CHAPTER 8

INFORMED CONSENT AND ORIENTATION GUIDE

8.1 PATIENT ORIENTATION

The majority of patients potentially eligible for the study will be admitted to one of several areas in the hospital including the emergency room, CCU, and stepdown units with a diagnosis of suspected or rule out myocardial infarction, or unstable angina. Some patients will already be in the hospital. They will have been admitted previously with a diagnosis of unstable angina or other medical problems and develop episode(s) of ischemic pain at rest. For the majority of patients who enter through these areas, a triage officer, a nurse or a house officer will call a member of the T3 team. The member of the team will be either the Principal Investigator or his/her designate. That individual may be a cardiac fellow or the T3 nurse. An initial decision concerning the eligibility of the patient will be made by the T3 team member.

The patient will then be approached by the Principal Investigator or his/her designate. If possible, the primary physician will also be involved in this phase of recruitment. If the family of the patient is available, they will also be consulted.

The background of the proposed study and the benefits and risks of the procedure and study will be explained to the patient and to the family if present. Informed consent will be requested from the patient prior to initiation of treatment.

Whenever possible the study physician will contact the patient's private physician in order to apprise the private physician at all phases of the study concerning the patient's progress.

8.2 INFORMED CONSENT

After it has been determined that a patient meets all of the inclusion criteria and none of the exclusion criteria for enrollment and after the study has been explained to the patient, he/she will be asked to sign a consent form. Failure to give informed consent renders the patient ineligible for the study. Copies of recommended consent forms will be made available to each participating Clinical Center. The Principal Investigator has the option of preparing consent forms for local use but those consent forms must be approved by the T3 Operations Committee. The local form may not substantially reduce the patient information in the model consent form. A model consent form for centers participating in the T3A protocol is given in Exhibit 8-1. A model consent form for centers participating in the T3B protocol is given in Exhibit 8-2.

EXHIBIT 8-1 10/21/91

INFORMED CONSENT: THROMBOLYSIS IN MYOCARDIAL ISCHEMIA

Purpose of Study

Your doctors have determined that you are either experiencing episodes of severe heart pain (unstable angina pectoris) that may lead to a heart attack, or that a mild heart attack may be in progress. The purpose of this study is to determine the best method of treatment for reducing these attacks, possibly preventing a heart attack and improving your quality of life. One possible treatment is alteplase (a clot dissolving drug) which may reduce the severity of blockages in coronary arteries. If you choose to participate in the study, you will be asked to undergo cardiac catheterization within the next 12 hours to evaluate the ability of alteplase to reduce the severity of blockages caused by clot formed on top of plaque, which remains in your heart's arteries. If your study doctors confirm that you are a candidate for this study during your cardiac catheterization, you will be assigned by chance (50% likelihood) to immediately receive either alteplase or an inert substitute (placebo) for 90 minutes. You will then return to the Coronary Care Unit under continued observation for 18 to 48 hours. Following this time period, you will be asked to undergo a second cardiac catheterization procedure to evaluate the effect of the drug on your heart's arteries. Whether or not you receive alteplase, heparin (a blood thinning drug) will be administered intravenously prior to the first cardiac catheterization and continuing at least until after the second cardiac catheterization. A tablet of aspirin (a drug shown of benefit in coronary artery disease) may be given to you too if a blockage is found that needs balloon dilatation.

Cardiac catheterization is a commonly performed procedure which assesses heart function and detects blockages in heart arteries. Following local anesthesia, a small plastic tube (catheter) is inserted into a groin artery and advanced to the heart. Pictures of the heart pumping chamber and its arteries are obtained by injecting x-ray dye through the catheter.

Your study doctors plan to analyze about eight tablespoons (4 ounces) of your blood during the first day of the study and a total of 16 tablespoons (8 ounces) over the course of your hospital stay. Your electrocardiogram will be externally monitored (Holter monitoring) for 24 hours between the two cardiac catheterization procedures to evaluate the heart's response to the therapy you have received. We will also telephone you at six weeks and one year from now to ask how well you are. The study doctors may contact you some time in the future after these treatments to ask about long-term results.

Participation in this study may extend your hospital stay by a day. There will be no charge to you for the blood clot dissolving medications or extra tests performed solely as part of the experimental study design. These extra tests include Holter monitoring and the second cardiac catheterization, unless balloon dilatation is performed.

Benefits

The possible benefits from participating in this study include reducing both the number of anginal attacks and chances for developing a heart attack. In addition, your participation may increase your chances for survival. Your doctors will evaluate the results of your cardiac catheterization and recommend additional therapy. Possible options include continued therapy with medicines, balloon dilatation, or coronary bypass surgery.

Discomforts and Risks

Alteplase has been approved for use in persons having a heart attack, but is considered an investigational new drug for unstable angina. However, preliminary analysis of patients treated with alteplase has demonstrated it may be beneficial in the treatment of unstable angina. The doctors in this study have used it to treat over 3,000 patients with major heart attacks.

Previous studies with alteplase and heparin have shown that bleeding may occur (10-15%) and may be severe enough to require blood transfusion (3-5%). Rarely, (less than 1 in 200 cases), and usually using a dose of alteplase larger than you will receive, a stroke may occur which may cause death or permanent disability. A minor risk exists of bruising, bleeding, or inflammation at the site where blood samples are drawn. Heparin is not an investigational drug and is commonly given to patients with your condition. It can also cause minor bleeding (10%) that may require transfusion (3%). The addition of aspirin may increase this risk slightly. The personnel involved in the study are well aware of all of these problems and are prepared to care for you should any of them arise.

The cardiac catheterization procedure carries a small risk of stroke or death (1 in 1,000) each time it is performed.

Alternatives

Your alternative to participation in this study is to receive your doctor's routine medical care for unstable angina. Routine medical care does not include use of alteplase to dissolve clot in the coronary arteries, Holter monitoring, and in most cases a second cardiac catheterization. These procedures are part of the experimental study design.

Cost/Payment

There will be no cost to participants, nor payment for participation. The same billing procedure will apply for the days of your hospital stay whether you participate in this study or not. Extra costs may be incurred with extended stay.

Confidentiality

In this study, your doctors will make note of your initials, sex, weight, height, and other facts about you. These details will be stored in a private coordinating center on a computer. The facts on the computer may be seen by staff at the National Heart, Lung, and Blood Institute, the drug companies which provide the study drugs and the Food and Drug Administration. You will not be identified personally in any reports from this study. Every effort will be made to keep your own personal medical data confidential.

Refusal and Withdrawal

You may refuse to take part in or you may withdraw from this study at any time without affecting your present or future care at this hospital.

Rights

Your study doctors do not expect any unusual risks as a direct result of this project. However, should an unforeseen injury occur, appropriate medical care as determined by the hospital will be provided and charged to the same account as your other hospital bills, but no financial compensation will be given. Should you have any questions about your rights in the study, you may call _____. You will be given a copy of this form to keep if you agree to take part in this study.

I have fully explained to the Subject, _____, the nature and purpose of the procedures described above and such risks as are involved in its performance. I have asked the Subject if any questions have arisen regarding the procedures and have answered these questions to the best of my ability.

_____ _____

Date Investigator's Signature

I have been fully informed about the above procedures, with its possible benefits, risks, and consequences. I recognize that I am free to ask any questions. I understand that participation in this study is voluntary and I am free to withdraw from this study at any time without affecting my care or my relationship to _____ Hospital.

I will receive a copy of this consent form. _____ Hospital maintains an "Institutional Assurance of Compliance," a document which explains how the hospital provides for protection of human subjects, a copy of which is available on request.

In the event injury occurs to me resulting from the research procedures, medical treatment will be available, if appropriate, at _____ Hospital. However, no special arrangements have been made for compensation or for payment for treatment solely because of my participation in this research study.

I HEREBY AGREE to become a subject in this investigation.

Date	Subject's Signature or Subject's Legal Representative when appropriate

I HAVE WITNESSED the explanations made by the Investigator and heard the responses to questions. I have no conflicting interest in the activity proposed.

Date	Witness

EXHIBIT 8-2 10/21/91

INFORMED CONSENT: THROMBOLYSIS IN MYOCARDIAL ISCHEMIA

Purpose of Study

Your doctors have determined that you are either experiencing episodes of severe heart pain (unstable angina pectoris) that may lead to a heart attack, or that a mild heart attack may be in progress. The purpose of this study is to determine the best method of treatment for reducing these attacks, possibly preventing a heart attack and improving your quality of life. If you choose to participate in this study, you will be assigned by chance to one of two treatment alternatives. In addition to your doctor's prescribing routine medicines to help reduce your anginal attacks, you will be assigned by chance (50% likelihood) to receive either alteplase or an inert substitute (placebo) for 90 minutes. Whether or not you receive alteplase, heparin (a blood thinning drug) will be administered intravenously. Aspirin (a drug shown of benefit in coronary artery disease) will be given to you after the infusion of alteplase.

In addition, you will be assigned to undergo cardiac catheterization within 18-48 hours to evaluate your heart's arteries (50% likelihood) or to receive continued medical care without cardiac catheterization unless your study doctors determine it is necessary on the basis of your clinical condition or special tests.

Cardiac catheterization is a commonly performed procedure which assesses heart function and detects blockages in heart arteries. Following local anesthesia, a small plastic tube (catheter) is inserted into a groin artery and advanced to the heart. Pictures of the heart pumping chamber and its arteries are obtained by injecting x-ray dye through the catheter.

Your study doctors plan to analyze about eight tablespoons (4 ounces) of your blood during the first day of the study and a total of 16 tablespoons (8 ounces) over the course of your hospital stay. Prior to hospital discharge, your study doctors will use a small intravenous injection of radioactive particles and a special camera to see how well your heart muscle pumps while you rest and while you exercise (thallium exercise test). Also, prior to hospital discharge, your heart will be externally monitored (Holter monitoring) for 24 hours to evaluate its response to the therapy you have received. We will ask you to return six weeks from now to undergo an Exercise Treadmill Test. We will also telephone you at one year to ask how well you are. The study doctors may contact you some time in the future after these treatments to ask about long-term results.

Benefits

The possible benefits from participating in this study include reducing both the number of anginal attacks and chances for developing a heart attack. In addition, your participation may increase your chances for survival.

Discomforts and Risks

Alteplase has been approved for use in persons having a heart attack, but is considered an investigational new drug for unstable angina. However, preliminary analysis of patients treated with alteplase has demonstrated it may be beneficial in the treatment of unstable angina. The doctors in this study have used it to treat over 3,000 patients with major heart attacks.

Previous studies with alteplase and heparin have shown that bleeding may occur (10-15%) and may be severe enough to require blood transfusion (3-5%). Rarely, (less than 1 in 200 cases), and usually using a dose of alteplase larger than you will receive, a stroke may occur which may cause death or permanent disability. A minor risk exists of bruising, bleeding, or inflammation at the site where blood samples are drawn. Heparin is not an investigational drug and is commonly given to patients with your condition. It can also cause minor bleeding (10%) that may require transfusion (3%). The addition of aspirin may increase this risk slightly. The personnel involved in the study are well aware of all of these problems and are prepared to care for you should any of them arise.

The cardiac catheterization procedure carries a small risk of stroke or death (1 in 1,000) each time it is performed.

If you have been assigned to cardiac catheterization, however, your study doctors will evaluate the results and will recommend the usual therapy based on the findings. Possible options include continued therapy with medicines, or with your consent, balloon dilatation or coronary bypass surgery.

Participation in this study may extend your hospital stay. There will be no charge to you for the blood clot dissolving medications or extra tests required for this study which include Holter monitoring and some of the blood tests.

Alternatives

Your alternative to participation in this study is to receive your doctor's routine medical care for unstable angina which may include thallium exercise testing and cardiac catheterization. Routine medical care does not include use of alteplase to dissolve clot in the coronary arteries, Holter monitoring, or some of the blood tests.

Cost/Payment

There will be no cost to participants, nor payment for participation. The same billing procedure will apply for the days of your hospital stay whether you participate in this study or not. Extra costs may be incurred with extended stay.

Confidentiality

In this study, your doctors will make note of your initials, sex, weight, height, and other facts about you. These details will be stored in a private coordinating center on a computer. The facts on the computer may be seen by staff at the National Heart, Lung, and Blood Institute, the drug companies which provide the study drugs and the Food and Drug Administration. You will not be identified personally in any reports from this study. Every effort will be made to keep your own personal medical data confidential.

Refusal and Withdrawal

You may refuse to take part in or you may withdraw from this study at any time without affecting your present or future care at this hospital.

Rights

Your study doctors do not expect any unusual risks as a direct result of this project. However, should an unforeseen injury occur, appropriate medical care as determined by the hospital will be provided and charged to the same account as your other hospital bills, but no financial compensation will be given. Should you have any questions about your rights in the study, you may call _____. You will be given a copy of this form to keep if you agree to take part in this study.

I have fully explained to the Subject, _____, the nature and purpose of the procedures described above and such risks as are involved in its performance. I have asked the Subject if any questions have arisen regarding the procedures and have answered these questions to the best of my ability.

_____ _____

Date Investigator's Signature

I have been fully informed about the above procedures, with its possible benefits, risks, and consequences. I recognize that I am free to ask any questions. I understand that participation in this study is voluntary and I am free to withdraw from this study at any time without affecting my care or my relationship to _____ Hospital.

I will receive a copy of this consent form. _____ Hospital maintains an "Institutional Assurance of Compliance," a document which explains how the hospital provides for protection of human subjects, a copy of which is available on request.

In the event injury occurs to me resulting from the research procedures, medical treatment will be available, if appropriate, at _____ Hospital. However, no special arrangements have been made for compensation or for payment for treatment solely because of my participation in this research study.

I HEREBY AGREE to become a subject in this investigation.

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T3 MANUAL OF OPERATIONS

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