Participant Name: **Date:**

Title of Study: Tolerance & Responsiveness Improvement for Metformin (TRIM) Study

Principal Investigator: B. Layden, MD

Tolerance & Responsiveness Improvement for Metformin (TRIM) Study

Principal Investigator: Brian Layden, MD at JBVAMC

Study Sponsor: Principal Investigator funds

INTRODUCTION

You are being invited to take part in a research study that is being supported and conducted by the Department of Veterans Affairs (VA). Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below closely and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND AND PURPOSE

Many veterans have diabetes or increased blood sugar called prediabetes. In the United States nearly 26 million people have **type 2 diabetes (T2D).** Metformin is the most commonly used drug for type 2 diabetes. It is very good for lowering blood sugar and decreasing bad effects of diabetes on heart. Metformin could also help to lose weight or not to gain weight. One of the most common side effects of metformin is upset stomach and diarrhea. This prevents patients from using the drug and taking the necessary dose. Alternatively, patients take glipizide (pill for diabetes) for their high blood sugar.

The goal of **Tolerance & Responsiveness Improvement for Metformin (TRIM)** study is to see if certain supplements called prebiotic can reduce diarrhea due to metformin. The prebiotic is a specialized natural plant fiber called Psyllium that beneficially nourishes the good bacteria living in the large bowel or colon.

This study uses a medication for diabetes called Metformin. This pill has already been approved by the Food and Drug Administration (FDA) to treat diabetes and is allowed by FDA to be used for type 2 diabetes. The study also uses supplement called *Psyllium* (prebiotic). Psyllium is a natural fiber. Psyllium is an over-the-counter product used to help with bowel regularity.

You are being asked to take part in the TRIM study because you have type 2 diabetes and are using glipizide to treat it or you already have diabetes (increased blood sugar levels) but are not on medication for diabetes.

Principal Investigator (PI) Dr. Brian Layden, Attending Physician, Section of Endocrinology, Department of Medicine at Jesse Brown VAMC and his research team will be conducting this study.

Approximately 120 participants may be involved in this research from outpatient clinics at JBVAMC.

DURATION OF THE RESEARCH
This research study is expected to take approximately 2 years. Your individual participation may take approximately 3 months. You will be asked to visit JBVA for approximately 3 to 4 visits during those 3 months. Each of those visits will take about 1-2 hours. In addition, you will receive 5 phone calls to ask you about symptoms while on medications. You will have phone call every 2 weeks in between visits. Your diabetes control will be assessed with a blood test (called HbA1c) 3 months after study completion by your primary care provider (PCP) as usually done for diabetes care. At any point if you do not tolerate metformin you can withdraw from the study. However, only if you have tolerated at least 2 weeks of study medications, you will be eligible to come in for a Final Visit.

All visits for this study will be conducted at the JBVAMC.

STUDY PROCEDURES
If you decide to take part in this study, this is what will happen:

Visit #1 (Screening):
During this visit, you will be asked to read and sign this consent document. You will be asked questions about your medical history including smoking, alcohol intake, medical conditions and medications. If you consent and are suitable to participate in the study, the tests and procedures noted in the table 1 on page 4 of this consent form will be performed.

Visit #2 (Baseline):
During Baseline Visit the tests and procedures noted in table 1 on page 4 of this consent form will be performed. Your diabetes medication will be reviewed and questionnaires about your bowel health (called GIQ) will be administered. If you are not taking any diabetes medications you will start metformin (pill) 500mg (one pill) twice daily. If you are already taking glipizide, you will be changed from glipizide to metformin (pill) 500mg (one pill) twice daily. one week after baseline visit you will receive a phone call from the study staff, to ask you about your blood sugar levels and if you have any belly and bowel symptoms. Based on your responses you will be assigned to one of the two treatment groups as follows:

Group 1:
If you do not develop diarrhea or upset stomach with metformin your dose will be increased to 1000mg twice daily (4 pills per day). If you tolerate metformin 1000mg twice daily, you will be scheduled to come for Final visit at 3 months (13 weeks).

Group 2:
If you develop diarrhea or upset stomach while taking metformin, you will come in for an unscheduled visit (V4) for evaluation and will be prescribed psyllium fiber (powder).

Psyllium plus Metformin group:
If you are in psyllium group, you will start taking psyllium 1 powder pack with each metformin dose for one week. If you still have diarrhea, you will increase psyllium to 2 powder packs with each metformin dose. If you still have diarrhea, upset stomach you will you come for Final visit to finish the study, and continue diabetes care with primary care provider.

Medication adjustments will be made as described in the table 1 on page 4.

Visit #3 (Final Visit):
Final visit will happen approximately 13 weeks after baseline visit. The tests and procedures noted in the table 1 on page 4 of this consent form will be performed.

Unscheduled visit – In addition to the study visits described above, you may be asked to return to the clinic for unscheduled visit if you need evaluation for diarrhea and medication adjustments. If visit is for diarrhea evaluation, the tests and procedures performed are blood pressure, pulse, weight measurements, questionnaires to assess bowel health (GIQ), blood, stool test.

All oral diabetes medications used in TRIM are approved by the FDA to treat diabetes. The prebiotic psyllium is available over the counter for treatment of constipation. During your participation in the study all medications will be prescribed by the study doctors. You will receive these medications from JBVA research pharmacy via mail. After completion of the study, you can continue to use all medications according to standard of care and rules at JBVAMC pharmacy. Your PCP will be notified of your participation and progress in the study.

Participant Name: **Date:**

Title of Study: Tolerance & Responsiveness Improvement for Metformin (TRIM) Study

Principal Investigator: B. Layden, MD

Table 1: Study timeline and procedures

Study Visit	Procedures	Length of Visit
Screening (week 0)	• General health questionnaire and Eligibility assessment • Fill out consent form • Will be provided supplies to collect urine and stool specimens	1-2 hours
Baseline (2 weeks after screening)	• Height, weight, blood pressure, pulse • Questionnaires to assess bowel health (GIQ) • Blood and stool • Review of adverse events, diabetes control and medication adherence • Start Metformin (MF) 500mg 1 pill twice a day	1-2 hours
Ph #1 (1 week after V2)	• Questionnaire to assess bowel health (GIQ) • If no diarrhea, then increase MF 2 pills twice a day • If diarrhea, come for unscheduled visit, add Psyllium 1 packet twice a day (with MF) Within 1 week do the following: • If no diarrhea, continue Psyllium 1 packet twice a day (If taking Psyllium). • If diarrhea with Psyllium, then increase Psyllium 2 packets twice a day (taken with MF).	15 mins
Ph #2 (2 weeks after Ph1)	• Questionnaire to assess bowel health (GIQ) • If no diarrhea with MF 2 pills twice a day, continue the same • If no diarrhea with Psyllium plus MF, then increase MF 2 pills twice a day • If diarrhea with Psyllium plus MF, come in for unscheduled visit (V4)	15 mins
Ph #3 (2 weeks after Ph2)	• Questionnaire to assess bowel health (GIQ) • If no diarrhea, continue your pills as before • If diarrhea come in for unscheduled visit (V4) • If persistent diarrhea, come in for your Final visit to finish the study, and continue diabetes care with primary care provider	15 mins
Ph #4 (2 weeks after Ph3)	• Questionnaire to assess bowel health (GIQ) • If no diarrhea, continue your pills as before • If diarrhea, come in for unscheduled visit (V4) • If persistent diarrhea, you come for Final visit to finish the study, and continue diabetes care with primary care provider	15 mins
Ph #5 (2 weeks after Ph4)	• Questionnaire to assess bowel health (GIQ) • If no diarrhea, continue your pills as before • If diarrhea, come in for unscheduled visit (V4) • If persistent diarrhea, you come for Final visit to finish the study, and continue diabetes care with primary care provider	15 mins
Final Visit (13 weeks after Randomization)	• Height, weight, blood pressure, pulse • Questionnaires to assess bowel health (GIQ) • Blood and stool tests • Review of adverse events, diabetes control and medication adherence	1-2 hours

During the study, you will check your blood sugar by finger stick at least 3 times per week. You will be provided with a glucose log/worksheet to document your blood sugar during the week. Also, it will include a list of symptoms to monitor. You should call the study staff if your blood sugar is higher than 250 on 3 occasions. The study team will review your treatment and give advice on additional actions that you can take, including being sure you take all your medications, and discuss if you should make changes in diet or activity. If needed you will come to the clinic or have tests as appropriate for usual care of diabetes. For example, the study doctor can increase metformin dose. You could also have your primary care provider talk to the study doctor (Dr. Layden) before prescribing any new diabetes medication.

If your blood sugar remains elevated, you may need to add medications including insulin. At this point you will come for a final study visit, discontinue the study and your primary care provider will treat diabetes as per usual care.

During and after the study you will continue to see your primary care physician for your medical care. If your doctor prescribes you a medication for diabetes, please call study team and notify them of the change of medication.

Descriptions of tests and procedures:

Physical Measurements at baseline and final visits

Blood pressure will be measured in your arm. Your height and weight will be measured and pulse will be taken at baseline and final visits.

Blood samples will also be collected during your initial and final visits. This blood will be taken for the measurement of HbA1c (measure of the average blood glucose level control over 3 months' time) and tests related to diabetes biomarkers. These biomarkers are substances in the body used to evaluate disease. The total amount of blood drawn for these tests will be about 3 tablespoons.

Stool samples will be collected and used for tests related to diabetes biomarkers similar to blood samples. Approximately 1 teaspoon of stool samples will be collected during your baseline and final visits.

Questionnaires

You may also be asked to fill out questionnaires (surveys) about your general health, health behavior and digestive symptoms (belly and bowel symptoms) questionnaire called GIQ. An example of a question might be, "In the last week how often have you had loose stools? Bloating or abdominal pain?" You may choose not to answer any question.

Subject Responsibilities: You will be expected to do the following:

- Take the study drug as instructed.
- Keep your study appointments. If you miss an appointment, please contact the research staff to reschedule as soon as you know you will miss the appointment.
- Fill out your diaries and questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigator or research staff if you change your mind about staying in the study.

- While participating in this research study, do not take part in any other research project without approval from the investigators.
- Take and store your study drug as instructed and return the unused study drug and/or empty containers to the study doctor's office at each visit.
- Do not share your study drug with anyone.
- Do not start any new diabetes medications without checking with your study doctor.
- Tell the study staff about any health problems you are having.

POSSIBLE RISKS OR DISCOMFORTS
Any drugs and procedure have possible risks and discomforts. The drugs and procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur. If you experience any of the side effects described in this section, please tell your study doctor or a research staff member as soon as possible.

Procedure Risks
Side Effects from Blood Drawing: Pain, bruising, bleeding or other discomfort at the blood drawing site have been seen. Fainting or infection at blood drawing site may occur (very unlikely).

Questionnaires: Some of the questions may seem very personal or embarrassing. They may upset you. You may refuse to answer any of the questions. If the questions make you very upset, we will help you to find a counselor.

Other procedure-related risks: You may feel uncomfortable taking multiple pills for the study. You will be asked to check your blood glucose with a finger prick. This finger prick can be slightly painful.

Drug Risks
Metformin
Metformin has been used for many years to treat patients with diabetes. Side effects include the following:

- loss of appetite
- upset stomach
- vomiting
- stomach pain
- diarrhea
- bloating or gas
- a funny taste (like metal)

These are usually mild and decrease with continued use of the medicine. Mild side effects might happen in one out of five persons. Only one or two persons out of fifty are expected to have to stop metformin because of side effects. Low levels of Vitamin B-12 might also develop very rarely in some persons. Very rarely (3 in 100,000 and usually people with poor kidney function or with severe liver disease) develop a serious condition known as lactic acidosis that can result in death. Lactic acidosis has also occurred in people who are heavy or binge alcohol drinkers.

People with poor kidney function or severe liver disease, women planning to become pregnant, or people who are heavy or binge alcohol drinkers should not take metformin. Tests will be done regularly to check on kidney and liver function and blood cell count. If there is any change in your blood chemistries (liver and or kidney function) you will be advised whether you should stop taking the metformin, either temporarily or permanently. If you are hospitalized for any reason, other than for the visits related to the TRIM study, you will be advised to stop taking the metformin during that hospitalization.

Psyllium
Psyllium is a fiber used to induce regular bowel movements. This product generally produces bowel movements within 12-72 hours. Side effects could include the following:

- abdominal cramps
- minor bloating
- minor nausea

Taking this product without adequate fluid may cause swelling and blockage of your throat or esophagus and may cause choking. Obstruction of the esophagus, stomach, small intestine, and colon has occurred when bulk-forming laxatives are administered without adequate fluids or in patients with intestinal stenosis. This product may cause allergic reaction in people sensitive to inhaled or ingested psyllium.
Patients should avoid use of the medication if they have stomach/intestinal blockage, difficulty swallowing, appendicitis or symptoms of appendicitis (such as nausea/vomiting, sudden or unexplained stomach/abdominal pain), a sudden change in bowel habits that lasts for longer than 2 weeks, or bleeding from the rectum.

Side Effects from stopping glipizide: You may experience elevated blood sugars. Also, if you have a prior history of diarrhea on metformin, you may re-experience similar side effects when you are started on metformin again.

Loss of Confidentiality
There is a risk of potential loss of confidentiality. Information that identifies you will be used in this study and shared with the, research staff. A breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft, and could carry other risks affecting ability to get insurance, current or future job status, or could result in embarrassment. However, the research team will make every effort to protect your private health information and guard against any loss of privacy.

Unknown Risks
There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

POTENTIAL BENEFITS
We can't promise that you will get any benefits from taking part in this research study. However, possible benefits include better control of your diabetes with metformin. Taking metformin could provide health benefits for your body weight control, your heart and liver health. Psyllium is natural fiber. Fiber could be helpful for your digestive health and decreasing your cholesterol to promote heart health. The information we get from this study might help to treat future patients.

ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH

You may choose not to participate in this study. If this is your decision, there are other choices including approved drugs for diabetes treatment. If you choose not to participate, you should discuss your healthcare with your primary healthcare provider.

CONFIDENTIALITY

If you participate in the research, your authorization will be required to have access to your private medical records. You will be asked to sign a separate authorization form to allow us to have this access. If you do not provide this authorization, you may not participate in the research.

Taking part in this study will involve collecting private information about you. This information will be protected in the following ways:

Paper documents will be locked in a filing cabinet that is located in a locked JBVA office or restricted access area in the JBVA. Access to electronic research data will be limited to Dr. Layden and his designated study team and will be stored on a secure JBVA network server. Data will be stored with a code, without your name or identifiers. For security, the data and the master list linking your name and the code will be stored separately.

We will make every effort to keep the information collected for this study confidential.
We will include information about your study participation in your medical record. People who will know you are a research subject include members of the research team, your physicians and your nurses and others who may have access to your medical record due to their job at JBVAMC. Otherwise, no information about you, or provided by you during the research, will be disclosed to others without your written permission, except there are times when we might have to show your records to other people. For example,

- if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
- when the JBVAMC Institutional Review Board or the JBVAMC Research and Development Committee monitors the research or consent process; or
- when the Office for Human Research Protections (OHRP), the Office of Research Oversight (ORO), the VA Office of the Inspector General (OIG), or other governmental regulatory agencies monitor the research; or
- if required by law
- Food and Drug Administration (FDA).
- Members of data and safety monitor board (DSMB)

The VA uses your social security number as a medical record number. Study personnel will use your name and the last four digits of your social security number to identify you and to process payments for participation. If you do not agree to the use of the last four digits of your social security number you may not participate in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. The website will include a summary of the results. You can search this website at any time.

Participant Name: **Date:**

Title of Study: Tolerance & Responsiveness Improvement for Metformin (TRIM) Study

Principal Investigator: B. Layden, MD

The ClinicalTrials.gov Identifier is: NCT03670043

What will happen to my blood and stool samples?
Your samples will be stored at Jesse Brown VA awaiting analysis and will be sent to laboratories named below. All samples will be coded. The samples will not include your identity, and your identity cannot be revealed without the use of a specific code key, which is kept at the study site by your study team. The laboratories being used in this study are:

Blood:
Jesse Brown VA medical laboratory, 820 S Damen, Chicago, IL 60612

The laboratories listed below are added because these laboratories use special techniques to perform biomarkers testing, which is not available at the Jesse Brown VA laboratory.

Blood:

- UIC Medical Center
  835 S. Wolcott, University of Illinois at Chicago, Chicago, IL 60612
- University of Chicago Medical Center
  5841 South Maryland Avenue Chicago, IL 60637
- Rush University Medical Center
  600 S Paulina St, Chicago, IL 60612

Stool:

- UIC Medical Center
  Research Resource Center (RRC), University of Illinois
  835 S. Wolcott, Chicago, IL, 60612

All these laboratories are experienced in handling and testing samples from research studies. All samples (blood and stool) will be destroyed at the end of the study. Your blood samples will be used to perform laboratory test like glucose, HbA1c (glucose marker), heart and diabetes-related biomarkers. The blood and stool samples will only be used for study related purposes, and no other analyses other than study related analyses that have been described in this consent form will be performed. All samples will be appropriately disposed and destroyed at the end of the study by the participating laboratories.

Use of blood and stool for optional tests.
The research described below is optional. Please read each sentence below, think about your choice, and mark "**YES**" or "**NO**". **No matter what you decide to do, your decision will not affect your medical care or your participation in the primary study.**

Consent to Use blood and stool samples for testing diabetes biomarkers:
(Biomarkers are substances in the body used to evaluate disease)

☐ **Yes,** I do give my permission for the study staff to use my blood and stool for testing of biomarkers

☐ **No,** I do NOT give my permission for the study staff to use my blood and stool for testing of biomarkers

What will happen to the results of this study?
Information about you will be combined with information from other people taking part in the study. We will write about the combined data we have gathered. Any talks or papers about this study will not identify you.

COSTS TO PARTICIPANTS AND PAYMENT
You will not be charged for any treatments or procedures that are a part of this study.
If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Payment Offered for Participation:
If you decide to take part in this study and it is determined that you are qualified to participate in this study, you will get compensated for your time and to cover study related medications. You will be compensated according to the following schedule:

$30 after completing procedures for Baseline visit.
$45 after completing procedures for Final visit.
$35 after completing optional collection of blood and stool at Baseline visit
$35 after completing optional collection of blood and stool at Final visit
$35 after completing procedures for any unscheduled visit for diarrhea

If you complete all procedures, including optional collection of blood and stool, you will be paid a total $145 for the study (excluding any unscheduled visit). If you do not complete the study you will be compensated for the part of the study that you have completed. All compensations will be provided via a check. If you have any questions regarding your reimbursement for participation, please contact Dr. Layden or study coordinator.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY
Every reasonable effort to prevent any possible injury from this study will be taken. In the event the study results in any physical, mental or emotional injuries to you, VA will provide necessary medical treatment (not just emergency care) at no cost to you. This does not apply to treatment for injuries that result from if you do not follow the study procedures.

Note: The VA may not reimburse you for necessary medical care for treatment in non-VA facilities for injuries in research conducted collaboratively with VA by a non-VA organization.

Additional compensation, beyond paying for treatment, has not been set aside. For all study participants, compensation damages resulting from the negligence of federal government employees may be available in accordance with Federal Tort Claims Act. For additional information concerning claims for damages, you may contact VA District Counsel at (708) 202-2216. You have not waived any legal rights or released the hospital or its agents from liability for negligence by signing this form.

If you believe that you may have suffered a research related injury (physical, mental or emotional injury or injury caused by loss of confidentiality or privacy), contact:

DURING THE DAY: Dr. Brian Layden at 312-569-6430 and
AFTER HOURS: Dr. Brian Layden at 773-505-0169

Emergency and ongoing medical treatment will be provided as needed.

PARTICIPATION IS VOLUNTARY

It is up to you to decide whether or not to take part in this study. If you decide to take part, you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are entitled. If you don't take part, you can still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

The researchers also have the right to stop your participation in this study without your consent if they believe it is in your best interest. In the event you withdraw or are asked to leave the study, you will still be compensated as described above.

When you withdraw from the study for any reason, all study drug(s) and study drug bottles, including those unused and empty must be returned to the study site.
If you do not sign this form, you cannot be in the study.

PERSONS TO CONTACT ABOUT THIS STUDY

If you have any illness or injury during your time on this study, you should call us promptly. Dr. B. Layden, M.D. is the person in charge of this research study. You can call him at (312) 569-6430 Mon - Thu, 8am to 4pm. You can also call his research team at 312-569-6468 Mon – Fri, 8am to 4pm with questions about this research study. For problems arising evenings, Fridays or weekends, you may call at 773-505-0169.

If you want to talk to someone who is not involved in this research about your rights as a JBVAMC patient, you should contact the Patient Advocate Office at the Jesse Brown VA Medical Center at (312) 569-7959.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Jesse Brown VAMC Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the Jesse Brown VAMC IRB at 312-569-6166 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

SIGNIFICANT NEW FINDINGS

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your

best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

CONFLICT or PROPRIETARY INTEREST DISCLOSURE

The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study. Your doctor is also the person responsible for this research study. Your doctor is interested in both your clinical care and the conduct of this research study. You may choose to seek the opinion of another doctor or someone not related to this research study before enrolling in this research study. More importantly, you are not under any obligation to participate in any clinical research study offered by your doctor.

Additional Forms

- In addition to this consent form you will be asked to sign an Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research (HIPAA)

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

One of the research study personnel has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this research study as has been explained in this document.

Participant's Name	Participant's Signature	Date

Name of person obtaining consent	Signature of person obtaining consent	Date