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Appendix A SUGGESTED DRAFT

(INSTITUTION)

CONSENT TO PARTICIPATE AS A RESEARCH SUBJECT IN THE STUDIES OF LEFT VENTRICULAR DYSFUNCTION (SOLVD)

The National Institutes of Health is conducting research Studies of Left Ventricular Dysfunction at over one hundred medical centers in the U.S., Canada and Belgium. The purpose of the study is to evaluate the effects of long-term drug administration on patients who have moderate left ventricular dysfunction or those who have overt heart failure.

I have been found to have left ventricular dysfunction; that is, my heart does not pump blood adequately. Patients with this problem are more likely to suffer from premature death than those who have normal ventricular function.

Some of the patients in this study will be found to have overt heart failure and symptoms such as leg swelling and shortness of breath. Studies have shown that treatment of heart failure usually improves these symptoms. Doctors do not agree about whether or not treatment of heart failure prolongs life. The aim of this study is to evaluate whether or not one of the newer treatments (enalapril) for heart failure used routinely prolongs life in those who suffer from heart failure specifically or left ventricular dysfunction. It is also possible that the treatment being tested can benefit me directly. Regardless of the benefit I may get from the treatment of heart failure, the information gathered in this study will be very important for doctors in deciding how to treat persons who have left ventricular dysfunction.

During approximately the first three weeks of the study, I will receive for some period of time the active medication (enalapril) and during another part I will receive an inactive medication that appears to be similar (a placebo). My response during the first three weeks will determine whether or not I am continued in the study. During the remainder of the study, I will be on either enalapril or placebo.

The type of drug I will be taking during the remainder of the study is selected by chance rather than by clinic doctor. I have an equal chance of receiving enalapril or the placebo. In order for the study to be successful, neither the clinic doctor nor I will know what drug I am taking, although should a need arise to know the identity of the drug, it can be revealed. Further, all information being collected will be continually monitored by independent

researchers associated with the study. Additionally, a group of national experts will be reviewing the data at frequent intervals.

I will be taking one pill twice a day. The drug has been used in several thousand patients with high blood pressure and with heart failure and is generally considered quite safe. The drug can occasionally (in about 3% of cases) cause side effects which are rarely serious but can sometimes be bothersome. There is a small chance I could experience side effects such as: light-headedness, skin rash or protein in my urine. Rarely, an altered taste in the mouth or very rarely a low white blood count or an allergic reaction may occur which may result in redness or swelling of the skin or breathing difficulty. All these side effects are thought to be reversible. If any of these events happen, my drug dosage may be reduced or discontinued.

I also understand that safety precautions have been set up to ensure that if my condition worsens my doctor may change other aspects of my treatment other than the study drug to treat my heart failure. I will always be offered any treatment that my medical condition requires and participating in this study will not affect that. Alternative options for therapy of my left ventricular dysfunction are available if I choose not to participate in this study. Any extra tests or hospitalization required by the study will be covered and paid for by the study. Should my clinical condition require the active agent of this study, my personal physician will be able to prescribe it for me.

I agree to participate in the Studies of Left Ventricular Dysfunction Program which is currently scheduled to conclude in 1991.

I agree to take part in the procedures to be done at baseline visit and subsequent follow-up visits.

At these visits some or all the following will take place:

1. The information about my medical history and general well-being will be collected.

2. I will be given a brief physical examination.

3. Samples of my urine may be collected for tests. There are no risks involved in this procedure.

4. I may have blood drawn from my arm with a needle for test. I understand that the needle feels like a pin prick. Occasionally, bruising may result.

The baseline visit will take about 45 minutes.

The next visit will take place a few days after this visit, and subsequent visits are less frequent. After the first four months, I will only be required to visit the clinic every four months, unless certain special circumstances occur. Most of these visits will be considerably shorter than the first visit.

I will be given the results of all my examinations and procedures at all clinic visits and, if I give my permission, these results may also be reported to my private doctor.

I understand that my Social Security or Medicare number will be used to help the SOLVD Clinic know if I am in the hospital. I also understand that this will in no way affect my Medicare coverage. I understand that this and all information obtained as part of the study will be considered confidential and only used for research purposes. My identity and my social security number will be kept confidential within the limits of the law.

For this study to be a success, it is important that I remain in communication with the study and if I lose touch with the clinic, they will try to find me to ask about my health. For this reason, I agree to tell the clinic when I move and also to provide names, addresses and phone numbers of relatives who will know my state of health. I agree to try my best to keep appointments at the clinic and to let the clinic know if I need to change appointments or when I have any problems following the instruction of the clinic staff. It is also important that I take all the tablets prescribed to me, although when necessary the dose of the tablets may be increased or decreased.

[Federal Regulations requires a clinic specific statement regarding compensation related to participation as a human research subject.]

My participation in the study is entirely voluntary and will not affect any medical care to which I am entitled. Further, I am free to refuse to take part or withdraw at any time. I have been given a copy of this form.

_____has discussed this information with me and if I have any questions about the study at any time in the future, I can call _____.
(Name)

_____
(Telephone number)

Signature:_____

Witness: _____

Date: _____

GUIDELINES FOR OBTAINING INFORMED CONSENT

Every clinical trial depends for its success on the cooperative participation of its subjects. They must take their medication as prescribed, return for follow-up visits as indicated, and contact the SOLVD Clinic if side effects develop. It is therefore imperative that we try to obtain truly informed voluntary consent. If the consent process is simply a mechanical ritual, the trial could be jeopardized not only on ethical grounds, but also by a high number of early drop outs, poor adherence to therapy, and allegations of coercion will ensue.

A. Basic Elements of Informed Consent

According to DHEW guidelines, informed consent is interpreted to mean:

> "the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion."

The guidelines also set forth eight essential ingredients of informed consent as follows:

1. Patients must be advised of the procedures to be followed and their purposes, including identification of any experimental procedures, and the expected duration of the patient's participation.

The study drug, enalapril, has not been licensed for treatment of LVD, therefore it must be considered experimental in this study. However, the ACE inhibitors have been used to treat several thousands of patients with hypertension and heart failure. We must carefully explain that two kinds of medications (active and a placebo) are being prescribed in the study and that half the patients will be assigned by chance to each therapy group. It is essential that the patient understand that he or she will not necessarily be taking an active drug. It is just as likely that placebo tablets will be prescribed. (However, should it become clear that the patient needs the active medication by current standards, such treatment will be instituted.)

Health professionals are not in the habit of discussing with patients the pros and cons of placebo therapy, and there tends to be a feeling among physicians and patients that active treatment with some procedure or drug is always preferable to an inactive approach. Yet, a number of studies have shown that patients may be better off taking an inert placebo (less adverse effects) than an active medication (sometimes ineffective), if their health status is carefully monitored in both cases.

In our situation we have a special reason for including a placebo group, and patients should be given some understanding of its purpose. This calls for an explanation of the scientific approach to the study--the need to control as many variables as possible. By emphasizing the importance of the placebo group, we explicitly call attention to the fact that this is primarily a study, rather than a therapeutic program specifically designed for the individual. Each patient will receive additional therapy based on

individual needs when indicated. Although, the scientific design of the study requires that certain conditions must be similar in those receiving treatment and placebo (that is why randomization is essential), this will not interfere with the usual care of the patient.

We should carefully explain that this is a double-blind trial in which neither the patient nor the physician will know which medication the patient is taking.

To allay anxiety, it is important to note that not everyone connected with the trial will be "blinded" in the sense of the study. An appropriate person at each medical center will be able to identify the patient's medication in an emergency situation.

Furthermore, a panel of national experts will know which patients are taking which medication and what is happening to each therapy group. If it is clear that active therapy is beneficial then, the study will be stopped so that everyone can have an opportunity to take the active drugs; and if active treatment is found to be harmful the study will also be stopped, at least for those who might be harmed. Experts who have access to all the data from the trial are in the best position to judge the effectiveness or harm of active treatment not the patients as a whole and special subgroups of them. Only from such a large comparative study of many patients will it be possible to know whether the treatment is beneficial or harmful. In individual patients it is usually difficult to know whether the patient survives because of treatment or because he/she has inherently a good prognosis.

Patients should be told that they are expected to take their medication daily over the course of the trial and visit the SOLVD clinic at least every four months. While all of the laboratory procedures are standard medical practice, they need to be explained so the patients know what is expected at each visit (e.g., physical examination, laboratory tests, questionnaires). To avoid misunderstanding, it should be made clear that the study is expected to last until October 1991.

2. Anticipated benefits of the trial must be explained to patients.

Many participants appreciate the opportunity to be involved in relevant research and to contribute to medical knowledge. In the SOLVD trial the knowledge we gain will be specifically applicable to patients in the study as well as other persons with congestive heart failure and asymptomatic left ventricular dysfunction, and this is an added benefit of participation.

About 250,000 patients are newly diagnosed each year with congestive heart failure. Although we know that symptoms of congestive heart failure can be alleviated whether or not treatment delays death is not known. It is therefore in the best interest of the patients that this careful scientific evaluation of the treatment of heart failure be carried out.

All patients in the trial will be monitored closely. Furthermore, tests and medications associated with the study are provided at no cost to the patient. The patient will not be charged for the active or placebo

Close associates of the participant may raise questions and considerations that the patient is likely to overlook, and questions that concern the family are better answered sooner than later. Furthermore, there is evidence to suggest that family support for studies of this kind increases the probability of patient cooperation during the course of the research.

3. To be eligible for participation in the SOLVD, participants must have the capacity to give their own informed consent.

If a participant is incapable of understanding what is expected of him or her as a subject in the study, it is not permissible to obtain informed consent from a guardian. The study requires daily responsibilities that cannot be easily assumed by other persons.

4. The setting in which consent is obtained should be as private as possible so patients can freely ask questions without embarrassment.

If extraneous parties can hear the conversation, patients may be reluctant to ask appropriate questions.

5. To avoid pressuring the patient, only one person associated with the study should be present when the patient reviews the consent forms.

If a second witness is required, he or she should be as unobstrusive and non-committal as the situation permits.

6. The patient should be given a copy of the informed consent forms after they are signed and witnessed.

Even though patients are free to withdraw from the study at anytime, the consent form spells out our obligations to the patient and the patient's obligations to the study while he or she is a subject.

7. Patients should be encouraged to keep the consent forms because they contain useful information about the study which they can review from time to time.

8. The name and telephone number of a local individual who could be contacted in case of emergency should be included.

C. Reducing the Vulnerability of Participants

A participant's trust in his or her physician is not a substitute for truly informed voluntary consent. Where dependency is particularly evident, we must be especially careful to give patients all the freedom they need to say "no" if this is their inclination.

Where the person responsible for obtaining the participant's consent is also the person in charge of the participant's regular medical care, participants must be told in no uncertain terms that they will be treated with the same degree of interest and concern regardless of whether they participate in the study.

tablets, periodic examinations relevant to the study, or laboratory tests required for the study.

There is no way of knowing in advance whether a particular patient will personally benefit from active treatment during the course of the trial. That will depend on whether the drugs are effective and whether the patient is assigned to the active treatment group. We should be careful not to suggest that patients will benefit from active treatment simply by entering the trial. If we were convinced that the drugs were effective, we would not be conducting the trial. The study may show that patients on placebo therapy do as well or better than patients on acitve treatment.

3. Attendant discomforts and risks "reasonably foreseeable" must be described.

All drugs have side effects. What is important is their severity and frequency. In the SOLVD there is little likelihood that the subjects will be seriously harmed by participating. To reduce the risks, we have purposely excluded patients for whom active therapy is contraindicated. Further, the active drug in the study has been used in some tens of thousands of patients worldwide and is not a "new untested" drug.

In spite of extensive precautions, however some patients will experience adverse reactions. In the active treatment group some will have initial hypotensive reaction with the first dose. This hopefully will be a small number of participants and mild in nature because of the small initial dose. Skin rash, altered taste sensation, proteinuria, pre-renal azotemia

and neutropenia may occur, depending on the specific agent finally selected. If they know such problems can occur, they will be less surprised if they do occur, and we hope they will be less inclined to withdraw from the study. It should be made clear that patients will be monitored very closely, particularly when they begin taking study medication, so that any problems that arise can be immediately treated. Patients who have an exaggerated response to the medication will be taken off the study medication or have their dosage reduced, whichever is appropriate. These side effects are thought to be reversible. Further, neutropenia is thought to be extremely rare (1 in 7,000 patients who do not have an impaired renal function or collagen disorder). The FDA has approved the use of this agent for hypertension.

To avoid the implication that side effects and problems are only linked to the active drug, we should indicate that some patients on placebo therapy may also experienced discomforts and difficulties similar to those attributable to the active drug. Since placebo patients may think they are taking acitve drugs, they may experience and report more drug related difficulties than otherwise.

4. Appropriate alternative procedures that might be advantageous for the subject must be disclosed.

This mandate is often overlooked in written consent forms. It means that the participant should be told what options exist if he or she elects not to participate in the trial. They may elect to be treated for their CHF by their own physician, but it should be stressed that safety precautions have

been set up to ensure that if the symptoms and signs of CHF occur or are aggravated, active treatment will be initiated and any other necessary steps will be taken.

5. A statement describing the extent to which maintenance of confidentiality of records identifying the patient needs to be made.

Confidentiality of all patient information is assured in all participating centers. No unauthorized personnel should have access to patient records or resluts of interviews or tests. Additionally, all record storage rooms whould be appropriately secured, and should contain necessary locked files or other storage equipment.

It may be useful to explain that in studies of this nature, numerical and alphabetical codes are assigned by which central study files may be linked to individual patients. The Clinical Centers retain forms which permit such linkage. The Patient Identification Forms contain patient identifiers and study codes. If, in the future, it is necessary for patient safety resons to contact individual patients, these locally maintained forms will allow such contacts. Patients are not identified by name in any of the forms submitted central coding or in any reports or publications.

6. Persons responsible for the study must offer to answer any inquiries concerning procedures.

We suggest that one or more people associated with the trial be available to answer relevant questions while patients are contemplating participation.

7. Patients must be told that they can withdraw from the trial at any time without prejudicing their future care.

We obviously would like our subjects to remain in the study as long as possible, but they have the right to withdraw at any time. We must communicate this option to patients without luring them into the trial on a probationary "look and see" basis. Hesitant patients should be evaluated very carefully to screen out those who are likely to withdraw early.

The right to withdraw from a trial is meaningless if such behavior invokes penalties. If they drop out of the trial, the fact of dropping out will not jeopardize their regular care.

8. Prospective subjects must be advised of the availability or non-availabilty of medical treatment or compensation for physical injuries incurred as a result of participation in the study.

It may be useful to distinguish between providing study treatment and follow-up free of charge, and financial compensation for injuries incurred. The Federal Government is prohibited by law from commiting funds that have not yet been appropriated by Congress, and no funds have been allocated for compensating injured subjects in trials such as the SOLVD. The only

recourse for such patients is to seek compensation through the courts or through negotiation with the Clinical Center involved.

Reimbursing the cost of medical treatment for a research-induced injury is a separate issue. Every effort will be made by the Project Office and the cooperating centers to reimburse injured subjects for their medical expenses if the patients are required to pay such costs out of their own pockets. Any such problems will be dealt with on a case by case basis (and, indeed, in the rare instances where some additional costs have been incurred, the NHLBI has paid for this).

Policies regarding compensation and reimbursement vary from institution to institution, so we cannot recommend a standard approach for all participating centers. However, on the basis of our observations to date in other clinical trials using the active study medications, we offer several suggestions. Staff members should stress the fact that the chance of serious injury in the SOLVD is extremely small but the government requires that compensation be discussed with patients if there is any risk at all. Legal terms and concepts should be translated into layman's language, and the ideas should be made relevant to the SOLVD, not simply to research in general. Comments regarding compensation should be as brief as possible. Where every contingency is described, these statements tend to be lengthy and out of balance with the rest of the consent form. They give the impression that injuries are likely to occur, even though we say elsewhere that the probability of serious side effects is minimal.

B. <u>The Process of Obtaining Consent</u>

The eight ingredients of informed consent in the DHEW guidelines refer primarily to categories of information that enable patients to make rational decisions regarding participation in clinical trials. Except for the stipulation that patient inquiries should be answered, these basic elements do not refer to the process of obtaining informed consent.

Various studies indicate that the circumstances under which consent is obtained in clinical trials can have a profound influence on the patient's interpretation of information communicated during the consent discussion and on the freedom of patients to make their own decisions.

Given the data at hand, we are recommending the following guidelines to insure that the consent we obtain will be as informed and voluntary as possible:

1. Participants should be fully informed about the study and have adequate time to evaluate the pros and cons of participation.

If it is thought desirable, the Consent Form may be left with the participant after the Initial Contact, so that he or she may more carefully review it. (It should be returned unsigned) Time should be set aside for orientation to the SOLVD for eligible participants, in order to discuss the pros and cons of participation.

2. Participants should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (for example, persons who might be needed to provide transportation.)

In approaching the issue of informed consent, we should keep in mind its two essential components -- information and voluntary choice. When we share with patients important facts about the SOLVD trial, we treat them as potential partners in our research and enable them to rationally evaluate their capacity and willingness to participate. By fully disclosing information about the study, we are expressing respect for our patients and reducing their vulnerability to coercions.

APPENDIX B. Shipping Blood Samples

B.1 Sample Drawing

Blood for future SOLVD assays should be obtained at the Eligibility Visit. It will be the individual Clinical Center's responsibility to prepare the blood sample and ship it. The blood should be spun down. Sera should be divided into three equal aliquots and placed in 48 mm x 12 1/2 mm Nunc cryotubes with silicone seals, and labelled with the participant's name and ID number.

B.2 Sample Shipment

The samples must be shipped in a way that will keep them frozen. All plasma samples for shipment should be collected, and packaged together in a thick walled styrofoam container on dry ice. A minimum of 5 pounds of dry ice is to be packed with each carton of samples for each day of transit time. It is highly recommended that delivery time be kept within 48 hours. The styrofoam container should be placed in a protective carton and shipped to a central storage facility. The shipping containers and labels with the address of the central storage facility will be sent to each Clinical Center by the assay lab.

B.3 Central Laboratory Procedures-see Protocol, Appendix A.

Appendix C: Physical Examinations Procedures

C.1 Weight.

The participant should only wear underwear under surgical gown without socks and shoes. He should not have been eating a heavy meal before the measurement. Be sure that the scale is balanced so that the indicator is at zero when no weight is on the scale. The scale should be level and on a firm surface. The participant should be instructed to stand in the middle of the platform of the balance scale with the head erect and eyes looking straight ahead. Adjust the weight on the indicator until it is balanced. Record the results to the nearest 0.2 pound or 0.1 kg.

C.2 Heart Rate.

After every blood pressure recording the radial pulse will be counted for 15 sec and the value multiplied by 4.

C.3 Blood Pressure.

Supine Blood Pressure: The participant should be resting in supine position for 5 minutes in a quiet room and on a comfortable bench.

Sitting Blood Pressure: The participant should be seated comfortably in a quiet room. The arm muscles should be relaxed and the forearm supported. The arm should be at the heart level when the measurement is done.

Measurement: A mercury sphygmomanometer should be used and a cuff size selected according to the circumference of the arm (AC). Ordinary cuff up to AC of 33 cm, large cuff for AC of 33-41 cm and thigh cuff for AC above 41 cm. The cuff is then applied evenly and firmly to the exposed upper arm. If possible the right arm should be selected and the same side used in the future. The cuff should be inflated to about 30 mm Hg above expected systolic blood pressure. The cuff is then slowly deflated, about 2-3 mm Hg per beat, during which time the Korotkoff sounds are listened to through a stethoscope placed over the brachial artery. The pressure at which the sounds are first heard is the systolic pressure. The diastolic pressure, phase V, is defined as the pressure at which the sounds disappear. The systolic and diastolic blood pressures should be measured at least twice over a period of at least 2 minutes and the second value is to be recorded.

APPENDIX D: ASSESSMENT OF QUALITY OF LIFE

D.1 Schedule of Administration of Form

The Quality of Life form is to be completed by participants attending Visit 3 (the Baseline Randomization visit) and by randomized participants attending Visit 5 (6 weeks post-randomization), attending Visit 8 (12 months post-randomization) and at the end of the study.

D.2 Procedures for Administering Form

The Quality of Life form is a self-administered instrument and as such it has been carefully designed to elicit the desired information in a "user-friendly" mode. Thus, pertinent identifying information such as is found in all other SOLVD forms has been relegated to a separate sheet. This cover sheet containing the identifying information is to be completed by Clinical center staff while the Quality of Life form itself is to be given to the participant for completion. The instructions for completing the form are on the form and are self-explanatory. However, Clinical Center staff should be able to clarify questions if necessary. In addition, some participants that are unable to read the form may require some other means of administering the form. The form can be administered at any time during the visit although it may be advantageous to administer it while the participant is waiting. After the participant has completed the form, the Clinical Center staff should staple the completed cover sheet to the form.

D.3 Quality of Life Form

The form is designed as a self-administered form and thus the instructions for its completion are on the form. The only part of the form to be completed by Clinical Center staff is the unattached cover sheet of identifying information: Participant's name, ID number, and the Date of the Visit. These are self-explanatory. After the participant completes the form and the Clinical Center staff completes the cover sheet, the Clinical Center staff must staple the cover sheet to the form.