Title of research study: **Perioperative analgesia using gabapentin in head and neck free flap reconstruction surgery: A randomized controlled trial**

Investigator: Arnaud Bewley, MD

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you are undergoing head and neck surgery requiring concomitant free flap reconstruction, and we would like to study how to optimize pain control for patients such as yourself in the post-operative setting.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**
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Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at 916-734-2704, and ask for Dr. Bewley.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study, and you wish to talk to the Otolaryngology Resident on-call. In the case of an emergency, dial 911 from any phone.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to an IRB staff member at (916) 703-9151, hs-irbadmin@ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

Patients undergoing head and neck reconstructive free flap surgery often have a lot of pain after surgery, which can lead to a need for a lot of narcotic pain medication. These medications can have many side effects that can make recovery more difficult including nausea, vomiting, dizziness, being overly sleepy, itchiness, inability to urinate, confusion, inability to have a bowel movement, longer time before being able to start walking. These side effects can make the hospital stay longer. The use of gabapentin, which is a non-narcotic pain medication that focuses on nerve pain, has been used in smaller head and neck surgeries including removal of tonsils, sinus surgery, thyroid surgery. Studies in patients needing orthopedic or OB/Gyn surgery have shown improved pain control with gabapentin. Potential benefits to future patients include improved pain control, less narcotic associated side effects and faster functional recovery.

How long will the research last?

We expect that you will be in this research study for up to 45 days after your surgery.

How many people will be studied?

We expect about 100 people here will be in this research study.

What happens if I say yes, I want to be in this research?

If you want to be a part of the study, you will be randomly put into either the group that will receive gabapentin or the group that will receive the placebo, an inactive substance; a pill/liquid that contains no medicine. You will receive the first dose of either liquid one hour before surgery. The anesthesia plan during surgery will be the same for both groups. After surgery, both groups will receive the same routine baseline pain medications, which include scheduled Tylenol supplemented by oral oxycodone and IV dilaudid as needed. In addition, you will start the gabapentin or placebo at 300 mg three times daily on the morning after surgery as a part of being in this study. You will continue the gabapentin or placebo for 30 days after surgery at which time it will be slowly stopped by decreasing to 300 mg twice a day for 3 days, after which the dose will be reduced to 300 mg once a day for 4 days. At the end of these 7 days,

the drugs will be completely stopped. We will provide you with enough supply for 30 study-dose days and 7 taper days at your hospital discharge including a study medication diary. You will routinely follow-up in clinic 1 week after discharge and 4 weeks after surgery, which will be included in the 90-day Medicare global period and therefore your cost will not be increased. You will be asked to bring the study medication, diary, and any pain medication to your ENT clinic appointments. In clinic, we will ask you about your pain, daily need for narcotics and review the below patient questionnaires when applicable. You will have a 30-day follow up phone call with a study coordinator to review your medication use and pain.

If you are discharged from the hospital before 7 days post-surgery, you will be sent home with a daily questionnaire until you are 7 days out from surgery. This questionnaire will ask the following questions:

- Nausea (yes/no)
- Vomiting (yes/no)
- Bowel Movement (yes/no)
- Number of narcotic pills and dose in mg of narcotic taken in last 24 hours
- Activity scale [“how would you rate your activity today”] (0-4)
- Pain score (VAS)

Of note, whether you receive gabapentin or placebo will be determined by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will have an equal chance of being given each treatment. Neither you nor the study doctor will know which treatment you are getting. If any medical emergency occurs while you are participating in the study, your doctor can identify your study treatment if necessary.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to:

1. Describe your pain level, nausea, bowel movements, any incidence of vomiting to the team while in the hospital. If you are discharged home prior to post-operative day 7, you will go home with a Questionnaire Log to fill out daily. Questions will include the following:
    - nausea (yes/no), vomiting (yes/no), bowel movement (yes/no), activity scale [“how would you rate your activity today] (0-4), number of opioid doses today, rate your pain
2. You will be asked to obtain refills for pain medications only through the UC Davis ENT team during the first 30 days after surgery.
3. You will be required to complete a daily entry in your Research Dose Diary to document your medication use. And,
4. Bring your gabapentin and narcotic pill/liquid bottle to each post-operative appointment.

What happens if I do not want to be in this research?

You may decide not to take part in the research, and it will not be held against you. You will not be given a dose of gabapentin prior before surgery, and you will receive your regular care after surgery.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you. You can choose to leave the study entirely or you can choose to stop taking the study medication and remain in the study for follow up only.

If you leave the study entirely, you will be asked whether the study can use the data collected up until withdrawal from study and whether you agree to the proposed follow up procedures and data collection. You may decline this request, and it will not be held against you.

Is there any way being in this study could be bad for me?

The study poses the risk of loss of confidentiality. The risk will be minimized by deidentification of subject information.

Gabapentin drug-related risks include the following:

- Sleepiness
- Dizziness
- Weakness
- Headache
- Nausea
- Ataxia: lack of muscle control or coordination of voluntary movements
- Weight gain
- Lazy eye
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  a. This is a rare but potentially serious drug reaction that can result in skin eruption, enlarged lymph nodes, increased amounts of atypical immune cells in the blood (eosinophils and atypical lymphocytosis), and injury to organs such as the liver, kidneys and lung.
- Anaphylaxis and angioedema: severe allergic reactions including swelling. A serious and potentially life-threatening allergic reaction.
- Seizure caused by withdrawal from Gabapentin
- Suicidal thoughts
- Increased risk of pancreatic tumors (rats only)
- Sudden and unexplained death (in epileptic patients)

Moreover, there is a documented interaction between certain opioid medication and gabapentin that can increase or decrease the effect of gabapentin. The dose of gabapentin will be safely adjusted while you

are in the hospital under a strict monitoring protocol prior to discharge. On discharge, you will be advised to stop the gabapentin if experiencing sedation, dizziness or other distressing side effects.

The use of Maalox antacid can reduce the effect of gabapentin.

You should not drive or operate heavy machinery while taking gabapentin until you become familiar with the individual effect of the drug on your ability to drive.

Substance Use Disorder
Gabapentin has a potential risk for misuse. Although this is low, it has been reported. Patients who suffer from untreated substance use disorder (alcohol, opioids, stimulants) or have a history of substance use disorder are more at risk. Ask the study investigator if you have any concerns or questions about this issue.

Unknown Risks to Women of Child Bearing Potential and Pregnant Women:

There are/may be risks to a fetus if you become pregnant while participating in this study. The potential risks to a fetus or a nursing child are not known.

If you are pregnant or nursing a child you cannot participate in this trial. You will be tested to see if you are pregnant prior to surgery and you must confirm that you do not intend to become pregnant during the trial.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

Risks associated with randomization: You will be assigned to a study group at random (by chance). Your assignment is based on chance (like a coin flip) rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. It might also prove to be less effective or have more side effects than the other study groups(s), or standard treatments available for your condition.

Placebo risks: During this study there is a 50% chance that you will receive a placebo. There is no direct risk associated with being placed in the placebo group as you will still receive standard pain management plan after the surgery. If your symptoms worsen and make you uncomfortable, you can withdraw from the study.

Inpatient Pre-renal disease: There have been reports that patients can develop mild kidney disease while recovering from surgery. We will be monitoring your kidney health with routine inpatient and outpatient blood tests that are not collected as part of research. In the event that you develop this condition, you will be allowed to stay in the study with a lower dose of the study medication. If your surgeon feels that you cannot remain in the study, they will remove you from the research.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits to both yourself and future patients include improved pain control, faster return to physical activity, decreased the incidence of opioids associated side effects including nausea, vomiting, and constipation.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

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.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission.

Federal law provides additional protection for your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/legal/privacy/) and in an attached document.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval.

What else do I need to know?

You or your health plan will be billed for the costs of routine medical care you receive during the study. These costs may include operating room fees, pharmacy charges, treatments, hospitalization, scans, etc. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered. Only the costs of research or experimental procedures will be paid by the study, which includes the cost of the study drug.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at HS-IRBAdmin@ucdavis.edu.

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

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Do not write below this line. For IRB stamp and version date only.

APPROVED by the Institutional Review Board at the University of California, Davis	
Protocol	APPROVED
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