UNIVERSITY OF CINCINNATI
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation in patients with locally advanced head and neck squamous cell carcinoma. Dose Escalation Phase

UC IRB Study #: 2014-6312 **Sponsor Name:** Investigator initiated

Investigator Information:

Trisha Wise-Draper, MD, PhD 513-584-7698/513-584-7661
Principal Investigator Name Telephone Number/24 hr Emergency Contact

Subject Name: _____ Date of Birth: _____/_____/____

INTRODUCTION

A biomedical or health-related research study is performed to answer specific questions about a disease.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, benefits, risks, discomforts, and precautions of the research. You should also be told what alternative procedures are available to you if you do not participate in the research study. The informed consent document is a written summary of this information. Be sure to ask questions while you read this consent document and ask questions if there is anything that you do not understand.

Your participation in this research study is entirely voluntary.

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

The researcher and sponsor of this study do not promise that you will receive any benefits from this study.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to test the safety of *adding* metformin to treatment that you will already be getting for your cancer. You will be offered "standard of care" treatment whether you participate in this study or not. The standard of care treatment will be cisplatin once every 3 weeks for 3 treatments and radiation for 7 weeks. The risks and

benefits of the standard of care treatment will be discussed by your regular doctor. Metformin is a medication that is currently used to treat diabetes. Overall, patients do well on this medication and are often taking it for long periods of time. There is research in animals that suggest that metformin may be useful for treating cancer. We do not know if it will work in humans, which is why we are doing this study. We will be giving increasing amounts of metformin to groups of patients already receiving normal treatment for their cancer. We would like to see if metformin causes any good effects by killing your cancer or bad effects (side effects) on you.

This is a Phase I study. A Phase I study is the first step in testing an investigational (new) drug in humans. An investigational drug is a drug that has not been approved by the Food and Drug Administration for a certain disease (in this case, metformin can be used for diabetes but not for cancer). The purpose of a Phase I study is to find the best way to give an investigational drug and/or the best dose. In Phase I studies, the dose is usually increased a little at a time until participants have serious side effects (which may or may not occur even at high doses).

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you have head and neck cancer that requires treatment with cisplatin and radiation.

The study doctor will determine if you are eligible for participation in this study on a case by case basis.

HOW LONG WILL YOU BE IN THE RESEARCH STUDY?

You will receive treatment with metformin starting 2 weeks before starting cisplatin and radiation. You will continue taking the metformin every day until you have finished cisplatin and radiation treatment.

You will be followed by the research team for 2 years after completion of the study treatment, in addition to your regular follow up care.

The researcher may decide to take you off this research study if you experience severe side effects or your cancer worsens or if drug supply is insufficient or new information becomes available.

You may withdraw from the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first so that stopping can be done safely. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you.

You may be contacted in the future by representatives of the University of Cincinnati who are interested in asking you survey questions about your participation in this research study. If you choose to participate in the survey, your responses will be used for quality assurance purposes only.

WHO IS CONDUCTING THE RESEARCH STUDY?

The study is directed by Dr. Trisha Wise-Draper MD, PhD, a medical oncologist and researcher at The University of Cincinnati; University of Cincinnati and the facilities of the affiliated health system located at UCMC and UCPC, including West Chester Hospital.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

Up to 18 people will take part in this study at The University of Cincinnati.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

You will be asked to read and sign this consent before any study-specific tests or procedures are performed. If you wish to participate in this study, the following tests and procedures will be performed to find out if you can participate in the study.

Screening Visit:

- A medical history will be obtained from you to make sure you do not have any conditions or past treatments that could interfere with your taking part in this study.
- Samples of your tumor (that have already been removed by surgery or biopsy) will be obtained for testing. This may allow us to understand how the treatment works on your tumor.
- A review of the medications you are taking, including prescriptions for conditions as high blood pressure, diabetes, or allergies and non-prescription medications as vitamins, herbal supplements, aspirin, etc. will be done.
- Physical examination will be performed.
- Measurement of your weight, height, blood pressure, respiratory rate and temperature will be done.
- Either a CT scan (or MRI) of your neck and chest and/or a PET/CT will be performed to evaluate your tumor before treatment is started. You may already have this done by your regular oncologist.
- In women able to have children, a pregnancy test will be done. The results of the pregnancy test must be negative for you to participate in this study.
- Blood sample will be taken (approx. 1-2 tablespoons) for laboratory tests.

Treatment

You will receive treatment for a total of 9 weeks. It may be longer if breaks are needed. You will take metformin for the entire 9 weeks. You will be told how much metformin that you will take at the beginning of the study. This is not done at random. The dose will be decided by how well the patients did on the treatment prior to you. This is for your safety to try to avoid any severe side effects. You will start your normal required treatment with cisplatin and radiation the second week.

You will receive treatment in this study as follows:

- Day -14 – You will begin to take metformin orally (by mouth) on this day. You will take metformin either once in the morning and once at night or once in the morning, at lunch and at night. Your research doctor will let you know how often. This will be 14 days before the start of your normal treatment of cisplatin and radiation.
- Every day – you will take metformin orally (by mouth) every day until you finish cisplatin and radiation.
- Day 1, 22 and 43 – you will receive cisplatin through a vein in your arm (this will be described in detail by your regular doctor as part of your normal treatment)
- Day 1 through Day 49 – you will receive radiation every day, 5 days a week (details will be given by your radiation oncologist as part of your normal treatment)

Please see the following chart for your medication regimen:

Drug or radiation	Day -14to Day1	Day1	Day 2-21	Day 22	Day 23-42	Day 43	Day 44-49
Metformin (A) Everyday (2 or 3 times a day)	A	A	A	A	A	A	A
Cisplatin (B)		B		B		B	
Radiation(C) (M-F only)		C	C	C	C	C	C

There will be additional laboratory tests to find the amount of metformin in your blood over several hours for the first 2 days. We will also ask for additional blood to be taken during your normal lab times. The following tests will also be done:

- Blood samples will be taken to understand how your body reacts to the metformin and the chemotherapy (cisplatin). Blood will be collected as follows:
    - Day 1 - One teaspoon of your blood will be drawn just before you receive Metformin, then half an hour, one hour, two hours, four hours and eight hours afterwards (eight hour timepoint optional).

  - Day -14 - One teaspoon of your blood will be drawn just before you receive metformin, then half an hour, one hour, two hours, four hours and eight hours afterwards (The eight hour timepoint is optional). We will also collect a sample the next day.
  - Day -14, Day 1 and week 11 - Three extra teaspoons of your blood will be withdrawn. You will already be giving blood for routine labs so this will not require an extra blood draw. This blood will help us understand how metformin may be affecting the tumor.

- During your clinical visits:
  - You will be asked questions about side effects and health concerns to evaluate if you are doing well with the treatment or if you are having side effects.
  - Blood samples will be taken (approx. 1 tablespoon) to make sure you are not having side effects from either your normal treatment or from the metformin.
  - A review of the medications you are taking, including prescriptions for conditions as high blood pressure, diabetes, or allergies and non-prescription medications as vitamins, herbal supplements, aspirin, etc.
  - A physical exam will be performed.
  - Measurement of your weight, height, blood pressure, respiratory rate and temperature.

All the blood draws will take place in the infusion center location where you receive your treatment as well. The standard labs needed before your standard chemotherapy may be incorporated at the same time instead of having extra blood draws.

You will be provided with a glucometer to monitor glucose levels in case you develop symptoms of hypoglycemia.

The metformin doses given in this study may be higher than what would be given in other diseases such as diabetes.

Follow-Up:

- Follow-up will not be any different for this study than your normal follow-up.

WHAT ARE YOUR RESPONSIBILITIES IF YOU PARTICIPATE IN THIS STUDY?

You will be responsible for coming to the researcher's office or hospital throughout the treatment period and follow-up period of the study.

You will be asked not to participate in any other clinical research studies taking another investigational medicine during this study.

You will have to inform your health provider and research team about your medications or

any herbal supplements. We may ask you to choose alternative medications with no or minimal suppression of the study drug activity or toxicity.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. There may be unknown or unforeseen risks associated with study participation. Side effects may be mild or very serious.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects include:

Possible Side Effects of Metformin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Metformin, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Metformin, from 4 to 20 may have:
• Heartburn, passing gas • Headache • Tiredness

RARE, AND SERIOUS In 100 people receiving Metformin, 3 or fewer may have:
• Lactic acid build up which may cause muscle aches, shortness of breath, or severe belly pain • Renal (kidney) failure

Some side effects of metformin may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects.

Stop using metformin and call your doctor at once if you have a serious side effect such as:

- Severe uncontrolled vomiting
- Shortness of breath

Monitoring/Precautions/Safeguards for toxicity:

1. We will closely monitor your blood counts and treat any abnormality according to the standard guidelines.
2. We will have well planned visit schedules for physical exam and assessment of any toxicity.
3. Patients who are on any medications or herbal supplements that expose them to more toxicity or decreased effectiveness of therapy, will be counseled to either replace this medicine or not take part in the trial.

Risks of combining metformin with cisplatin:

We are not sure of all the risks of combining metformin with cisplatin. This is why we are performing this study. However, cisplatin can cause your kidneys not to work well. This could cause the amount of metformin in your body to stay longer. This could then result in increased side effects of metformin which are listed above.

Risk of hypoglycemia:

Metformin does not usually cause hypoglycemia in the treatment of diabetes, but in combination with cisplatin, metformin may cause hypoglycemia when caloric intake is deficient. Signs and symptoms of hypoglycemia include:

- Shakiness
- Nervousness or anxiety
- Sweating, chills and clamminess
- Irritability or impatience
- Confusion, including delirium
- Rapid/fast heartbeat
- Lightheadedness or dizziness
- Hunger and nausea
- Sleepiness
- Blurred/impaired vision
- Tingling or numbness in the lips or tongue
- Headaches
- Weakness or fatigue
- Anger, stubbornness, or sadness
- Lack of coordination
- Nightmares or crying out during sleep
- Seizures
- Unconsciousness

Hypoglycemia can be treated with the following:

1. Consume 15-20 grams of glucose or simple carbohydrates
2. Recheck your blood glucose after 15 minutes

3. If hypoglycemia continues, repeat.
4. Once blood glucose returns to normal, eat a small snack if your next planned meal or snack is more than an hour or two away.

Risks of combining metformin with radiation:

We are unsure if there are any risks of this combination. We will be watching for side effects while you are on study.

Blood Draws

There may be risks of drawing blood (venipuncture). Risks of having your blood drawn include faintness, inflammation of the vein, pain, bruising, bleeding at the site of the puncture and, rarely, infection.

WHAT ARE THE REPRODUCTION RISKS?

Because the drug(s) in this research study can affect an unborn baby, and metformin may increase these risks, you should not become pregnant or cause a pregnancy while in this research study. You should not nurse your baby while on this research study. You must notify the study doctor and your treating physician immediately if you become pregnant or suspect that you have caused a pregnancy. You should use an adequate method of birth control during this study. You should discuss birth control options with your study doctor.

If you or your partner become pregnant, the treatment used in this research study might involve unknown risks to the embryo or fetus. The study doctor will wish to follow the outcome of any pregnancy and condition of any newborn.

ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

If you agree to take part in this study, it is unlikely that there will be a direct medical benefit to you. The addition of metformin may allow better response to the standard treatment of cisplatin and radiation. However, we are conducting this research study to determine if this benefit seen in animals can also be confirmed in humans. We hope the information learned from this research study will benefit other patients with advanced head and neck cancer in the future.

The information obtained from this study may benefit the study Sponsor Trisha Wise-Draper, MD, PhD.

There is a small possibility that the tumor may decrease in size, cancer spread could be limited, and other problems associated with the tumor could decrease. However, these effects may not improve your quality of life or make you live longer.

WHAT OTHER CHOICES FOR CARE ARE THERE?

Your other choices may include:

- Receiving standard chemotherapy without the addition of metformin.
- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Getting no treatment.

Talk to your study doctor about your choices before you decide if you will take part in this study.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical and research records related to this study. The University of Cincinnati, the monitor, the auditor, the Institutional Review Board (IRB), and other regulatory authority(ies) will be granted direct access to your original medical and research records for verification of clinical trial (research study) procedures or study data without violating your confidentiality, to the extent permitted by the applicable laws and regulations. By signing this consent form, you are authorizing such access. The data from the study may be published; however, you will not be identified by name. Your identity will remain confidential unless disclosure is required by law.

Your research information will be saved in your UC Health medical record. UC Health employees providing service or care to you will be able to see it.

AVAILABILITY OF INFORMATION

You will receive a copy of this signed and dated consent form.

You will be told about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

You will receive the study medication, metformin, and the study-related blood draws at no cost.

You and/or your health plan/ insurance company will need to pay for some of the costs of treating your cancer in this study including the standard chemotherapy with cisplatin and radiation. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of

getting regular cancer treatment.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

You will not be paid to participate in this research study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. The University of Cincinnati will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You may choose either to take part or not to take part in this research study. If you decide to take part, you may decide to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to you. The investigators will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

If you have questions, concerns or complaints about this research study or to report a research-related injury, please contact the researcher Trisha Wise-Draper, MD, PhD at 513-584-7698.

Please call the University of Cincinnati Institutional Review Board at 513-558-5259 (Monday – Friday 8 am to 5 pm) if you:

- Think the research has hurt you.
- Have general questions about giving consent or your rights as a research participant in this research study.
- Have questions, concerns, or complaints about the research.
- Cannot reach the research team or you want to talk to someone else.

To report complaints or concerns to an independent agency in an anonymous and confidential manner, please call the Research Compliance Hotline at 1-800-889-1547.

UNIVERSITY OF CINCINNATI
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation in patients with locally advanced head and neck squamous cell carcinoma. Dose Escalation Phase

UC IRB Study #: 2014-6312 **Sponsor Name:** Investigator-Initiated

Investigator Information:

Trisha Wise-Draper, MD, PhD	(513) 584-7698	(513) 584-7661
Principal Investigator Name	Telephone Number	24 hr Emergency Contact

SIGNATURES

I have read or someone has read to me, this Informed Consent Document which describes the purpose and nature of this research. I have had time to review this information and have been encouraged to ask questions. I have received answers to my questions. If I do not participate or if I discontinue my participation, I will not lose any benefits. I will not lose any legal rights if I discontinue. My participation in this research is completely voluntary. I give my consent to participate in this study. I have received (or will receive) a copy of this form for my records and future reference.

Participant Date

PERSON OBTAINING CONSENT
I have read this form to the participant and/or the subject has read this form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information.

Signature and Title of Person Obtaining Consent and Identification of Role in the Study Date