SUMMARY OF CHANGES – Main Consent

NCI Protocol #: 10104
Local Protocol #: PHL-099
Protocol Version Date: 6-Mar-2025

Protocol Title: A Randomized Phase 2 Study of Cabozantinib in Combination with Nivolumab in Recurrent Metastatic Endometrial Cancer

Informed Consent Version Date: 6-Mar-2025

Reason for revision: Protocol amendment owing to change in CIMAC studies

#	Section	Comments
1.	ICD – All pages	Version date updated
2.	Page 4	Word ‘gender’ is replaced with the word ‘sex’ as per CTEP’s recommendation

Study Title for Study Participants: Testing the combination of cabozantinib and nivolumab in advanced, recurrent metastatic endometrial cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: PHL-099/NCI 10104 – A Randomized Phase 2 Study of Cabozantinib in Combination with Nivolumab in Advanced, Recurrent Metastatic Endometrial Cancer

What is the usual approach to my endometrial cancer?

You are being asked to take part in this study because have advanced, recurrent, or metastasized (cancer that has spread to other parts of the body) endometrial cancer. You have already been treated with platinum-based chemotherapy and your disease is now growing. People who are not in a study usually are treated with more chemotherapy.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- you may choose not to be treated for cancer. You may choose to get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using the drug cabozantinib along with the drug nivolumab to using the drug nivolumab alone. The addition of cabozantinib to nivolumab could shrink your cancer, but it could also cause side effects. This study will allow the researchers to know whether using cabozantinib and nivolumab together is better, the same, or worse than using nivolumab alone.

The drugs nivolumab and cabozantinib have been FDA-approved for other cancers, but they have not been approved for metastatic endometrial cancers.That means that these drugs are investigational, meaning we don't know whether or not they will work on your cancer.

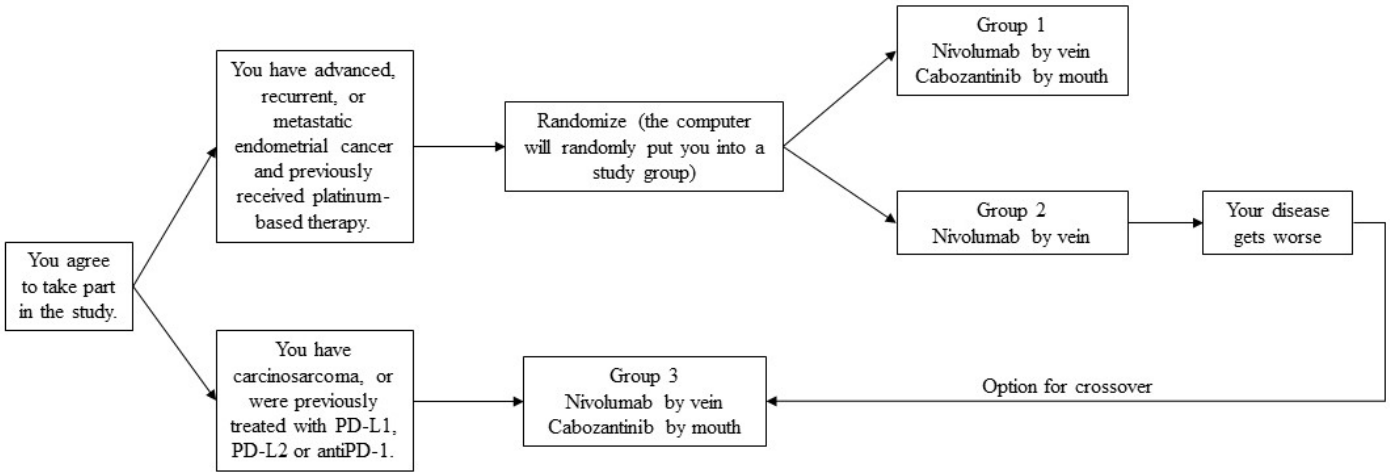
What are the study groups?

This study has three study groups. Groups 1 and 3 will receive the study drugs cabozantinib and nivolumab and Group 2 will receive only nivolumab. Group 3 is for patients who have previously had PDL-1 immune therapy, or have carcinosarcoma. Your study doctor will inform you if you could be part of Group 3. Nivolumab will be given through your vein using a needle. Cabozantinib will be taken by mouth; if you take cabozantinib, you will be given a pill diary to keep track of the pills you take.

If you have advanced, recurrent, or metastatic endometrial cancer, a computer will by chance (like flipping a coin) assign you to either Group 1 or Group 2. This is called randomization. This is done by chance because no

one knows if one study group is better or worse than the other. Randomization will be 2:1, meaning you will have a 2 in 3 chance of being in Group 1, and a 1 in 3 chance of being in Group 2. Patients who could be in Group 3, as described above, will not be randomized.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



If you are put into Group 2 and your disease starts to get worse, you will be given the option of crossing over into Group 3. Your study doctor will speak to you about this when it becomes applicable. If you do decide to cross over, you will need to repeat the extra tests and procedures described below as if you were starting the study from the beginning, including the biopsy.

There will be about 54 people taking part in this study.

How long will I be in this study?

You will receive the study drug(s) nivolumab with or without cabozantinib until your disease gets worse. After you finish taking nivolumab with or without cabozantinib your doctor will ask you to visit the office for a follow up exam about 30 days after your final dose of the drug (s). Your doctor will continue to watch you for side effects until any that you might have experienced resolve. Your doctor will follow your condition for the rest of your life, and they will let you know if you need to return at any time after that.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra procedures, exams and tests to find out if you can be in the study:

- You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements. Some medications may interact in harmful ways with cabozantinib and nivolumab, and it is important that your study doctor and

prescribing physician are aware of any possible risks so that they can prescribe alternative medications if necessary. Please consider carrying a list of your medications at all times.

- You will have your demographics (age, sex, race, ethnicity) and medical history documented
- You will be asked to provide blood samples for pregnancy testing (for women who are able to get pregnant)
- You will have an electrocardiogram (ECG) to trace the natural electrical activity of your heart
- You will have scans done to check on the size of your tumors
- You will be asked to have a tumor biopsy done
- You will be asked to provide archival tumor tissue: A sample of your tumor tissue that was removed previously by biopsy or surgery prior to your participation in this study will be collected. The tumor tissue will be tested to see what effects the study drugs have on your tumor.

A tumor biopsy will be taken for the study prior to randomization, before you take the first dose of the study drug. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. You will be given a separate consent from the team doing your biopsy confirming that you agree to the procedure. The research biopsy is done in a similar way to biopsies done for diagnosis. The tumor tissue will be tested for certain genes that will provide the study team with information about your cancer.

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the biopsy that will be used for this study.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra exams, tests and procedures. They are not part of the usual approach for your type of cancer.

During the study:
You will receive nivolumab every 2 weeks for the first 4 cycles, and every 4 weeks from cycle 5 onward and participants in Group 1 and 3 will take cabozantinib once per day. A 4-week period is referred to as one cycle. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day that is considered extra.

Day	What you do
Within 28 days of starting study	• Sign consent form • Have CT or MRI scans done • Have tumor biopsy done • Have ECG done
Day 1	• Get nivolumab by IV (outpatient) • Provide research blood samples • Take first dose of cabozantinib if applicable • Have ECG done if taking cabozantinib
Day 15	• Get nivolumab by IV (outpatient) • Provide research blood samples

Future cycles

Day	What you do
Days 1	• Have scans done (every 8 weeks) • Provide research blood samples • Get nivolumab by IV • Have ECG done if taking cabozantinib • Return pill diary from previous cycle if taking cabozantinib
Day 15	• Get nivolumab by IV (up to and including Cycle 4 only) • Have blood tests done

Follow-Up

Day	What you do
30-37 days after stopping study drug(s)	• Have scans done every 8 weeks until progression (if not done previously) • Provide research blood samples • Have ECG done if taking cabozantinib • Return pill diary if taking cabozantinib • Optional tumor biopsy, if you agree to provide one (described later in this form)
Long term	• Every 12 weeks via phone, or medical records review

At any point after signing consent, your clinical team may ask to collect an additional blood sample for research analysis. They may ask to collect this while on-treatment in the study or during the follow-up visit.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that the drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You may also have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.
- May not be able to take part in future studies.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and may even result in death.

You can ask your study doctor about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about nivolumab. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Nivolumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving nivolumab. In clinical trials, most immune-mediated side effects were reversible and managed by stopping nivolumab temporarily, administration of corticosteroids and supportive care.

Special precautions Side effects of nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab is used in combination with cabozantinib. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving Nivolumab, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Nivolumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection

- Bruising, bleeding
- Pain or swelling of the joints
- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving Nivolumab, 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck, confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

The tables below show the most common and the most serious side effects that researchers know about cabozantinib. Keep in mind that there might be other side effects that doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cabozantinib, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste • Redness, pain or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cabozantinib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin • Sores in mouth which may cause difficulty swallowing • Swelling of arms, legs • Infection • Bruising, bleeding • Dehydration • Muscle weakness • Dizziness, headache • Cough, shortness of breath • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Bleeding from multiple sites including the nose • Changes in voice • Hair loss, rash • Change in hair color • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Cabozantinib, 3 or fewer may have:
• A tear or hole in internal organs that may require surgery • Non-healing surgical site • Damage to the jawbone which may cause loss of teeth • Bleeding in the brain which may cause confusion

- Stroke which may cause paralysis, weakness
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Lung collapse

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant or breastfeed while in this study. The drug(s) used in this study could be very damaging to an unborn baby. Women of child bearing potential should avoid pregnancy for 7 months after the last dose of nivolumab or cabozantinib. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

This study has only a small chance of helping you because we do not know if the study drug(s) is/are effective. It is not possible to know at this time if the study drug(s) is/are better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The nivolumab and cabozantinib will be supplied at no charge while you take part in this study. The cost of getting the nivolumab ready and giving it to you is not paid for by the study sponsor, so you and your insurance company may have to pay for this. It is possible that the nivolumab and/or cabozantinib may not continue to be

supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating and caring for your cancer while in this study, including the cost of tests (i.e. scans, ECGs), procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study
- The Institutional Review Board (IRB), or Research Ethics Board (REB) is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- Monitors and auditors
- LAO-11030 (University Health Network Princess Margaret Cancer Centre, its affiliated institutions/companies and its associated laboratories

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for the following study.

1. Optional Sample Collections for Laboratory Studies

Researchers are trying to learn more about cancer, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect a tumor biopsy when you stop study medications for research on how your cancer changed after having taken nivolumab with or without cabozantinib.

If you choose to take part, a biopsy will be collected when you stop study medications.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample of tissue will be collected in a similar way to biopsies done for diagnosis.
2) Your sample and some related health information will be sent to a researcher for use in the study described above.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. *(For non-US participants, please verify existence of such laws before including the following text.)* There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers who receive your sample and information for testing will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance for this optional laboratory study. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in the optional study:

SAMPLES FOR THE LABORATORY STUDIES:

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____