Study Title:	Phase I/II Trial of Gabapentin plus Ketamine for Prevention and Treatment of Acute and Chronic Pain in Locally Advanced Head and Neck Cancer Patients Undergoing Primary or Adjuvant Chemoradiation
Version Date:	08/22/21
PI:	Dianne Lou, M.D., Ph.D.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
This purpose of this study is to determine the optimal doses of two pain medications, gabapentin and ketamine. We will be observing side effects and your ability to tolerate these medications. These medications will be started before you begin chemotherapy and radiation and you will continue to take them until you are finished with treatment unless significant side effects occur. We believe that the combination of these pain medications will decrease your pain during treatment and also your chance of developing long term, chronic pain after your completely finished with cancer treatment. The doses of the medications we are testing have been used for pain in different populations and we do not expect many significant side effects. However, some of the side effects may include (but are not limited to) fatigue, weight gain, drowsiness, dizziness, blurry vision, confusion, euphoria, swelling of the arms and legs, and hallucinations. It is expected that these study medications will not take away all your pain and that you will likely need other pain medications such as opioids. There are no restrictions or limitations on your daily activities while taking gabapentin or ketamine.

During this study, there will be daily, weekly, monthly time commitments. You can expect to participate in the following activities.

- ***Initial Study Visit:*** This visit will include education about medications, filling out questionnaires to assess your baseline pain and function, and initiation of the medications *BEFORE you start cancer treatment*. At this time, you will meet with the study nurses who will follow you during the length of the study. In addition, the Pharmacist will provide information about the medication and how to use the medications. Gabapentin will be prescribed to you in the pill form and this should be covered by insurance. We will provide

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ketamine nasal spray, free of charge. Lastly, we will draw blood for future research studies. *These activities will take about 1-2 hours to complete.*

- ***Daily Activities:*** You will complete a daily medication compliance form and list any side effects that you experience. You will take both of these medications three times a day. One is a pill and the other is a nasal spray. Every week, we will increase your doses until you reach the pre-determined dose. *These activities my take anywhere from 5 minutes to up to 15 minutes a day.*
- ***Weekly Activities:*** You will fill out a questionnaire during your weekly in-person study visits with the research nurses. If we are unable to see you in-person, we may conduct this visit over Zoom or other communication platform. Your compliance and side effect form will be reviewed during this time. Your dose may be either decreased or you may be taken off the medications completely if your side effects are significant or intolerable. You will meet with the pharmacist to continue managing your medications. *These activities may take anywhere from 30-45 minutes to complete.*
- ***End of Treatment Visit:*** This visit will take place around your last day of chemotherapy or radiation treatment. In addition to the same weekly activities as described above, we will ask you to complete several questionnaires regarding your pain and functional status. Lastly, we will perform blood draws at this time for future research studies. *These activities will take about 1-2 hours to complete.*
- ***1, 2, and 3 Month Follow-up Visits:*** These visits will occur around the time of your follow-up visits with your cancer doctors. It is anticipated that you will be weaned off these pain medications under the guidance of your treating physician. During these visits, we will have you fill out the same questionnaires regarding your pain and functional status. We will continue to monitor any side effects. We will collect one last blood sample at the 3 month follow-up visit. These activities will take about 1-2 hours to complete.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have been diagnosed with head and neck cancer and will be treated with chemotherapy and radiation therapy. These treatments, along with the cancer itself, may cause pain that could potentially be long-lasting.

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Gabapentin is a medication that is commonly used to treat nerve related pain. Specifically, it has been used to treat pain involving the mouth, throat and nasal passages in head and neck cancer patients treated with radiation. We have already completed a large 150 patient study of head and neck cancer patients who were started on gabapentin before receiving cancer treatment. This study showed that pain is significantly reduced throughout the course of treatment and at the end of treatment. To further decrease pain (and ultimately prevent it), we want to explore the use of another pain medication called ketamine. The purpose of this current study will be to see how patients tolerate the combination of gabapentin and ketamine and to find the correct dosing for ketamine in those taking gabapentin. This will be the basis for a future, larger study to look at how effective this combination is at reducing and/or preventing pain in head and neck cancer patients.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:
Common side effects ($\geq$10%): dizziness, drowsiness, unsteady on your feet, fatigue

Uncommon side effects (<10%): tremor, twitching, mood swings, hostility, nervousness, difficulty with focus or memory loss, headache, diarrhea, vomiting, impotence, visions changes, swelling, high blood pressure, high heart rate, rapid eye movements, hallucinations/vivid dreams or imagery, euphoria, confusion.

Rare side effects ($\leq$1%): allergic reaction, liver or kidney issues, abnormal heart rhythm, double vision, potential for abuse, seizure-like state.

These side effects are only related to gabapentin and ketamine. Some of these side effects are common to your cancer treatment as well.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. Currently, Gabapentin is listed as an FDA Pregnancy Category C (i.e. risk cannot

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be ruled out) and ketamine is Category N (not classified). Women of childbearing age who undergo chemotherapy and radiation are already stringently counseled regarding the need to avoid pregnancy. The added risk of Gabapentin and ketamine to a developing embryo or fetus is nothing in comparison to active chemotherapy radiation. However, if Gabapentin or ketamine is continued following active chemotherapy for management of pain, the risk to a fetus cannot be ruled out.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study:

- This study is the first step in determining whether the routine use of gabapentin and ketamine can diminish pain in head and neck patients undergoing radiation.
- This study will establish a safe and tolerable dose of ketamine when taken with gabapentin.

The benefits you might get from being in this study:

- You may get pain relief from the medications that are being studied.

Procedures to be followed:
If you agree to participate, you will undergo the activities listed in above which include:

- Filling out questionnaires
- Daily use of gabapentin and ketamine
- Daily compliance and toxicity diary
- Weekly study site visits with study nurse and pharmacist
- 3 total blood draws (to be drawn with other labs that your cancer doctor orders)

Payments for your time spent taking part in this study or expenses:
There will be no payment as part of this study.

Costs to you if you take part in this study:
There is no additional cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred, then you and/or your insurance may be billed for the cost of medical care provided at Vanderbilt to treat the injury. You will be responsible for any copayments or deductibles associated with the treatment of that injury.

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There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Dianne Lou, MD, PhD or Dr. Barbara Murphy, MD at 615-322-4967. If you become injured or hurt as part of your participation in this study, they can help discuss any medical treatments available to you.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
You may be taken off of the study if it is deemed in your best interest by the principal investigator, if you are having toxicities from gabapentin and/or ketamine, or for failure to comply with study procedures.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:
You will be given a unique identifier that will link your name to the study related information. Only the principal investigator and study staff will have access to this information. Electronic study related information will be kept on a password protected database on a secure server. Paper copies of study related information will be kept in a locked office. After the study has been completed and the results reported, all electronic and paper information will be destroyed.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form including the National Cancer Institute. Vanderbilt, Dr. Lou, Dr. Murphy and her staff

will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you. Please see additional information in the "Genetic Screening Rider" at the end of this consent form.

Study Results:
The results of this study will not be shared with you unless you request it. A copy of the MRI scans and any processing of blood samples may be made available upon request upon the discretion of the research team. Please contact the study investigator for additional information.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors,

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government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____

Time: _____

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Genetic Screening "Rider" for Consent Forms

Consent for Genetic Research

The purpose of this study is to look at genes (DNA, RNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

A *blood sample of* up to 3 tablespoons will be drawn from a vein in your arm using a needle. This will take about 1 minute of your time since this sample will be taken during your routine blood draws for studies ordered by your cancer doctor.

Blood samples – You may feel bothered or pained from the needle stick. You may have a bruise or the site may get infected. It is rare, but some people faint.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Dianne Lou, Dr. Barbara Murphy, study nurses, and study staff will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

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Your sample will be used to make DNA and RNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

At any time, you may ask to have your sample destroyed. You should contact Dr. Dianne Lou or Dr. Murphy at 615-322-4967 to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in _____.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature: _____ Date: _____