CONSENT FORM

Subject Name _____

Title of Protocol A randomized pilot study evaluating dapagliflozin and metformin, alone and in combination, in overweight/obese women with a recent history of gestational diabetes mellitus (GDM): treatment effects on body weight, anthropometric measurements and cardiometabolic abnormalities

Principal Investigators: Renee Harris MD
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Sponsor: The Metabolic Health Clinic
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(225) 231-5275

Drug/Funding Support: Astra Zeneca, L.P.

Please read this form carefully. This consent form contains important facts to help you decide if it is in your best interest to take part in this study. Take time to ask the study doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, please ask the doctor. The study doctor or study staff will explain them to you. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. If you decide to take part in the research study, you must sign your name to the final page. Your taking part is entirely voluntary.

Purpose of the Study:
You are being asked to take part in a clinical research study because you had gestational diabetes mellitus (GDM) in your recent pregnancy. Women with prior GDM do not metabolize (digest) enough of the carbohydrates (simple and complex sugars) found in food. This study is being done to compare the ability of different medications to improve carbohydrate metabolism in women with prior GDM. All of the study medicines are pills that you take by mouth. The medications will be dapagliflozin and metformin XR together (Xigduo XR), or dapagliflozin (Farxiga) alone, or metformin XR (glucophage) alone. The effects of the dapagliflozin plus metformin XR (Xigduo XR), both good and bad, will be compared to treatment alone with the metformin XR (Glucophage) or dapagliflozin (Farxiga). You will need to take the oral medicines for about 24 weeks. Dapagliflozin (Farxiga), metformin XR (Glucophage XR) and combination (Xigduo XR) are approved by the U.S. Food and Drug Administration (FDA) for use in patients with type 2 diabetes, but are considered investigational drugs in this study. This means they are not yet approved by the FDA for use in women with prediabetes (women who had diabetes during their pregnancy

Sixty women will take part in the study at The Woman's Hospital in Baton Rouge, Louisiana. The length of time you will be in this study is about 24 weeks

STUDY PROCEDURES

If you volunteer to take part in this research study, you will be asked to read and sign this consent form. You will then have a screening visit. Tests will be done during this visit to see if you meet all of the entry conditions to take part in this study. These will include:

- review of your reproductive history
- a medical history
- physical measurements of height, weight, waist, hips, and blood pressure
- a blood pregnancy test will be done to confirm that you are not pregnant

You will also provide information about the following:

- race
- last pregnancy
- current method of birth control
- menstrual bleeding cycle length
- current drug use
- cigarette smoking/tobacco use
- alcohol intake

If you are eligible to take part in the study and you meet the medical conditions, you will be placed in one of three treatment groups:

- Dapagliflozin and metformin XR (Xigduo XR)
- Dapagliflozin (Farxiga)
- Metformin XR (Glucophage XR)

Your treatment will be chosen on a **randomized** basis, which is similar to rolling dice. A computer will choose which of the medicines you will get. Neither your doctor nor you will be able to choose which treatment you will be given. You have an equal chance of getting dapagliflozin plus metformin XR, metformin XR, or dapagliflozin. The principal investigator **will not know** which group is getting the dapagliflozin plus metformin XR, metformin XR, or dapagliflozin.

Once you have enrolled and been randomized to study drug, you will be taught how to take the medicine. All study participants are on oral (by mouth) medicines. You will be instructed when to take the medicine and how many times a day. Study staff will explain how to take medications. In addition, written instructions will be included with your medicine. If there are any questions about the medications and how to take them, you can call the Woman's Hospital Research Department at 225 231-5275.

Procedures during the Study

You will have clinical and laboratory testing over 24 weeks. There will be a total of 6 visits (3 to the outpatient laboratory and 3 clinic visits) over a 24-week period.

With each of the clinic study visits, you will have the following clinical measures (vital signs) taken:

- height
- weight
- measurement of your waist and hips with a tape measure
- blood pressure

There will be a baseline lab visit, a 10-12 week lab visit and a final study lab test visit. These visits will be scheduled before you start treatment (baseline), 10-12 weeks after starting treatment and during study weeks 22-24. During the baseline and final testing visits, you will need to give blood (around 1 ½ teaspoons) for laboratory tests of your hormones and blood chemistries. This blood test is to find out if your thyroid, liver, kidneys, and lipid levels are normal and to be sure you are not pregnant. At the 10-12 week visit, only a blood test to check that you are not pregnant will be done.

In addition, at the baseline visit and the study test visit, you will take an oral glucose (sugar) tolerance test. For the sugar tolerance test to work, the night before the test you cannot eat anything after midnight and the only liquid you can drink after midnight is water. This test requires that blood samples be taken when you arrive, 30 minutes, 1 hour and 2 hours after drinking a sugar solution. In total, this test requires that you have your blood taken 4 times within 2 hours. The total amount of blood to be taken during each visit will be about 3 tablespoons. A total of 6 tablespoons of blood will be drawn during your taking part in this study, which will take about 16 weeks to complete.

In addition to the lab visits, you will see the Metabolic Health Clinic physician before starting the medicine and at the end of the study during your clinic visits. The clinic physician and nurse will also see you about 10-12 weeks after starting the medication to find out how you are tolerating the medicine and dispense new medicine.

See patient study procedure chart with a review of your study visits.

2. Risks/Side Effects

The treatments used in this study may cause some or none of the side effects listed. In addition, there is always the risk of some very uncommon or unknown side effects taking place.

<u>Risks Associated with Study Procedures</u>

In this study you will need to have blood drawn from your arm several times. You may have some tenderness from having blood taken from a vein in your arm. You may also have

unpleasant effects from using the pills. Possible risks and side effects from each of these tests and drugs are listed below. The risks of drawing blood include local pain, bruising and swelling, bleeding and infection at the site of the vein puncture. As well, an infrequent risk of lightheadedness, dizziness, and, rarely, fainting is possible.

Risks/Side Effects Associated with Study Medications

Dapagliflozin (Farxiga), metformin XR (Glucophage XR), and combination dapagliflozin and metformin extended-release (Xigduo XR) are medicines that the U.S. Food and Drug Administration (FDA) has granted marketing authorization for use in diabetic women. These drugs have not been granted marketing authorization for use by pregnant women. A pregnancy test will be done before you start drug treatment and at the end of the study. Please notify your treating physician that you may be on Farxiga, Xigduo XR or Glucophage XR if you are scheduled for a scan or medical procedure that uses an IV or tests that may use contrast dyes. Possible risks from these medicines are listed below:

Dapagliflozin (Farxiga)

Dapagliflozin works by decreasing the amount of sugar the body absorbs and increasing the amount of sugar that leaves the body in the urine. It is used along with diet and exercise.

In this study, you will be instructed to take one pill the same time every day. Each tablet must be swallowed whole, so do not crush or chew the pills. You should drink plenty of fluids while taking this medicine. Remember to take dapagliflozin on a regular schedule to get the most benefit from it. Taking your pill at the same time each day will help you remember to take it. If you miss a dose of dapagliflozin, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once.

The most common side effects of dapagliflozin include:

- yeast infections of the vagina
- change in urination, including urgent need to urinate more often, in larger amounts, or at night.
- urinary tract infections
- reduced blood pressure
- runny or stuffy nose; sore throat

Dapagliflozin may cause dizziness, light-headedness, or fainting. Alcohol, hot weather, exercise, or fever may increase these effects. This effect may be worse if you take it with alcohol or certain medicines. To prevent them, sit up or stand slowly, especially in the morning. Sit or lie down at the first sign of any of these effects.

Low blood sugar (hypoglycemia) is uncommon when **dapagliflozin** is taken alone but it may happen if you do not eat enough calories (from food, juices, fruit, etc.). Some of the common signs include:

- chills
- drowsiness

- dizziness
- shaking
- weakness
- fainting
- tingling of the hands or feet

cold sweat
rapid heartbeat
headache
hunger

Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery, or do other unsafe activities where you could hurt yourself or others. Severe cases of low blood sugar could cause loss of awareness, and in extreme cases, death. Tell your doctor right away about the reaction. To help prevent low blood sugar, eat meals on a regular schedule and do not skip meals.

Dapagliflozin will cause your urine to test positive for glucose. Be sure your doctor and lab personnel know you are taking dapagliflozin.

Serious allergic reactions to this drug are unlikely, but seek medical attention right away if it occurs. **Some symptoms of allergic reactions are:**

- rash
- itching
- swelling around the mouth, throat or eyes
- a fast pulse
- sudden drop in blood pressure
- sweating

A severe allergic reaction could be fatal. If you notice other effects not listed above, contact your doctor

Dapagliflozin may be associated with an increased risk of bladder cancer. Tell your doctor right away if you notice symptoms that could be associated with bladder cancer (eg, a red color or blood in the urine, difficult or painful urination, an increased need to urinate). Discuss any questions or concerns with your doctor.

Seek medical help at once if you have any of these serious side effects:

- symptoms of kidney problems or urinary tract infection (eg, blood in the urine, change in the amount of urine produced, difficult or painful urination, unusual or persistent pain in the mid to lower back, unexplained swelling). Urinary tract infections may be life-threatening, leading to sepsis or kidney infections if not treated immediately.
- vaginal discharge, itching, or odor
- feeling short of breath (even with mild exertion), fast or irregular heartbeat, muscle weakness, severe or persistent headache, dizziness, or light-headedness
- severe skin reaction -- fever, sore throat, swelling in your face or tongue, burning in your eyes, very dry mouth or eyes skin pain, followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling

There have been reports of serious and sometimes life-threatening cases of ketoacidosis in patients treated with dapagliflozin . Ketoacidosis is a condition where the body makes high levels of blood acids called ketones. This condition may lead to hospitalization.

Seek medical attention immediately and alert us if you experience symptoms consistent with ketoacidosis, such as: nausea, vomiting, abdominal pain, confusion, change in breathing pattern, fruity or acetone smell to your breath, and unusual fatigue or sleepiness.

If left untreated, diabetic ketoacidosis can cause death.

There have been cases of a rare but serious infection of the genitals reported with sodium-glucose cotransporter-2 (SGLT2) inhibitors, like Farxiga. This condition is a serious, rare infection called necrotizing fasciitis of the perineum, also referred to as Fournier's gangrene.

You should seek medical attention immediately if you have tenderness, redness, or swelling of the genitals or the area from the genitals to the rectum, and have a fever above 100.4F, or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to seek treatment right away.

Metformin extended release (Glucophage XR)

Glucophage extended release (XR) is an oral medicine that works by helping to return your body's correct response to the insulin you naturally make. It lowers the amount of sugar that your liver makes and that your stomach and intestines absorb. It is used along with a diet and exercise program to control high blood sugar in patients with type 2 diabetes. This medicine is taken by mouth with meals. Each tablet(s) must be swallowed whole, so do not crush or chew the pills. You should drink plenty of fluids while taking this medicine. Inactive parts of the drug may be passed in your stool as a harmless soft mass that may look like the original tablet. This is normal for this drug. Since this is an extended-release tablet, it lowers the number of times you have to take a pill each day. Extended-release metformin delivers the drug to your body in the same amounts as instant-release metformin over a longer period of time.

The most common side effects of metformin include:

- nausea
- stomach upset
- diarrhea
- loss of appetite
- acid stomach
- a metallic taste
- increased abdominal gas
- vomiting

Side effects usually decrease over time. Taking metformin right before meals may lessen nausea and vomiting. Food decreases the rate the drug is absorbed, so taking the medicine with food can reduce the side effects of metformin. In this study, metformin will be started at a low dose (2 pills once a day with dinner) for 3 weeks and increased to 4 pills with dinner as you are able to tolerate it.

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A rare side effect of metformin use is a condition called lactic acidosis. If the liver is not able to change the lactic acid into sugar, the acid builds up in the blood. If not treated, this acid buildup can lead to coma and death. Lactic acidosis is more likely to occur in patients who:

- have kidney or liver failure
- have low levels of oxygen in their blood (hypoxia) or poor blood flow
- abuse (drink too much) alcohol
- have excess loss of body fluids (dehydration)
- are undergoing X-ray or scanning measures that require an injectable iodinated contrast drug, surgery, or have a serious infection

Seek medical help right away if you develop any of the following signs of lactic acidosis:

- unusual tiredness (fatigue) or severe drowsiness
- cold skin
- muscle pain
- breathing trouble or rapid breathing
- unusually slow or irregular heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital setting. If you have an illness that results in severe vomiting, diarrhea, and/or fever, or if drinking of fluids is really decreased, you need to call your physician. If your stomach symptoms come back (after you are on the same dose for several days or weeks), tell your doctor right away. A late comeback of stomach signs may be due to lactic acidosis. Alcohol is known to intensify the effect of metformin and you should never drink excess amounts (greater than 2 glasses of wine, or beer, or 2 ounces of hard liquor a day) of alcohol (all the time or "short-term binge") while taking metformin. Taking metformin should be briefly stopped for all surgical procedures that include reducing fluids. You should not take metformin again until normal fluid intake is started again and renal (kidney) function is back to normal.

When taken alone, metformin will not cause low blood sugar (hypoglycemia), but it may happen if you do not eat enough calories (from food, juices, fruit, etc.). Some of the common signs include:

- chills
- cold sweat
- dizziness
- drowsiness
- shaking
- rapid heartbeat
- weakness
- headache
- fainting
- tingling of the hands or feet
- hunger

Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery, or do other unsafe activities where you could hurt yourself or others. Severe cases of low blood sugar could cause loss of awareness, and in extreme cases, death. Tell your doctor right away about the reaction. To help prevent low blood sugar, eat meals on a regular schedule and do not skip meals.

Serious allergic reactions to this drug are unlikely, but seek medical attention right away if it occurs. **Some symptoms of allergic reactions are:**

- rash
- itching
- swelling around the mouth, throat or eyes
- a fast pulse
- sudden drop in blood pressure
- sweating
- dizziness
- trouble breathing

A severe allergic reaction could be fatal. If you notice other effects not listed above, contact your doctor

Less serious side effects of metformin may include:

- cold symptoms such as runny or stuffy nose, sneezing, sore throat.
- hepatic (liver) enzyme elevations
- interference with vitamin B12 absorption that is rapidly reversed by taking vitamin B12 supplements

Dapagliflozin plus metformin XR (Xigduo XR)

Metformin and dapagliflozin are oral diabetes medicines that help control blood sugar and insulin levels in patients with type 2 diabetes. It is used along with a diet and exercise program to control high blood sugar in patients with type 2 diabetes. Farxiga works by helping the kidneys get rid of glucose from your bloodstream. Metformin works by decreasing glucose (sugar) production in the liver and decreasing absorption of glucose by the intestines. These medicines are taken by mouth with meals. Each tablet(s) must be swallowed whole, so do not crush or chew the pills. You should drink plenty of fluids while taking this medicine. Possible risks and side effects for the combination are noted above, under dapagliflozin (Farxiga) and metformin XR (Glucophage XR) sections.

Risks/Side Effects Associated with All Study Medications

Dapagliflozin (Farxiga), metformin XR (Glucophage XR), and combination dapagliflozin and metformin extended-release (Xigduo XR) can interact with other medicines. This includes some common medications such as certain decongestants, diuretics, cimetidine (Tagamet), corticosteroids and niacin. Know the medicines you take including prescription and non-prescription drugs, vitamins, and herbal supplements. Keep a list of them to show the study doctor or study staff throughout the time you are taking part in this research study.

Pregnancy

The FDA has created guidelines for drug companies to follow in regards to labeling medications and their impact on pregnancy. Dapagliflozin and Xigduo XR are FDA pregnancy category C medication (one in which the risk to the pregnancy cannot be ruled out). Many medications pregnant women use fall into this category. For medications in this category, adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are

lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk. Metformin XR (Glucophage) is an FDA pregnancy category B medicine (not expected to be harmful to an unborn baby). However, because of possible or unknown side effects of the study drugs on a fetus, you must not be pregnant during the study. Tests to determine if you are pregnant will be done before starting the medicine, halfway through your taking part in the study, and at the end of the study. Patients in all treatment groups will have the same tests done. You will be required to be using a birth control method (unless you have a tubal ligation) in order to participate in the study. This birth control method must be maintained during the study. Do not use Farxiga, Xigduo XR, and Glucophage XR without telling your doctor if you are breast-feeding a baby. It is not known whether metformin or dapagliflozin passes into breast milk or if they could harm a nursing baby.

Any drug can cause side effects. The drugs used in this study may cause some or none of the side effects listed. This study may also have risks not known at this time. There is always the risk of some very uncommon or unknown side effects occurring which have not been explained in this consent. Risks to subjects are minimized by using procedures consistent with sound research dosing. In addition, a listing of other known side effects of all drugs is on hand through the pharmacy, or from the drug company.

If you do not understand any of the above risks you may discuss them with Dr. Harris or Dr. Elkind-Hirsch. Although the risks of developing the above complications are small, they do exist. If they occur, Dr. Harris, Dr. Elkind-Hirsch and their team will watch you closely and take appropriate medical action. This may include stopping the use of the drug. Your primary care physician is still responsible for your medical care.

3. Benefits

As a result of taking part in the study, you will receive medical care. You will be checked throughout the study. Both medicines have been used in diabetic patients and have shown to improve sugar tolerance. However, this benefit cannot be certain in women with prior GDM. It is possible that you may <u>not</u> receive any benefit from this study. Society will gain from learning if the use of certain "anti-diabetic drugs" has a positive influence on sugar metabolism in women with prediabetes.

4. Alternative Treatment

Caloric restriction, weight loss, and exercise are alternative methods which are used to reduce glucose and insulin levels. A number of other anti-diabetic medicines, like the ones described in this consent but made by the same or other drug companies, are another choice that may be right for you. You may talk over the use of these with your primary health care professional or the health care professionals in this study. You do not need to take part in this study to receive treatment for your condition.

5. Costs

There will be no charge for any of the study measurements or blood tests. All study medications and exams will be provided free of charge throughout the time you are in this trial. Test results will be offered to you as well as your private doctor(s) if you give separate written consent for information to be sent to your doctor(s). You will get $75 after study baseline screening and $75 after the final study testing visit (in which you have a 2-hour lab test at the hospital) to pay for local travel, meals and other costs from your study visit. Your health insurance company or you will pay for all other costs associated with your medical care. Woman's Hospital will be given payment from the study sponsor to cover some of the costs for carrying out the study and data collection.

6. Confidentiality

The results of this study may be published. Your name and identity will be kept private. Absolute confidentiality cannot be guaranteed. Your study records will be part of your medical chart. Your study chart will be kept in a locked filing cabinet. Your study chart and study data will be kept for a minimum of three years. An agent from Astra Zeneca, the company supplying the medicine, may look at your records. The data will not be shared with other researchers. The Woman's Hospital Foundation Institutional Review Board, Woman's Hospital Research and Development Committee, research and study staff, as well as Woman's Health Research Department, and the Food and Drug Administration may also check your study records.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by 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 Web site at any time.

7. Contacts for Extended Medical Care

If an injury happens while you are taking part in this study, medical care will be given to you. No funds have been set aside to pay your costs in the event of an injury as a result of this study. If an injury does occur, medical care can be gotten easily. The cost of this medical care will be the responsibility of you and/or your insurance company.

If you are hurt while taking part in this study, you should contact the Woman's Metabolic Health Clinic at (225) 924-8550. For more information about this research or patients' rights in research, you may also contact Ericka Seidemann, Human Protections Administrator, at (225) 231-5296.

8. Termination of Participation

At any time, you may ask that your test results not be used for research. Your decision to not take part will not have a penalty. You can leave the study at any time without changing your further care. Please call Dr. Elkind-Hirsch at (225) 231-5278 if you no longer wish to take part in the study. The researchers may need to stop your taking part in the study for any of the following reasons:

- you become pregnant
- an adverse event that leads to stopping of treatment by your physician

- you develop a related sickness, which increases the risk to you or halts the analysis of the study facts
- you have to take an unacceptable medicine at the same time
- not following study instructions
- finding out that you are not eligible
- new information about the study drug is discovered that may affect your wish to continue taking part
- the study doctor feels it is in your best interest

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Acknowledgement Of Receipt Of Information And Consent To Participate

I HAVE HAD AMPLE OPPORTUNITY TO ASK ANY QUESTIONS CONCERNING THE STUDY AND MY PARTICIPATION IS VOLUNTARY AS REFLECTED BY THE SIGNED STATEMENT BELOW.

I have read the preceding description and have heard the verbal explanation of these procedures from my doctor. I freely give my consent to participate in this research. I have the right to ask questions and may refuse to continue in the study any time that I so desire. If I refuse to participate or if I withdraw from the study, the doctors will continue to care for me and treat me as necessary for my condition

During the course of the research study, I will be informed of any new significant findings that may relate to my willingness to continue to participate.

At any time during treatment I am free to discuss with my doctor or his/her designee or the WHF Human Protections Administrator my rights as a participant and any side effects that might occur.

I AM MAKING A DECISION WHETHER OR NOT TO PARTICIPATE IN THIS STUDY. MY SIGNATURE INDICATES THAT I HAVE DECIDED TO PARTICIPATE, HAVE READ (OR BEEN READ) THE INFORMATION PROVIDED HEREIN, AND THAT I HAVE RECEIVED A COPY OF THIS INFORMED CONSENT.

Patient Name	Date	Witness Name	Date
Patient Signature	Date	Witness Signature	Date
Investigator Signature Date			

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Figure 1: Flow of Patients through Trial