CHAPTER FIVE : SECTION TWO SAMPLE CONSENT FORMS : PRIMARY/ECONOMICS

(Division, Department or School Letterhead)Institutional Review Board
University of Pittsburgh
IRB Number:
Consent Form Approved: _____
Protocol Renewal Date: _____

Consent for Participation in the Research Study Entitled Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)

Sponsor: National Institutes of Health
National Heart Lung and
Blood Institute (NHLBI)

Principal Investigator: _____

As a diabetic patient with heart disease, you are being asked to take part in a research study known as BARI 2D. This 2400 patient, 7-year study in the U.S., Canada, and other countries is designed to compare whether initial treatment of coronary artery disease with angioplasty (PTCA) or surgery (CABG) is better than starting with a medical program. At the same time, this study will compare two approaches for treatment of diabetes.

BACKGROUND:

CORONARY ARTERY DISEASE: Coronary artery disease is a condition where the arteries which deliver blood with oxygen and energy sources to the heart muscle itself become narrowed by a process called atherosclerosis. Patients with type 2 diabetes develop coronary artery disease and other cardiovascular complications 2-3 times as often as similarly aged persons without diabetes. In some cases, coronary artery disease can best be treated by optimal medical therapy with diet, exercise programs and drugs. In other cases, invasive procedures, like percutaneous coronary intervention (PCI) or bypass surgery (CABG), which increase blood flow to the heart (revascularization), offer the best chance of improving outcome. There are patients for whom we do not know whether optimal medical treatment alone or coronary revascularization combined with optimal medical treatment is better. You are being asked to volunteer for this research study because you are such a patient.

TYPE 2 DIABETES: Diabetes is a disease in which blood sugar (glucose) levels are abnormally high, causing damage to many organs, such as the eyes, the kidneys, and the nerves. Lowering blood glucose levels to normal helps to prevent such damage. We suspect that high blood glucose is also bad for the heart, because diabetic individuals with especially high blood glucose levels are more likely to suffer heart attacks and death.

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In type 2 diabetes, high blood glucose results from two things: (1) the pancreas does not supply enough insulin; and (2) the body does not react well enough to whatever insulin it receives. We now have drugs to improve both of these problems and bring blood glucose levels down close to normal. "Insulin providers" are drugs that increase the supply of insulin, and "insulin sensitizers" are drugs that increase the reaction of the body to insulin. However, we do not know whether insulin providers or insulin sensitizers are better, particularly for type 2 diabetic patients, like yourself, who have coronary artery disease.

THE RESEARCH QUESTIONS

This research study seeks to learn the answer to two main questions.

QUESTION 1: When pictures (coronary angiograms) show definitely narrowed coronary arteries, but not to the point that demands immediate intervention (revascularization), is it better to go ahead and do elective coronary bypass surgery, open arteries with a balloon catheter (angioplasty) or put in a tube for blood to get past a blockage (stent), or is it better to treat in a medically optimal way with diet, exercise and drugs and hold revascularization procedures for use later, should they become more urgently needed?

QUESTION 2: Is it better to lower blood glucose levels close to normal by giving insulin provider drugs or by giving insulin sensitizer drugs?

For each question, "Is it better?" means "will there be a better chance to live longer and avoid future heart attacks".

An additional goal in the BARI 2D study is to evaluate the effect of the treatments on your use of medical services and the cost of those services.

EXPLANATION OF TREATMENT

If you agree to join this study, several tests will be performed (if not already recently done) to verify that you are eligible for the study:

(1) Blood will be drawn (about 2 tablespoonfuls) to check levels of glucose, kidney function and other standard blood components
(2) A test for ischemia (abnormal blood flow to the heart) will be done. This may be one of many standard clinical tests, for example, an exercise or chemical heart stress test.
(3) Coronary arteriography (pictures of blood flow through your heart arteries) will be performed.

If the above tests show that you are eligible for BARI 2D, you will be randomly allocated (like flipping a coin) by a computer to one of 4 treatment groups:

(1) Optimal medical therapy and insulin providing drugs
(2) Optimal medical therapy and insulin sensitizing drugs

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(3) Surgical or catheter-based revascularization plus optimal medical therapy and insulin providing drugs
(4) Surgical or catheter-based revascularization plus optimal medical therapy and insulin sensitizing drugs

OPTIMAL MEDICAL THERAPY will consist of medically approved medications to help improve supply of blood to your heart and reduce the heart's demand for oxygen. Additionally, you may receive medications to lessen the likelihood of blood clot formation in your heart's arteries as well as cholesterol-lowering and blood pressure-lowering medication, if needed.

You will receive detailed advice on steps to reduce your risk of progression of coronary heart disease including information on (1) stopping smoking, if you smoke; (2) a heart-healthy diet; and (3) exercise. Patients assigned to optimal medical therapy may still undergo revascularization in the future, should their symptoms worsen or do not improve.

If you are assigned to optimal medical therapy and revascularization, you and your doctor will decide whether percutaneous coronary intervention (PCI) or bypass surgery (CABG) is better for you. During PCI, which is performed under local anesthesia, a small plastic tube is inserted in your narrowed heart artery to open the narrowing. In many cases, a small tubular structure called a stent is placed in the artery at the site of the narrowing to help keep the artery open. Two major types of stent are used: bare metal stents and drug-eluting stents. Drug-eluting stents contain medications that are released over time to help reduce the chance that re-narrowing of the artery will occur. CABG is open heart surgery where a vein from your leg or an artery from your chest is used to bypass the narrowed heart artery.

If you are assigned to optimal medical therapy and insulin providing drugs and your blood glucose is only moderately elevated, you will receive a pill to cause your body to produce and release more insulin. If your blood sugar is very high, or later becomes very high, you will be given insulin injections, either alone or in combination with the pill.

If you are assigned to optimal medical therapy and insulin sensitizing drugs, you will receive a pill to reduce the body's need for insulin by making the available insulin act more strongly on the body's tissues.

Whichever blood glucose-lowering treatment you receive, you may receive medication from the other treatment arm if your blood glucose fails to come under control. Also, you may receive an additional pill to help lower your blood glucose by slowing the digestion of starches and sugars in meals.

The usual method for measuring how well diabetes is controlled is the hemoglobin A1c (HbA1c) level. HbA1c indicates the average level of blood glucose (sugar) that was present during the previous 4-12 weeks. Non-diabetic persons have a HbA1c of 4.0 to 6.0%. The usual target level of diabetes glucose control in BARI 2D will be a HbA1c less than 7.0%, and action must be taken if HbA1c is greater than 8.0%. We will strive to lower HbA1c to less than 7.0% in each research subject, so long as that can be accomplished using drugs from the assigned treatment arm. If necessary, we will use drugs from the opposite treatment arm if we cannot otherwise

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bring HbA1c to below 8.0%. We may also need to prescribe several injections of insulin per day to some research subjects to achieve these objectives, just as we would in excellent clinical practice. Research subjects with low risks of eye, kidney, or nerve complications, compared to the danger of cardiovascular complications, may be targeted to HbA1c levels of 7.0 to 8.0%. Your BARI 2D diabetes investigator will use his/her best judgment in selecting and seeking to achieve an optimum HbA1c for you within the framework of the BARI 2D research plan and your personal diabetes situation. You are encouraged to discuss these goals and the appropriate means to achieve them, with your BARI 2D diabetes caregivers.

Once you have been randomly assigned to either the insulin sensitizing or insulin providing treatment arm, to start with you will be prescribed only diabetes drugs from that treatment arm. If you were already taking only such drugs, there would be no change in diabetes medications for you. On the other hand, if you were previously taking diabetes drugs from the opposite treatment arm, they will be discontinued and you will be prescribed different drugs appropriate to your assigned treatment arm. This will be done even if your diabetes control had been satisfactory on your former pre-BARI 2D drug regimen. Therefore, at first your blood glucose level might actually go up temporarily, before the new drugs fully take hold. However, we will raise the doses of the new drugs as quickly as we can, with due regard for safety, in order to return your blood glucose to satisfactory levels. If this cannot be achieved with the new drugs, we will add back as necessary any of your old drug(s), including insulin, until your diabetes control becomes satisfactory again. This process might take several months, and in some instances a temporary increase in urinary and intake of fluids might occur. We will ask you to test your blood glucose at home more frequently during such a transition period. We will frequently review those numbers with you by phone, fax, or e-mail on a regular basis, so that we can make prompt changes in drug doses and prevent symptoms.

You will be asked to prick your finger and test your own blood glucose levels at home on a schedule that may vary from 3 times a day to only several times a week, depending upon what drugs you are receiving. In addition, you will return to our clinic to meet with a diabetologist (doctor who is an expert in diabetes management) and/or cardiologist (doctor who is an expert in cardiac management) once a month for the first six months, then every three months afterward. During these visits, up to 2 tablespoonfuls of blood will be drawn from an arm vein to check how well your diabetes, cholesterol and other blood components are being controlled with treatment. It may be necessary to redraw some of these samples if for some reason the first sample is unusable. You will also be offered counseling for smoking cessation, nutrition and physical activity, and will be given a pedometer and other materials as appropriate to help you monitor and manage your risk factors (such as smoking, obesity, and sedentary lifestyle). You will be asked questions about your symptoms.

You will have an electrocardiogram (ECG) at study entry and every year afterward until the end of the study. You should expect to be followed for at least 5 years in this study.

You will have a nuclear imaging test one year after study entry and every other year afterward until the end of the study. Nuclear imaging of the heart is a standard of care technique used to detect blockages in the arteries feeding the heart muscle and to examine the degree of damage and also the heart function. The study is a stress study done with a radioisotope and a special camera.

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ECONOMIC METHODS: An interviewer at Stanford University in California will contact you by phone every three months to ask you about recent doctor visits, outpatient procedures or hospital stays you may have had. If you have been in the hospital, a copy of the hospital bill will be requested. The interview will take only a few minutes to complete.

BENEFITS

Your benefits from participating in this study may include better control of your diabetes and heart disease related to the intensive follow-up you will receive. Your participation in this study will also provide future benefits to society as we find out which approach to treating diabetes and heart disease is better for patients like you.

Some of the medications and supplies to manage your diabetes and heart disease may be made available to you at no cost. These are standard of care medications that would normally be prescribed independent of the fact that they are being provided free of charge. Your BARI 2D physician will choose the best medications for your care independent of whether the medication may be available to you at no cost.

If you are assigned to revascularization, your BARI 2D physician may determine that a drug-eluting stent is most appropriate. This device is available at many institutions as part of standard medical care, and either you or your insurance provider will be responsible for this payment. If a drug-eluting stent is not available as standard medical care at your institution, the study will provide it at no cost to you.

RISKS OR DISCOMFORTS

You will receive medically approved treatments, and there are no risks beyond those of standard clinical care. Blood drawing can cause temporary discomfort or bruising at the skin puncture site, and, in rare instances, fainting can occur. Stress testing may cause abnormal blood pressure, fainting, disorders of the heart beat, and, in rare instances, heart attack and a 1 in 10,000 chance of death. Coronary arteriography can cause temporary discomfort at the skin puncture or incision site in the arm or groin, bleeding, bruising, clot formation, infection, irregularities in the heart beat, and in very rare instances (less than 0.5 %) stroke or death.

Nuclear cardiology imaging uses a pharmacologic agent that simulates cardiac stress. Intravenous injections could produce bruises or infection. Adenosine could produce chest pains, shortness of breath, flushing, dizziness, headaches, and stomach pains. On rare occasions, it produces changes in EKG or heart rhythm. These tend to be short lived because the drug is short lived. More serious side effects such as heart attack or death are extremely unusual for nuclear imaging tests. The amount of radiation is well below the limits set for research uses. Emergency equipment and trained personnel are available at all times.

A common risk (occurring in 10-20 out of 100 patients) associated with stenting -- one form of Percutaneous Coronary Intervention (PCI) -- that occurs within the first 6 months is re-narrowing of the artery. This complication occurs less frequently in most patient subgroups by use of drug-eluting stents as compared to procedures performed with conventional bare metal stents. The

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risk of thrombosis (clotting) in the stent is infrequent irrespective of whether a bare-metal or drug-eluting stent is implanted (approximately 1 in 100 patients). On average, patients who undergo a stenting procedure can be expected to remain in the hospital for about 1 to 2 days.

Re-narrowing of the artery within the first six months is also a common risk (occurring in 10-25 out of 100 patients) associated with balloon angioplasty without stenting – another form of PCI (performed infrequently today due to the overall benefits of stenting). Usually, this re-narrowing can be successfully treated with a second angioplasty procedure. On average, patients who undergo balloon angioplasty can be expected to remain in the hospital for about 1 to 3 days.

Other infrequent (occurring in 1 to 5 out of 100 people) procedural-related complications in all types of PCI (bare-metal stent, drug-eluting stent, or balloon angioplasty) include emergency bypass surgery, failure to completely open the heart artery, damage to the heart including myocardial infarction, spasm (twinge) of the artery, permanent scarring and damage to the artery, stroke and/or paralysis (loss of speech, inability to understand, weakness or inability to move your arms or legs), transient ischemic episodes (small temporary strokes, where symptoms go away), increase or decrease in blood pressure, chest pain, change in heart rhythm (including a slow heart rate or fast heart rate), internal hemorrhage (bleeding inside the body), fever, infection, and death. On rare occasions (occurring in less than 1 out of 100 people), the dye used during the PCI procedure may cause renal (kidney) insufficiency, and bleeding may occur with anti-clotting drugs that are used at the time of the procedure.

With the Cypher drug-eluting stent, there have been reports, including some deaths, that are considered possible hypersensitivity reactions. The symptoms reported include pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. The FDA does not have sufficient data to establish rates for these events, nor can it determine whether these rates are different from those experienced with bare metal stents.

For patients who undergo CABG, an infrequent risk (occurring in 1-10 out of 100 patients) is a temporary change in cognitive status (such as memory difficulty). Other infrequent complications (occurring in 1 to 5 out of 100 people) include bleeding that requires re-operation, infection, heart damage during the procedure including myocardial infarction, stroke, renal (kidney) failure, respiratory failure, prolonged need for insertion of a tube in the chest after surgery, and death. In addition, in rare instances (occurring in less than 1 out of 100 people), patients may experience reactions to anesthesia. On average, patients who undergo CABG can be expected to remain in the hospital for approximately 5-7 days. Many patients may require a blood transfusion during surgery.

All insulin providing drugs can cause an abnormally low blood glucose (hypoglycemia). None of the insulin sensitizing drugs cause hypoglycemia when used by themselves, but they can provoke hypoglycemia when added to one of the insulin providing drugs. Each of the FDA-approved drugs for diabetes treatment used in this study is currently in widespread use, but complications can occur such as diarrhea, abdominal cramping, nausea, vomiting, gas, liver test abnormalities, weight gain, leg swelling or other rare side effects.

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ALTERNATIVE TREATMENTS

The alternative to joining this study is to receive your doctor's standard treatment for coronary heart disease and diabetes which can include some or all of the medications being used in this study as well as PCI and CABG.

MEDICAL RECORDS

Your medical records will be reviewed and information collected for the purpose of this research study. Information resulting from your participation in this research which may be important for your current or future medical care will be placed in your medical record and may be shared with others to address standard payment, treatment, and health care operations.

COSTS AND PAYMENTS

You will be billed in the standard fashion for routine medical care for which you are scheduled and either you or your insurance provider will be responsible for this payment. Neither you, nor your third-party insurance provider will be billed for any research procedures that are not part of your routine medical care. **Optional: There will be no payment to you for participating in this study but you will be reimbursed for parking expense during clinic visits.**

PAYMENT FOR RESEARCH-RELATED INJURIES ****Statement will vary by institution****

(Your Hospital) and the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI), have made no provision for monetary compensation to you in the event of physical injury resulting from this study. Should physical injury occur, treatment is available, but treatment is not provided free of charge.

CONFIDENTIALITY

In this study, the doctors will make note of your initials, sex, age, weight, height, and other facts. These details will be stored in a private Coordinating Center on a computer. The facts stored in 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. Some patient data and samples (e.g. blood, urine) collected during the course of the study will be sent to research laboratories. Whenever possible, the data, samples and medical information are coded such that the individual patient cannot be identified. However, some information may still contain patient identifiers when it reaches the core laboratories, and complete confidentiality cannot be guaranteed. All computer data used for analysis of the study results includes only a research ID code for each patient without name or personal information. You will not be identified personally in any reports from this study. Every effort will be made to keep your personal medical data confidential.

WITHDRAWAL FROM STUDY AND NEW INFORMATION

You are free to withdraw your consent and to stop participation in any part of this project at any time without affecting future medical care you may receive at this institution. Your refusal to

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answer any of the questions will not result in any loss of benefit to which you are otherwise entitled. Any significant new findings that develop during the course of the study which may affect your willingness to continue in the research will be provided to you by the study physician.

Your study doctor may end your participation in this research study without your consent for any reason which they feel is appropriate, including an adverse event, failure to take the medication as instructed, failure to keep your scheduled appointments, cancellation of the study by the Sponsor, injury or medical condition which may place you at risk of further complications if you continue to participate, or other administrative reasons. If this occurs, you will be informed by your doctor of the reason for your withdrawal from the study and you will be advised of available treatment that may be of benefit at that time. Being removed from study participation will not result in any loss of benefit to which you are otherwise entitled.

QUESTIONS

If you have any questions about the research, Dr. _____ will be glad to answer them. Dr _____'s number is _____. If you have any questions about your rights as a research subject, _____ (title _____) will answer them. Mr. (Ms) _____ number is _____.

LEGAL RIGHTS AND SIGNATURES

You will receive a copy of this informed consent. You are not waiving any of your legal rights by signing this consent form.

(1) Your signature below indicates that you agree to participate in the **primary BARI 2D** study as described above.

_____ _____
DATE PARTICIPANT'S SIGNATURE

_____ _____
DATE WITNESS'S SIGNATURE

(2) Your signature below indicates that you agree to participate in the **economic research** of cost data related to medical care costs of the BARI 2D study as described above.

_____ _____
DATE PARTICIPANT'S SIGNATURE

_____ _____
DATE WITNESS'S SIGNATURE

I confirm that I have explained to this patient the nature and purpose, and the possible benefits and risks of the study procedures and drugs.

_____ _____
DATE INVESTIGATOR'S SIGNATURE

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