The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness **Study (GRADE Study)**

NCT01794143

Phase 1 Informed Consent V1.6.1

March 17, 2017

Phase 2 Informed Consent V1.7

October 5, 2017

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

GRADE Study Coordinating Center
Biostatistics Center
George Washington University
6110 Executive Boulevard
Rockville, Maryland 20852

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Template Informed Consent- Phase 1

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

PRINCIPAL INVESTIGATOR:

SITE PRINCIPAL INVESTIGATOR:

DESCRIPTION OF SUBJECT POPULATION: Adults with type 2 diabetes

(Consent for Screening and Trial Run-in)

About this consent form

Please read this form carefully. It tells you important information about a research study called the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study or GRADE Study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "participants." This term will be used throughout this consent form.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

The consent form you are being asked to sign today is for the screening and run-in period (**Phase 1**) of the GRADE study. **By signing this form, you are giving your permission for Phase 1 – Screening and Run-In. Phase 1 will determine whether you are eligible for the GRADE clinical trial (Phase 2). Once you have completed the screening and run-in period you will be given a separate consent form to review and sign. It will explain the details of the clinical trial (Phase 2).** This consent form gives a description of the clinical trial (Phase 2) to help you decide whether or not to participate in the screening and run in period (Phase 1). You may also ask to review the full Phase 2 consent document now if you would like.

Why is this research study being done?

The GRADE study is a research study for people with type 2 diabetes. This research study will compare the effectiveness of four different medications that are used to treat type 2 diabetes.

Each of the 4 medications will be used together with metformin. Metformin is the medication used most often to treat type 2 diabetes. Each medication combination used in the GRADE study has been approved by the U.S. Food and Drug Administration (FDA) and is commonly used to treat type 2 diabetes in adults. However, no study has ever compared these combinations "head-to-head". Therefore, which combination treatment is best for adults with type 2 diabetes is not known. The GRADE study will compare how well the different medication combinations control blood sugar levels. We will also look at other benefits or side effects of each medication combination. Information from the GRADE study will help to determine the best treatment for type 2 diabetes.

Who can be in this research study?

To be in the GRADE study, you need to have type 2 diabetes for less than 10 years. You must have been at least 30 years of age when you were diagnosed (if you are an American Indian, you must have been at least 20 years old at the time of diagnosis). You also must be taking metformin to treat your type 2 diabetes. You cannot currently be taking any diabetes medications other than metformin. If you take less than 2000 mg of metformin per day, that dose will be increased during the first few weeks of the study (called the "run-in" period). You must be able to take at least 1000 mg of metformin per day (goal being 1000 mg twice per day) to be in the GRADE study.

To be in the GRADE study, you must be willing to take a second randomly assigned study medication by self-injection or pill every day along with your metformin. You must be willing to test your blood sugar by finger stick (or from an alternate site, such as your arm) up to 2 times daily at home. If needed to keep your blood sugar levels within the recommended range, you must be willing to take more than one type of insulin and more than one injection per day, and take up to 3 medications daily.

Once you successfully complete the screening and run-in period you will be randomized to one of the four study diabetes medications. Being randomized means that the medication will be assigned by chance, like the flip of a coin. **You will not have a choice about the second diabetes medication that will be assigned to you**. Some of the medications are taken by injection and some as pills. You will stay on that randomly assigned medication, in addition to your metformin, for the duration of the GRADE study assuming that you tolerate the assigned medication. If your diabetes control worsens we may ask you to add one or more types of insulin given by injection, as is usually done in clinical practice when a combination of two different drugs is not enough to keep blood sugar levels in the recommended ranges.

You must have a regular health care provider (primary care provider) by the end of the run-in period in order to be in the study. If you do not have a primary care provider, the GRADE study

may be able to help you identify one. While you are in the GRADE clinical trial, the study team will help you with your diabetes treatment plan and will provide all study medication free-of-charge. You and your primary health care provider will still be responsible for other parts of your health care, including general preventive measures such as monitoring blood pressure, blood cholesterol, foot exams, eye exams, and immunizations. The GRADE Study will send results of your GRADE blood tests that are part of "usual care" reports to your primary care provider. If the study medications fail to lower your glucose levels to an acceptable range, we will reach out to your own care provider to discuss adding non-study medications. Any additional medications prescribed by your care provider would be billed to your insurance and would not be provided by the study.

We expect to enroll about 5000 people with type 2 diabetes at GRADE study sites throughout the United States. We will enroll about 150 participants ***(OR INSERT LOCAL INSTITUTION TARGET NUMBER IF GREATER THAN 150)*** at (***INSERT LOCAL INSTITUTION***). The GRADE study is sponsored by the National Institutes of Health (NIH), meaning that they are providing funding and other support to carry out the study. Medications used in the GRADE study are being donated by the following companies: Bristol-Myers Squibb, Merck, Novo Nordisk, and Sanofi. Roche Diagnostics will donate blood sugar monitors and test strips. BD Medical is providing insulin starter kits and the needles to be used for insulin injections. None of the companies has had any part in designing or carrying out the study and they will not be involved in evaluating the study results. The Centers for Disease Control and Prevention (CDC) is providing financial support for the economic analysis. The National Diabetes Education Program (NDEP) is donating copies of the booklet, *4 Steps to Control Your Diabetes for Life,* to the study.

How long will I take part in this research study?

The screening and run-in period (Phase 1) will take about 6-12 weeks to complete. During screening and run-in, we will ask you to make 2 or 3 study visits to (***INSERT SITE NAME***). Each visit will take about 60-120 minutes. We will be in contact with you between visits to review how you are doing taking metformin.

Your participation in the GRADE clinical study (Phase 2) will be for 4 years up to 7.5 years depending on when you enroll. The study is planned to end in 2021. Phase 2 visits will be every 3 months. Most of these visits will take about an hour. Once each year you'll have a longer visit (3-4 hours) that will require that you fast (nothing to eat for at least 8 hours before the visit). The visit will start between 8 and 9:30 AM. We may occasionally ask you to come in for an extra visit from time to time to re-check a blood test result or to adjust your medications. Extra visits will generally take an hour or less.

What will happen in this research study?

Phase 1: Screening and Run-in

Screening Visit

The first visit (screening visit) will be done to find out whether you initially qualify for the study. It will take about 60 to 90 minutes. Your medical history will be reviewed and we will measure your blood pressure and weight. About 3 tubes of blood (about 3 teaspoons total) will be collected. We will test your blood for red blood cell count, liver function, kidney function, and hemoglobin A1c, a test that tells us about your average diabetes control. If you are a woman of childbearing age, we will do a urine pregnancy test.

It will take a few days to get the results of your tests. We will check the results to make sure that you qualify for the study and that any of the 4 study medications would be safe for you. If you are eligible, we will ask you to come for another appointment to start the run-in part of the study. If you do not qualify for the study, we will tell you why. In some cases, such as a temporary condition or blood test that made you ineligible, we can schedule a repeat screening visit and/or blood test.

Run-in Visits

The purpose of Run-In Visits is:

- To be sure you can tolerate taking the study medication metformin, which you will be required to take twice per day.
- To make sure that you are able to come to your appointments, give yourself an injection and test your blood sugar as requested.
- To make sure that you understand what you will be expected to do over the next 4 to 7 years of the study.

The first run-in visit will take place within one to two weeks of your screening visit. It will take about 60 to 90 minutes. We will give you the study-supplied metformin and, if necessary, begin to adjust the dose. We will teach you how to test your own blood sugar by pricking your finger (also called “doing a finger stick”) or testing from an alternate site, such as your arm, and ask you to demonstrate it. We will also show you how to give yourself a practice injection without medicine (there are two medicines in the study that are given by injection), and we will ask you to give yourself a practice injection before you leave the visit so that you can be confident that you will be able to give yourself an injection during the study.

You must be able to take at least 1000 mg of metformin per day and the goal is to have you taking 1000 mg twice daily. If you are already taking the recommended study dose of 1000 mg twice per day, no changes will be made and you will continue on that dose. If you take more than that, we will reduce the dose to 1000 mg twice per day. If you take less than that, we will increase your dose weekly until you are taking 1000 mg twice per day. If, by increasing the dose you start having side effects (the most common problems are stomach upset and diarrhea), we will decrease the dose and try again. If you still have side-effects, we will change you to a longer-acting/slower release type of metformin, which may reduce the side effects. If you need to have your metformin dose adjusted, we may ask you to come for an additional run-in visit about 4 to 6 weeks after the screening visit.

During run-in, you will meet with the GRADE staff for diabetes education. The GRADE staff will review the basics of diabetes self-management, exercise goals, and healthy eating. Your final run-in visit will be about 6 to 12 weeks after your screening visit. This visit will take about 2 hours to complete. We will ask you to bring back any unused study medication (metformin). We will check to see that you have been able to take the recommended amount of metformin and collect some blood samples (about 1 teaspoon) for kidney function and diabetes control.

You will be asked to sign the clinical trial (Phase 2) consent form either at the final run-in visit or at your next visit, which would be the start of the clinical trial. That visit will be scheduled for a week or two after the final run-in visit, when we will have received the results of your blood tests to make sure that you are still eligible to participate in the study. We will let you know the results and if you are not eligible for the clinical trial we will tell you why. If you are not eligible, we will provide a small amount of metformin so you won't run out as you go back to your own health care provider.

Phase 2: GRADE Clinical Trial

We will give you a consent form for Phase 2 if you are eligible for the clinical trial after the screening and run-in phase. However, you may ask to review the consent form at any time. We describe the clinical trial in general terms below so that you will know what would be expected of you should you enroll in the clinical trial.

Once you have enrolled into the GRADE clinical trial, your participation will be for 4 up to 7.5 years depending on when you enroll. You will continue to take metformin and you will start a second diabetes medication. **As a reminder, the second diabetes medication is assigned by chance. Neither you nor any member of the GRADE study team will be able to decide which medication is assigned.** There are four possible medications. Two are taken by mouth (pills) and two are given by injection (one injection per day). You will have a visit with the study staff

every three months. At each visit, the study staff will perform a blood test (hemoglobin A1c) that measures your average blood sugar control to see if it is in the desired range. If your hemoglobin A1c is not "at target" with the combination of metformin and the assigned study medication, we will ask you to add insulin. If one type of insulin does not keep your hemoglobin A1c in an acceptable range, we may ask you to add a second type of insulin.

Clinical Trial: Treatment and Follow-up

Your first visit in Phase 2 of the GRADE clinical trial is called the baseline randomization visit. This visit will take about 5 hours to complete. We will ask you to be "fasting" (no food for 8 hours; you may drink water). Please take your usual morning medications (except for your diabetes medications) with a small amount of water. We will ask you not to take your metformin on the morning of your visit but would like you to bring your metformin with you to take when the visit is over.

At this first visit, you will be assigned to your second study medication, to be taken in combination with the metformin. The medications that will be used in Phase 2 of the GRADE study are glimepiride, sitagliptin, liraglutide, and glargine. All of these medications are taken daily, all are commonly used to treat type 2 diabetes, and all are approved by the FDA for use with metformin. Glargine and liraglutide are taken by injection once per day. Glimepiride and sitagliptin are taken by mouth as a pill once or twice daily. If you are assigned to take glargine or glimepiride we will give you a blood glucose meter, testing supplies, and instructions on testing your blood sugar by finger stick at home since both of these medications will be adjusted based on your home blood sugar test results. The other two medications, liraglutide and sitagliptin are not adjusted based on blood sugar results. The study staff will review your assigned medication with you in detail during this visit. This will include a review of how to take the medication, when to take the medication, how to store the medication, and common side effects and risks of the medication. If you are assigned to glargine or liraglutide we will teach you how to give an injection and have you demonstrate how it is done before the end of the appointment.

Blood and urine samples, questionnaires, measurement of your blood pressure, electrocardiogram (ECG), height, weight, waist and hips, and a foot exam will be done at the baseline visit. We will test your memory with standard testing.

If time permits, some of your testing, measurements or other questionnaires can be completed at your final run-in visit (blood pressure, height, weight, waist and hips, foot exam, ECG, the memory test, and/or questionnaires about your quality of life, diabetes symptoms and care). Your waist and hips will be measured with a tape measure and we will test your memory with

standard testing. You will have an ECG, a heart tracing, to measure the electrical activity of your heart. The ECG will be repeated at some annual visits during the study.

The memory testing will require about 20-30 minutes to complete. At your baseline randomization visit you will also have an Oral Glucose Tolerance Test (or OGTT). The OGTT measures your glucose and insulin response to carbohydrate and takes about 2 hours to complete. You will be given a flavored drink with glucose (sugar), and we will take blood samples periodically during the test. The OGTT will be performed at baseline and at some annual visits (years 1, 3 and 5).

At the conclusion of the baseline randomization visit we will give you a 3 month supply of study medication and will schedule you for a follow-up visit in 3 months. The study team will be available by phone to talk with you in between visits. You will continue to have visits every 3 months for the duration of the GRADE clinical trial. Most visits will take 60 to 90 minutes. One visit per year (scheduled around the time of your anniversary of your baseline randomization visit) may take up to about 3-4 hours to complete (depending on whether or not an OGTT is scheduled).

What are the risks and possible discomforts from being in this research study?

There is a small risk of infection at the site of the needle stick for blood drawing. This occurs in less than 1 in 1,000 people. The risk is minimized by standard blood collection practices, such as cleaning the skin before the needle stick, and wearing gloves/washing hands. In some cases, a person may faint or become sick to the stomach at the sight of a needle or when blood is drawn. In about 1 in 4 people, there may be minimal discomfort or bruising at the site of the needlestick. The GRADE staff who perform these procedures have special training and experience in drawing blood. This should help keep these risks at the lowest possible level.

If the blood tests done in GRADE show abnormal results, this may be stressful to you. However, studies have shown that the sooner health problems are found and treated, the better the outcome. In addition, many of the problems identified by the GRADE staff might be easily treated. For example, we may find an abnormal amount of fat (cholesterol, lipids) in your blood. We know this problem can be treated by changing your diet and/or prescribing cholesterol-lowering medications.

The total amount of blood obtained annually during the GRADE study is somewhat more than the amount of blood that would be obtained during usual clinical care, but is not unsafe for adults and will not cause low blood counts (anemia). Also, the results of the blood tests during GRADE may take the place of some of the tests that your own care provider would otherwise perform.

There is a slight amount of pain associated with checking blood sugar levels using finger sticks. There is also a very low risk of infection at the site of the finger stick. The GRADE staff will help you find the best ways to check your blood sugar levels and how to minimize discomfort and avoid infection.

There may be a small amount of pain associated with injection of medications into the fatty tissue in your abdomen or thigh (the most common sites for injections). The GRADE staff will help you find the best place to inject to keep the pain as little as possible.

Some people may get slightly nauseated or get an upset stomach from the glucose (sugar) drink given during the OGTT. These symptoms are rare and disappear within 15 to 30 minutes.

Metformin

The FDA has approved the use of metformin for treating diabetes in adults. It is the most common diabetes medication used worldwide, and all potential participants will be treated with metformin before entering screening. There are, however, risks associated with metformin that you should know.

The most common side effects of metformin include nausea, headaches, diarrhea, vomiting, bloating, excessive gas, loss of appetite, and an unpleasant taste in the mouth. These are more common when the medication is first started and lessen or disappear over time. About 10 out of 100 people using metformin may experience these symptoms to some degree. However, these side effects are rarely severe enough to result in needing to stop the medication. Other side effects include lower-than-normal levels of vitamin B12 in the blood, which can rarely lead to anemia (low blood count). Hypoglycemia (low blood sugar) rarely occurs when metformin is taken by itself, but it can occur when metformin is combined with some other diabetes medications.

In very rare instances (fewer than 3 in 100,000), a condition called lactic acidosis has been reported in patients taking metformin. When lactic acidosis occurs it is usually in persons who have other severe medical problems, such as kidney disease, liver disease, or severe circulatory problems. We will check blood tests and ask about symptoms to make sure it is safe for you to continue to take this medication. In addition, you must notify the GRADE study team if you experience any severe disease that results in hospitalization since, for safety, we will want to stop metformin during the illness. If ignored or untreated, lactic acidosis can lead to serious health problems that can progress to coma or death.

You should talk to the study team before you undergo any surgery, X-ray procedures, or CT scans that use any type of injection (such as a dye that makes X-rays easier to see) as you will need to stop your metformin during the time of the procedure. Alcohol should not be used in excess while taking metformin. Inform your study doctor if you now have (or develop during the course of the trial) kidney or liver disease, heart failure, or severe infections.

Other Study Medications

The FDA has approved the use of all the medications used in the GRADE study for treating diabetes in adults. However, there are risks associated with each medication that you should know. For example, allergic reactions may occur. Any medication may be associated with an allergic reaction. Although the medications studied in GRADE are only rarely associated with an allergic reaction, one may still occur. If you develop any symptoms of an allergic reaction (itching, rash, hives, difficulty breathing) while you are taking the study medication you should contact the study staff.

According to most treatment guidelines, younger people, for example less than 65 years of age, should aim for HbA1c less than 7% in order to decrease their risk of developing diabetes complications. Higher levels of HbA1c, such as 7.5% or higher, may be appropriate for older people with longer duration diabetes who have other diseases, such as heart disease. A recent large study showed that patients treated to achieve near-normal blood sugar levels (an average HbA1c level of 6.4%) had a higher risk of death, including death from heart attacks and strokes. The risk of having one of these events was higher in patients with a prior history of heart disease and with diabetes for longer than 10 years. Several other studies with persons who were more similar to those who will be recruited in GRADE have not shown any increased risk for heart attacks, stroke, or deaths when their HbA1c levels were reduced to an average of 6.4%.

In order to reduce possible increased risk, GRADE will include lower risk persons who have had diabetes for less than 10 years. In addition, GRADE is excluding persons who are very ill or who have had a heart attack, stroke or a surgical procedure to prevent or treat such diseases in the previous year. It is unknown whether the GRADE protocol will increase the risk for heart attacks and strokes in some persons whose HbA1c level is decreased to less than 6.8%.

The effects of some diabetes medications on how an unborn baby grows and develops are not known. None of the medications in the study are known to be associated with specific birth defects. In fact, three of the medications are commonly used during pregnancy. However, because we do not know for certain the effects of some of the diabetes medications used in the study on a baby before it is born, it is important that you do not

become pregnant while you are taking study medications. We will do a urine pregnancy test at the screening and randomization visit if you are a woman of childbearing age. We may also ask you to provide a urine sample for pregnancy testing at other times during the study. If you suspect that you are pregnant or are concerned you may have become pregnant while taking the study medications, you should advise the GRADE study team immediately. If you become pregnant you will be advised to stop taking the study's medications and switch to medications specifically prescribed by your own health care provider during the pregnancy. We will recommend that your primary care provider find a doctor for you who specializes in taking care of pregnant women who have diabetes.

Each of the study medications has some known side effects. These are carefully described in the Phase 2 (Clinical Trial) consent form. Two of the study drugs have a side effect of weight gain. We will counsel you to minimize that risk and monitor you for that possibility.

Any time that a diabetes medication is started, stopped, or changed, there is a risk that you may have high blood sugar levels (hyperglycemia) or low blood sugar levels (hypoglycemia). The symptoms of high blood sugar levels include drowsiness, thirst, excessive urination, and loss of appetite. If you start to go to the bathroom more often than usual, you may need to check your blood sugar levels more often, and also check your urine for ketones.

The symptoms of low blood sugar levels include sweating, fatigue, nervousness, shakiness, rapid heartbeat, nausea, and confusion or personality changes. If a person drinks or eats sugar-containing food right away, the symptoms will often stop. In the most severe cases, low blood sugar can cause unconsciousness and seizures. If you have any of these symptoms, you will need to check blood sugar levels to be sure the symptoms are caused by low blood sugar. As part of the GRADE diabetes education, we will teach you about the signs and symptoms of high and low blood sugar levels and what to do about them.

We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may not be effective to control their blood sugar levels. If this happens, long-term treatment with insulin or a more intensive insulin regimen (more than 1 injection of insulin daily) may be required. However, we cannot tell beforehand which participants will be able to tolerate the study medications and which will not; or which participants will be able to successfully control their blood sugar levels with the assigned medications and which will not. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels and has the most favorable long-term outcomes, every participant randomized into the study is equally important. Even if you are no longer taking your originally assigned medications, it is just as important for us to know your long-term outcomes as it is for any other participant. That is

why it is important for you to attend all study visits even if you aren't taking some or all of your study-assigned medications, or if you are taking other diabetes medications prescribed by your care provider.

What are the possible benefits from being in this research study?

If you decide to take part in this study, there is no guarantee that your health will improve. We will follow your diabetes closely. You will receive additional education about diabetes and how to take care of it. The GRADE study team will help you manage your diabetes free-of-charge. You will have blood tests and procedures to monitor your health at no charge and the results will be shared with you and, with your permission, with your primary care provider who may use them to help with your medical care. In addition, you will receive the following at no charge:

- Glucose testing equipment as needed at no cost to you
- Diabetes medication at no cost
- Diabetes care from a team of diabetes experts at no cost

What other treatments or procedures are available for my condition?

You do not have to take part in this study to be treated for type 2 diabetes. Other treatments or procedures that are available to treat diabetes include receiving care for your diabetes from your primary care provider or other health care providers rather than the GRADE study. You are not obliged to take part in the GRADE study to receive treatment for diabetes.

Can I still get medical care within (*INSERT INSTITUTION NAME*) if I don't take part in this research study, or if I stop taking part?

Yes. Your decision will not change the medical care you get within (***INSERT INSTITUTION NAME***) now or in the future. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to join the study. If you decide to join now, you may change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed. It is possible that we will have to ask you to stop your participation before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?
You will not be paid for your participation during the screening and run-in phase (the "tryout"). We will pay for local travel costs and provide parking vouchers and meal replacements if we ask you to fast for an appointment.

There is no cost to you for being in this study. There will be no charge for procedures or medications required by the study.

What happens if I am injured as a result of taking part in this research study?
Taking part in this research study may hurt you (this was explained in the section called "Risks and Discomforts"). If you need to get medical care right away, you should go to the nearest emergency care center. Be sure to explain that you are participating in a research study. If you do not need emergency care, you should contact your primary care provider. The GRADE investigators may also take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. You will be responsible for any costs not covered by your health insurance. GRADE and the clinical site you go to will not pay for your care. Likewise, GRADE and your clinical site will not pay you for pain, worry, lost income, or non-medical costs that might occur from being in this research study.

If I have questions or concerns about this research study, whom can I call?
You will receive a copy of this consent form. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, primary care provider, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may ask your questions to _____ at phone _____.

You can contact the local Institutional Review Board at _____ for further information about your rights as a research subject.

Confidentiality
Your consent to be in this study includes consent for the GRADE researchers to review your health records as may be needed for the purposes of this study. Your consent also gives GRADE researchers permission to collect study information (data) related to this study and to use it for research purposes. Your consent also includes permission for the sponsor of this study (NIH) to review your study records.

Information from your medical records and information obtained about you during the GRADE study will be sent to the GRADE central coordinating center at The George Washington University for statistical analysis. No personal information that directly identifies you will be

included with this data. Personal information is information such as your name that directly identifies you. Instead, you will be assigned a unique study code. The key to the code, linking it to you, will be kept in a locked file here at ***(INSERT NAME OF STUDY SITE)***. Only ***(INSERT NAME OF PI AND HIS/HER STUDY STAFF AT STUDY SITE)*** will have access to the key to the code. Research records will be stored securely. After the study is completed, the study data may be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever this information is used.

Your study data and information from your medical records may be reviewed for safety monitoring purposes by pharmacists and nurses at the GRADE Drug Distribution Center or by the GRADE safety monitor. Your study data may be shared with companies that are donating the study medications for purposes of reporting safety information to the Food and Drug Administration (FDA). As described above, no personal information that directly identifies you will be included with any data or medical information reviewed by the Drug Distribution Center, the GRADE safety monitor, drug companies, or the FDA.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, GRADE researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether at the federal, state, or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others, if you wish.

There are some rare exceptions to the protection offered by the Certificate of Confidentiality. GRADE researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

GRADE researchers will consider your records private. Rarely, representatives of the U.S. Department of Health and Human Services (DHHS) or GRADE may review or request a copy of your study records. If this happens, these requests will be honored. Also employees of the ***(INSTITUTION'S NAME)*** _____or its agents could be allowed to see your study records to make sure that the study is being done properly.

A description of this clinical trial will be available on www.ClinicalTrials.gov. as required by the U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this site at any time.

The results of this study may be published for scientific purposes. These results could include laboratory tests. By signing this form, you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

Informed Consent

Study Doctor or Person Obtaining Consent	Date/Time

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date/Time

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Template Informed Consent- Phase 2

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

PRINCIPAL INVESTIGATOR:

SITE PRINCIPAL INVESTIGATOR:

DESCRIPTION OF SUBJECT POPULATION: Adults with type 2 diabetes

(Consent for GRADE Clinical Trial)

About this consent form

Please read this form carefully. It tells you important information about a research study called Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study or GRADE. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "participants." This term will be used throughout this consent form.

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

The GRADE Study is a 7-year clinical trial designed to compare the effects of combining each of 4 different medications that are currently used to treat type 2 diabetes with a drug called metformin in individuals who have had type 2 diabetes for less than 10 years.

The medication combinations are all commonly used, but studies comparing each of these drugs in combination with metformin over a number of years have not been done. The GRADE study has been designed to compare how well each of these 4 drugs work (in combination with metformin) in controlling type 2 diabetes and in addition to examine any other benefits and potential side effects of the medications. All medications and the medication combinations used in the GRADE study have been approved by the U.S. Food and Drug Administration (FDA).

The GRADE trial is a multicenter study and we expect to enroll a total of about 5000 people with type 2 diabetes within the United States. We expect to enroll about 150 participants ***(OR IF >150 INSERT LOCAL INSTITUTION TARGET NUMBER)*** at (***INSERT LOCAL INSTITUTION NAME***).

You have already completed Phase 1 of the GRADE study, called the screening and run-in phase. During Phase 1, you were found to be eligible for the GRADE study.

This consent form focuses on **Phase 2** of the GRADE clinical trial, the long-term treatment and follow-up study. It describes in detail what will happen during the clinical trial.

By signing this consent, you are giving your permission to be entered into Phase 2 of the GRADE clinical trial. You will be asked to participate in the study up to its planned end in 2021. The GRADE study is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which is a branch of the National Institutes of Health (NIH). NIDDK is providing funding and other support to carry out the study. The National Heart, Lung, and Blood Institute (NHLBI) is providing funding for the electrocardiogram (ECG) tests to measure the electrical activity of the heart. Medications used in the GRADE study are being donated by the following companies: Bristol-Myers Squibb, Merck, Novo Nordisk, and Sanofi. Roche Diagnostics will donate blood sugar monitors and strips. BD Medical is providing insulin starter kits and the needles to be used for insulin injections. None of the companies has had any part in designing or carrying out the study. The Centers for Disease Control and Prevention (CDC) is providing financial support for the economic analysis. The National Diabetes Education Program (NDEP) is donating copies of the booklet, *4 Steps to Control Your Diabetes for Life,* to the study.

How long will I take part in this research study?

If you enroll in the GRADE clinical trial, you will be asked to come for visits every three months until the end of study follow-up that is projected to be reached in 2021. So, depending on when you enroll, you will have as few as about 16 visits or as many as about 28 visits to your GRADE clinical center during the entire study. Most visits will take about an hour but once per year you will have an "annual" visit that will take about 3-4 hours. We may occasionally ask you to come in for an extra visit to re-check a blood test result or to adjust your medications. These extra visits should take an hour or less.

What will happen in this research study?

GRADE Clinical Trial

You will continue to take metformin. When your eligibility to participate has been established you will attend a baseline (or randomization) visit at which time you will start to take a second

diabetes medication that will be assigned at random or by chance, like a flip of a coin. **Neither you, nor your study team will select the second medication that will be assigned to you**. The second medication will be one of four possible medications which will be described later on in this document.

You will be asked to come to the study clinic for a visit every 3 months until 2021. The GRADE staff will be available by phone to talk with you in between visits. Most of these every 3-month visits ("quarterly visits") will take about an hour. Once per year, on about the anniversary of your baseline visit, you will have a longer "annual visit" that will take about 3-4 hours. At each quarterly and annual visit, one of the blood tests will be a hemoglobin A1c test (called a HbA1c which measures your average level of blood sugar over the past 3 months). If your HbA1c is higher than 9%, which means that your blood sugar levels are very high, you will be asked to come to the GRADE clinic for a repeat test 3 to 6 weeks after the initial test. There may be additional or interim visits scheduled if we think that you would benefit from additional monitoring.

If you enroll in this study, the study medical team will treat your diabetes according to the GRADE protocol, and provide all study medications at no cost to you. You and your primary health care provider are still responsible for other parts of your care, including general preventive measures such as treating high blood pressure and elevated cholesterol levels, if you have those conditions, and giving vaccinations and providing foot care and eye care. The results of some of the tests done by the GRADE study will be shared with your regular health care provider (for example, blood pressure and cholesterol levels), which should help them provide you with care.

Baseline Randomization visit

Your first visit in Phase 2 of the GRADE clinical trial is called the baseline randomization visit. Prior to the visit we will check the results of your blood tests done at your last run-in visit to make sure that you are eligible for the GRADE clinical trial. We will also assess how many metformin pills you have taken during run-in. You will need to bring all unused study medication with you to the visit. If you are a woman of childbearing age, we will ask you for a urine sample to test for pregnancy before the randomization process starts. If you are pregnant or planning a pregnancy during the course of the study, you cannot be in the study.

The baseline randomization visit will take about 5 hours to complete. We will ask you to be "fasting" (no food for 8 hours; you may drink water) on the day of your visit. Please take your usual morning medications (except for your diabetes medications) with a small amount of water. Do not take your diabetes medications on the morning of the visit. We will provide visit instructions and will remind you about your appointment either by phone, email, or mail.

We will collect blood and urine samples. The blood samples (about 13 teaspoons) will be collected to measure lipids (blood fats including cholesterol), sugar, insulin (the hormone in your body that controls glucose levels), and C-peptide (a protein that is produced by your body and tells us how much insulin your body is making). Blood and urine samples will be collected for long-term storage and future analyses. The urine sample will be used to measure albumin (a type of protein) and creatinine (a waste product) to see how well your kidneys are working.

During this visit, we will perform an oral glucose tolerance test (OGTT). The OGTT measures your blood glucose levels in response to a sweet drink and measures your body's ability to make insulin. It requires frequent blood sampling (5 times) over a period of 2 hours. You must be fasting for at least 8 hours before this test, which will be started before 10:30 AM.

We will ask you to drink a flavored sweet drink and we will check blood tests before and afterwards to see your body's response. At the start of the test we will place an IV (intravenous catheter) in a vein in your arm or hand. An IV is a small plastic catheter inserted into a vein that will stay in your vein during the 2-hour test so that we can draw several blood samples without doing a needle stick each time. When the test is done we will remove the IV from your vein.

You will have a brief physical exam at your baseline randomization visit. Your evaluation will include blood pressure, electrocardiogram (ECG), height, weight, waist and hip measurement, and a foot exam, unless any of those measurements were completed during your final run-in visit. During the foot exam we will test your reflexes and do other simple measurements to assess nerve function in your feet. These include using a soft filament on your foot to see whether or not you can feel it and test light touch sensation. The filament is a soft flexible piece of nylon, like a bit of fishing line. It does not hurt, and does not puncture the skin. We will also use a tuning fork to test if you can feel vibration on your big toe. This feels like a slight buzzing sensation and is not painful. We will ask you some questions about your past medical history. We will measure your waist and hips with a tape measure. You should wear loose-fitting comfortable clothing. You will have an ECG, a heart tracing, to measure the electrical activity of your heart.

We will ask you to complete about 6 brief questionnaires. Two of these questionnaires ask about your quality of life and one asks about symptoms you may be having. Another will give us information about costs of caring for diabetes. If not completed at your final run-in visit, we will test your memory with standard testing. The memory testing will require about 20-30 minutes to complete.

Medication assignment

You will be assigned a second diabetes medication at the baseline randomization visit. As stated earlier, **neither you, nor your study team will be able to select the second medication**

that will be assigned to you. The second medication (one of 4 second medications used in this study) will be assigned by chance, like a flip of a coin. It is therefore important that you have considered and are willing to accept an assignment to any one of the four medications. That includes being willing to take one of the two diabetes medications that are given by injection. In this case, you must be willing to give yourself medication by injection daily in order to take part in the study.

As long as your blood sugar levels remain under acceptable control, you will take the assigned medication along with your metformin for the duration of the study. If your blood sugar control worsens, once per day insulin therapy will be started for the three groups that weren't assigned initially to insulin. Insulin therapy will be further increased, with more than once per day injections, if once per day insulin doesn't adequately control your diabetes. We will provide you with the study medication at no charge, and provide instructions for taking it. Each of the 4 possible medications that will be added to your metformin at the baseline randomization visit are commonly used to treat diabetes. They are glimepiride, sitagliptin, liraglutide, and glargine. Glargine and liraglutide are taken by injection once per day. Glimepiride and sitagliptin are taken by mouth as a pill once or twice daily. If you are assigned to take glargine or glimepiride, we will give you a blood glucose meter, testing supplies and instructions on testing your blood sugar by fingerstick (or sticking another site like your arm) at home. The doses of these two medications will be adjusted based on your home blood sugar test results. The other two medications, liraglutide and sitagliptin are not adjusted based on blood sugar results.

We will teach you how to take the medication, when to take the medication, how to store the medication, and common side effects and risks of the medication. If you are assigned to glargine or liraglutide we will teach you how to give an injection and have you demonstrate how it is done before the end of the appointment. If it is later determined that you need to add insulin to your treatment regimen in order to maintain acceptable control, we will also teach you how to give yourself an injection.

Quarterly Visits

You will be asked to come to the GRADE clinical center for routine visits every 3 months. There will be 4 visits a year. Each year there are 3 quarterly visits and one annual visit from the date that you entered the study. The scheduled quarterly visits are listed below.

Year 1 at 3, 6, and 9 months after your randomization visit

Year 2 at 15, 18 and 21 months after your randomization visit

Year 3 at 27, 30 and 33 months after your randomization visit

Year 4 at 39, 42 and 45 months after your randomization visit

Year 5 at 51, 54 and 57 months after your randomization visit

Year 6 at 63, 66 and 69 months after your randomization visit

Year 7 at 75, 78 and 81 months after your randomization visit

If you were enrolled in the first year of the study, 2013, you may be asked to complete two more quarterly visits at 84 and 87 months (after your randomization visit) until the study ends in 2021.

At each quarterly visit the GRADE staff will talk with you about the medication you are taking, review your blood sugar levels if needed, give you a new supply of study medication, review any side effects or problems that you are having from the medication, measure your weight and blood pressure, review any other medications you are taking, and ask you some questions about your medical history. You will have a blood sample taken to check your average glucose control over the past 3 months (HbA1c test). This is about ½ teaspoon of blood. Twice per year, we will ask you for a urine sample to check your kidney function. Twice during the study we will do a blood test for a vitamin B12 level. This may require about ½ teaspoon of blood if done at a semi-annual visit. If done at an annual visit no additional blood is needed. If you are using a glucose meter we will review the fingerstick readings that are recorded in your meter or log book. The quarterly visits will take about one hour to 90 minutes.

It is important that you bring your unused medication with you to each study visit.

Annual visits

You will have a scheduled annual visit each year that you are in the GRADE study. We will ask you to be fasting (no food or drinks except for water for 8 hours) before the visit. Please take your usual morning medications (except for your diabetes medications) with a small amount of water. Do not take your diabetes medications on the morning of the visit if you are having an OGTT. We will ask you to arrive at the appointment by 9:30 AM or earlier. The annual visits that include an OGTT will take about 4 hours each. Annual visits without an OGTT will be about 3 hours each. Your study team will inform you prior to the visit if you will be receiving an OGTT. The schedule of annual visits is listed below.

Annual fasting visits

- Year 1 at 12 months after randomization
- Year 2 at 24 months after randomization
- Year 3 at 36 months after randomization
- Year 4 at 48 months after randomization

- Year 5 at 60 months after randomization
- Year 6 at 72 months after randomization
- Year 7 at 84 months after randomization

Because special tests are conducted at these annual visits, you should fast for 8 hours before the visit.

At each annual visit the GRADE staff will talk with you about medication taking, review your blood sugar levels if needed, give you a new supply of study medication and collect any study medication you have returned, review any side effects or problems that you are having from the medication, examine your feet, measure your weight, blood pressure, waist and hips, review any other medications you are taking, and ask you some questions about your medical history. We will ask you to complete the same brief questionnaires that were completed during the randomization visit and were described above.

You will have blood samples collected which include a test to check your average glucose control over the past 3 months (HbA1c), and a test to check your kidney function (creatinine) at each annual visit. Lipids (fats in your blood such as cholesterol) will be tested at some of the annual visits. Your blood level of vitamin B12 will be measured at your next semi-annual or annual visit, whichever comes first, after this is started in about April, 2017, and again at your year 4 annual visit. Your vitamin B12 results will be provided to you and your primary care physician (PCP). We will tell you if the result is in the normal or abnormal range. We are measuring vitamin B12 levels because long-time use of metformin may cause vitamin B12 levels to be low. Low vitamin B12 levels can usually be easily treated with a daily vitamin pill. The GRADE study will not provide the vitamin as part of the study but will provide you with information about B12 supplements and where to purchase them or will provide a prescription for you if you prefer. If your vitamin B12 level is considered to be very low, we will repeat the test in about 6 months to check that the vitamin pill is working.

In addition, we will perform the same oral glucose tolerance test (OGTT) that was performed at the baseline randomization visit at some annual visits (years 1, 3 and 5). If an OGTT is performed, an IV catheter will be placed to limit the number of “sticks” necessary to obtain the blood samples. We will also ask you for a urine sample to check your kidney function every year. If you are using a glucose meter we will review the fingerstick readings. In addition, 4 tubes of blood will be collected for long-term storage and future analyses. In total, all of the blood tests performed at the annual visit will add up to a maximum of 200 cc (or 13 tablespoons) of blood. Rarely, a tube of blood may be damaged or lost during preparation or shipment. If this happens, we may ask you for an extra tube of blood at a later visit.

The electrocardiogram (ECG) will be done at baseline and at some annual visits to measure the electrical activity of your heart .

Long-term Follow-up

GRADE is a long-term study to look at the effectiveness of the 4 drugs (plus metformin) used in the study. This study is planned to end in 2021. Each participant's long-term follow-up information is important to the study. We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may prove to be ineffective. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels, and has the most favorable long-term outcomes, every participant randomized into the study is equally important. It is important for study participants to attend all quarterly and annual study visits until the end of the study even if they are not taking some or all of their study-assigned medications, or if you are taking other diabetes medications prescribed by your care provider.

We realize there may be circumstances that prevent you from attending all of your study visits at the clinic. If that happens, the study staff may arrange for a phone call or a visit to your home to perform some of the study visit at your convenience. In addition, you may be asked to collect a small blood sample in your home from your finger. If you are willing to collect the sample, we would mail a collection kit to you and review the details of the procedure with you to make sure you understand how to collect the sample, and to allow you to ask questions. The sample will be mailed to the GRADE laboratory by you and the GRADE study will cover the postage. We hope that when you are able you will return to the clinic to resume your usual study visits.

GRADE study staff will ask your permission to get copies of your medical records if you are hospitalized during the study. Review of the records will be used to determine the cause of the hospitalization.

Monitoring Your Blood Sugar and Changes to Your Diabetes Medications

The effectiveness of each diabetes treatment will be measured by HbA1c. HbA1c is a blood test which measures your average level of blood sugar over the previous 3 months. After your first 6 months in the study, an HbA1c level that is above 7.5% for two consecutive visits will require that additional medication be added. However, if your HbA1c level is >9% during the first 6 months you are in the study, we may add another medication sooner.

If you were randomly assigned to the glargine insulin (a long-acting insulin) treatment group and your HbA1c result goes above 7.5% for two consecutive tests despite dose adjustments, we will add an injection of rapid-acting insulin in addition to your long-acting glargine insulin and

your metformin. If you are randomly assigned to the other medication groups (glimepiride, sitagliptin or liraglutide) and your HbA1c goes above 7.5% for two consecutive tests, you will continue the metformin and your second randomly assigned diabetes medication, and we will ask you to start taking once per day glargine insulin. If your HbA1c stays above 7.5% on these 3 medications we will ask you to add a second type of insulin, which is rapid-acting. When you add the rapid-acting insulin we will ask you to stop the 2nd diabetes medication that was assigned at randomization. You will continue to take metformin and 2 types of insulin.

At each study visit the study staff will monitor your lab test results, talk with you about any side effects you are having and will adjust medication doses as needed. If the side effects are frequent or severe we will decrease or discontinue the study medication. If at any time during the study, your HbA1c level goes above 9%, we will ask you to come back for a repeat measurement within 3 to 6 weeks instead of the usual 3 months between visits.

If the study medications fail to lower your glucose levels to an acceptable range, we will reach out to your own care provider to discuss adding non-study medications. Any additional medications prescribed by your care provider would be billed to you or your insurance and would not be provided by the study.

What are the risks and possible discomforts from being in this research study?

There is a minor risk of infection at the site of the needle stick for blood drawing or intravenous (IV) insertion. This occurs in less than 1 in 1,000 people. The risk is minimized by following standard clinical practices such as cleaning the skin before the needle stick, and washing hands prior to blood collection. In some cases a person may faint or become sick to the stomach at the sight of a needle or when blood is drawn. In about 1 in 4 people, there may be some discomfort or bruising at the site of the needlestick. The GRADE staff who conduct these procedures have special training and experience in drawing blood and placing IVs. This should help keep these risks at the lowest possible level.

If the blood tests done in GRADE show abnormal results, this may be stressful to you. However, studies have shown that the sooner health problems are found and treated, the better the outcome. In addition, many of the problems identified by the GRADE staff might be easily treated. For example, we may find an abnormal level of fats (such as cholesterol) in your blood that, once identified, can be treated by changing your diet and/or having your own physician prescribe cholesterol-lowering medications.

There is a slight amount of pain associated with checking blood sugar levels using fingersticks. There is also a very low risk of infection at the site of the fingerstick. The GRADE staff will help you find the best ways and places to check your blood sugar.

There is a very slight amount of pain associated with the injections of the study medications (long-acting and rapid-acting insulins and liraglutide) into the fatty tissue in your abdomen, arms or legs. The GRADE staff will help you find the best place to inject to keep the discomfort as minimal as possible. Do not share the pen devices which are used to administer the injected medications or the pen needles with others as it could cause transmission of infection like hepatitis or HIV.

Some people may get slightly nauseated or get an upset stomach from the glucose (sugar) drink given during the OGTT. These symptoms are rare and disappear within 15 to 30 minutes.

The FDA has approved the use of all the medications used in the GRADE study for treating diabetes in adults. However, there are risks associated with each medication that you should know. For example, allergic reactions may occur. Any medication may be associated with an allergic reaction. Although the medications studied in GRADE are only rarely associated with an allergic reaction (itching, rash, hives, or difficulty breathing for example), it may still occur. If you develop any symptoms of an allergic reaction while you are taking the study medication, you should stop the medication and contact the study staff as soon as possible.

According to most treatment guidelines, younger people, for example less than 65 years of age, should aim for HbA1c less than 7% in order to decrease their risk of developing diabetes complications. Higher levels of HbA1c, such as 7.5% or higher, may be appropriate for older people with longer duration diabetes who have other diseases, such as heart disease. A recent large study showed that patients treated to achieve near-normal blood sugar levels (an average HbA1c level of 6.4%) had a higher risk of death, including death from heart attacks and strokes. The risk of having one of these events was higher in patients with a prior history of heart disease and with diabetes for longer than 10 years. Several other studies with persons who were more similar to those who will be recruited in GRADE have not shown any increased risk for heart attacks, stroke, or deaths when their HbA1c levels were reduced to an average of 6.4%.

In order to reduce possible increased risk, GRADE will include lower risk persons who have had diabetes for less than 10 years. In addition, GRADE is excluding persons who are very ill or who have had in the previous year a heart attack, stroke or a surgical procedure to prevent or treat such diseases. It is unknown whether the GRADE protocol will increase the risk for heart attacks and strokes in some persons whose HbA1c level is decreased to less than 6.8%.

The effects of some diabetes medications on how an unborn baby grows and develops are not known. None of the medications in the study are known to be associated with specific birth defects. In fact, three of the medications are commonly used in diabetic patients during pregnancy. However, because we do not know for certain the effects of some of the diabetes medications used in the study on a baby before it is born, it is important that you not become pregnant while you are taking study medications. We will do a urine pregnancy test at the screening and randomization visit if you are a woman of childbearing age. We may also ask you to provide a urine sample for pregnancy testing at other times during the study. If you suspect that you are pregnant or are concerned you may have become pregnant while taking the study medications, you should advise the GRADE study team immediately. If you become pregnant you will be advised to stop taking the study's medications and switch to medications specifically prescribed by your own health care provider during the pregnancy. We will recommend that your primary care provider find a doctor for you who specializes in taking care of pregnant women who have diabetes.

Any time that a diabetes medication is started, stopped, or changed, there is a risk that you may have high blood sugar levels (hyperglycemia) or low blood sugar levels (hypoglycemia).

The symptoms of high blood sugar levels include thirst and increased frequency of urination, including the need to urinate more often than usual during sleeping hours. If you start to go to the bathroom more often than usual, you may need to check your blood sugar levels more often.

The early symptoms of low blood sugar levels include sweating, fatigue, nervousness, shakiness, and rapid heartbeat. If a person drinks or eats sugar-containing food right away, the symptoms of low blood sugar will stop, usually within 10 minutes. Most cases of low blood sugar, if treated rapidly and appropriately, cause only minimal symptoms and no harm. However, if low blood sugar episodes are not detected and treated quickly, they can become more severe, causing confusion. In the most severe cases, low blood sugar can cause unconsciousness and seizures. If you have any of the early warning symptoms, you will need to check blood sugar levels to be sure the symptoms are caused by low blood sugar. If you cannot check your fingerstick blood sugar for some reason, you should treat yourself with a sugary snack as if your blood sugar is low. As part of the GRADE diabetes education, we will teach you about the signs and symptoms of high and low blood sugar levels, how to prevent them and what to do about them.

We know that some participants will not be able to tolerate the assigned medications, and that for some participants the assigned medications may prove to be ineffective. If this happens, long-term treatment with insulin or a more intensive insulin regimen (more than 1 injection of insulin daily) may be required. However, we cannot tell beforehand which participants will be

able to tolerate the study medications and which will not; or which participants will be able to successfully control their blood sugar levels with the assigned medications and which will not. In order to answer the study questions as to which medication provides the best long-term control of blood sugar levels and has the most favorable long-term outcomes, every participant randomized into the study is equally important. Even if you are no longer taking your originally assigned medications, it is just as important for us to know your long-term outcomes as it is for any other participant. That is why it is important for every study participant to attend all study visits even if you are not taking some or all of the study-assigned medications.

The actions, side effects, and risks of metformin, as well as of each of the 4 secondary medications and the fast acting insulin used in this study are described below.

GRADE Trial Medications, Risks and Side Effects

Hypoglycemia:

Medications used to treat high blood sugar in persons with diabetes can sometimes cause blood sugar to become too low (hypoglycemia). Hypgolycemia can result from diabetes medications or from a change in your diet, activity level, or exercise routine. Symptoms of hypoglycemia can range from mild to severe. Mild to moderate symptoms of hypoglycemia include increased hunger, anxiety, shaking, or feeling dizzy or light-headed. More severe symptoms can include confusion or loss of consciousness and may require emergency treatment or hospitalization. Severe episodes of hypoglycemia may cause brain damage, coma or death. Your study team will teach you how to recognize and treat hypoglycemia.

Metformin

If you have advanced to the clinical trial phase informed consent, you are taking metformin and tolerating at least 1000 mg per day. Metformin is used to help control blood sugar in patients with type 2 diabetes. This medication decreases the amount of glucose absorbed from your diet and made by your liver. It also makes the body more sensitive to insulin.

The most common side effects of metformin include nausea, headaches, diarrhea, vomiting, bloating, excessive gas, loss of appetite, and an unpleasant taste in the mouth. These are more common when the medication is first started and lessen or disappear over time. About 10 out of 100 people using metformin may experience these symptoms to some degree. However, these side effects are rarely severe enough to result in needing to stop the medication. Other side effects include lower-than-normal levels of vitamin B12 in the blood, which may rarely lead to anemia (low blood count). Numbness and tingling in the extremities can also be caused

by low levels of vitamin B12. Low vitamin B12 levels can generally be treated with a vitamin B12 supplement tablet. Hypoglycemia (low blood sugar) rarely occurs when metformin is taken by itself, but it can occur when metformin is combined with some other diabetes medications.

In very rare instances (fewer than 3 in 100,000), a condition called lactic acidosis has been reported in patients taking metformin. When lactic acidosis occurs it is usually in persons who have other severe medical problems, such as kidney disease, liver disease, or severe circulatory problems. We will check blood tests and ask about symptoms to make sure it is safe for you to take this medication. In addition, you must notify the GRADE study team if you experience any severe disease that results in hospitalization since, for safety, we will want to stop metformin during the illness. If ignored or untreated, lactic acidosis can lead to serious health problems that can progress to coma or death.

You should talk to the study team before you undergo any surgery, X-ray procedures, or CT scans that use any type of injection (such as a dye that makes X-rays easier to see) as you will need to stop your metformin during the time of the procedure. Alcohol should not be used in excess while taking metformin. Inform your study doctor if you now have (or develop during the course of the trial) kidney or liver disease, heart failure, or severe infections.

Glimepiride (Amaryl)

Glimepiride is in a class of type 2 diabetes medications called sulfonylureas. This class of drugs stimulates your pancreas to produce more insulin and makes your body more sensitive to insulin. Insulin is the hormone naturally made by your pancreas which helps you to absorb glucose (sugar) into your muscles and tissues. Without enough insulin the glucose remains in your bloodstream causing your blood sugar levels to rise.

Glimepiride may cause low blood sugar (hypoglycemia) or weight gain. Other common side effects include upset stomach, nausea, dizziness, itching, and sensitivity to light. Rare complications include blood cell abnormalities including low platelet count with easy bruising and allergic reactions causing itching, rash, swelling, wheezing or shortness of breath. If you have low blood sugars when following your usual diet and activity plan, we will adjust your dose of this medication to be sure it is safe for you. You will need to check your fingerstick blood sugar levels in order to help your team adjust your doses. We will provide supplies and education for testing your blood sugar by fingerstick at home and teach you how to recognize and treat low blood sugar levels. Tell your study doctor if you now have (or develop during the trial) an inherited condition called G6PD disease, heart, liver or kidney disease or a disorder of the thyroid, adrenal or pituitary glands.

Sitagliptin (Januvia)

Sitagliptin is in a class of type 2 diabetes medications called dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 is an enzyme in your body that breaks down certain hormones in your body known as incretins. Sitagliptin inhibits DPP-4 and slows the breakdown of incretin hormones in the body. When the body's blood sugar rises in response to a meal, Sitagliptin helps to increase the body's production of insulin and decreases the amount of glucose (sugar) produced by the liver.

Sitagliptin is generally well-tolerated. Because incretin hormones are more active in response to higher blood sugar levels (and are less active in response to low blood sugar), the risk of dangerously low blood sugar (hypoglycemia) is low with sitagliptin. Sitagliptin has been associated with more frequent infections such as bladder infections (urinary tract infection), cold-like symptoms (upper respiratory infection), headache, diarrhea, inflammation and muscle or joint pains. It has also been associated, although very rarely, with pancreatitis (an inflammation of the pancreas), and rarely with painful skin blisters or sores. Symptoms of pancreatitis include severe abdominal pain, nausea, and vomiting. Tell your study doctor immediately if you experience any of these symptoms. If you have ever had pancreatitis, you are not eligible for the GRADE study. Similar drugs that work like Sitagliptin have been associated with heart failure in patients who have a prior history of heart disease. If you have shortness of breath, difficulty doing your usual daily activities, or unexplained weight gain, tell your study doctor about these symptoms.

Liraglutide (Victoza)

Liraglutide is a form of natural hormone called Glucagon-like peptide (GLP-1). It is one drug in a class of type 2 diabetes medications called incretins. When the body's blood sugar rises in response to a meal, GLP-1 works by helping your pancreas to increase production of insulin. It also slows down the emptying of the stomach and decreases the amount of glucose (sugar) produced by the liver. Liraglutide is given by injection once daily. We will teach you how to give the injections and provide the supplies necessary. Liraglutide (Victoza®) is now approved by the FDA to reduce the risk of major adverse cardiovascular (CV) events which include CV death, non-fatal heart attack, or non-fatal stroke in adults with type 2 diabetes mellitus and known cardiovascular disease.

Common side effects of liraglutide include nausea, vomiting, diarrhea, decreased appetite and stomach discomfort, which may affect from 15 to 40% of people. Liraglutide may cause low blood sugar (hypoglycemia). These side effects are often temporary and disappear or decrease with continued treatment. In addition, by starting with a smaller dose and increasing it, the risk for these side effects can be reduced. An increased risk of pancreatitis has also been reported. If you develop nausea, vomiting or have abdominal pain that last for more than a few hours,

you will be advised to hold the liraglutide and call the study team. A recent clinical trial reported an increased risk of gallbladder inflammation (cholecystitis) and/or gallstones in the gallbladder (cholelithiasis) in those taking liraglutide when compared to those who were assigned to a placebo. Contact your study doctor if you develop sudden abdominal, shoulder or upper back pain, fever, chills or yellowing of the skin. High levels of calcitonin, a substance in your blood that is associated with a rare form of thyroid cancer, have been reported. You are not eligible for the GRADE study if you have had pancreatitis or medullary thyroid cancer.

Glargine (Lantus) Insulin

Glargine is a long-acting insulin that is administered by injection once per day. Insulin is a hormone in your body that helps you absorb sugar and other nutrients into your muscles and other body tissues and cells. It also decreases the amount of glucose produced by the liver.

We will teach you how to give the injections and provide the supplies necessary. We will provide supplies and education for testing your blood sugar by fingerstick at home and teach you how to adjust your dose based on the blood sugar results. If you are assigned to glargine, the dose of glargine will be adjusted based on your self-tested blood sugar levels and the hemoglobin A1c blood tests performed every 3 months so that you can achieve the study targets with minimal hypoglycemia.

Side effects of glargine include low blood sugar (hypoglycemia) and weight gain. Other side effects may include itching, redness, or swelling at the injection site, allergic reaction and low potassium. Tell your study team if any of these symptoms are severe or persistent.

Aspart (Novolog) Insulin

Some participants in the study who do not achieve the goal blood sugar control with their assigned study medications may take aspart insulin in addition to glargine. Aspart is a rapid-acting insulin that is given by injection to help control blood sugar levels when other medications don't achieve the study goals. Although aspart may be given up to 3 times daily, most participants who need the rapid-acting insulin added will only take 1 injection per day. The dose of aspart will be adjusted based on the results of self-monitoring of fingerstick blood sugar testing. We will provide supplies and education for testing your blood sugar by fingerstick at home and teach you how to recognize and treat low blood sugar levels.

Side effects of aspart insulin include low blood sugar. Other side effects may include weight gain, or itching, redness or swelling at the injection site. Tell your study team if any of these symptoms are severe or persistent.

What are the possible benefits from being in this research study?

If you decide to take part in this study, there is no guarantee that your health will improve. We will follow your diabetes closely. You will receive education about diabetes and how to take care of it. The GRADE clinic team will help you manage your diabetes at no cost to you. You will receive tests and procedures to monitor your health at no charge and the results will be shared with you and, with your permission, with your primary care provider who may use them to help with your medical care. In addition, you will receive the following at no charge:

- Glucose testing equipment as needed at no cost to you
- Diabetes medication at no cost
- Care from a team of diabetes experts at no cost

Use of Stored Samples during and after Study End

With your permission, we would also like to store blood and urine samples for possible use during GRADE or after GRADE is over. Your samples will be stored indefinitely. Your blood and urine samples could be used to help health researchers learn more about what causes diabetes and how to treat it better. They could also help them learn more about diabetes, its complications (such as eye, nerve, and kidney damage), and other conditions for which people with diabetes may be at increased risk.

Your blood and urine samples will be stored at the GRADE central laboratory during the study and some of the extra "storage" samples at a place that is maintained for research purposes by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (sample repository). The samples stored at the sample repository will not have your name or any other identifying information that could directly link them with you. However, even with this confidentiality measure, there is no absolute guarantee that your identity will be protected.

As long as GRADE continues, it is possible for you to change your mind about having your blood and urine samples stored for future use. When GRADE is over, your remaining samples will be stored under the control and protection of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Researchers will not be able to use your samples without the permission of the NIDDK. You should understand that you can still be in this study without permitting the storage of your samples for further testing after GRADE is over.

Genetic Testing

We will ask your permission to allow us to study your DNA to understand how genes may affect the immune system, diabetes, complications associated with diabetes, or the response to the study medications. We will not provide the results of your testing to you or anyone else.

Although we will try very hard to keep any information about your testing private, there is a very small possibility that someone else could learn about your testing. Some people worry that genetic information could be used to discriminate against them. To prevent misuse, the researchers will take special precautions to protect your information. The data will be collected and stored with a code number only. We have obtained a Certificate of Confidentiality from the National Institutes of Health to protect the information we obtain about you. In addition, a law was passed in 2008 by the Federal Government that prohibits many forms of discrimination based on genetic information.

With your permission, DNA samples, which will be used to study the genetic (inherited) basis of diabetes, its complications, and response to therapy, will also be stored in the sample repository.

What other treatments or procedures are available for my condition?
You do not have to take part in this study to be treated for type 2 diabetes. Other treatments or procedures that are available to treat diabetes include receiving care for your diabetes from your primary care provider or other health care provider rather than the GRADE study. You are not obliged to take part in the GRADE study to receive treatment for diabetes.

Can I still get medical care within (*INSERT NAME OF INSTITUTION*) if I don't take part in this research study, or if I stop taking part?
Yes. Your decision will not change the medical care you get within (***INSERT NAME OF INSTITUTION***) now or in the future. There will be no penalty, and you will not lose any benefits you receive now or have a right to receive.
Taking part in this research study is up to you. You can decide not to take part. If you decide to join now, you may change your mind and stop participating later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?
Your choice to be in this study is completely voluntary. At any time you may choose to stop taking your study medications or to stop attending your study visits. If you wish to do so, you should tell us. We will make sure that you stop the study medications safely and will provide you with instructions about follow-up care.

What if I have difficulty with my study medication?
Your study doctor may choose to discontinue your study treatment at any time if it is felt that continuing treatment may hurt you. If this happens, we will tell you why. We will also help

arrange other care for you, if needed. You will be told of any new findings that affect your being in this study.

Will I be paid to take part in this research study?

You will be provided an honorarium of $100 per year during your participation in the GRADE study. The honorarium will be provided after the annual visit each year. We will also pay for local travel costs and provide parking vouchers and meal replacements if we ask you to fast for an appointment. By signing this consent you understand and agree that, if this research study results in the development of any product that can be sold, you will not receive a share of any money that is made.

What will I have to pay for if I take part in this research study?

There is no cost to you for being in this study. There will be no charge for procedures or medications required by the study.

What happens if I am injured as a result of taking part in this research study?

Taking part in this research study may hurt you (this was explained in the section called "Risks and Discomforts"). If you need to get medical care right away, you should go to the nearest emergency care center. Be sure to explain that you are participating in a research study. If you do not need emergency care, you should contact your primary care provider. The GRADE investigators may also take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. You will be responsible for any costs not covered by your health insurance. GRADE and the clinical site you go to will not pay for your care. Likewise, GRADE and your clinical site will not pay you for pain, worry, lost income, or non-medical costs that might occur from being in this research study.

If I have questions or concerns about this research study, whom can I call?

You will receive a copy of this consent form. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, primary care provider, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may ask your questions to _____ at phone_____.

You can contact the local Institutional Review Board at _____ for further information about your rights as a research subject.

Confidentiality

Your consent to be in this study includes consent for the GRADE researchers and representatives of the sponsoring agency (NIDDK/NIH) to review your health records as may be needed for the purposes of this study. Your consent also gives GRADE researchers permission to collect study information (data) related to this study and to use it for research purposes. Information from your medical records will be sent to the GRADE central coordinating center at The George Washington University for statistical analysis. No personal information that directly identifies you will be included with this data. Personal information is information such as your name that directly identifies you. Instead you will be assigned a unique study code. The key to the code, linking it to you, will be kept in a locked file here at *(**INSERT NAME OF STUDY SITE**)*. Only *(**INSERT NAME OF PI AND HIS/HER STUDY STAFF AT STUDY SITE**)* will have access to the key to the code. Research records will be stored securely. After the study is completed, your study data, without any personal identifying information, will be placed in a government information bank and may become available to researchers under the supervision of the NIDDK/NIH. Your privacy will be protected whenever these data are used.

Your study data and information from your medical records may be reviewed for safety monitoring purposes by pharmacists and nurses at the GRADE Drug Distribution Center or by the GRADE safety monitor. Your study data may be shared with companies that are donating the study medications for purposes of reporting safety information to the Food and Drug Administration (FDA). As described above, no personal information that directly identifies you will be included with any data or medical information reviewed by the Drug Distribution Center, the GRADE safety monitor, drug companies, or the FDA.

In the event that the study team loses contact with you during the trial, they will contact your primary care doctor and/or consult your medical record to collect information about your medical condition.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, GRADE researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether at the federal, state, or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others, if you wish.

There are some rare exceptions to the protection offered by the Certificate of Confidentiality. GRADE researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

GRADE researchers including representatives of NIH will consider your records private. Rarely, representatives of the U.S. Department of Health and Human Services (DHHS) or GRADE may review or request a copy of your study records. If this happens, these requests will be honored. Also employees of the ***(INSTITUTION'S NAME)*** _____or its agents could be allowed to see your study records to make sure that the study is being done properly.

A description of this clinical trial will be available on www.ClinicalTrials.gov. as required by the U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this site at any time.

The results of this study may be published for scientific purposes. These results could include laboratory tests. By signing this form you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

AUTHORIZATION INFORMATION:

Use of DNA samples:

Please indicate whether you are willing to provide a DNA sample to help us understand how genes may affect diabetes or related diseases. You can still be in the GRADE study even if you decide not to provide a DNA sample.

☐ Yes, I am willing to provide a DNA sample for use during this study ____ Initials

☐ No, I do not give permission to obtain or use a DNA sample during GRADE ____ Initials

Stored Samples:

Please indicate whether you are willing to allow blood and urine samples to be stored after GRADE is over, including DNA samples. These samples could be used to help researchers learn more about diabetes and its treatment. These samples could also be used to help them learn more about diabetes, its complications (such as eye, nerve, and kidney problems), and other conditions for which people with diabetes are at higher risk. You can still be in the GRADE study even if you decide not to have blood or urine samples stored once the GRADE study is over.

I give permission to have my blood and urine samples and/or DNA stored: (check one below)

☐ Yes, store my blood and urine samples including DNA _____ Initials
☐ Yes, store my blood and urine samples but not DNA _____ Initials

☐ Yes store my DNA, but not my blood or urine samples _____ Initials

☐ No, I do not give permission to have my blood, urine samples or DNA stored _____ Initials

Permission for Use of Social Security Number for Future Contact:

In the event that we have lost contact with you and cannot reach any of the individuals you have listed as contacts if we are having difficulty reaching you, we would like to have your permission to use your social security number to assist in locating you. We would ask public services that assist in locating individuals for your address and contact information or ask state and/or federal agencies to check their survival reports. We will only use these services as a last resort if we are unable to locate you. You can still be in this study if you decide not to give us permission to use your social security number to help us contact you.

Please indicate whether you are willing to provide your social security number to help us locate you.

☐ Yes, I am willing to provide my social security number for use to locate me for the study.
____ Initials

☐ No, I do not give permission to use my social security number to locate me during the study
____ Initials

Informed Consent

Study Doctor or Person Obtaining Consent	Date/Time

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date/Time