicting and avoiding digoxin toxicity. The one-month data will be reviewed by the Steering Committee and the Data and Safety Monitoring Board (DSMB), which will then make recommendations whether or not this practice should be continued or modified.

Although these goals have been accomplished, recent data from two other studies indicate that elevated digoxin levels even within the currently accepted therapeutic range correlate with a higher mortality. These studies are small and retrospective and, therefore, the conclusions may not be reliable. The DSMB recommended the following:

a) All patients have a one month and a twelve month routine digoxin blood levels.
b) Serum potassium level supplement at baseline on all patients already randomized and to be randomized.
c) Serum potassium, creatinine, and magnesium levels on all routine one month and twelve month samples and in cases of suspected digoxin toxicity.
d) Serum potassium and creatinine levels on the first day of hospitalization or at diagnosis of suspected digoxin toxicity. In addition, obtain serum votassium and creatinine on all past cases of suspected digoxin toxicity.

The data forms have been revised to incorporate these changes.

15) Central Laboratory for Digoxin Analyses

A Central Laboratory will be available for the study. All routine blood samples from the first 500 patients must be drawn 6-24 hours after the last dose. In order to facilitate this, patients should be advise.1 not to take their study medication until after their clinic visit. A Digoxin Blood Level Form (Appendix IID) with patient identifiers, dose of digoxin/placebo and time between last dose and the blood sampling should be sent with the blood sample. These samples will be picked up by the Central Laboratory in batches. The serum digoxin concentration in individual patients will not be reported to the clinic,;. These data will be reviewed centrally and presented to the DSMB.

Blood samples from patients with a high likelihood of toxicity should be sent by express mail to the Central Laboratory. An Event Form (Appendix IIC) is also completed and mailed to the Data Coordinating Center. If possible, the sample should be drawn 6-24 hours after the previous dose.

(This page revised 7/92)

In cases of suspected toxicity, the result of the analysis is transmitted from the Central Laboratory to the Data Coordinating Center. The Data Coordinating Center informs the clinic of the results by fax or by telephone (backed by a written report). The result is reported as one of three levels: Probably toxic (> 2.5 ng/ml), therapeutic or possibly toxic (0.8-2.5 ng/ml) or subtherapeutic (< 0.8 ng/ml). Placebo patients will be reported to be in the low group. It is expected that the results will be available at the clinic within three to four working days of mailing the blood tubes.

16) Emergency Unblinding

Emergency unblinding can be done by telephone 24 hours a day. This should be done in all cases where unblinding is necessary or if blood levels are drawn and analyzed locally. In case of milder side effects, the treating physician has the option of decreasing the dose or temporarily discontinuing the blinded drug. Similarly, patients who are felt clinically to be unresponsive to therapy and in need of digoxin, after all other therapy has failed, can have the study drug stopped, and then be started on open-label digitalis. In this case, unblinding should not be necessary. All patients will, however, continue to be part of the study and be followed until the scheduled end of the study. They will be included in the analysis of efficacy and will remain in the group to which they were-originally allocated.

17) Training, Meetings and Monitoring Data Quality

Meetings will be held with investigators to familiarize them with all the procedures of the study at the start of the study and regularly during the course of the trial. Staff from the Project Office and both of the Coordinating Centers will provide additional assistance to the clinics in answering questions about the protocol and helping to solve problems. In addition, a videotape that describes the study protocol, randomization procedure, study aids and drug distribution process will be provided to each clinic. Because the integrity and credibility of the study depends on high quality data, the data collection will be regularly monitored. The Data Coordinating Center will perform edit checks on the data as they are entered and will generate reports for the Steering Committee that depict timely receipt of data, consistency over forms, error rates, and randomization rates.

18) Evaluation of Protocol and Procedures

To achieve the goals of the trial, a large organization involving about 200 to 250 centers in the United States and Canada is necessary. To evaluate whether this organization is adequate, whether it is feasible to enroll a sufficient number of patients with heart failure, and whether all aspects of the protocol can be satisfactorily implemented, the main study will be preceded by an initial phase. During this phase, about 100 centers (about 50 in each country) will recruit a total of 1000 patients. When 1000 patients have passed their first follow-up visit, the data will be evaluated by the Steering Committee and the independent Data and Safety Monitoring Board. The specific goals of this review are to evaluate:

a) the overall study organization, timeliness and completeness of the data forms.
b) the overall availability of Patients for the study.
c) the distribution of the enrolled patients among the subgroups which have been designated as important.
d) the quality of the data.
e) whether the proposed method of drug dosing results in adequate serum digoxin concentrations.

C. STUDY SIZE AND MONITORING

1) Study Size

In reviewing the available data from previous studies of heart failure, several factors have the potential to affect the mortality rate in the control group and the observed impact of digoxin on mortality. Among these are the proportion of NYHA class III and IV patients, the percent of patients randomized to placebo who begin to use digitalis ("drop-in rate"), and the percent of patients randomized to digoxin who stop using the drug ("dropout" rate).

Currently available data from the CASS registry and the VHeFT-1 trial indicate a three-year mortality rate of about 40% to 45% among heart failure patients not receiving vasodilator therapy. Vasodilator therapy could potentially decrease the mortality by, one-fifth or one-sixth. Therefore it would be more realistic to assume a lower event rate if a' high proportion of patients are receiving an ACE-inhibitor and also because patients entering trials often experience a lower than expected event

rate. A three-year mortality rate, in the range of 27% (i.e., about 9% per year) to 30% (about 10% per year) is considered likely and is used for sample size calculations in Table 2. Based upon experiences from previous trials, it is assumed that at the end of follow-up 15% of patients will use open-label digoxin in the placebo group and that 15% of patients randomized to the digoxin group will stop taking digoxin. Assumed treatment effects of long term (i.e., over three years) digoxin are 20% and 15%. Accounting for noncompliance, the observed effects are in the range of 10% to 15%. For example, a three-year mortality rate of 27% in the placebo group and 23% in the digoxin group is equivalent to a 15% treatment effect. When taking account of the assumed drop-in rate and dropout rate, this is equivalent to an observed 12% to 13% treatment effect. Table 2 provides the numbers of patients that are required to have a 90% probability of detecting a difference using a two-tailed alpha of 0.05 under a variety of assumptions. Based on Table 2, the Steering Committee decided that the main study should consist of at least 7,000 patients with an EF $\leq$ 0.45. If the treatment effects are' larger than 15%, then clear results are likely to emerge early. If the observed treatment effects are 101, then the study will still have moderately high power (80%) to detect such differences. Patients with an EF > 0.45 will be entered into a ancillary study to assess if the effects of digoxin on the combined end point of mortality and hospitalization for CHF are consistent with the overall results.

TABLE 2: RANGE OF STUDY SIZE UNDER A NUMBER OF ASSUMPTIONS

Common Assumptions For All Calculations:

a) Option A: Placebo drop-ins, 115% over three years (5% per year); Digoxin dropouts, 15% over three years (5% per year)

b) Option B: 5 % dropouts/drop-ins the first month, then 5 % in the remaining 11 months and each subsequent year (total of 20% at the end of the study)

Three-year Mortality Rate	Hypothesized Percentage Reduction in Mortality*	
	15%	20%
27% (15 % noncompliance)	6700 (13%)	3700 (17%)
(20% noncompliance)	7500 (12%)	4100 (16%)
30% (15% noncompliance)	5800 (13%)	3200 (17%)
(20% noncompliance)	6500 (12%)	3600 (16%)

*Observed risk reductions are in parentheses.

2) Statistical Analyses

The primary measure of efficacy is mortality from any cause. The analysis will include all deaths up to a common termination point. Subsidiary analyses of mortality due to progressive heart failure and deaths at two years will be performed. Additionally, the effect of treatment on vascular deaths, hospitalizations due to worsening CHF, and hospitalization for digitalis toxicity will be analyzed. Survival curves will be estimated by the Kaplan-Meier method and compared using the log-rank statistic.

All prior subgroup hypothesis will be examined by tests of interactions. In particular a regression analysis will assess whether ejection fraction modulates the effect of digoxin on mortality and morbidity. If tests of interaction or regression are significant, then estimates of treatment effects within each subgroup will be derived. The tests for significance within a subgroup will be adjusted for multiplicity using Bonferroni's inequality. No p-values will be assigned for data-derived subgroups.

3) Interim Monitoring

The Data Coordinating Center is responsible for collection of the study data and for preparing reports ta the Steering Committee and the Data and Safety Monitoring Board (DSMB). Reports to the DSMB will include information on the progress of the study, data quality, end points and toxicity. A recommendation to stop the study early can be made by the DSMB to the NHLBI if convincing evidence of benefit or harm is detected. At an early meeting of the DSMB, a thorough discussion of monitoring methods will be presented and they will choose to adopt an appropriate scheme. However, the results of these analyses are not binding on the DSMB, but merely provide a framework in which to consider other relevant external or internal data in making recommendations regarding early termination or modification of the study.

D. STUDY ORGANIZATION

1) Steering Committee

The Steering Committee is composed of experts on heart failure, digitalis, and clinical trial design; and representatives of the NHLBI Project Office, the VA, the Data Coordinating Center, and the Pharmacy Coordinating Center. All members of the Steering Committee are appointed by the NHLBI Director. The Steering Committee will oversee all aspects of the study, including protocol development, patient recruitment and follow-up, data completeness, and analyses and publication of results.

The members of the Steering Committee are:

- Richard Gorlin, M.D., Chairman
  Mount Sinai Hospital
  New York, NY 10029

- Jay N. Cohn, M.D.
  Univ. of Minnesota Medical School
  Minneapolis, MN 55455

- Gilles R. Dagenais, M.D.
  Institut de Cardiologie DeQuebec
  Quebec, CANADA G1V 4G5

- Richard Davies, MD., Ph.D.
  Univ. of Ottawa Heart Institute
  Ottawa, CANADA K1Y 4E9

- Daniel Deykin, M.D.
  Boston VA Medical Center
  Boston, MA 02130

- Gary S. Francis, M.D.
  University of Minnesota
  Minneapolis, MN 55455

- David Johnstone, M.D.
  Victoria General Hospital
  Halifax, Nova Scotia
  CANADA B3H 2Y9

- Tenence Montague, M.D.
- Koon Teo, M.D.
  Univ. of Alberta Hospital
  Edmonton, Alberta
  CANADA T6G 2R7

- Bramah N. Singh, M.D., Ph.D.
  VA Medical Center
  West Los Angeles, CA 90073

- Thomas W. Smith, M.D.
  Brigham and Women's Hospital
  Harvard Medical School
  Boston, MA 02115

Data Coordinating Center:

- William 0. Williford, Ph.D.
- Joseph F. Collins, Sc.D.
  Cooperative Studies Program
  Coordinating Center
  VA Medical Center
  Perry Point, MD 21902

Pharmacy Coordinating Center:

- Carol Fye, R.Ph., M.S.
- Mike Sather, R.Ph., M.S.
  Cooperative Studies Program
  Clinical Research Pharmacy
  Coordinating Center
  VA Medical Center
  Albuquerque, NM 87106

Project Office:

- Salim Yusuf, MRCP, D.Phil.
- Rekha Garg, M.D.
  Clinical Trials Branch
  National Heart, Lung and
  Blood Institute
  Bethesda, MD 20892

2) Data and Safety Monitoring Board

The Director of NHLBI has appointed a Data and Safety Monitoring Board (DSMB). The DSMB will carefully monitor the study. The DSMB will recommend if changes should be made in the conduct of the study based on review of the proportion of patients with various baseline features who are recruited, outcome variables, toxicity, and other blinded data. The DSMB will monitor the study to assess if the results are sufficiently compelling or adverse to terminate the study early. In addition, the DSMB will review the event rates, compliance and use of ACE-inhibitor: and suggest modifications should these be necessary. The members of the DSMB will have no other direct participation in the study.

The members of the Data and Safety Monitoring Board (DSMB) are:

David Bristow, M.D., Chairman
Oregon Health Sciences University
Portland, OR 97201

Hugo T. Engelhardt, M.D., Ph.D.
Baylor College of Medicine
Houston, TX 77030

Michael Gent, M.D.
Hamilton Civic Hospitals Research Center
Hamilton, Ontario
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William B. Hood, M.D.
University of Rochester
Rochester, NY 14642

Paul Meier, Ph.D.
University of Chicago
Chicago, IL 60637

Bertram Pitt, M.D.
University of Michigan Medical Center
Ann Arbor, MI 48109

David Waters, M.D.
Montreal Heart Institute
Montreal, Quebec
Canada H1T 1C8

E. PUBLICATIONS POLICY

All main publications emerging from the study results will be in the names of all full collaborators in the study.

F. TIME TABLE

The study will be carried out in three phases. The first phase, during which the protocol has been developed and approved, has been completed. During the second phase the protocol will be implemented in about 100 centers. One thousand patients will be enrolled and the experience will be assessed. If the second phase meets its goals, the study will proceed to phase three. In this phase, it is expected that about 200 centers will participate. Recruitment will last a total of three years and will be followed by a further two years of follow-up of all patients until a common termination date.

A detailed study time-table is outlined below:

Oct-Dec 1990	Regional meetings and training of investigators.
Jan 1991 to Dec 1993	Recruitment of patients
Summer or Fall of 1991	Review of study organization and enrollment after inclusion of 1000 patients. Modifications of the protocol if necessary.
Jan 1994 to Dec 1995	End of follow-up
March 1996	Publication of study results

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APPENDIX I

OUTLINE OF SAMPLE CONSENT FORM - "Digitalis Investigation Group"

Local Center Name _____ Randomization No.:

Patient Name _____ - - - / - - - -

You have been found to have heart failure which means that the heart does not pump blood adequately. The symptoms of heart failure include leg swelling and shortness of breath Digitalis is a drug that has been commonly used for more than 200 years to treat patients with heart failure. In spite of this, it is unclear whether digitalis is beneficial, harmful, or has no effect in most patients with this condition. The National Heart, Lung and Blood Institute and the Department of Veterans Affairs are, therefore, conducting a large research study in the U.S. and Canada. The aim of this study is to find out whether or not the use of digitalis prolongs or shortens life and reduces symptoms.

You will have an equal chance of receiving digitalis or placebo; neither you nor your doctor will know which. You will be asked to take one, two, three or four tablets a day. All tablets are to be taken together once a day. Digitalis can occasionally cause side effects which are rarely serious but can sometimes be bothersome. The side effects include nausea, vomiting and rarely irregular heart rhythm. If side effects occur your doctor may stop or decrease the drug The treatment may or may not be of personal benefit for you but the information gathered from the study will be very important for the treatment of patients with heart failure,

If your heart failure worsens your doctor will re-evaluate your treatment. You will always be offered any treatment that your clinical condition requires and participating in this study will not affect that. Any extra tests required by the study will be free of charge.

Study visits will be scheduled about three times a year and would usually coincide with your regular visits to your physician. At the visits, information about your medical history will be collected and a brief physical examination will be made. Participation in this study will not prolong your usual visit to your physician. Each visit will take at out 15 minutes. The study is currently scheduled to conclude in 1995.

Your Social Security or Medicare number may be used to help the clinic know if you have needed hospital care. All information obtained as part of the study will be confidential and only used for research purposes. Your identity and social security number will be kept confidential within the liits of the law.

Your participation in the study is entirely voluntary and will not 'affect any medical care to which you are entitled. An alternative to participation is continued individualized care by your physician. You are free to refuse to participate or withdraw from the study at any time without penalty. If you have any questions please contact Dr. _____ at this telephone number _____. Questions about research related risks can be answered by _____ at this telephone number _____.

[A clinic specific statement regarding compensation related to participation as a human research subject should be inserted here. Generally, the study does not provide compensation for medical injury.]

I agree to pat-tic ipate in the digitalis study and I have been given a copy of this form.

_____ _____
Patient's Signature Date

_____ _____
Witness' Signature Date

_____ _____
Participating Investigator's Signature Date

(This page revised 10/91.)

General Guidelines From Federal Regulations Regarding Informed Consent

CODE OF FEDERAL REGULATIONS
Title 45 • Public Welfare
Department of Health and Human Services
Revised as of October I, 1988

PART 46 • PROTECTION OF HUMAN SUBJECTS

46.116 General requirements for informed consent.

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to particil ate and that minimize the possibility of coercion or undue influence. Theinformation that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpato ry language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights" or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of thii section, it seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be folk owed, and identification of any procedures which are experimental:

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject:

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs ar d, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to he subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) 4dditional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided-to each subject;

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent:

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent. set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Programs under the Social Security Act, or other public benefit or service programs: (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and document that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, tlhe subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in these regulations are not intended.20 preempt any applicable Federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, state, or local law.

[46 FR 8386, Jan. 26, 1981; 46 FR 29883, June 3, 1981, as amended at 48 FR 9270, Mar. 4, 19831

APPENDIX **IIA**

NHLBI-VA Study #995
Revised FER 1992

DIGITALIS INVESTIGATION GROUP

BASELINE FORM

Local Center Name _____

PRINT Patient Name _____
Last First M.I.

Randomization Number
___ ___ ___ / ___ ___ ___ ___

Date of Randomization Mo _ _ Day _ _ Yr _ _

Items 1 through 9 must be transmitted over the telephone at the time of randomization

1. SOCIAL SECURITY NUMBER ..... ___ ___ ___ - ___ ___ - ___ ___ ___ ___
2. DATE OF BIRTH ..... Mo ___ ___ Day ___ ___ Yr ___ ___
3. EJECTION FRACTION (percent) ..... ___ ___
   A. METHOD (1=Radionuclide, 2 =Angiography, 3=2-D Echo) ..... ___
4. SEX (1=Male, 2=Female) ..... ___
5. RACE (1=White, 2=Black, 3=Other) ..... ___
6. CHEST X-RAY (CT-ratio) ..... 0 ___ .
7. WEIGHT ..... ___ Kg OR ___ ___ ___ lbs.
8. HEIGHT ..... ___ ___ ___ cms OR inches
9. SERUM CREATININE LEVEL ..... ___ ___ . ___ mg/dl OR ___ ___ ___ µ mol/l

9A. SERUM POTASSIUM LEVEL ..... ___ . ___ mEq/l OR ___ . ___ mmol/l

10. PLEASE RECORD RECOMMENDED DIGOXIN DOSE ..... 0 ___ .
11. PLEASE RECORD RANDOMIZATION NUMBER ..... ___ ___ ___ ___ ___ ___

Complete the following information - not to be transmitted by telephone.

12. APPROXIMATE DURATION OF CHF (months) ..... ___ ___ ___

SIGNS OR SYMPTOMS: O=None or Unknown, 1=Present, 2=Past, 3=Present and Past (Present is defined as ≤ 1 month. Pest is > 1 month prior to randomization.)

13. RALES ..... ___
14. ELEVATED JUGULAR VENOUS PRESSURE ..... ___
15. PERIPHERAL EDEMA ..... ___
16. DYSPNEA AT REST OR ORTHOPNEA ..... ___
17. DYSPNEA ON EXERTION .....
18. LIMITATION OF ACTMTY ..... ___
19. S J ..... ___
20. RADIOLOGIC EVIDENCE OF PULMONARY CONGESTION ..... ___
21. HEART RATE (beats/minute) ..... ___ ___ ___
22. BLOOD PRESSURE (mm Hg) ..... ___ ___ ___ / ___ ___ ___
23. CURRENT NYHA FUNCTIONAL CLASS (use codes below) ..... ___

1 = Class I (Patients with cardiac disease hut without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea).
2 = Class II (Patients with cardiac disease resulting in slight limitation of physical adivity. They are comfortable at rest. Ordinary physical activity causes fatigue or dyspnea).
3 = Class III (Patients with cardiac disease resulting in marked limitation of physical adivity. They are comfortable at rest. Leas than ordinary activity causes fatigue or dyspnea).
4 = Class IV ((Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency are present even at rest. If any physical activity is undertaken, symptoms are increased.)

STUDY #995 - BASELINE FORM (PAGE 2 OF 2) RANDOMIZATION NO. /_____ _____

24. ETIOLOGY OF CHF ..... PRIMARY ___

1=Ischemic 4=Idiopathic
2 = Hypertensive 5 = Alcohol related SECONDARY
3=Valvular 6=Other
Specify _____

CODE: YES = 1
NO OR UNKNOWN = 0

25. PREVIOUS MYOCARDIAL INFARCTION ..... ___
26. CURRENT ANGINA ..... ___
27. HISTORY OF DIABETES ..... ___
28. HISTORY OF HYPERTENSION ..... ___

CURRENT DRUG USE:

29. USE OF DIGOXIN WITHIN ONE WEEK PRIOR TO RANDOMIZATION ..... ___
30. POTASSIUM-SPARING DIURETICS .....
31. OTHER DIURETICS ..... ___
31A. POTASSIUM SUPPLEMENT ..... ___
32. ACE INHIBITOR ..... ___
33. NITRATES (ORAL OR PASTE) ..... ___
34. HYDRALAZINE ..... ___
35. OTHER VASODILATORS, SPECIFY _____ .....
36. DOSE OF DIGOXIN/PLACEBO (D-995) PRESCRIBED (mg/day) ..... ___
(For all doses, give the patient one bottle of study drug.)
37. PATIENT ADDRESS: _____

_____

TELEPHONE: AREA CODE: _____ NUMBER: _____

38. NAME, ADDRESS AND TELEPHONE NO. OF FAMILY OR PRIVATE PHYSICIAN:

NAME: _____

ADDRESS: _____

TELEPHONE: AREA CODE: _____ NUMBER: _____

39. NAME, ADDRESS AND TELEPHONE NO. OF CLOSE FRIEND OR RELATIVE NOT LIVING WITH PATIENT:

NAME: _____

ADDRESS: _____

TELEPHONE: AREA CODE: _____ NUMBER: _____

40. DATE OF NEXT VISIT ..... Mo ___ Day ___ Yr ___

41. LAST NAME AND FIRST INITIAL OF INDIVIDUAL RANDOMIZING PATIENT (IN CAPITALS) ..... _____
Last First Initial

Signature _____

PLEASE RETURN FORM TO DATA COORDINATING CENTER AT PERRY POINT.

VA Form 10-20914a(F R)
JAN 1991

APPENDIX IIB

DIGITALIS INVESTIGATION GROUP

NHLBI-VA Study #995
Revised FEB 1992

FOLLOW-UP FORM

Local Center Name _____

PRINT Patien Name _____
Last First M.I.

Randomization Number
___ ___ ___/___ ___ ___ ___

Date of Follow-Up Visit Mo _ _ Day _ _ Yr __ __

CIRCLE CLOSEST VISIT (MONTH) NUMBER:	**01***	04	08	**12***	16	20	24	28	32	36	40	44	46	52	56	60

(*Please draw Digoxin blood level at this visit if instructed by the Data Coordinating Center.)

1. **DID PATIENT COME TO THIS SCHEDULED VISIT? (1=Yes, Go to Q.4; 0=No, Go to Q.2) . .** _ _

2. **IF PATIENT DID NOT COME TO VISIT, INDICATE REASON . . . . . .**
   1=Missed visit (visit should be rescheduled)
   2=Refuses further participation (try to keep the patient in the study, at least by telephone contact)
   3=Lost to follow-up (contact private physician, relative, or friend)
   4=Died (complete Q. 3)

   If the patient has not come to the visit, please make every effort to contact the patient and complete another copy of this form at least by telephone conversation.

3. **IF PATIENT DIED:** **(Please call 1-800-336-2309 to inform the Data Coordinating Center of the date of death if there is a delay of greater than 4 weeks in obtaining the information in Q. 3B.)**

   A. **DATE OF DEATH . . . . . Mo _ _ Day _ _ Yr _ _**

   B. **PRIMARY CAUSE OF DEATH . . . . . .**
   1=Presumed arrhythmic and no evidence of worsening CHF
   2=Progressive heart failure (include patients with worsening CHF, even if the terminal event is an arrhythmia)
   3=Other cardiac, specify _____
   4=Stroke
   5=Embolism, specify _____
   6=Other vascular, specify _____
   7=Noncardiac, nonvascular, specify _____
   8=Unknown

4. **SINCE LAST VISIT, HOW MANY TIMES HAS THE PATIENT BEEN HOSPITALIZED? . . . .** ___
   (If none, enter "0")
   (Hospitalization, for study purposes, is defined as admission to hospital for at least 24 hours.)

PLEASE COMPLETE A SEPARATE EVENT FORM FOR EACH HOSPITALIZATION.

5. **CURRENT NYHA FUNCTIONAL CLASS (use codes below) . . . . . .** _ _
   1 = Class I (Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea).
   2 = Class II (Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. *Ordinary* physical activity causes fatigue or dyspnea).
   3 = Class III (Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue or dyspnea).
   4 = Class IV ((Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency are present *even* at rest. If any physical activity is undertaken, symptoms are increased.)

6. **SINCE LAST VISIT, HAS THE DOSE OF DIURETICS, ACE-INHIBITORS OR ANY OTHER NON-TRIAL THERAPY BEEN INCREASED FOR WORSENING HEART FAILURE? (1=Yes, 0=No)** ___

A. IF YES, HOW MANY TIMES HAS THE PATIENT REQUIRED ANY OF THE FOLLOWING: (If none, enter "0")

1) unscheduled office visit(s) .....

2) emergency room visit(s) .....

3) hospitalization(s) for less than 24 hours .....

(Code: 1=Yes 0=No)

7. CURRENT ACE INHIBITOR USE ..... ___

8. NITRATES (ORAL OR PASTE) ..... ___

9. HYDRALAZINE .....

10. OTHER VASODILATORS, SPECIFY _____ .....

11. POTASSIUM SPARING DIURETICS .....

12. OTHER DIURETICS .....

12A. POTASSIUM SUPPLEMENT .....

13. HOW MANY STUDY TABLETS (D-995) HAVE BEEN RETURNED? ... ___ mls OR ___ tabs
(cylinder) (tablet count)

14. WHAT PROPORTION OF STUDY TABLETS DOES THE PATIENT REPORT HAVING TAKEN SINCE LAST VISIT? ..... ___
1=None/few (<20%)
2=Some (20-80%)
3=Most/all (>80%)
} ACTION: Please encourage patient to take tablets regularly if possible.

15. IS THE PATIENT CONTINUING STUDY DRUG? (1=Yes, 0=No) ..... __

IF YES:

A. CODE DOSE PRESCRIBED AT THIS VISIT (For doses of 0.125 or 0.25 mg give one bottle; for 0.375 or 0.5 mg give 2 bottles of study drug.) .....
1=0.125 mg/day (1 tab/day) 3=0.375 mg/day (3 tabs/day)
2=0.25 mg/day (2 tabs/day) 4=0.50 mg/day (4 tabs/day)

B. INDICATE NUMBER OF BOTTLES DISPENSED AT THIS VISIT (270 tablets/bottle) ... __

IF NO:

C. CODE REASON FOR STOPPING ..... __
1=Side effects, specify _____
2=Renal insufficiency
3=Prescription of open label digoxin due to CHF
4=Prescription of open label digoxin due to atrial fibrillation/flutter
5=Other, specify _____

*If patient **has stopped** etudy medication, **please** try to restart at a lower **dose.** If **not possible,** the **patient should** remain in the study **until follow-up is** completed,*

16. HAS DOSE BEEN. CHANGED SINCE.THE LAST VISIT? (1=Yes, 0=No) .....

A. IF YES, SPECIFY REASON .....
1=Renal insufficiency
2=Side effects, specify _____
3 = Other, specify _____

17. HAS PATIENT'S ADDRESS CHANGED? (1=Yes, 0=No) .....

A. IF YES, SPECIFY NEW ADDRESS BELOW:

_____

_____

TELEPHONE: AREA CODE: _____ NUMBER: _____

18. DATE OFNEXTVISIT ..... Mo __ Day __ Yr __

19. LAST NAME AND FIRST INITIAL OF INDMDUAL COMILETING THIS FORM (IN CAPITALS) .....
Last First Initial

Signature _____

VA Form 10-20914b(NH) JAN 1991 **PLEASE RETURN FORM TO DATA COORDINATING CENTER AT PERRY POINT.**

APPENDIX IIC

DIGITALIS INVESTIGATION GROUP

NHLBI-VA Study #995
Revised FEE 1992

EVENT FORM

Local Center Name _____

PRINT Patient Name _____
Last First M.I.

Randomization Number
___ ___ ___ / ___ ___ ___ ___

Date of Event Mo _ _ Day _ _ Yr _ _

PLEASE COMPLETE A SEPARATE EVENT FORM FOR EACH HOSPITALIZATION OR EPISODE OF SUSPECTED DIGOXIN TOXICITY. CODE DISCHARGE DIAGNOSES FOR EACH HOSPITALIZATION.

A. HOSPITALIZATION (Defined as admission to hospital for at least 24 hours.)

CODE 1=YES 0=NO

01. **WAS PATIENT HOSPITALIZED? (If No, Go to Section B)** ..... ___
IF YES, COMPLETE QUESTIONS 02 THROUGH 17.
02. **WORSENING** HEARTFAILURE ..... ___
03. DIGOXIN TOXICITY (If YES, **complete** Section B below) ..... _ _
04. **MYOCARDIAL** INFARCTION ..... ___
05. **UNSTABLE ANGINA** ..... ___
06. **STROKE** ..... ___
07. **ARRHYTHMIA - SUPRAVENTRICULAR** ..... ___
08. **ARRHYTHMIA** -VENTRICULAR ..... ___
09. **CORONARY** ARTERY BYPASS **GRAFT** SURGERY **(CABG)** ..... ___
10. **PERCUTANEOUS TRANSLUMINAL** CORONARY **ANGIOPLASTY (PTCA)** ..... ___
11. CARDIAC TRANSPLANTATION ..... _ _
12. VALVE OPERATION ..... ___
13. OTHER CARDIAC SURGERY, SPECIFY _____ ..... ___
14. OTHER CARDIOVASCULAR REASON, SPECIFY _____ ..... ___
15. **RESPIRATORY INFECTION** ..... ___
16. OTHER NONCARDIAC, NONVASCULAR REASON, SPECIFY _____ ..... ___
17. **ENTER NUMBER OF PRIMARY REASON FOR HOSPITALIZATION (USE QUESTIONS 02-16 TO CODE)** ..... _ _

B. SUSPECTED/CONFIRMED SYMPTOMS AND SIGNS OF DIGOXIN TOXICITY

18. DID PATIENT HAVE AN EPISODE OF SUSPECTED/CONFIRMED DIGOXIN **TOXICITY?** ..... ___
IF YES. COMPLETE QUESTIONS **19-27b.** IF NO, **GO** TO QUESTION **28.**
19. **VENTRICULAR TACHYCARDIA** ..... ___
20. **VENTRICULAR FIBRILLATION** ..... ___
21. **SUPRAVENTRICULAR** ARRHYTHMIA ..... ___
22 **AV-BLOCK** ..... ___
23. NAUSEA OR VOMITING ..... ___
24. VISUAL DISTURBANCES ..... ___
25. **DIARRHEA** ..... ___
26. OTHER, SPECIFY _____ ..... ___
27. SERUM DIGOXIN CONCENTRATION (IF KNOWN) **(ng/ml)** ..... _._

C. PLEASE PROVIDE THE FOLLOWING BLOOD LEVELS ON THE FIRST DAY OF HOSPITALIZATION OR AT DIAGNOSIS OF SUSPECTED DIGOXIN TOXICITY

2 % **SERUM POTASSIUM LEVEL** ..... _._ mEq/l OR _._ mmol/l

27b. SERUM CREATININE LEVEL ..... mg/dl OR _ _ _ µ mol/l

*REMINDER: If knowledge of **digoxin** blood **levels** is **essential** for **the** immediate management of the patient, obtain digoxin blood **levels** from the most **convenient** and quick source. **Please report the level to the Pharmacy Coordinating** Center at (505) 265-1 711. ext. 2580. In other situations where **digoxin** toxicity **is** suspected but the **situation is not** urgent, please reduce or **stop trial** medication and send the blood **sample** to **SmithKline Beecham Clinical Laboratories, Inc. by calling 800-877-7004. You will receive results within 4 working days. In such circumstances,** PLEASE **AVOID OBTAINING DIGOXIN BLOOD LEVELS** WCALLY.*

28 LAST NAME AND FIRST INITIAL OF **INDIVIDUAL** COMPLETING **THIS FORM** (IN **CAPITALS)** ..... _____
Last First Initial

Signature _____

PLEASE** RETURN FORM TO THE DATA **COORDINATING CENTER** AT PERRY **POINT.

VA **Form 10-20914c** NR)
JAN 1961

SmithKline Beecham
Clinical Laboratories
7600 Tyrone Ave.. Van Nuys. California 91405 PHONE (800) 877- 7004

APPENDIX IID
DIGOXIN BLOOD LEVEL (Test Request Form)

DIGITALIS INVESTIGATION GROUP

ACCT NO. LAB NO.
99999999 573670.9

SAMPLE REQUISITION
ATTENTION CDT
ADDRESS
CITY
STATE00000
PHONE
VAHR

SBCL STUDY ID: VAH

PROTOCOL: DIG STUDY-VA/NHBLI

INVESTIGATOR #: *** INV ID ** *

REV: 03/12/92 BY:(GLD J

PATIENT SECTION

PATIENT

INITIALS: |___|___|___|
F M L

RANDOMIZATION #:***|___|___|___|___|___|
(REQUIRED AT ALL VISITS)

Birthdate: |__|__| MO |__|__| DAY |__|__| YR Sex: |__| M |__| F

Collection Information:

Date: |__|__| MO |__|__| DAY |__|__| YR Time: |__|__|__|__| 24HOUR CLOCK

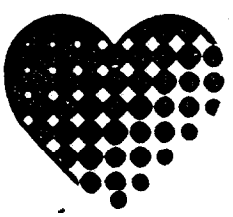
CURRENT STUDY DRUG DOSE: 0._ _ _ MG/DAY
HOURS FROM LAST DOSE TO BLOOD DRAW:__HRS *
* (DRAW 6 HRS AFTER LAST DOSE OF STUDY DRUG)

REQUEST SECTION

SCHEDULED VISITS:
(CHECK CORRECT VISIT NUMBER)

	FOR SBCL USE ONLY.	
( )1M (ROUTINE ONE MONTH)	VAH1	CREATININE POTASSIUM MAGNESIUM
( )12M (ROUTINE 12 MONTH)	J030 STORAGE SAMPLES	DIGOXIN CREATININE POTASSIUM MAGNESIUM
( )SDT (SUSPECTED DIGOXIN TOXICITY)	VAH2	DIGOXIN CREATININE POTASSIUM MAGNESIUM

D I G



Digitalis
Investigation
Group

UNSCHEDULED VISITS: CHECK VISIT TYPE, VISIT #, AND TEST(S) REQUESTED BELOW.

1. VISIT TYPE:	2. VISIT NUMBER:	3. TEST(S): **
( )RET RETEST *	( )1M ( )12M	( )DCX1 DIGOXIN ( )DC9 CREATININE ( )KB POTASSIUM ( )BAG MAGNESIUM
* CHECK PRIOR VISIT #.	( )SDT	

INSTRUCTIONS: ** TESTING OUTSIDE OF THIS STUDY MUST BE PREAPPROVED BY THE DIGITALIS INVESTIGATION GROUP.

SUBMIT IN BLUE LET-ERED BAG ANY **FROZEN** SPECIMENS WITH BLUE COPY OF THIS REQUISITION
SBCL COPY -WHITE (G)

APPENDIX III

NOTES ON MEASUREMENT OF EJECTION FRACTION

Background

The purposes of measuring ejection fraction in this study are to identify those at high risk and to examine the effect of digoxin on survival in patients characterized by severity of LV dysfunction. The experience from the first 5000 patients followed for an average of 18 months in SOLVD has been used. An EF measured within four months prior to randomization was accepted as long as the patient's clinical condition had not changed or the patient had not undergone any procedure (e.g., PTCA) that could alter EF. EF could be measured by any one of three techniques: a) Badionuclide b) Angiogram and c) 2-dimensional echocardiogram using the area length method or modiied Simpsons' rule. The experience from SOLVD indicates that this approach adopted provided adequate discrimination for the purposes of predicting mortality. EF was the most powerful predictor of mortality. The means and distributions of EF for each of the time periods of measurement and for the three different techniques were similar. Moreover, the predictive value and increment in risk of death for a given change in EF were identical for all three techniques and time periods.

Acceptable Methods of Measuring Ejection Fraction

1) Measured from a contrast angiogram
2) Radionuclide: First pass or MUGA
3) 2-D echocardiogram:
   a) using a commercial computer program that already exists in currently available equipment;
   b) using a modified Simpsons' rule;
   c) area length method; or
   d) a simplified method described by Quinones et al. (Circulation 64, No. 4, 1981). Details are provided in the **Manual** of Operations.

Estimates by "eyeballing" an angiogram, radionuclide or echocardiographic recording are not acceptable. In general, the last EF performed within the previous six months prior to randomization should be used. If the patient's clinical condition has changed or if he has suffered an infarction or undergone a procedure such as PTCA or surgery, an EF should be obtained at least seven days after the event. In several measurements were done within a short period prior to randomization during which the patient was stable, the EF derived from angiographic or radionuclide measures are preferable to echocardiographic methods.

APPENDIXIV

Nomograms for Calculating Digoxin Daily Maintenance Dose Requirements (mg)
For Estimated Peak Body Stores of 10 Micrograms/kg

		Body Weight (Kg/lbs)					
		501110	60/132	70/154	80/176	90/198	100/220
	10	0.125	0.125	0.125	0.125	0.250	0.250
Correct4 d	20	0.125	0.125	0.125	0.250	0.250	0.250
Creatinine	30	0.125	0.125	0.250	0.250	0.250	0.250
Clearance	40	0.125	0.250	0.250	0.250	0.250	0.250
(ml/min	50	0.125	0.250	0.250	0.250	0.250	0.250
70kg	60	0.250	0.250	0.250	0.250	0.250	0.375
	70	0.250	0.250	0.250	0.250	0.250	0.375
	80	0.250	0.250	0.250	0.250	0.375	0.375
	90	0.250	0.250	0.250	0.250	0.375	**0.500**
	100	0.250	0.250	0.250	0.375	0.375	**0.500**

Corrected creatinine clearance/70 kg is estimated by the formula: 140-age/serum creatinine. For women, the resulting value will be multiplied by 0.85.

The dosage will be calculated by the Data Coordinating Center based on age, creatinine level, gender, and body weight.

APPENDIX V

RESPONSIBILITIES OF PARTICIPATING PHYSICIANS AND COMPENSATION

One physician (study physician) from each participating center will be responsible for the conduct of the study in a particular center. The study physician will be responsible for assuring that the study protocol is implemented and that at least 36 patients are enrolled in the study. Each center is encouraged to maximize the rate of recruitment. There is no upper limit to the number of patients a center may enroll. All patients should be followed until the end of the study or until their death. If the study physician chooses to relocate, it is his (her) responsibility to identify a colleague that will complete the study. Periodic study meetings will be held (approximately twice a year during recruitment and once a year thereafter) and travel expenses will be covered. A fixed payment of $350.00 will be provided for the randomization of each patient and $50.00 for each completed Follow-Up and Event Form. When a patient dies, and both sections 3A and 3B are completed, $100.00 will be provided. In addition, investigators participating in the quality of life and six-minute walk test substudy will be reimbursed $400 for each patient who completes the substudy. This substudy consists of a series of questionnaires and the walk test to be completed four times - at randomization, 1-, 4- and 12-month visits. The payments are to cover the cost of any ejection fraction or other tests done solely to enter a patient into the study, any administrative costs, and is also a small payment in appreciation for the investigator's efforts on behalf of the study. All wholehearted collaborating physicians will be recognized in all publications.

(This page revised 10/91.)

APPENDIX VI

WOMEN AND MINORITIES IN THE STUDY POPULATION

The Digitalis Study depends upon the participation and cooperation of many physicians who see large numbers of patients meeting study criteria. These physicians are willing to participate in the study at no cost, other than reimbursement of incurred expenses, with the only benefit of reimbursement for expenses incurred in travel to periodic study meetings. Study goals dictate the need for about 7,000 patients recruited from approximately 200 institutions throughout the United States and Canada.

After considering the degree to which this could be achieved, it was concluded that an efficient source of participating physicians are the Department of Veterans Affairs hospitals. Therefore, the study is a collaborative endeavor with the Department of Veterans Affairs and will involve a substantial number of VA hospitals. In addition, a sizeable number of non-VA hospitals will participate. (The ratio of VA to non-VA hospitals is expected to be about 1:3 or 1:4.) It was further judged necessary to include participating institutions in Canada in order to achieve overall recruitment goals.

The substantial involvement of VA hospitals and Canadii hospitals will result in a mix of females and minorities which may not be precisely that of the U.S. heart failure population. There are no national data available on the exact demographic characteristics of patients with heart failure. National mortality data indicate age-adjusted death rates from heart failure are about SO-50% higher in men compared to women and 50% higher in blacks compared to whites. However., cohort data from the Studies of Left Ventricular Dysfunction (SOLVD) indicate that once a subject has heart failure, women have about 35% to 40% higher mortality compared to men. In SOLVD, one of the largest trials to recruit women, the patient population distribution was as follows: 25% females, 75% males;; and 81% non-Hispanic Caucasian, 15% Black, and 4% Other. In the Studies of Left Ventricular Dysfunction registry, the patient population distribution was as follows: 26% females, 74% males; and 89% non-Hispanic Caucasian, 9% Black, and 2% Hispanic. The Digitalis Study does not restrict the entry of patients based on gender or race. It is possible that the proportions of women and minorities may-be-slightly different in the Digitalis Study compared to the SOLVD registry because of differences in the mix of hospitals and their locations. The study should be able to recruit about 15-20% (1100-1400) minorities given that a large number of minorities receive their medical care at VA hospitals. However, women are expected to be recruited only from the non-VA hospitals, i.e., from about 150 to 160 hospitals. It is expected that given the experience of SOLVD (which also had VA hospitals), we should be able to recruit about 15-20% (1100-1400) women into the trial. This proportion is very similar to the 28% to 30% estimated from the national statistics.

We have made several concerted efforts to enhance the recruitment of women and minorities. First, many women investigators have expressed interest in being collaborators. Second, in developing the video that provides an overview of the study for the collaborators, a black female portrays the type of patient who is eligible for the study. Third, the informed

consent and patient information booklets have been translated into Spanish to assist Hispanic patients n achieving a better understanding of the study and, thus, encourage their participation. Fourth, we will have collaborators who will represent a wide array of medical practices from family practitioners in a rural setting to major universities and academic centers ix urban settings. Finally, Dr. Rekha Garg, co-project officer and minority female, has a primary interest to ensure that we have a large number of women and minorities in this study.

Alternative recruitment strategies have been considered, but the cost of obtaining a representative sampling of the U.S. population would have been prohibitive.

The scientific merit of the study with its anticipated population mix has been considered. There is no clinical experience to suggest that gender or race are significant influences on clinical responses of patients to digitalis (such as acute hemodynamic responses in heart failure or control of the heart rate in atrial fibrillation). The large sample size coupled with high event rates in this trial will permit evaluation of whether the response to therapy differs for women and minorities when contrasted with the experience of the entire group with relatively high degree of confidence. No heterogeneity of response by gender or race has been found in SOLVD. The trial results are expected to be applicable to patients of both genders and different races.

We conclude that it is appropriate to proceed with the anticipated levels of women and minority participants.

(This page revised 10/91.)

October, 1992