PERIOPERATIVE ANALGESIA USING GABAPENTIN IN HEAD AND NECK FREE FLAP RECONSTRUCTION SURGERY: A RANDOMIZED CONTROLLED TRIAL

Protocol Number:	CCOL026
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Protocol History:	11/26/2019

PROTOCOL SIGNATURE PAGE

Protocol Number: CCOL026

Protocol Title: Perioperative analgesia using gabapentin in head and neck free flap reconstructive surgery: A randomized controlled trial

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

PROTOCOL SYNOPSIS

Protocol Title: Perioperative analgesia using gabapentin in head and neck free flap reconstructive surgery: A randomized controlled trial

Protocol Number: CCOL026

Phase of Development: N/A

Investigational Product, Dosage Form, Route, and Dose Regimen:

Gabapentin: 900 mg of oral/enteral, 1 hour before surgery and 300mg TID, 37 days post-operatively.

Primary Objective: Determine differences in morphine equivalent units between experimental and control group from the immediate perioperative setting to 30 days post operatively

Secondary Objectives: To evaluate for possible associations between pain control and history of opioid use, functional outcomes, location of tumor, presence and type of flap reconstruction
Study Design and Investigational Plan / Methodology: A superiority double blind randomized controlled placebo trial examining the effect of perioperative supplementation with gabapentin in head and neck patients undergoing free flap reconstructive surgery

Study Population and Sample Size: Patients undergoing head and neck surgery with concomitant free flap reconstruction at UCDMC, N=100

Eligibility Criteria: Adult patients naïve to gabapentin undergoing head and neck surgery with concomitant free flap reconstruction at UCDMC

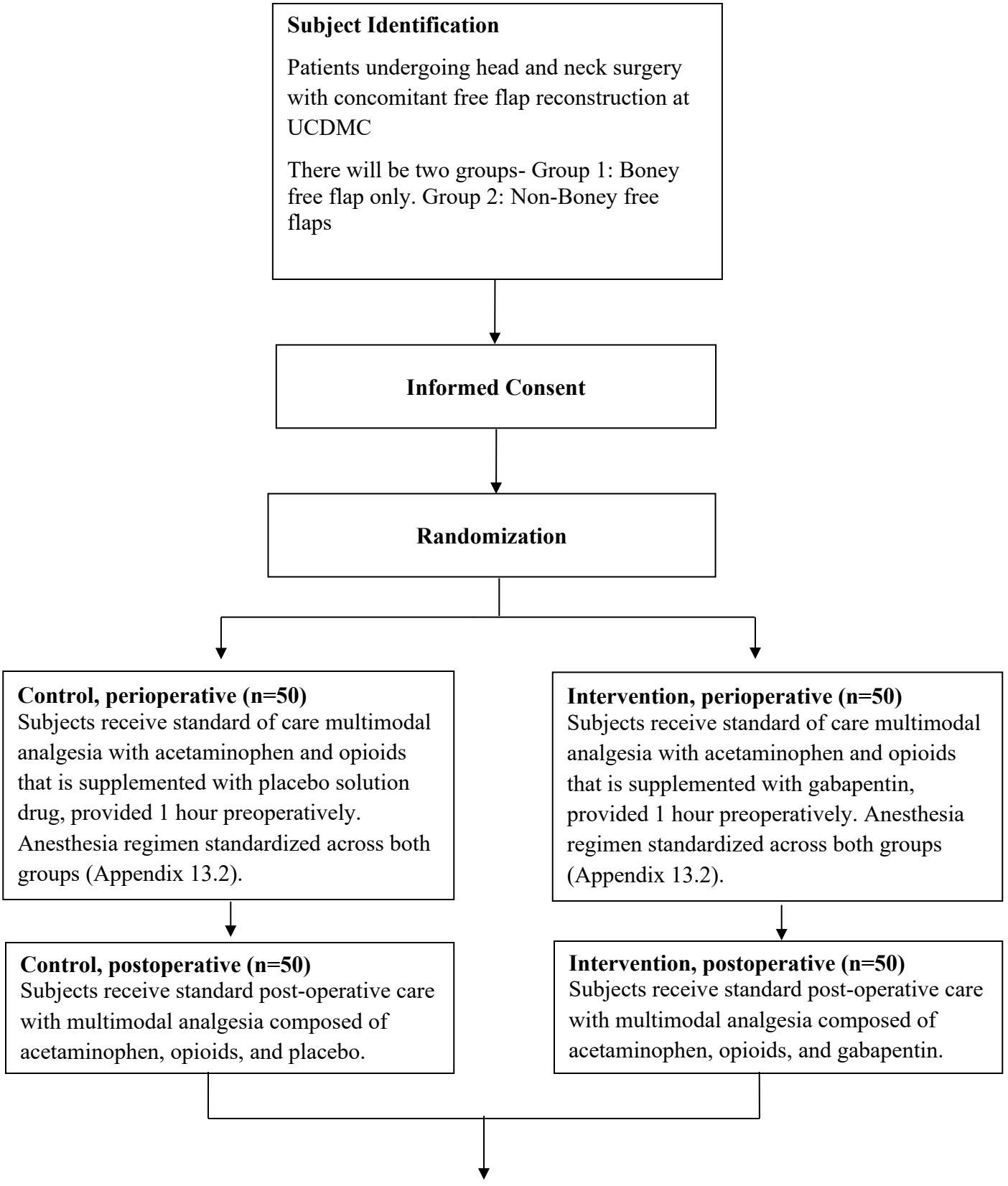
Endpoints: Daily morphine equivalent units, Pain score assessed via visual analog scales (VAS), Difference in length of stay and cost, Difference in narcotic related side effects, Difference in narcotic related, and incidence of postoperative complications.

Duration of Study and Follow-up: Patients will be enrolled to the study for 37 days starting the day of the surgery. Patients will be discharged from the hospital with a 37-day supply of gabapentin. Subjects will routinely follow up in clinic 1 week after discharge and 4 weeks post-surgery for wound check and routine postoperative care

Enrollment period: 24 months

Statistical Considerations: Intention-to-treat analysis will be performed to the data. ANOVA test will be used to evaluate the effect of the intervention on daily morphine equivalent units over the 1st week to address the primary objective

STUDY SCHEMA



Post-Operative Monitor and Follow-Up for Data Collection (n=100)
Subjects will be provided study medication 300mg TID for 30-day with a 7 day taper. This will be given during their hospital stay and they will be discharged with the remaining medication.

POD 1-7 (while inpatient):

- Pain level will be assessed by research assistant/resident daily between 9 and 11 am via Visual Analog Scale (VAS)
- Calculation of daily morphine equivalents
- The following information will be obtained from chart review for each day of hospitalization: nausea, vomiting, bowel movement [BM], physical therapy assessment (time to graduation), delirium/altered mental status (AMS), incidence of sedation requiring holding of medication

If discharged prior to POD 7 (earliest discharge will be POD 2): all patients will receive daily questionnaires as seen in Appendix 13.1.

- nausea (yes/no)
- vomiting (yes/no)
- BM (yes/no)
- Amount of narcotic taken in 24 hours (# of pills and dose in mg)
- Activity scale [“how would you rate your activity today] (0-4)
- Pain score (VAS)

Provider assessment at 1-week post discharge and 4-week postoperative outpatient clinic follow up:

- Obtain pain scores (VAS)
- Calculate daily morphine equivalent units based on residual narcotic requirement as well as number of remaining pills in the bottle, taking into account any refills
- Review patient’s questionnaires
- Measure home study medications

30-Day Follow-Up Phone Call:

- Obtain pain scores (VAS)
- Finalize Adverse Event reporting
- Review final pain medication reporting

After 30 days post-surgery, the patient will taper off the study medication to 300mg BID for 3 days and then 300mg once a day for 4 days. The study will then be completed.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation/Term	Definition
ACS	Acute coronary syndrome
AE	adverse event
AMS	Altered mental status
BM	Bowel movement
CAD	Coronary artery disease
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DLT	dose-limiting toxicity
DVT	Deep vein thrombosis
ENT	Otolaryngology (Ear, Nose, Throat)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GT	Gastrostomy tube
IDS	Investigational Drug Services
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous
MI	Myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NG	NasoGastric
NSAID	Nonsteroidal anti-inflammatory drug
OCR	Office of Clinical Research
OS	overall survival
PAD	Peripheral artery disease
PD	progressive disease
PE	Pulmonary embolism
PET	positron emission tomography
PI	principal investigator
PO	Per oral
POD	Postoperative date
PR	partial response
RASS	Richmond Agitation-Sedation Scale
RCT	Randomized Controlled Trial
SAE	serious adverse event
SBP	Systolic blood pressure
SRC	Scientific Review Committee
TID	*ter in die*, three times a day
UCDCCC	UC Davis Comprehensive Cancer Center
UCDMC	University of California, Davis Medical Center
UTI	Urinary tract infection
VAS	Visual Analog Scale

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1.0 INTRODUCTION

1.1 Background and Study Rationale

Patients undergoing head and neck surgery requiring concomitant free flap reconstruction frequently experience significant post surgical pain, which often necessitates the use of narcotic pain medication. However, opioids can have multiple side effects that can complicate the postoperative care including nausea, vomiting, dizziness, sedation, pruritis, urinary retention, delirium, constipation, and time to ambulation of patients undergoing head and neck surgery with concomitant free flap reconstruction. This, in turn, may affect patient length and cost of hospital stay. Consequently, a multimodal approach to analgesia is often employed with a focus on use of scheduled acetaminophen +/- NSAIDs supplemented with narcotics [1,2] [3]

The use of gabapentin in the head and neck surgery literature has largely been limited to outpatient surgeries, including tonsillectomy in children and adults, functional endoscopic sinus surgery, and thyroidectomy [4-15] Indeed, a recent systematic review by Sanders et al examined 15 RCT comparing multimodal analgesia with gabapentin to analgesia without gabapentin in the otolaryngology literature [4]. The majority of these studies employed preoperative dosing only, with only 1 study providing a single postoperative dose as well. The control group pain regimen among these studies did vary and included a combination of acetaminophen, NSAIDs, dexmedetomidine, or clonidine supplemented with opioids. The studies focused on the impact of gabapentin on acute postoperative pain determined by subjective measurement of reduction in visual analog pain scale. Of note, these patients were not hospitalized for longer than 24 hours. The thyroid and sinus studies consistently demonstrated improved pain control with use of gabapentin compared to control. The data was slightly more variable across the tonsillectomy studies. Moreover, 7 studies also measured the need for breakthrough pain medication and supplemental analgesia; each of these studies demonstrated significantly less supplemental analgesia consumption in the gabapentin group.

The only study examining the utility of gabapentin in pain management in head and neck cancer patients (glossectomy with anterolateral thigh free flap) examined the utility of a single preoperative dose.[16] The authors concluded that this led to a significant reduction in subjective postoperative pain scores, morphine requirement, and nausea and vomiting compared to controls. This study did not employ postoperative gabapentin.

Furthermore, Doleman et al[17] performed a recent meta analysis (133 RCT) examining literature across multiple surgical specialties pertaining to the efficacy of perioperative gabapentin supplementation vs placebo. The meta analysis indicated both the efficacy of gabapentin supplementation in decreasing opioid requirement (measured via morphine equivalent units) in the experimental group during the first 24 hours ($P<0.001$), as well as a good safety profile across a wide range of loading and maintenance doses (200 to 1200 mg) of gabapentin. The significant reduction in opioid requirement was independent of surgery type. Moreover, the

gabapentin group demonstrated a significant decrease in VAS postoperative pain scores, nausea, vomiting and itching; however, sedation scores were increased. Only 8 of these 133 RCT examined the effect of gabapentin outside the immediate 24 hour period, and all 8 trials demonstrated improvement in chronic pain scores at 3 months post operatively. Finally, patient satisfaction scores and preoperative anxiety were also significantly improved with the use of gabapentin compared to controls.

Here, we propose, for the first time, a superiority double blind randomized controlled placebo trial examining the effect of perioperative supplementation with gabapentin in head and neck patients undergoing surgery requiring free flap reconstruction. The primary purpose of this study is to determine the difference in morphine equivalent units between the experimental (i.e. perioperative gabapentin) and control group (i.e. no perioperative gabapentin). The secondary purpose of this study is to determine differences across the two groups in relation to the following: visual analog pain scores, cost and length of stay, medication side effects, and incidence of postoperative complications. Of note, in order to maximize reliability of the visual analog scale (VAS), prior studies have employed the Jadad scoring system, which we will also implement in our study.[18]

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- Determine differences in morphine equivalent units between experimental and control group from the immediate perioperative setting to 30 days post operatively
    - The morphine equivalent units will be recorded every day; we will examine the daily average amount received at POD 7 and then again at the 4-week post operative visit for each patient.

2.2 Secondary Objectives

- Obtain pain scores (Visual analog score filled by patient) on a standardized 1-10 scale once daily between 9 am and 11 am by the same research coordinator while inpatient among each group on weekdays. On weekends, same standardized scale will be given between the same hours by the ENT resident on call.
- If patient discharged home prior to POD 7, will go home with a Questionnaire Log (Appendix A) to fill out daily. Each patient will receive a phone call from the research coordinator between 9 and 11 am to remind them to fill out the log

- One set of below questions for each day until POD 7:
- nausea (yes/no), vomiting (yes/no), BM (yes/no), activity scale ["how would you rate your activity today] (0-4), number of opioid doses today (1, 2, 3, 4, 5, 6, 7, 8), rate your pain according to VAS (0-10 likert scale)
    - activity scale:
        - 0 - did not make it out of bed
        - 1 - out of bed to bathroom or chair
        - 2 - ambulated around house
        - 3 - ambulated outside of house
        - 4 - return to baseline activity
- Patients will also be reminded to bring in their gabapentin and narcotic pill/liquid bottle (i.e. oxycodone or hydrocodone-acetaminophen) to each post operative appointment (i.e. at 1 week post discharge and 4 week post surgery) and not to obtain pain prescriptions from any physician not part of the UCDMC Otolaryngology staff during the first 30 days after surgery, as this will provide another means by which to calculate morphine equivalent units

- At post operative appointments: Obtain pain scores (Visual analog score filled by patient) & morphine equivalent units (ie how much oxycodone still requiring/how many pills left in the bottle taking into account any refills/review of home log when applicable) at the 1 week post discharge visit and again at the 4 week post surgery visit (will be obtained by the physician/NP)
- Calculate total cost of inpatient stay among the two groups
- Record narcotic related complications among the two groups (determined from chart review, recorded by ancillary staff including physical therapist and nurses): time to "discharge from physical therapy," time to reach goal enteral bolus/oral feeds, occurrence of hypotension as defined by SBP < 90 or DBP <60 , incidence of delirium, time to first BM, incidence of nausea, dizziness, vomiting, constipation, urinary retention
- Incidence of common postoperative complications: pneumonia, UTI, DVT, PE, ACS
- We plan to evaluate for possible associations between pain control and history of opioid use, functional outcomes, location of tumor, presence and type of flap reconstruction

2.3 Study Endpoints

All subjects will complete a 1-month follow up course and will be examined for:

Outcome measures:

- Daily morphine equivalent units during the first week, at 1 week post discharge, and at 4 weeks post operation
- Pain score assessed via visual analog scales (VAS) at following intervals: daily morning VAS questionnaire during the first week, at 1 week post discharge, and at 4 weeks post operation
- Difference in length of stay and cost

- Difference in narcotic related side effects: nausea, vomiting, dizziness, sedation, pruritis, urinary retention, delirium
    - We will use RASS score to evaluate sedation. Will hold opioid and/or gabapentin if RASS sedation score between -2 and -5 which will be recorded prior to administration of each dose of opioid/gabapentin. This is the current UCDMC Pain Pharmacy Department standard of practice.
    - RASS -1 indicates a drowsy state where patient is able to maintain > 10 seconds of eye contact to voice [25]
    - RASS -2 indicates light sedation where patient awakens to voice with eye contact but holds it for less than 10 seconds before closing eyes again[25]
    - RASS -3 indicates moderate sedation where patient demonstrates movement to voice but does not awaken[25]
    - RASS -4 indicates deep sedation where patient does not demonstrate any movement to voice but does move to physical stimulation[25]
    - RASS -5 indicates unarousable state where there is no response to voice or stimulation[25]
    - Per standard UCDMC protocol, we will also hold opioid and/or gabapentin for respiratory rate less than 10
    - Based on discussion with the UCDCM Pain Pharmacy team and per the standard UCDMC policy, during the inpatient stay, every patient on Gabapentin will have the following nursing order to ensure safety and prevent falls: “Monitor for sedation and dizziness. Out of bed with assistance only.”
    - If patient becomes symptomatic we will reduce Gabapentin to 100 mg TID immediately and place a pain pharmacy consult to reassess dosing.
- Difference in narcotic related complications including days to mobilization (measured by physical therapy phase 4), days to tolerating oral or enteral feeding, hemodynamic instability, delirium, nausea
- Incidence of postoperative complications: pneumonia, wound infection, wound dehiscence, wound fistula, UTI

- Demographic information
    - Gender, age, history of cigarette smoking, history of alcohol use, history of diabetes, CAD, PAD, MI, PE, history of prior radiation, history of prior chemotherapy

3.0 STUDY DESIGN

3.1 Method

The current otolaryngology and general surgery literature has demonstrated the safety of administering a single perioperative dose of gabapentin across a wide range (i.e. 100 mg to 1200 mg) [4,17] with no clear efficacy advantage of one dose over another. Moreover, in the orthopedic literature, safety for gabapentin daily dosing of up to 1200 mg has been established.[19] Moreover, Peng et al[19] demonstrated significant improvement in pain occurring with doses >/= 900 mg once

daily but not <900 mg once daily. Thus, our experimental group will receive a single perioperative dose of 900 mg of oral/enteral gabapentin 1 hour before surgery, while the control group will receive the same amount of placebo syrup 1 hour before surgery. Per the current standard of practice by the UCDMC Pain Pharmacy department, we will initiate study dose at 300 mg TID on the AM of POD 1.[17] Patients in the study will continue the study drug for 30 days postoperatively at which time it will be weaned off by decreasing to 300 mg BID for 3 days after which the dose will be reduced to 300 mg once daily for 4 days. At the end of the 7-day tapering, the study medication will be completely stopped. At the start of the study, we will create a 37-day supply of gabapentin (concentration of 250 mg/5ml) or placebo syrup for each patient. A total of 18 mls of 50 mg/ml would be required for a 900mg daily dose. Thus, a 30-day supply which would be 540 mls. Including the tapering doses, this amount would bring the total per patient study medication to 600mL. With a 1:1 randomization, 50 patients would require a total of 30,000 ml of gabapentin and another 50 patients will require 30,000 ml of the placebo syrup.

Our study proposes a protocol in which all patients will receive standardized postoperative pain regimen which includes scheduled 24 hours total of 3000 mg acetaminophen daily that is supplemented by 5-10 mg of oxycodone liquid via per oral (PO) (if tolerated) or enteral route via NasoGastric(NG) or Gastrostomy Tube (GT) as needed for breakthrough pain every 3 hours. Nursing will be advised to provide 5 mg for moderate breakthrough pain (VAS 4-6) and 10 mg for severe breakthrough pain (VAS 7-10) at these 3 hours intervals. In addition, for pain not controlled by liquid acetaminophen and liquid oxycodone, we will prescribe intravenous (IV) hydromorphone. Nursing will have orders to provide a single dose of 0.3 mg IV hydromorphone at least 30min after their last dose of oral oxycodone, only as needed for breakthrough pain rated as moderate (VAS 4-6) that is not controlled by the combination of acetaminophen, gabapentin/placebo and oxycodone. For severe breakthrough pain (VAS 7-10) not controlled with the acetaminophen, gabapentin/placebo and oxycodone, nursing will have orders to provide 0.6 mg of IV hydromorphone at least 30min after their last dose of oral oxycodone. If pain is still not well controlled (ie VAS is > 4), the nurse will call the on call resident who can then prescribe any additional opioid medication and consult pain pharmacy, as needed. Prn IV pain medication may be provided until they day of discharge. If pain not well controlled on this regimen, as indicated by inability to work with physical therapy due to pain, the pain pharmacy team will be consulted.

There is a documented interaction between opioid medication and gabapentin. Specifically, the co-administration with hydrocodone can reduce the exposure to the hydrocodone, whereas co-administration with morphine can increase the effect of gabapentin.[27](Pfizer 2017) The majority of head and neck patients undergoing free flap reconstruction surgery require baseline opioid post-operatively. For this reason, as mentioned above, we will be implementing the RASS score

as well as nursing orders to "Monitor for sedation and dizziness. Out of bed with assistance only." This is in accordance with the current UCDMC Pain Pharmacy Department standard of practice. In this way, the dose of gabapentin will be safely titrated while inpatient under these monitoring procedures prior to discharge on this titrated dose with continued instructions to stop medication if experiencing sedation, dizziness or other distressing side effects. Finally, the use of Maalox antacid can also decrease bioavailablity of Gabapentin; since this is a decrease and not increase in the bioavailablity of gabapentin, it should not increase risk of gabapentin related sedation and dizziness side effects compared to taking gabapentin by itself.

As mentioned briefly, perioperative gabapentin supplementation has also been studied in other surgical subspecialties, such as thoracic surgery, orthopedics surgery, and obstetrics/gynecology, often via RCT [20-24]

Indeed, several RCT in the orthopedics and obstetrics literature assess efficacy of the gabapentin group compared to control by measurement of morphine equivalent units, which is the same proposed primary outcome of our study. For this similarity in outcome measure, and the overall lack of similar otolaryngology literature, we used the following two studies to perform our power analysis. Paul et al[23] examined patients undergoing primary total hip arthroplasty. He compared an experimental group receiving preoperative gabapentin followed by two days of postoperative dosing to the placebo group. The authors demonstrated no statistically significant difference in morphine equivalent units across these two randomized groups. Reagan et al[20] examined patients undergoing reconstructive pelvic surgery. He similarly compared morphine equivalent units across the same two randomized groups (gabapentin vs placebo) and demonstrated that the gabapentin group had less need for opioid at time of discharge, as well as decreased overall need for opioid analgesia.

Finally, after discussion with the UCDMC Department of Anesthesia a standardized anesthetic plan was adopted to be used during all study enrolled head and neck surgeries with concomitant free flap reconstruction (please see Appendix B). Of note, post operatively, study patients will be transitioned to oral/enteral acetaminophen as soon as medically safe, at a dose of 1000 mg every 8 hours. Will plan for IV acetaminophen the first night after surgery with initiation of oral/enteral acetaminophen on the morning of POD 1 in most cases. This scheduled acetaminophen will thus be timed and scheduled with the study drug on a q8hr basis.

We think that perioperative administration of gabapentin in addition to a standardized postoperative pain regimen will help improve postoperative analgesia and reduce narcotic pain medication requirements when compared to patients randomized to the non-gabapentin pain regimen as evidence by an overall decrease in morphine equivalents. Moreover, we propose that the gabapentin group will have improved time to mobilization and tolerance of bolus enteral

feeds, in addition to a reduction in occurrence of pneumonia, DVT and PE (opioid complications).

For morphine equivalent comparison, the following exchanges will be used:

- oral hydrocodone = 1:1.5, oral oxycodone = 1:1.5, and oral hydromorphone = 1:4
- IV hydromorphone: oral hydromorphone = 1.5:7.5

3.2 Procedures Involved

Randomization

The study is a superiority, blinded, randomized controlled trial. Randomization will be done by the UCDMC Investigational Drug Services (IDS) as simple block randomization via electronic randomizer. All research and surgical staff involved including nursing, surgeons, pain management, patients, and PI will be masked. The IDS team will remain the sole unmasked group.

Study Medication

IDS will purchase, prepare, and dispense both study solutions for oral or enteral route administration. At the start of the study, we will create a 37-day supply of gabapentin (concentration of 250 mg/5ml) or placebo syrup for each patient. Inpatient dispensing will remove medication from the patient specific bottle stored in IDS. Once the patient is ready for discharge, they will be given the remaining solution, a study diary (Appendix C), and a study discharge handout (Appendix D) to take home.

Recruitment

Patients will be head and neck patients at UCDMC Otolaryngology who will undergo surgery requiring free flap reconstruction requiring at least 2 days of inpatient stay. Indications for head and neck surgery with concomitant free flap reconstruction include, but are not limited to, cutaneous and mucosal malignancies, soft tissue (muscle, fat, bone, nerve, vascular) malignancies, including all malignancies involving cranial skull base; additional indications for free flap reconstruction include osteoradionecrosis of the head and neck, as well as functional laryngectomy. All patients will be screened based on the inclusion and exclusion criteria. Patients meeting study criteria will be approached at their pre-op visit by the primary investigator and approved research staff to obtain informed consent. Once informed consent is signed, each subject will be assigned a numeric code. This code and patient information will be provided to

IDS for treatment randomization. Study data that is collected will be reference under this code. Informed consent will be obtained prior to any study related procedures.

Pre-operation

Upon the completed of informed consent, the following information will be extracted from the patient's medical charts:
Name, DOB, MRN, demographics, pertinent history of present illness, medical history, surgical history, current medications, allergies, social history, substance use, pertinent imaging (CT, MRI, PET, Angiography), physical examination findings, endoscopy videos. In addition, relevant medical and surgical history will be collected and confirmed with the patient. Confidentiality will be maintained as explained in Section 11.5: Patient Confidentiality.

Inpatient

The patient will arrive on the day of surgery and given oral or enteral 900mg study treatment 1 hour prior to surgery. The patient will begin the 300mg TID regiment starting the morning of post-op day 1. IDS will individually dispense three times a day to the nursing staff. Nurses will follow the breakthrough pain protocol outlined in the Methods section. All relative medication (including surgery anesthesia) will be collected and converted to morphine equivalent units during pre-operation, perioperation, and post-operation. Patient vitals, hematology and biochemistry lab draws, and VAS pain levels are routinely checked daily as part of inpatient care. This information will only be collected if it is available. No additional orders will be placed to collect this information.

Discharge Outpatient Follow up

Patients will be discharged with a research dose diary (Appendix C), study discharge instructions (Appendix D), and study medication. If the patient is discharged early, they will be given an additional questionnaire to complete until Day 7 postop (Appendix A).

The patient will continue the 300mg TID regiment until a total of 30 days has passed since the surgery. After 30 days, the patient will taper off the medication by taking 300mg BID for 3 days (Day 31-33) and 300mg QD for 4 days (Day 34-37). At the point of discharge, the patient will be asked to return to clinic at 1 week and 4 weeks post-surgery for standard assessments. During these visits, the patient will return with their diary, bottle of study medication, and their post-operative narcotics. Copies will be made of the diary, the study bottle amounts will be recorded, and any pills will be counted at each office visit. Within 2-3 days after the patient has completed their 30-day study regiment they will receive a phone call from a study researcher. The researcher will follow up on any outstanding adverse events, pain medication use, and VAS pain. This phone call will also provide the patient an opportunity to ask final research questions, review tapering instruction, and how to dispose of extra medication.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

a) Patients undergoing head and neck surgery with concomitant free flap reconstruction surgery at UCDMC. There will be two groups; group 1 will include reconstruction with boney free flap only. Group 2 will include any non-boney free flap reconstruction.
b) Patients naïve to gabapentin
c) Adult patients >18 years of age and able to consent

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

a) Patients who are already taking scheduled gabapentin
b) Patients allergic to gabapentin
c) Chronic opioid use not from active head and neck disease
d) Illicit drug use (per report)
e) Patients with known renal compromise, such that Creatinine clearance is < 30
f) Patient with known hepatic insufficiency or cirrhosis
g) Adults unable to consent
h) Individuals < 18 yo
i) Pregnant women
j) Prisoners

4.3 Inclusion of Women, Minorities, and Other Underrepresented Populations

Recruitment is open to all minorities and both genders.

5.0 CONCOMITANT MEDICATION

Because there is a potential for interaction of gabapentin with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator (or Protocol Chair) should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.1 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. They will be given two options:

1) Removal from the study entirely (no medication and no follow up); or
2) Removal from taking the study medication and remain in the study for follow up only.

Patients who wish to stop taking the study medication will have the opportunity to remain in the study for long-term follow-up. The study will continue to monitor these patients for safety and to ensure that their pain is appropriately monitored and documented.

The investigator also has the right to withdraw patients from the study for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient demonstrates disease progression;
- Patient experiences unacceptable toxicity;
- Start of a new treatment cycle is delayed for > 28 days as a result of toxicities at least possibly related to study treatment;
- Patient becomes pregnant;
- Patient is lost to follow-up;
- The study is terminated.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the Final Visit.

Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the IRB The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to institutional, federal and any other appropriate committees and/or sponsors.

6.0 STUDY EVALUATIONS

6.1 Treatment Phase

- Treatment will consist of daily gabapentin or placebo during the first 30 days post operatively from head and neck free flap surgery

6.2 End of Treatment Visit

- Treatment will end on post-operative day 30 after which the drug (gabapentin or placebo) will be weaned over the next 7 days

6.3 Follow-up Phase

- Patients will have daily in-person follow-up while admitted (usually POD 1-7). Patients that are discharged prior to POD 7 will receive daily questionnaires as seen in appendix A. Patients will also follow up in clinic 1 week after discharge and 4 weeks post operatively from surgery.

6.4 Efficacy and Safety

- Gabapentin is a commercially available medical drug that has been shown to be safe and effective in the clinical setting, including in the Otolaryngology patient population.

7.0 DRUG INFORMATION

7.1 Gabapentin

7.1.1 Formulation, Packaging, and Handling

The investigational product will be prepared, stored and dispensed by the Investigational Drug Service (IDS) Pharmacy. The contents of each dose will be blinded by IDS and the unblinding key stored in IDS.

7.1.2 Disposal and Destruction

Drug supply will be disposed of according to institutional standard operating procedure. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

8.0 STUDY CALENDAR

Evaluation	Pre-operative	Peri-operative	POD 1-7 (daily)[1]	1 week after discharge	4 weeks after surgery	30 days post-op (Phone Call)
Inclusion/exclusion criteria	X			± 4 days	± 4 days	
Demographics	X					
Medical History	X					
Physical Exam[3]	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Basic Metabolic Panel lab	X		X[2]	X[6]		
Visual Analog Scale for Pain Assessment	X	X	X	X	X	X
Daily morphine equivalents[5]	X	X	X	X	X	X
Narcotics-related complications[4]	X		X	X	X	X
Study Medication Compliance				X	X	X
Post-operative complications			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medications		X	X	X	X	X

Evaluation	Pre-operative	Peri-operative	POD 1-7 (daily)[1]	1 week after discharge	4 weeks after surgery	30 days post-op (Phone Call)
1: If discharged before Post-Operative Date 7, patients will keep track of narcotics-related complications with a home data collection form (Appendix A). Patients must remain inpatient at least 2 days. 2: Lab data will be required during pre-operative and on the day of discharge. 3: Physical Exam includes height, weight, performance status, clinical tumor measurements (if applicable). 4: Narcotic-related complications includes nausea, hypotension, delirium, and syncope. 5: Daily morphine equivalents extracted from medication provided during pre-operation, surgery (APPENDIX B), and post-operation. 6: Only patients who experience a clinically significant change in creatinine that leads to a study dose adjustment will be required to have a 1 week post-discharge follow up lab draw to review creatinine stability.						

9.0 SAFETY AND REPORTING REQUIREMENTS

9.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol, an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

9.2 Adverse Event Documentation

Any patient enrolled in the trial who signed the consent form and received at least one dose of Gabapentin will be eligible for adverse event reporting.

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, action taken and outcome.

9.3 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction, which hypothetically might have caused death if it were more severe).

- Requires inpatient **hospitalization or prolongation of an existing hospitalization**
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event or reaction**. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Clarification should be made between the terms serious and severe because they ARE NOT the same. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.4 Procedures for Reporting Serious Adverse Events (SAEs)

9.4.1 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

9.4.2 Follow-up of Adverse Events and Serious Adverse Events

The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented on the CRF.

In addition, any known untoward event of any severity that occurs subsequent to the AE reporting period that the Investigator assesses as at least possibly related to the study therapy (i.e., the relationship cannot be ruled out) should also be reported as an AE.

10.0 RISKS TO SUBJECTS

10.1 Risk of loss of Confidentiality

The study poses the risk of loss of confidentiality. The risk will be minimized through the data collection and banking processes described in Section 12.

10.2 Risk of Gabapentin

Gabapentin Drug related risks include: [26](Kaye 2017)

- Somnolence (15.2%)
- Dizziness (10.9%)
- Asthenia (6.0%)
- Headache (4.8%)
- Nausea (3.2%)
- Ataxia (2.6%)
- Weight gain (2.6%)
- Amblyopia (2.1%)

Additionally, rare and serious side effects of gabapentin include [27](Pfizer 2017)

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),
- Anaphylaxis and angioedema,
- Withdrawal-precipitated seizure,
- Suicidal ideation,
- Increased risk of pancreatic tumors (rats only), and
- Sudden and unexplained death (in epileptic patients)

Patients taking gabapentin are advised against driving or operating heavy machinery until they have sufficiently assessed the individual effects of the medication impairing their ability to drive.[27](Pfizer 2017)

Addiction

Gabapentin abuse is considered low due to its low potential for addition compared to opioids. However, there is a new trend of gabapentin abuse in group of patients who are already abusing opioids. The abuse not been clinically validated, but spikes in gabapentin-related fatalities have led several states to register Gabapentin as a controlled substance (Virginia, Ohio, Kentucky, and West Virginia). A meta-analysis study by Bonnet and Scherbaum (2017) examined the addictive potential of gabapentin through evaluating several dimension and concluded that current literature does not offer strong evidence to support the addictive effects of gabapentin.[28] Although recent health care policy has reclassified gabapentin as a controlled substance in certain states, this reclassification is based on its potential for abuse.[29] Potential for abuse does not reflect potential for addiction. The medication has been deemed an opportunistic drug for

abuse due factors such as low cost, national classification as a non-controlled substance, and increasing rates of on- and off-label prescribing, and not necessarily due to addictive potential.[29]

10.3 Placebo Risk

During this study, there is a 50% chance that a subject will receive a placebo. There is no anticipated risk associated with placebo treatment, as both groups of study participants will receive standard anesthesia and pain management plan post-surgery. The patients in placebo group may take higher amount of narcotic pain medication compared to those in the gabapentin group. This is not proven yet, and the narcotic medication intake amount is the primary outcome measure of the study. The researchers will carefully monitor the pain score reported by the participants. Study participants may withdraw from the study if the pain is not managed.

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

There are/may be risks to a fetus if a participant become pregnant while participating in this study.

A patient will not be a surgery candidate if she is pregnant, and therefore pregnant patients will not be eligible for the study.

10.5 Risk Associated with Randomization

The patient will be assigned to a study group at random (by chance) in order to avoid any bias in data collection or data analysis. The treatment group a subject is assigned to might not be the group the subject 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.

10.6 Mitigating Potential AE: Post-op Prerenal Disease

In the event that a patient develops increased serum creatinine levels during their inpatient stay, they will be allowed to remain in the study at the discretion of the PI and placed on a pharmacy adjusted at-home dose. Serum creatinine will be routinely screened pre-operatively and prior to discharge. If the patient develops a clinically significant increase in serum creatinine, the IDS will be informed and will provide a dose adjustment for the at-home patient dosing (See Table 2). Patients who have clinically significant changes in their inpatient labs will routinely require follow-up labs to be reviewed during their outpatient appointments. The study will review the 1-week post-discharge routine basic metabolic panel lab draws for patients that experience post-op prerenal disease. Further dose adjustments or patient withdrawal will be required if the creatinine level have worsened at the 1-week post-discharge office visit. Patient withdrawal will occur at the PI's discretion. The underlined sections in the Patient Discharge Instructions (Appendix D) will be corrected based on PI discretion using the following dose adjustment guidelines:

Table 2: Dose adjustment guidelines

Creatinine Clearance (mL/minute)	Normal Titration Schedule	Tapering Schedule
30–59	300mg TID	300mg BID 3 days, 300mg QD 4 days
15–29	300mg BID	300mg QD 7 days
<15 not on hemodialysis	300mg QD	100mg QD 7 days

10.7 Mitigating Suicidal Ideation

Patients will be routinely evaluated for suicidal ideation during their office visits. Standard of care evaluations will be used to identify and manage treatment options for study patients. Patients will be removed from the study at the discretion of the PI.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design and Overview of Primary and Secondary Endpoints

The subjects will be randomly assigned to control group and intervention group. Intention-to-treat analysis will be performed to the data. The intervention and control groups will be compared for similarity of age, sex, weight, prior therapy, type of surgery, and the presence or absence of pre-operative opioid use to ensure adequate randomization.

- **Primary outcome: daily morphine equivalent units measured repeatedly over the 1st week**
- **Exploratory outcome: total morphine equivalent units accumulated over 1 month**
- **Secondary outcomes for side effects:**
    a. Pain score (measured as 0-10) measured daily over 1 month.
    b. Binary outcomes measured daily over 1 month (including nausea, vomiting, dizziness, sedation, pruritis, urinary retention, and delirium).
    c. Length of stay and costs over 1-month (readmission is not included).

We expect to have about 15% attrition during the 1-month follow-up time, and most dropouts will occur after 1 week due to discharge at Day 7. To handle the dropouts, longitudinal analyses will be performed to explore the effects and association with covariates, using likelihood-based method based on missing-at-random (MAR) assumption. In addition, imputation methods will be performed whenever necessary, and sensitivity analysis will be conducted.

11.2 Sample Size Estimation /Accrual Rate

The primary outcome measure is the daily morphine equivalent units measured repeatedly over the 1st week. Each subject is measured 7 times at consecutive 7 days after surgery. Assume the null hypothesis is that the difference of daily morphine equivalent means between two groups is 0 over the 1st week. Based on previous studies, we expect that the intervention will reduce 50%

daily morphine equivalents from 40mg/day in control group (ie, 20mg/day in intervention group). Due to the fact that previous studies did not have data for the repeated measures over the 1st week, we assume that the means of daily morphine equivalent at the consecutive 7 days are constantly 20mg/day in intervention group, and constantly 40mg/day in control group under alternative hypothesis. We assume the standard deviation is 30 for both groups, and the correlation between repeated measures is 0.9. Therefore, sample sizes of 45 patients per group (total 90) achieve power of 91% to detect the above difference of means between two groups, with a significance level (alpha) of 0.05. This is based on a two-sided repeated-measure ANOVA test. Considering 5-10% attrition over the 1st week, we will need additional 5 patients per group, resulting total 50 patients per group (total 100). We will plan an interim analysis after enrollment and data collection of the first 50 total patients (25 in each group) to assess statistical significance.

Due to no precise data from previous studies, the above sample size justification is based on some assumptions. After 50 patients have been enrolled, we will further refine the sample size calculation with the obtained data.

11.3 Evaluation of Efficacy

For the primary outcome, repeated-measure ANOVA test will be used to evaluate the effect of the intervention on daily morphine equivalent units over the 1st week. Exploratory longitudinal analysis will also be conducted, using linear mixed-effect model to explore the treatment effect change over time and association with covariates.

For total morphine equivalent units accumulated over 1 month, Wilcoxon rank sum test will be performed to test the effect of intervention. Additionally, multivariate linear regression analysis adjusted with covariates will be conducted.

11.4 Evaluation of Safety

Daily pain score over 1 month will be tested using repeated-measure ANOVA test. Linear mixed-effect model will also be performed to explore the change of pain score over time and association with covariates.

Daily binary outcomes over 1 month (including nausea, vomiting, dizziness, sedation, pruritis, urinary retention, and delirium) will be analyzed used mixed-effect logistic regression to evaluate the side effect of intervention over time and the association with covariates.

Length of stay and costs over 1-month will be compared between two groups using Wilcoxon rank sum test. Additionally, multivariate linear regression analysis adjusted with covariates will be conducted as exploratory analysis.

12.0 ADMINISTRATIVE REQUIREMENTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The protocol, Investigator's Brochure, informed consent, advertisements, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

12.3 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Patient Registration Form.

12.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the patient prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

12.5 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the Glassrock building. Medical records of patients

will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from UC Davis Office of Research or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.6 Protocol Compliance and Deviations

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies. Any departures from the protocol must be fully documented in the source documents.

12.7 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of the drug

12.8 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.9 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan. Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

12.10 Provisions to Monitor the Data to Ensure the Safety of Subjects

a) The PI will be responsible that the following are carried out:
- Ensure that the protocol is being followed
- Ensure that informed consent is documented
- Ensure that changes to the protocol are approved by the UC Davis IRB
- Ensure that accurate and complete records are being maintained by the site
- Ensure that accurate and complete reports are being made to UC Davis IRB
- Ensure that the information in the investigator's report is complete, accurate, and legible
- Ensure that there are no omissions in the reports of data that may be directly or indirectly relevant to the study
- Ensure that missing examinations are noted in the reports
- Ensure that subjects failing to complete the study are noted along with the reason for such failure
- Follow IRB policies for reporting of Adverse Events/Serious Adverse Events

12.11 Data Banking

Data sheets used in the collection of PHI and generation of the recruitment database will be destroyed upon completion of the recruitment process. No data will be disclosed from the study. We assure that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

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14.0 APPENDICES

14.1 APPENDIX A:

HOME DATA COLLECTION SHEET

TO BE FILLED OUT BY THE PATIENT IF DISCHARGED EARLY UNTIL POD 7

Patient Name:

Patient MRN:

1st day after discharge

1. Did you have nausea over the last 24 hours? (yes or no)
2. Did you vomit over the last 24 hours? (yes or no)
3. Did you have a bowel movement over the last 24 hours? (yes or no)
4. How would you rate your activity over the last 24 hours? (please circle only 1)
    a. 0 - did not make it out of bed
    b. 1 - out of bed to bathroom or chair
    c. 2 - ambulated around house
    d. 3 - ambulated outside of house
    e. 4 - return to baseline activity
5. How many times did you take narcotic medication over the last 24 hours? ____
6. How many mg total of narcotic did you take over the last 24 hours? ___
7. Please rate your pain right now on a scale of 1-10 ___

Patient Name:

Patient MRN:

2nd day after discharge

1. Did you have nausea over the last 24 hours? (yes or no)
2. Did you vomit over the last 24 hours? (yes or no)
3. Did you have a bowel movement over the last 24 hours? (yes or no)
4. How would you rate your activity over the last 24 hours? (please circle only 1)
    - 0 - did not make it out of bed
    - 1 - out of bed to bathroom or chair
    - 2 - ambulated around house
    - 3 - ambulated outside of house
    - 4 - return to baseline activity
5. How many times did you take narcotic medication over the last 24 hours? ____
6. How many mg total of narcotic did you take over the last 24 hours? ___
7. Please rate your pain right now on a scale of 1-10 ___

Patient Name:

Patient MRN:

3rd day after discharge

1. Did you have nausea over the last 24 hours? (yes or no)
2. Did you vomit over the last 24 hours? (yes or no)
3. Did you have a bowel movement over the last 24 hours? (yes or no)
4. How would you rate your activity over the last 24 hours? (please circle only 1)
    - 0 - did not make it out of bed
    - 1 - out of bed to bathroom or chair
    - 2 - ambulated around house
    - 3 - ambulated outside of house
    - 4 - return to baseline activity
5. How many times did you take narcotic medication over the last 24 hours? ____
6. How many mg total of narcotic did you take over the last 24 hours? ___
7. Please rate your pain right now on a scale of 1-10 ___

Patient Name:

Patient MRN:

4th day after discharge

1. Did you have nausea over the last 24 hours? (yes or no)
2. Did you vomit over the last 24 hours? (yes or no)
3. Did you have a bowel movement over the last 24 hours? (yes or no)
4. How would you rate your activity over the last 24 hours? (please circle only 1)
    - 0 - did not make it out of bed
    - 1 - out of bed to bathroom or chair
    - 2 - ambulated around house
    - 3 - ambulated outside of house
    - 4 - return to baseline activity
5. How many times did you take narcotic medication over the last 24 hours? ____
6. How many mg total of narcotic did you take over the last 24 hours? ___
7. Please rate your pain right now on a scale of 1-10 ___

Patient Name:

Patient MRN:

5th day after discharge

1. Did you have nausea over the last 24 hours? (yes or no)
2. Did you vomit over the last 24 hours? (yes or no)
3. Did you have a bowel movement over the last 24 hours? (yes or no)
4. How would you rate your activity over the last 24 hours? (please circle only 1)
    - 0 - did not make it out of bed
    - 1 - out of bed to bathroom or chair
    - 2 - ambulated around house
    - 3 - ambulated outside of house
    - 4 - return to baseline activity
5. How many times did you take narcotic medication over the last 24 hours? ____
6. How many mg total of narcotic did you take over the last 24 hours? ___
7. Please rate your pain right now on a scale of 1-10 ___

14.2 APPENDIX B:

INTRA OP DATA COLLECTION SHEET

TO BE FILLED OUT BY THE ANESTHESIA PROVIDER AT THE END OF SURGERY

PLACE IN STUDY ENVELOPE WHEN COMPLETE

Anesthesia Provider(s):

Anesthetic agents used:

- Request standard anesthetic to include Inhalational anesthetics (sevoflurane/desflurane), +/- propofol drip, and IV narcotic infusion of choice (remifentanyl, fentanyl, sufentanil). Please specifically avoid nitrous oxide and as an anesthetic agent and ketorolac as pain adjunct.
- Request that anesthetic adjuncts such as IV ketamine (drip or bolus) and IV Dexmedetomidine (drip or bolus) be withheld by the anesthesia team, unless deemed medically necessary.
- Request that 1000 mg of IV Tylenol be provided as first dose 1 hour prior to surgery and then be dosed at a dose of 1000 mg every 8 hours intra operatively for surgery lasting > 8 hours

Induction:

Versed IV dose: _____

Fentanyl IV dose: _____

Propofol IV dose: _____

Neuromuscular blocking agent: agent:_____ dose: _____

Maintenance:

Inhalational anesthesia:

Agent: _____ %: _____

Propofol drip: Total dose:_____

IV narcotic:

Remifentanyl: Total dose: _____

Sufentanil: Total dose _____

Adjuncts (if used)

Agent 1 _____

Dose and timing (from incision start): _____

Reason? _____

Agent 2 _____

Dose and timing (from incision start): _____

Reason? _____

Agent 3 _____

Dose and timing (from incision start): _____

Reason? _____

14.3 APPENDIX C:

RESEARCH DOSE DIARY

TO BE FILLED OUT BY PATIENTS AFTER DISCHARGE

	Did you take all three doses?	If no, please check which dose you missed	Did you take any medications other than your discharge medications?	If Yes, please list what you took: Drug Name, Amount taken (mg or mL), and why
Day 1	Yes No	Morning □ Afternoon □ Night □	Yes No	
Day 2	Yes No	Morning □ Afternoon □ Night □	Yes No	

Day 3	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 4	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 5	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 6	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 7	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 8	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 9	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 10	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 11	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 12	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 13	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 14	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 15	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 16	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 17	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 18	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 19	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 20	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 21	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 22	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 23	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 24	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 25	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 26	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 27	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 28	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 29	Yes No	Morning □ Afternoon □ Night □	Yes	No	
Day 30	Yes No	Morning □ Afternoon □ Night □	Yes	No	

You have completed your 30-day regiment and you can begin to wean off the medication. For the next **3 days**, please take the medication **300mg Twice a Day** (Morning and Night). After 3 days, lower the dose again to **300mg Once a day** for **4 days**. After this, you will be done with the study medication.

If you have any questions, Call Angela (Study Coordinator) at 916-734-2704

If you miss a dose, wait and take your normal next dose. Do not double up your doses.

14.4 APPENDIX D:

STUDY DISCHARGE INSTRUCTIONS

TO BE PROVIDED TO PATIENT PRIOR TO DISCHARGE

STUDY DISCHARGE INSTRUCTIONS

You are participating in a randomized research study that requires you to take medication at home. You have been provided a bottle of the study medication and a home diary. Please avoid driving until after at least 7 days post-op.

Instructions for Medication Use

Your study medication bottle holds enough liquid for _____days.

Since you have been in the hospital, you have been given 300mg three times per day. Continue this medication routine while you are at home. Most patients will take it in the morning, afternoon, and at night. This medication can be taken with or without food. Below are instructions on how to measure the correct volume of medication.

- Ensure that you fill the syringe until the **6mL** mark for the full 300mg dose.
- Once you have finish taking your oral dose, clean the syringe by flushing it with water.

If you missed a dose, document it in your dose diary. Skip the missed dose if it is almost time for your next scheduled dose. **Do not** take extra medicine to make up the missed dose.

Do not stop taking this medication without first talking to your Study Doctor.

After 30 days, we will ask you to wean yourself off the medication. For 3 days (Day 31-33), take 300mg twice a day. You will then take 300mg once for 4 days (Day 34-37).

Follow up

Your next scheduled appointment with Dr. _____ is _____

***Please bring all your discharge and study medications to this visit.**

Diary

You have been provided a Research Dose Diary to help you keep track of your compliance. Complete this form once a day while taking this medication at home.

***Please bring your diary to your next office visit.**

Contact

If you start to feel any of the following unnatural side effect, please contact the Clinical Trials team at 916-734-2704: Lack of coordination, unusual changes in mood or behavior, or seizures.

Non-emergent medical problems or questions, please call the Otolaryngology-HNS clinic at 916-734-5400 during the daytime on weekdays. For emergent issues, please proceed immediately to the ER.