Appendix I:
Model Informed Consent Document

(Consent Version Date: May 11, 2005)

ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD)

Principal Investigator(s)_____

You are invited to join in a research study called Action to Control Cardiovascular Risk in Diabetes (ACCORD), which is sponsored by the National Heart, Lung and Blood Institute (part of the U.S. federal government). The investigators listed above are in charge of the study. Other professional persons may help them or act for them.

What are some general things you should know about research studies? Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. You do not have to participate in research in order to receive treatment.

Details about this study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

STUDY PURPOSE

What is the purpose of the study and how long will it last? Type 2 diabetes is very common in North America. People with Type 2 diabetes have a higher chance of getting heart disease or stroke than people without diabetes. The purpose of the ACCORD study is to determine the best approaches to lower the risk of heart disease and stroke in people with Type 2 diabetes.

ACCORD will answer three research questions. In diabetes, the level of sugar in the blood is too high. So the first question is to determine the effects of lowering blood sugar to a level below that normally targeted in current clinical practice, compared with a level that is usually targeted. Many diabetic patients have high blood pressure. So the second question is to determine the effects of lowering blood pressure to a level below that normally targeted in current clinical practice, compared with a level usually targeted. Many diabetic patients also have problems with their blood lipids (like cholesterol, fat-like materials in the blood). So the third question is to determine the effects of treating several components of blood lipids compared with treating only one component. Each of these questions is described in more detail below.

You are being invited to participate in ACCORD because you have Type 2 diabetes along with other factors that increase your chance of having future heart disease and stroke, or you may already have had heart disease or stroke. Your participation in the study will last until 2009. However, study results will be reviewed regularly to see if the trial should be stopped earlier than this. Most participants will be in the ACCORD study between 5 ½ and 8 ½ years.

The total number of participants will be about 10,000 from 77 clinics throughout the United States and Canada. The study will involve approximately ___ patients at the _____ clinical site. ACCORD recruited about 1,200 participants during the Vanguard (pilot) portion of the trial in 2001 and these participants are still being treated and followed.

STUDY SUMMARY

What will happen if you take part in this study? Initial visits will be conducted to determine whether you qualify for the study. These are called "screening" visits. Your medical history, blood pressure, and past blood sugar and cholesterol measurements will be reviewed to determine whether you qualify for the study. You will have a short physical exam, and one tube (about 2 teaspoonfuls) of blood may be collected and tested for creatinine (a measure of kidney function), lipids and liver function. Some urine will also be collected and tested for protein.

If you qualify for the study and volunteer to participate, your study doctor will treat your blood sugar and either your blood pressure or your blood lipids according to the ACCORD study protocol. You and your personal physician are still responsible for other parts of diabetes care, including general preventive measures, foot care, and eye care. If you are not in the blood pressure part of ACCORD, your personal physician will still be responsible for treating your blood pressure. If you are not in the blood lipids part of ACCORD, your personal physician will still be responsible for treating your blood lipids (such as blood cholesterol). In addition, you will still need to see your personal physician(s) for all other medical care.

Blood sugar treatment groups. If you qualify and consent, you will be randomly assigned (like the flip of a coin) to one of the two blood sugar goals. The "intensive" goal is a blood sugar level lower than the current recommended value. The "standard" goal is a blood sugar level similar to the current recommended value. Your current treatment for diabetes (if any) will be changed to study treatment based on the goal to which you are assigned. Your study treatment will use available and approved diabetes treatments (oral medications and/or insulin as may be required).

If you are randomized to the intensive blood sugar goal, it is very likely that you may need one or more of the following: a) at least 2 oral medications; b) 3 or more insulin injections per day; c) frequent self-adjustment of insulin; and d) frequent home glucose monitoring. This means you will probably have to take several pills, give yourself insulin injections with a small needle, and do finger sticks to test your blood sugar up to eight times a day.

The degree of control of blood sugar is best measured by a test called hemoglobin A1c. This test gives an average of your sugar values during the past 2 to 3 months. If you are in the intensive blood sugar treatment group, the goal will be to keep your hemoglobin A1c at less than 6.0% (which is about an average blood sugar of 115 mg/dl (6.4 mmol/L)). This level is much lower than usually achieved in clinical practice. If you are in the standard blood sugar treatment group, the goal will be to keep your hemoglobin A1c value between 7.0% and 7.9% with the average around 7.5% (average blood sugar of 160 mg/dl (8.9 mmol/L)). This level is also lower than that usually achieved in clinical practice. Lowering hemoglobin A1c to this level from higher levels has been shown to reduce complications of diabetes like eye and kidney diseases. Your diabetes medications may be adjusted upwards or downwards, as your study doctors try to reach these blood goals safely.

Compared to the intensive target of a hemoglobin A1c of less than 6.0%, the standard hemoglobin A1c target of 7.5% has a somewhat higher risk for some diabetes complications. These include eye disease (retinopathy), kidney disease (nephropathy), and abnormal nerve function (neuropathy). On the other hand, a hemoglobin A1c of less than 6.0% will increase somewhat the risk for developing serious low blood sugar reactions (hypoglycemia) and weight gain. Whether the lower hemoglobin A1c target gives more or less protection against cardiovascular disease (such as heart attack or stroke) is not known. This is what ACCORD is trying to find out.

In the standard group, ACCORD will take action and recommend treatment to lower your blood sugar if your hemoglobin A1c value becomes greater than 7.9%. If your hemoglobin A1c drops below 7.0% and you are taking insulin or a secretagogue (like glimepiride or repaglinide) , we may reduce your diabetes treatment to try to bring your value above 7.0%. In the intensive group, if your hemoglobin A1c value becomes even slightly greater than 6.0%, we will increase your treatment.

Depending on your initial blood pressure and blood cholesterol results, you will also be asked to participate in either the blood pressure or cholesterol parts of the study. You must participate in one or

the other (based on your qualifications) to participate fully in ACCORD.

Blood pressure treatment groups. Blood pressure lowering can prevent heart disease, stroke, and kidney disease. There is some evidence that lowering blood pressure further than current practice might help prevent heart disease and stroke in people with diabetes. This possibility needs careful testing in a study such as this one.

If you qualify for the blood pressure portion of the study, you will be randomly assigned (like the flip of a coin) to one of two blood pressure goals. The "intensive" goal is a blood pressure level lower than that already proven to reduce heart disease and stroke. The "standard" goal is a blood pressure level similar to that already proven to reduce disease. Your study doctor will choose the medications he/she feels will be best for treating your blood pressure. Therefore, your current blood pressure medication (if any) could be changed or continued. If you do not reach your blood pressure goal, your study doctor will change your treatment until you do.

Blood lipid treatment groups. Lowering blood cholesterol can prevent heart disease and stroke. There is also some evidence that changing other blood lipids by lowering triglycerides (a type of fat in the blood) and raising HDL-cholesterol (the good cholesterol) may prevent heart disease in people with diabetes. This possibility needs careful testing in a study such as this one.

If you are eligible to participate in the blood lipid study, your current cholesterol medication treatment (if any) will be stopped and changed to the study medication. You will be treated with cholesterol-lowering medication commonly known as a "statin". The statin used in ACCORD is called simvastatin.

The dose of simvastatin you are started on will depend on your medical history. If you have had a heart attack, stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG), you will be started on 40 mg of simvastatin. If you have not had any of those, you will receive 20 mg a day of simvastatin.

Regardless of your assigned dose of simvastatin, you will be randomly assigned (like the flip of a coin) to a medication known as a fibrate to lower your triglycerides and raise your HDL-cholesterol, or to a placebo (a pill that does not contain any medicine). The fibrate used in ACCORD is called fenofibrate. Neither you nor your doctor will know which study treatment (placebo or fibrate) you are receiving. If it becomes necessary to know for medical reasons, the information will be made available.

If you begin ACCORD at the 20 mg dose of simvastatin and your cholesterol levels remain higher than the currently recommended level, or if you have a heart attack, stroke, heart surgery, surgery on your arteries (blood vessels) or angina (chest pain) with changes in an electrocardiogram (ECG or EKG) during the study, your dose of simvastatin will be increased to 40 mg per day. If your cholesterol level remains too high despite treatment with the increased dose of simvastatin, you will be taken off the lipid study medications and sent to your personal doctor to get appropriate treatment to reduce your cholesterol level.

Genetic component. Genetic research will be done as part of this study. You may, if you wish, volunteer for the genetic portion of the study. If you volunteer to participate in the genetic portion of ACCORD, your blood will be stored for genetic (DNA) analysis. The genetic portion of ACCORD is described in more detail below. You do not need to agree to participate in the genetic studies to participate in the main ACCORD study.

Visit schedule and measurements. If you qualify for ACCORD and are assigned to the standard blood glucose group and either the lipid trial or the standard blood pressure group, you will be asked to visit the clinic at one month, four months, and every four months thereafter for the duration of the trial. If you are assigned to any of the other groups, you will be asked to come every month for the first four months of the study and then at least every two months thereafter until the end of the study.

At each clinic visit, your health will be reviewed, and any symptoms you may have will be discussed with the study doctor or nurse or other study staff. Your weight, blood pressure, and heart rate will be measured, and your study medications will be reviewed to make sure you are taking them correctly. You

will receive nutrition and physical activity recommendations and will be taught how to follow them. In addition, a member of your ACCORD study care team may contact you by phone between your clinic visits to determine how you are feeling and whether or not further action is required to control your blood sugar or blood pressure levels.

You will have blood specimens (up to five tablespoons) drawn every four months for the first year and once a year thereafter. These tests will measure blood sugar, potassium, kidney function, and liver function. You will also be asked to allow blood and urine specimens to be taken and stored for future non-genetic studies. Also, additional blood samples may be taken occasionally to monitor your treatments for safety, which may require you to come in for additional visits.

Some urine will be collected at the baseline visit and every two years thereafter so that it can be examined for urine protein and creatinine (a measure of kidney function). You will also have an electrocardiogram (a recording of the electrical activity of the heart, also called an ECG or an EKG) at baseline and every two years thereafter. A limited eye exam will be done every other year.

If you are in the cholesterol study, your blood cholesterol will be measured every four months during the first year and every year thereafter until the end of the study. You will also have blood drawn every four months throughout the study to check your kidney function. If you are not in the cholesterol study, you will have your cholesterol measured every year.

As part of diabetes management, you will be expected to check your own blood sugar, as discussed later. If you are assigned to the "intensive" blood sugar goal you will have more frequent blood sugar testing by the clinic. This testing will range from once per month during the first 4 months of treatment to every two months thereafter.

You also have about a 1-in-5 chance of being chosen to complete questionnaires about your quality and activities of life, and your diet and physical activity levels. These questionnaires will be given at the beginning of the study, your 1 year visit, 3 year visit, and 4 year visit. The questionnaires will take about one hour of your time. In addition, you may be chosen to participate in a group where health care costs will be monitored (and you would be asked to give permission to obtain records from any hospitalizations).

Certain medical procedures are recommended for people with diabetes that are not part of the research study. These include annual eye exams by an ophthalmologist, annual foot exams, annual flu and pneumococcal vaccinations, and electrocardiograms (ECGs or EKGs). The study eye examination does not replace the recommended annual eye exams by an experienced eye care professional, such as an ophthalmologist (a doctor who specializes in the diagnosis and treatment of eye diseases).

During the course of the trial, our central Coordinating Center at Wake Forest University School of Medicine, or its representatives may contact you, about your participation in the trial. For example, you may be asked if you are having any trouble taking any of your medications. You may also be asked how you are feeling and whether you have been in the hospital for any reason, why and where you were hospitalized.

POTENTIAL RISKS OF PARTICIPATING IN THE ACCORD STUDY

What are the possible risks and discomforts? Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation (tubes tied), or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method, involves the careful use of condoms and/or a spermicidal foam or gel along with a diaphragm, cervical cap, or sponge. We encourage you to discuss this issue further with your doctor if you have any questions.

If you are a pregnant woman, you cannot participate in this study. Because some methods of birth

control are not 100% reliable, a negative pregnancy test is required at least 10 days after your last normal menstrual period if you are a sexually active woman of childbearing potential.

This study requires that blood be drawn from a vein in your arm several times during the study. Drawing blood may result in pain at the point of puncture, a feeling of faintness, irritation of the vein, and bruising or bleeding at the site of the needle stick. There is also a very slight possibility of an infection at the needle puncture site. The study visits, procedures, and lab work might be more often than your medical conditions usually require, but they are very important for the study.

This study requires daily finger-stick measurements of your blood sugar level. You probably have experience testing your blood sugar by finger-stick before coming into the study. You need to test your blood sugar daily because it is very important for the study that you keep your blood sugar values at the assigned goal. If you are assigned to the intensive blood sugar goal, there is a good chance that at some point you will be asked to do up to eight finger sticks a day to properly correct your blood sugar. Your blood sugar checks will be reviewed by clinic personnel and will be used to figure out your treatment plan. Clinic personnel, or others working for ACCORD, may contact you to discuss your blood sugar results.

Treating blood sugar in persons with diabetes can sometimes cause blood sugar to be too low. This condition, called "hypoglycemia", can result from changing diet, exercise, or medication. Symptoms are usually mild but sometimes can be more serious.

Mild symptoms of hypoglycemia include hunger, anxiety, dizziness, or light-headedness. Sometimes there is sweating, fatigue or mild confusion, tremors (shaking) or palpitations (feeling your heart beating in your chest). Hypoglycemia may cause loss of consciousness. If this occurs while operating machinery such as driving a car, it can result in injury or even be life threatening.

In rare cases, hypoglycemia can be very severe and require emergency treatment or hospitalization. Severe hypoglycemia may cause brain damage, coma, or death. Severe hypoglycemia can occur in any patient taking medication to lower blood sugar. It is more likely to occur in those treated with insulin to achieve lower glucose targets, as in the intensive treatment group of this study.

A sugar-containing drink such as fruit juice usually quickly relieves the milder symptoms. You may be given sugar pills to raise your blood sugar if you have symptoms. Medications are sometimes needed to treat severe hypoglycemia. These may include intravenous (I.V.) fluids or injections of glucagon, a medication that rapidly increases blood sugar.

Regardless of which blood sugar treatment group you are assigned to, safety will always be of first importance when changes in the management of your blood sugar are made. Based on data from previous studies it is estimated that, in the intensive group, about six out of 100 participants will have a serious complication (such as hospitalization or emergency room visit for hypoglycemia) every year. In the standard group about 2 participants may have such a complication every year. In either group, ACCORD doctors and nurses will take action to lessen the risk of hypoglycemia should it occur too often or in a severe form. On the other hand participants in the standard group may have a somewhat higher risk of complications related to diabetes (like eye, kidney disease or abnormal nerve function). It is estimated that, in the intensive group, about one out of 100 participants will have such a complication every year. In the standard group about 1.5 participants may present such a complication every year.

If you are assigned to the intensive blood pressure group, you may experience blood pressure that is too low. Symptoms of low blood pressure may be mild, such as feeling a little lightheaded, or less often may be more severe, such as dizziness, fatigue, or fainting. Sitting or lying down often relieves these symptoms. You should notify your clinic doctor or nurse if you have these symptoms. Clinic staff will follow you closely to lower your chances of having too-low blood pressure.

What are the side effects of the medicines used in the study? All drugs have a potential risk of an allergic reaction, which if not treated quickly, could become life threatening.

You may have side effects from the specific medications chosen as treatments. Medications that may be

used at this time in ACCORD are listed below. Additional medications may be chosen in the future. The ACCORD staff will tell you about any new medicines that they may give you.

Possible side effects for the classes of medications include the following. Your doctors have ways to manage these effects.

Blood sugar treatments

Sulfonylureas [glimepiride]: The most common side effects associated with this family of medicines include hypoglycemia (low blood sugar), weight gain, and allergies. Very rarely, blood cell abnormalities may occur. Your doctor has ways of managing the blood cell abnormalities.

Biguanides [metformin]: Common side effects associated with this drug class include nausea, vomiting, diarrhea, bloating, loss of appetite, or metallic taste in the mouth. These usually get better after the first few weeks of treatment. If these treatments are stopped, the side effects will go away over a day or two. Very rarely, people can have a severe reaction known as lactic acidosis (a condition that occurs when your body fluids and tissues have too much acid in them). Lactic acidosis almost always occurs in people with advanced kidney disease, liver disease or heart failure, and in people who drink alcohol heavily. Every effort will be made to avoid using this drug in people with those conditions.

Thiazolidinediones (TZDs) [rosiglitazone, pioglitazone]: The most common side effects related to this group of medicines include fluid retention (a condition that occurs when your body holds in too much water) and weight gain. Although the 4 mg/day dose of rosiglitazone (the TZD to be used in ACCORD) is the only dose of rosiglitazone that has been approved by the U.S. FDA for use with insulin, higher doses of rosiglitazone, which you may be placed on, have been combined with insulin in medical practice. The use of drugs like rosiglitazone together with insulin may cause fluid retention, which could lead to or worsen heart failure. Heart failure is a decreased ability to pump enough blood throughout the body. Symptoms of heart failure include shortness of breath, cough, fatigue, tiredness, ankle swelling, or weight gain. If your doctor prescribes insulin together with rosiglitazone, you will be monitored closely for these symptoms, so that the medications can be adjusted or, if necessary, stopped.

Although there has been no report of liver difficulties with rosiglitazone, a related medication was removed from the market due to rare, severe liver reactions. Thus, if you require this medication, you will need to have blood tests looking for liver problems every two months for the first year after you begin the medication and once a year thereafter.

Insulin [various short-, intermediate-, or long-acting forms, including aspart and glargine]: Potential side effects related to insulin use include: low blood sugar, low potassium in the blood, allergies or skin changes.

Meglitinides [repaglinide]: Common side effects include headache, upper respiratory infections, nausea, vomiting, constipation, and diarrhea. The most serious side effect is hypoglycemia.

Alpha-Glucosidase Inhibitors [acarbose]: Side effects include flatulence (gas), diarrhea and abdominal discomfort These are generally mild to moderate in severity and usually diminish in frequency and intensity with time. Very rarely, this medication may cause skin reactions, hepatitis, and/or jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems).

Blood pressure treatments

Angiotensin Converting Enzyme Inhibitors (ACE-I) [benazepril, lisinopril, ramipril]: Potential side effects associated with this type of medicine include: dizziness, headache, fatigue, nausea, diarrhea, cough, rash, high potassium in the blood, low blood pressure upon standing, harm to kidney function and rarely angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death).

Diuretics [chlorthalidone, hydrochlorothiazide]: Potential side effects associated with this class of medication also known as "water pills" include: muscle cramps, nausea, vomiting, diarrhea, dizziness, rash, weakness, low blood pressure, low potassium, high blood sugar, partial or total lack of ability to

perform sexual function, and gout (a painful joint condition that occurs when too much acid and salt build up in the blood stream and joints).

Beta Blockers [metoprolol]: The most common side effects associated with this group of medicines include: dizziness, fatigue, stomach upset, depression, cold hands and feet, low blood pressure, changes in heart rhythm and heart rate, and decrease in sexual function. Beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar. If you begin taking these medications, you should not stop taking them without talking to your study doctor first.

Calcium Channel Blockers [isradipine, diltiazem, amlodipine, nifedipine]: The most frequent side effects associated with these medications are: ankle or foot swelling, dizziness, flushing, palpitations (awareness of your heartbeat), headache, fatigue, nausea and abdominal discomfort. Occasionally, severe hypotension (abnormally low blood pressure) may occur when starting these medications or adjusting their dose. Rarely, increased angina (chest pain) and myocardial infarctions (heart attacks) may occur in people with severe coronary artery disease. When combined with a Beta Blocker, the medication nifedipine may cause congestive heart failure (a decreased ability to pump enough blood through the body), which can be serious but is very rare.

Alpha Blockers [terazosin]: Potential side effects associated with this category include: fainting, dizziness, fatigue, swelling, low blood pressure, partial or total lack of ability to perform sexual function, changes in heart rhythm and certain blood cell abnormalities.

A-II Receptor Blockers [candesartan, valsartan]: The most common side effects are dizziness, headache, fatigue, diarrhea, muscular-skeletal pain. More serious side effects are angioedema (swelling of the face, lips and tongue that can result in difficulty breathing or in rare cases, death) and severe hypotension. This family of drugs may also affect your kidney function. Your doctor may do blood tests to see if your kidneys are performing properly.

Loop Diuretic [furosemide]: rare side effects include thrombocytopenia (low platelet count), rash, pancreatitis (inflammation of the pancreas), and jaundice (yellowing of the skin or whites of the eyes, indicating possible liver problems). Serious side effects include abnormalities in blood cells.

Sympatholytics [reserpine]: The most common side effects include dizziness, dry mouth, nausea, vomiting, nasal congestion, peripheral edema (too much fluid in the body's tissues), stomach cramps, headache, impotence, depression, nervousness, shortness of breath, nightmares, difficulty with urination, shaky hands, and anorexia (poor appetite). More serious side effects include dysrhythmias (heart rhythm abnormalities), black tarry stools, hematemesis (vomiting blood), bradycardia (slow heart rate), chest pain, and thrombocytopenia (low platelet count).

Vasodilators [hydralazine]: Side effects include headache, tachycardia (fast heart rate), angina (chest pain), and palpitations. Rare but more serious side effects include abnormalities in blood cells and lupus-like syndrome.

Potassium Sparing Diuretics [triamterene]: The most common side effects include diarrhea, nausea, vomiting, gastrointestinal distress, dizziness, dry mouth, pruritis (itching), rash, sensitivity to light, weakness, hypotension, muscle cramps, blood chemical imbalances (such as too much potassium), impaired kidney function, elevated uric acid, blood cell abnormalities and reduced folic acid stores. More serious possible side effects include increased acid in the blood and shock due to an allergic reaction to the medication.

Alpha-beta blockers [carvedilol]: The most common side effects are dizziness and fatigue. The more serious side effects include AV block (a heart rhythm disturbance), bradycardia (slow heart rate), thrombocytopenia (low platelet count), and bronchospasm (tightening of breathing airways). Alpha-beta-blockers may also hide some of the symptoms but not the hazards of low blood sugar.

Lipid treatments

HMG-CoA Reductase Inhibitors (statins) [simvastatin]: Common side effects associated with this class of cholesterol-lowering medications include: headache, dizziness, stomach upset. Rare, but more

serious side-effects are muscle aches, rash and elevated liver enzymes (indicating possible liver problems) in the blood. (Also, see 'Drug Interactions' discussed below.)

Fibrates [fenofibrate]: Potential side effects associated with these medications include: abdominal pain, stones in the gall bladder, jaundice (yellowing of the skin and/or whites of the eyes, indicating possible liver problems), headache, change in taste, elevated liver and kidney function tests, and certain abnormalities in blood cells. Your study doctor has ways to manage these blood cell abnormalities.

Fenofibrate could possibly harm the kidney. Blood tests will be done regularly to look at your kidney functioning. If your results are not normal your dose of fenofibrate or placebo (whichever you are on) will be reduced. If your values do not improve, the medication will be stopped entirely. After your dose is reduced or stopped, your study doctor will continue to monitor your kidney function. (Also, see 'Drug Interactions' discussed below.)

Drug Interactions

What are some of the ways the study drugs can interact? The Food and Drug Administration (FDA) has approved all drugs that will be used in ACCORD. Most have been used for many years. Therefore, we know much about the way these drugs work and how they interact with other drugs - especially other treatments that will be used in this study.

Researchers know that using a sulfonylurea (a type of drug that lowers blood sugar) with certain other drugs should be avoided. Your study doctor will make sure that you do not take these kinds of medicines together.

Researchers also know that using statins and fibrates together may increase the chance for certain side effects such as liver problems and muscle pain and inflammation. These side effects are rare, but are more likely at higher statin doses. If your dose of simvastatin is increased to 40 mg per day, your chance of side effects may be increased. Many doctors use simvastatin and fenofibrate together, and the ACCORD trial will use caution whenever you are given this combination. Additionally, the ACCORD clinic will be checking your blood to make sure that the study medications are not harming your liver or muscles. These tests will be done at 1, 4, 8, and 12 months after you begin the medications, and every year after that. If your study doctor thinks that the statin and fibrate medicines are causing problems for you, then he/she may take you off one or both these medicines.

If you are eligible to be in the lipid portion of ACCORD and if you are on warfarin (also called Coumadin), your personal doctor will be informed both by phone and in writing that you may be on fenofibrate. Because the use of fenofibrate generally means that your dose of warfarin should be reduced to avoid excessive risk of bleeding, you will be tested to see how fast your blood clots. This blood test can be done by either the ACCORD clinic or by your private doctor. You will not be randomized until the ACCORD clinic staff speaks with your private doctor about monitoring the appropriate dose of warfarin for you. If you are placed on warfarin during the study, you will need to make sure that your private doctor is reminded that you may be on fenofibrate.

POTENTIAL BENEFITS

What are the possible benefits? The ACCORD treatment may or may not be of personal benefit to you. The information gathered from the study will be very important for the treatment of diabetes in the future. There will be no charge to you for any of the required tests and procedures performed during your participation in this study. Clinic visits, physical exams, laboratory tests, electrocardiograms and any other procedures associated with the research aspects of this study are paid for by the study. In addition, your medications for the blood sugar control as well as for the blood pressure control portion or blood lipid control portion of ACCORD (whichever part you are in) will be provided to you free of charge. You will not be paid for your participation in this study.

ALTERNATIVE TREATMENTS

If you chose not to participate, what other options do you have? You do not have to participate in this research study in order to receive treatment. A number of treatments are available for diabetes, high blood pressure, or high cholesterol. These treatments include drugs, diet, exercise, and weight loss. If you decide to stop participating in this study, your personal doctor should manage your medical care.

NEW INFORMATION

What if we learn about new risks during the study? You will be given any new information gained during the course of the study that might affect your health, welfare, or willingness to stay in the ACCORD study. Results of your laboratory tests and clinical measurements will be provided to you to share with your personal physician.

PRIVACY

How will your privacy be protected? Any information obtained about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you. Your name and any other potentially identifying information will not be used on any data or samples you provide. However, your name and Social Security and Medicare numbers will be recorded and stored centrally to help the study keep track of any illnesses you may experience. Also, in order to receive supplies (glucose strips) to measure your own blood glucose during the trial, you will need to provide the information that will permit billing for Medicare (if you are covered) and/or other insurance you may have (if you have it.) You will not be identified in any report or publication about this study.

Your records for this study may be reviewed by authorized representatives from the National Heart, Lung, and Blood Institute, the Food and Drug Administration (FDA) and monitoring personnel from the _____ Clinical Center Network Office for the study at _____and by the committee in charge of protecting research participants at_____.

At the end of the study, all forms with your name or other identifying information will be kept in a locked room for a period of five years. Only your study doctor or co-workers assisting the doctor will have access to these forms. After five years, the forms will be destroyed.

Also at the end of the study, the Coordinating Center will provide the National Heart, Lung, and Blood Institute (NHLBI) data from the study, without personal identifying information such as your name, address, Social Security number, or Medicare number. Blood, urine, and/or tissue samples or other materials taken from you during the study will be considered donated by you to medical research. These materials may also be provided to the NHLBI at the end of the study, again without personal identifying information. The data and/or materials may be shared with other scientists who meet NHLBI requirements including treating the data or materials as medically confidential, obtaining approval from their Human Subjects review boards, and agreeing not to share the data or materials with other parties. Drug companies that have contributed drugs, and in some cases money, to the ACCORD study also will be provided study data without any personal identifying information.

U.S. Federal Certificate of Confidentiality. It is particularly important to you to know that ACCORD has been granted a Certificate of Confidentiality from the United States Federal Government to make sure we can best protect your privacy. This certificate means that the ACCORD researchers cannot be forced to tell anyone not connected with the study about your participation. This includes courts and police. The researchers will only release information if you request it.

There are some limits to the researcher's ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put someone else we know about in danger, then we will have to tell the appropriate agencies to protect you or the other person.

INJURY

What will happen if you become ill during the study or suffer a complication related to the treatment that you are receiving as part of the study? While it is not likely that you will suffer major health problems as a result of your participation in this study, the medical treatment that is a part of this study carries a small risk of serious health problems. Of course, should a problem occur, or should you need emergency medical help, necessary emergency care would be provided and the investigator working with you would help you find a doctor to continue your care if needed. Any cost of medical care that results from such a health problem will be your responsibility and will not be paid for by the National Heart, Lung, and Blood Institute, the study investigators, or the hospital or clinic conducting this study.

QUESTIONS ABOUT THE STUDY AND YOUR RIGHTS

What if you have questions about this study? For questions about the study or in the event of a research-related injury, contact the study investigator, _____, at _____ [INCLUDE AFTER-HOURS NUMBER].

What if you have questions about your rights as a participant? For questions about your rights as a research participant, you may contact the Chairman of the Institutional Review Board, which is a group of people who review the research to protect your rights as a research participant, at _____. You will be given a copy of this consent form.

What if you want to stop before your part in the study is complete? Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your study doctor also has the right to stop your participation in this study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

GENETIC STUDIES

What is the goal of the genetic studies? One goal of ACCORD is to examine your genetic material (DNA) and its relationship to the effects of the treatments. If you volunteer to participate in the genetic studies you will be asked for a sample of blood (about 1 teaspoon) to obtain DNA from your blood cells. Information gained from research on your DNA may be used to develop new ways to detect or treat major diseases.

Will the DNA samples be shared with other institutions? If you agree to participate in the genetics portion of the study, the ACCORD Central Laboratory may share DNA samples with researchers participating in ACCORD. If you give permission, samples may also be shared with other research laboratories studying the genetics of type 2 diabetes and the development of heart and blood vessel diseases, other major diseases, health conditions, or risk factors. The scientists from these laboratories would be given the DNA without any information to identify you.

How will genetic information be kept private? Only the ACCORD Central Laboratory will have access to the samples. No other individual, including your spouse, parents, children, physician or employer will have access to the stored sample or information gained from your stored sample. At the end of the study, your samples may be provided to other investigators under certain conditions, without any personal identifying information (See Privacy section above).

How long will the DNA samples be kept? Your sample may be kept until it is no longer of scientific value. If, at any time during the study, you decide that you do not wish to have your DNA sample stored any longer, you may notify your ACCORD study coordinator and the sample will be destroyed.

Who owns the samples? By checking "yes" at the end of this document, you volunteer to provide

genetic samples for medical research purposes. Your DNA will not be sold to anyone or to institutions or companies for financial gain or commercial profit without your consent. Also, neither you nor your heirs will receive money from any discoveries or inventions made using the information and/or specimens you provide. There is no cost to you or your insurance company for the storage and use of the samples.

Will you receive study results of research involving your samples? You will not be informed of the results of the research performed on your genetic blood sample, although genetic tests may be developed after a study of samples in the ACCORD study. If there is any new information about genetic testing for type 2 diabetes and its relationship to heart and blood vessel diseases or other health conditions, you will be informed by your study doctor if this information may be important to you or your family.

PARTICIPANT'S AGREEMENT FOR THE GENETIC PORTION OF ACCORD

*Please check **one** of the following choices:*

____ **Yes**, I agree to participate in the genetic portion of ACCORD

____ **No**, I do not agree to participate in the genetic portion of ACCORD

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding diseases to be studied:

____ I agree to allow my genetic sample to be studied for genes related to any major disease or health condition or risk factors.

____ I agree to allow my genetic sample to be studied **ONLY** for genes related to diabetes, blood pressure, blood cholesterol abnormalities, heart disease, other cardiovascular diseases, kidney diseases, or other risk factors for heart disease or for diabetes.

If you agreed to participate in the genetic portion of ACCORD, please check one of the following regarding investigators who will have access to the genetic samples:

____ I agree to allow my genetic samples to be used for research by ACCORD investigators as well as by other researchers who meet NHLBI standards and procedures.

____ I agree to allow my genetic samples to be used **ONLY** for research by ACCORD investigators.

PARTICIPANT'S AGREEMENT FOR ACCORD STUDY

I have read the information provided above. I voluntarily consent to participate in the ACCORD study.

_____ _____
Participant's signature Date

_____
Printed name of participant

_____ _____
Signature of person obtaining consent Date

_____
Printed name of person obtaining consent